

**Dissertation**

**Functional Proteomics and Metabolomics for the Study of  
Cancer Metabolism**

submitted by

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## Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research of this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I follow the guidelines of “Good Scientific Practice”

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## Abbreviations

|         |                                                           |
|---------|-----------------------------------------------------------|
| ABP     | Activity based probe                                      |
| ATGL    | Adipose triglyceride lipase                               |
| bp      | base pair                                                 |
| BSA     | Bovine serum albumin                                      |
| Cas     | CRISPR associated                                         |
| CRISPR  | Clustered regularly interspaced short palindromic repeats |
| DNA     | Deoxyribonucleic acid                                     |
| DSB     | Double strand break                                       |
| DTT     | Dithiothreitol                                            |
| FACS    | Fluorescence assisted cell sorting                        |
| FBS     | Fetal bovine serum                                        |
| GLDC    | Glycine dehydrogenase                                     |
| HCD     | Higher-energy collisional dissociation                    |
| HDR     | Homology directed repair                                  |
| HPLC    | High performance liquid chromatography                    |
| Kb      | kilpbase                                                  |
| KO      | Knockout                                                  |
| MS      | Mass spectrometry                                         |
| MTBSTFA | N-methyl-N-[tert-butyl-dimethylsilyl]trifluoroacetamide   |
| NHEJ    | Non-homologous end joining                                |
| NHS     | N-Hydroxysuccinimid                                       |
| ORF     | Open reading frame                                        |

|       |                                                |
|-------|------------------------------------------------|
| PAM   | Protospacer adjacent motif                     |
| PBS   | phosphate buffered saline                      |
| PCR   | Polymerase chain reaction                      |
| PLBD2 | Putative Phospholipase B-like 2                |
| PSM   | peptide spectrum match                         |
| PTM   | Post translational modification                |
| PVDF  | Polyvinylidene fluoride                        |
| RFP   | Red fluorescent protein                        |
| RP    | Reversed phase                                 |
| SIRM  | Stable isotope resolved metabolomics           |
| SDS   | Sodium dodecyl sulfate                         |
| TALEN | Transcription activator-like effector nuclease |
| TCA   | trichloroacetic acid                           |
| TEAB  | Triethylammonium bicarbonate                   |
| TLC   | Thin layer chromatography                      |
| WT    | Wildtype                                       |
| ZFN   | Zinc-finger nucleases                          |

## Zusammenfassung

Krebserkrankungen sind unter anderem durch Veränderungen im Metabolismus von Zellen charakterisiert. Die wahrscheinlich bekannteste metabolische Anpassung von Krebszellen ist die erhöhte Aufnahme von Glukose, 1930 von Otto Warburg beschrieben. Allerdings sind die Veränderungen nicht nur auf den Glukose-Metabolismus beschränkt. Auch der Auf- und Abbau von Lipiden kann sich in Krebszellen wandeln. Diese Arbeit beschäftigt sich mit dem Schlüssel-Enzym im Abbau von Triglyzeriden, der „Adipose Triglyzerid Lipase“ (ATGL), und dessen Einfluss auf den Krebsstoffwechsel. In vorangegangenen Experimenten wurde entdeckt, dass der Verlust von ATGL (ATGL-KO) zu einem Wachstumsvorteil von B-Zell-Tumoren führt. Im ersten Kapitel dieser Arbeit sollen nun die genauen Mechanismen, die für diesen Wachstumsvorteil verantwortlich sein könnten, untersucht werden. Überraschenderweise konnten mittels stabiler Isotopen aufgelöster Metabolomik, radioaktiven Nährstoffaufnahme- und Einbau-Experimenten keine metabolischen Unterschiede im zentralen Kohlenstoff- und Fettsäuremetabolismus in den Zellen gefunden werden, die diesen Wachstumsunterschied erklären. Mit der Hilfe von aktivitätsbasierten Proteom-Analysen konnte aber eine unbekannte Serinhydrolase mit potentieller Phospholipase Aktivität (PLBD2) identifiziert werden, die eine höhere Aktivität in ATGL-KO Zellen aufweist und die Abwesenheit von ATGL partiell kompensieren könnte. Das native Substrat von PLBD2 ist allerdings noch unbekannt. Mittels quantitativer Proteom-Analysen konnte außerdem eine erniedrigte Expression der Glyzin Dehydrogenase (GLDC), ein Enzym des Einkohlenstoffmetabolismus, in ATGL-defizienten B-Zellen erkannt werden. Ein direkter Zusammenhang mit dem Wachstumsvorteil durch die erniedrigte GLDC Proteinexpression muss aber erst noch gezeigt werden. Des Weiteren wurde CRISPR-Cas9 dazu genutzt eine Lungenkrebs-Zell-Linie (A549) zu generieren welcher ATGL fehlt. Dieses neue Modell konnte die Ergebnisse in den B-Zellen nicht bestätigen, da die ATGL-defizienten Lungenkrebszellen keinen Wachstumsvorteil aufweisen. Dies führt zu der Annahme, dass ATGL gewebe-spezifischen Einfluss auf das Fortschreiten von Krebs hat und könnte in Zukunft für die Diagnose und Beobachtung von Krebserkrankungen dienen.

Das zweite Kapitel dieser Arbeit beschäftigt sich mit der Bedeutung von korrekten Datenbankeinträgen auf die Identifikation von Proteinen bei der Auswertung von Massenspektrometrie-Daten. Trypsin ist ein Enzym, das häufig in Standard-Proteomikexperimenten zum Verdau von Proteinen verwendet wird. Dieses Trypsin ist in den meisten Fällen modifiziert, um einen Selbstverdau und den daraus resultierenden Verlust der Enzymaktivität zu minimieren. Modifiziertes Trypsin jedoch befindet sich nicht unter den Datenbankeinträgen, die zur Identifizierung von Peptiden und Proteinen aus Massenspektren verwendet werden. Hier wird nun gezeigt, dass modifiziertes Trypsin unbedingt in der Datenbank vorhanden sein sollte, da es sonst zu schwerwiegenden falsch-positiven Identifizierungen von Proteinen kommt. Des Weiteren wird hier eine einfache und schnelle Lösung für die Implementierung von modifiziertem Trypsin in Datenbanken dargestellt, welche die falsch-positive Zuordnung sowie negative Einflüsse auf die Ergebnis-Statistik verhindert.

## Abstract

Altered metabolism is one of the hallmarks of cancer. This is not limited to the well-known changes in glucose metabolism, but also includes changes in anabolism and catabolism of lipids in cancerous tissues and cells. The first chapter of this thesis investigates the impact of adipose triglyceride lipase (ATGL), the rate limiting enzyme in lipid degradation, on metabolism of cancer. As cancer model, B-cell tumors lacking ATGL (ATGL-KO), which have been shown to exhibit a growth advantage in mice, were used. The aim here was to depict metabolic mechanisms which might be responsible for this enhanced growth rate. However, no significant metabolic changes could be observed in ATGL-KO as compared to control cells by stable isotope resolved metabolomics, radioactive nutrient uptake and tracing and other biochemical tests in central carbon and fatty acid metabolism, which could explain the growth advantage. Interestingly, activity-based proteomics revealed an increased unknown serine hydrolase activity (of a putative phospholipase like protein named PLBD2) which might partly compensate for the loss of ATGL. However the native substrate of PLBD2 remains to be identified. Moreover, quantitative proteomics showed the downregulation of glycine dehydrogenase (GLDC), among other proteins, in ATGL-KO cells. This enzyme is involved in one-carbon metabolism. But a causal relationship remains to be established. The use of CRISPR-Cas9 to knock out ATGL in lung cancer cells (A549) led to a complete depletion of the enzyme and thus provided another cell model for the investigation of ATGL in cancer. However, in contrast to B-cells, the lack of ATGL rather decreased growth of the lung cancer cells. These contradictory results may hint toward a tissue-specific role of ATGL that can be very important in diagnosis and progression of cancer.

In the second chapter this thesis shows the importance of including modified trypsin in proteomic database searches. Trypsin is the most common protease used in bottom-up proteomics workflows. In order to avoid the autolysis of trypsin, the enzyme is usually chemically modified. However, here it is shown that the modification is not complete and furthermore does not fully protect from autolysis. This results in the presence of modified peptides of trypsin in the sample. During downstream analysis, the modified peptides, if not included in the protein database, can lead to false positive identifications. Due to the high abundance of

trypsin in digests modified peptides could be identified in large amounts. If modified trypsin was not included in the database these modified peptides were found to lead to misassignments in 18 % of analyzed publically available projects. Here a database search method is presented which includes modified trypsin. This easily implementable method avoids false positive assignments, while the increase in search space stays minimal and thus omits impaired result statistics.

## **Chapter One – Metabolic Changes in Cancer related to ATGL**

## 1. Preamble

This work aims to investigate the influence of the lipolytic enzyme adipose triglyceride lipase on cancer progression. Little is known about the impact of this enzyme and further knowledge might contribute to the development of potential drug targets in cancer therapy.

## 2. Introduction

In 1930 Otto Warburg first described the unusually high consumption of glucose by cancer cells even in the presence of oxygen. Today known as the “Warburg effect”, glycolysis under aerobic conditions only partially accounts for reprogrammed energy metabolism, one of the hallmarks of cancer. Besides glucose, other metabolic fuels like amino acids and lipids have an essential impact on cancer progression.

### 2.1. Hallmarks of cancer

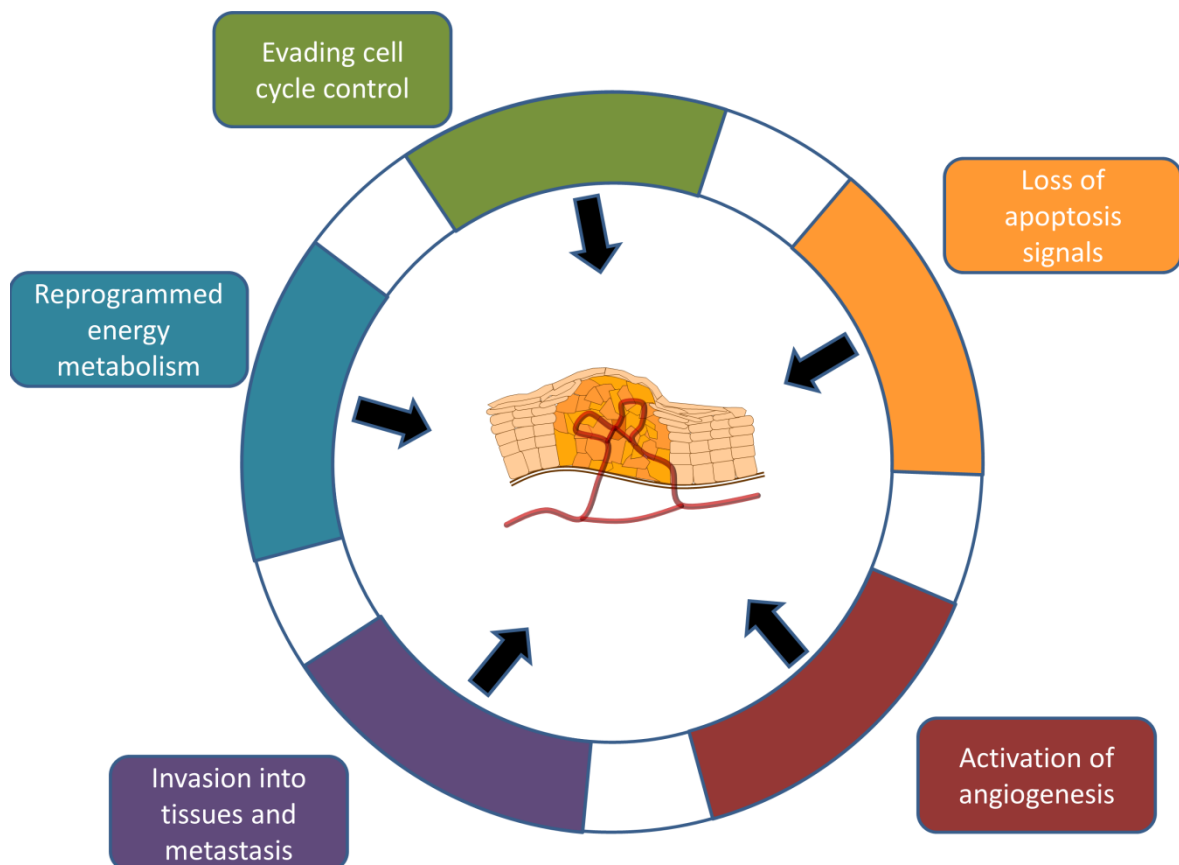


Figure 1: Overview of cancer hallmarks. Figure adapted from Hanahan and Weinberg (1)

The uncontrolled growth of cancer cells is made possible by several different mechanisms (reviewed in (1, 2); Figure 1). First, cell cycle control, which in normal

cells ensures maintenance of cell number, can be altered in a way that allows cancer cells to keep proliferating. On the one hand this can be achieved by the constant/uncontrolled expression of growth factors (or sustained activation of growth factor receptors) or on the other hand by escaping natural growth suppressors. Second, apoptosis, programmed cell death, is avoided in cancer cells, thereby eliminating natural clearance of cells. Third, with increasing tumor size nourishment of tumors becomes challenging and requires angiogenesis, the formation of new blood vessels. Permanent activation of angiogenesis enables the tumor not only to be supplied with nutrients and oxygens but also to dispose of metabolic wastes and carbon dioxide. Fourth, cancer cells are characterized by their ability to invade other tissues and form metastases. Epithelial-mesenchymal transition, a process adapted from wound-healing and embryonic morphogenesis, enables cancer cells to invade other tissues and compartments. Fifth, in order to meet the requirements of enhanced growth, cancer cells reprogram their energy metabolism. This involves a metabolic switch to glycolysis, even under aerobic conditions, which requires an increased glucose import to meet the energy requirements and results in the increased production of lactate. This switch, however, also enables the production of necessary biosynthetic building blocks like nucleotides and amino acids. Metabolic reprogramming is now known to also include changes in metabolism of amino acids (e.g. glutamine and serine) and lipids (e.g. fatty acids).

## **2.2. Changes in central carbon metabolism in cancer**

Reprogramming of energy metabolism in cancer is very distinct in the pathways of central carbon metabolism. Central carbon metabolism (Figure 2) describes the conversion of carbon through glycolysis, gluconeogenesis, the pentose phosphate pathway, and the citric acid cycle (TCA cycle). Besides the increased production of lactate in cancer cells many other changes in central carbon metabolism have been observed.

Catalyzing the essential first step in glycolysis, hexokinases are involved in the progression of cancer. Especially levels of the isoform hexokinase 2 (HK2) have been shown to be elevated in cancer cells (3, 4). Coelho et al reported that the activity of hexokinase (and phosphofructokinase) is highly enhanced in human

breast carcinoma tissues compared to non-tumorous tissues. Furthermore they found that the activity of both enzymes is positively correlated with aggressiveness and invasiveness of the tumor (5).

Increased lactate production, prominent in many tumor cells, has been reported to be induced by the M2 isoform of pyruvate kinase (M2-PK) (6). This isoform found in tumors is, unlike the M2 isoform present in e.g. lung cells, dimeric (in non-tumorous proliferating cells it is tetrameric). Hence this tumor specific isoform M2 is also called “Tumor M2-PK”. The dimeric M2-PK is close to being inactive, enabling an accumulation of metabolites upstream of phosphoenol-pyruvate which are then available as precursors for amino acid-, nucleotide- and phospholipid-synthesis (7).

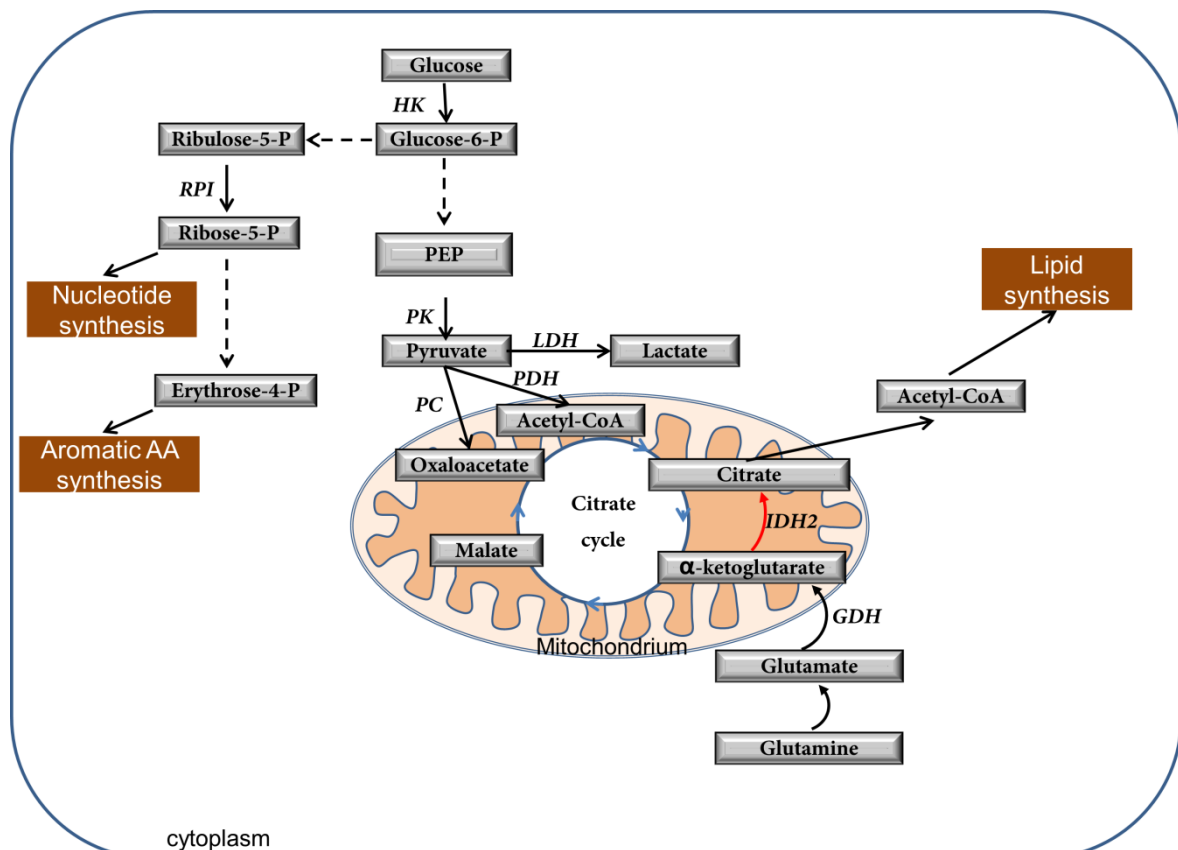


**Figure 2: Central carbon metabolism.** Shown is a simplified excerpt from central carbon metabolism. Enzymes HK: hexokinase; PK: pyruvate kinase; PC: pyruvate carboxylase; PDH: pyruvate dehydrogenase; LDH: lactate dehydrogenase; GDH: glutamate dehydrogenase; IDH2: isocitrate dehydrogenase 2; RPI: ribulose-5-phosphate isomerase.

Reductive carboxylation of  $\alpha$ -ketoglutarate in cancer cells supports the conversion of glutamine in the reverse citrate cycle in order to produce lipids and has been shown to be the pathway of choice in cancer cells with defective mitochondria (8).

### 2.3. One carbon metabolism

As cancer cells grow quickly they have an enhanced need for all cellular components. Cell growth requires not only glucose as fuel in order to produce ATP but also building blocks for the synthesis of e.g. proteins, lipids and nucleic acids. These building blocks can be provided by the metabolism of amino acids, e.g. serine and glycine. These two amino acids provide single carbon units that are cycled through folate metabolism and into catabolic processes to create the aforementioned building blocks (Figure 3).

This pathway was investigated in detail over the last years and it has been reported to be altered in cancer cells (9-11).

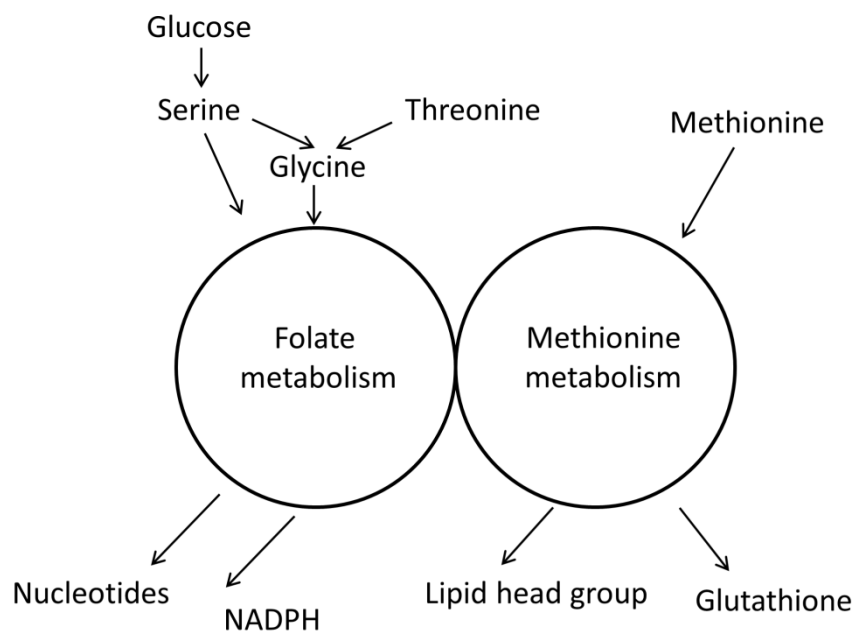


**Figure 3: Overview of one-carbon metabolism, adapted from (11)**

Serine and glycine are non-essential amino acids and degradation of both leads to the same set of metabolic precursors. Labuschagne et al proved that the two amino acids have different impact in different cell lines. Serine, even though it is a non-essential amino acid, is required in the growth medium for proliferation of cancer cells and a lack of extracellular serine attenuates nucleotide production (10).

## **2.4. Lipid metabolism and cancer**

Obesity, a condition characterized by excess body fat, has been linked to the occurrence of many types of cancer (12). The most common explanation for this connection is increased insulin resistance and higher levels of inflammation (reviewed in (13) and (14), respectively). Another explanation was provided by Louie et al who found that the incorporation of exogenous fatty acids into structural and oncogenic signaling lipids is significantly increased in aggressive cancer cell lines (15).

Besides the systemic accumulation of fat, lipids play an important role in cancer on a molecular basis. Excess carbohydrates can be stored as fat (Figure 4). The first enzyme in that pathway is citrate lyase, catalyzing the generation of acetyl-CoA from citrate. Acetyl-CoA carboxylase (ACC), the primary rate-limiting enzyme in fatty acid synthesis, then synthesizes malonyl-CoA. The chemical inhibition of ACC has been shown to result in impaired growth of cancer cells (16). Likewise the inhibition of fatty acid synthase, a multi-enzyme protein synthesizing palmitate from acetyl-CoA and malonyl-CoA, leads to growth inhibition in some cancer cell lines and was reported to be expressed at high levels in human cancer cells (reviewed in (17)). Both enzymes play a critical role in cancer which underlines the dependence of cancer cells on endogenous fatty acids (18).

Cholesterol is one of the main components of cellular membranes and is also involved in cell signaling. Several studies report that high cholesterol levels in the blood increase prostate cancer risk and that cholesterol accumulates in prostate cancer cells (19). Llaverias et al also reported a positive correlation between blood cholesterol levels and growth rate and metastatic potential of breast cancer (20).

Phospholipids are important building blocks for cellular membranes. Lysophosphatidic acid (LPA), one of the simplest phospholipids, contains only one fatty acid residue and serves as a precursor for more complex phospholipids. Furthermore LPA is an important signaling molecule which has been associated with cancer. The broad spectrum of LPA's involvements includes the stimulation of cell proliferation, migration and survival, but also the promotion of wound healing. LPA levels in serum were found to be increased in malignant effusions (reviewed by Mills and Moolenaar (21)).

Also catabolic pathways have been shown to be involved in cancer progression. Monoacylglycerol lipase (MGL), the final enzyme in triglyceride degradation, is more active in aggressive cancers than their less aggressive counterparts. It was shown that the increased activity of MGL leads to an elevated availability of protumorigenic signaling lipids such as LPA and prostaglandin E2, which in turn promote cell migration (22).

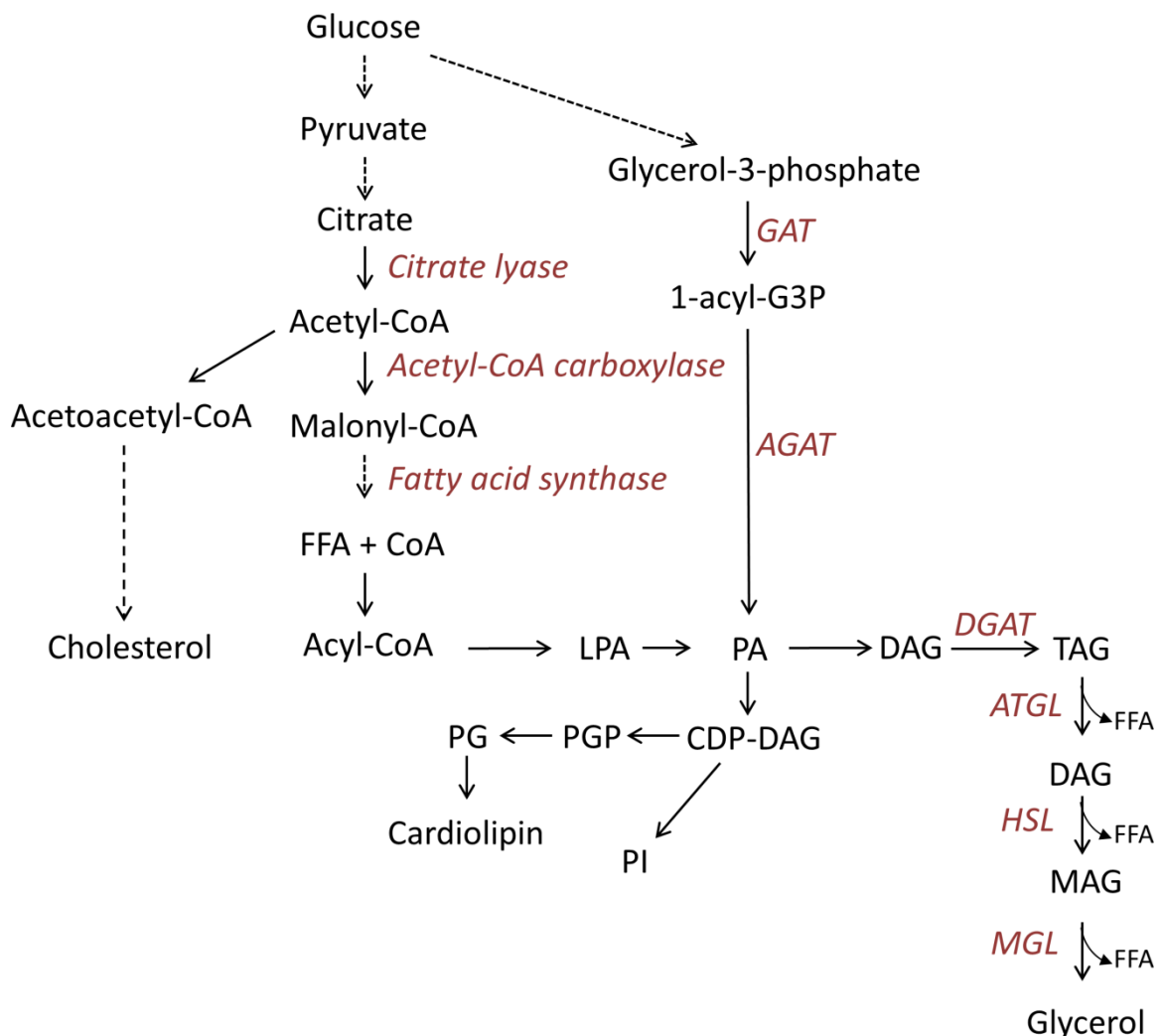


Figure 4: Simplified depiction of lipid metabolism reactions. In red are the enzymes that catalyze the reaction. GAT: Glycerol-3-phosphate acyltransferase; AGAT: 1-acyl-glycerol-3-phosphate acyltransferase; DGAT: Diacylglycerol-acyltransferase; ATGL: Adipose triglyceride lipase; HSL: Hormone sensitive lipase; MGL: Monoacylglycerol lipase

## 2.5. Adipose triglyceride lipase

Hormone-sensitive lipase (HSL) was once assumed to be the major enzyme in triglyceride degradation. About a decade ago, two groups independently published the discovery of adipose triglyceride lipase (ATGL) (23, 24) and showed that it catalyzes the first and rate-limiting step in triglyceride degradation with a ten times

higher affinity for triglycerides than HSL. This could explain the observation that HSL-KO mice were not obese and accumulated diglycerides instead of triglycerides (25).

The loss of ATGL has been shown to be protective against cancer-associated cachexia (26). However the impact of ATGL in cancer has been poorly investigated. Zagani *et al* claim that inhibition of ATGL would attenuate the growth of cancer cells (27). This contradicts Ou *et al* who showed that the loss of the ATGL activator CGI-58 promotes colon cancer growth, but they propose a cancer enhancing role independent of ATGL (28).

Considering the impact of ATGL on metabolism it might play a very important role in the progression of cancer.

## **2.6. Serine hydrolase activity based proteomics**

Activity based probes (ABP) are powerful tools to observe changes in enzymatic activity. The influence of ATGL on the lipase activity profile in cells can be investigated using ABP targeting serine hydrolases, as most lipases belong to the enzyme class of serine hydrolases.

ABP typically consist of a reactive group, a binding group and a reporter tag (29). The latter can, dependent on the application, be a fluorophore, an affinity tag or a so called biorthogonal linker group. These biorthogonal linker groups enable the use in living cells due to their small size and biological inertness. Once within the cell, the group can then be targeted with high specificity in a subsequent step for example by a click chemistry reaction.

Using click chemistry different fluorophores can be added to the ABP-labeled enzymes in a subsequent step. Then, just like in a differential gel electrophoresis (DIGE), samples labeled with different fluorophores can be mixed and analyzed together in a two-dimensional gel electrophoresis (2-DE) experiment (Figure 5). This approach was called differential activity based gel electrophoresis (DABGE) (30) and originally employed activity based probes already linked to fluorophores. These probes were used in homogenates rather than living cells. The smaller ABPs without fluorophore can directly target enzymes in living cells, thus all

enzymes are within their native subcellular compartment and optimal conditions for each individual target enzyme are ensured.

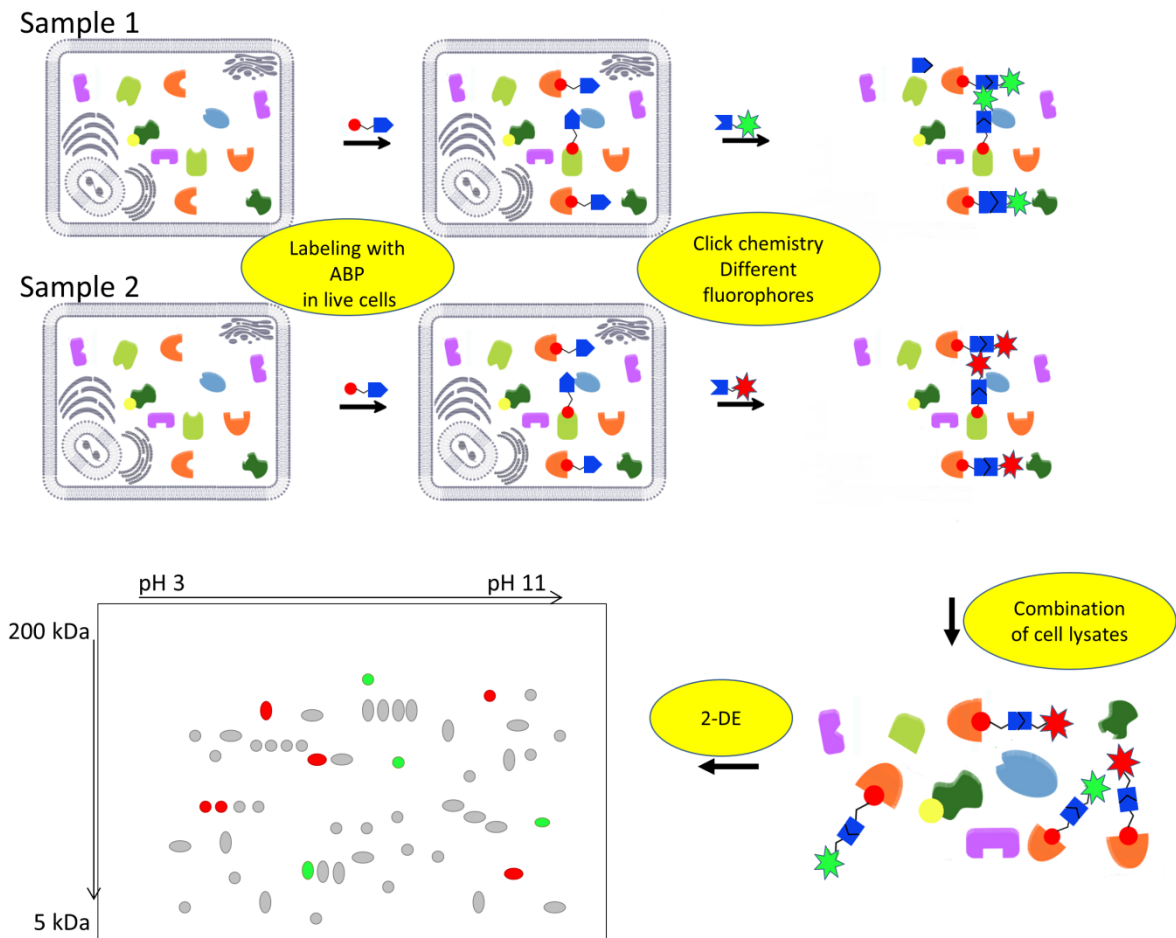


Figure 5: Differential activity based gel electrophoreses (DABGE). Shown here is the 2D-gel grey spots are unregulated

## 2.7. Genome editing

In order to investigate gene functions the complete inactivation of a gene is very helpful as it provides crucial information about the biological function, either in a cell line or a whole organism.

Knocking out genes in mice is done via homologous recombination in murine embryonic stem cells (ES cells). ES cells are totipotent and can differentiate into any cell type. If a targeting vector is provided exogenously, the gene of interest can be altered by homologous recombination in these ES cells. Once the vector is integrated into the genome of the ES cell, the ES cell can be injected into a blastocyst of a mouse and the resulting chimeric mouse will have the desired mutation in every cell of the organism (31). This process, however, is tedious and

inefficient due to the rare occurrence of homologous recombination events compared to random insertions.

The occurrence of homologous recombination can be increased by the introduction of double strand breaks in the target gene. New gene editing methods rely on this. Within the last 15 years Zinc-finger nucleases (ZFN) and transcription activator-like effector nucleases (TALEN) have emerged. Both, ZFN and TALEN induce double strand breaks by nucleases and have been extensively used in cell culture and whole animal knockout models (reviewed in (32) and (33), respectively).

The performance of zinc-finger nucleases is based on the cleavage domain of the nuclease *FokI* which is linked to a zinc-finger protein (34). The zinc-finger protein can be designed in a way to target the gene of interest; however, this design is not trivial.

TALENs are also based on the fusion of a DNA binding protein, here the TALE protein, to the nuclease *FokI*.

When the knockout of a protein is desired one can rely on Non-homologous end joining (NHEJ), which is error-prone and thus can lead to insertions or deletions (indels) in the target gene and a shift in the open reading frame (ORF) leading subsequently to the loss of the gene product. The other possibility is to use an exogenous repair template which allows the insertion of specific mutations via homology directed recombination (HDR) (as described above), but also the introduction of selection markers.

Similar to ZFNs and TALENs, the CRISPR-Cas9 system can be used for gene editing due to its ability to introduce a double strand break into target DNA (Figure 6). First discovered as an adaptive immune system in microorganisms, CRISPR-Cas9 has become a valuable method for genome editing in the last couple of years, due to its simplicity and efficiency.

Even though the first CRISPRs (clustered regularly interspaced short palindromic repeats) were first discovered in 1987 in *Escherichia coli* (35) the term only evolved in 2002 (36). Cas (CRISPR associated) genes translate into a family of

proteins which can function as nucleases, helicases, polymerases and polynucleotide-binding proteins.

Different Cas genes have been identified from different organisms. Today, the most commonly used is Cas9 from *Streptococcus pyogenes*. Cas9 targets a specific gene (via the “guide RNA” - gRNA) and, when adjacent to a protospacer adjacent motif (PAM), introduces a double strand break into the gene.

Hence CRISPR-Cas9 can be used for the complete and permanent loss of a targeted gene function and thereby generate stable protein knockouts (KO).

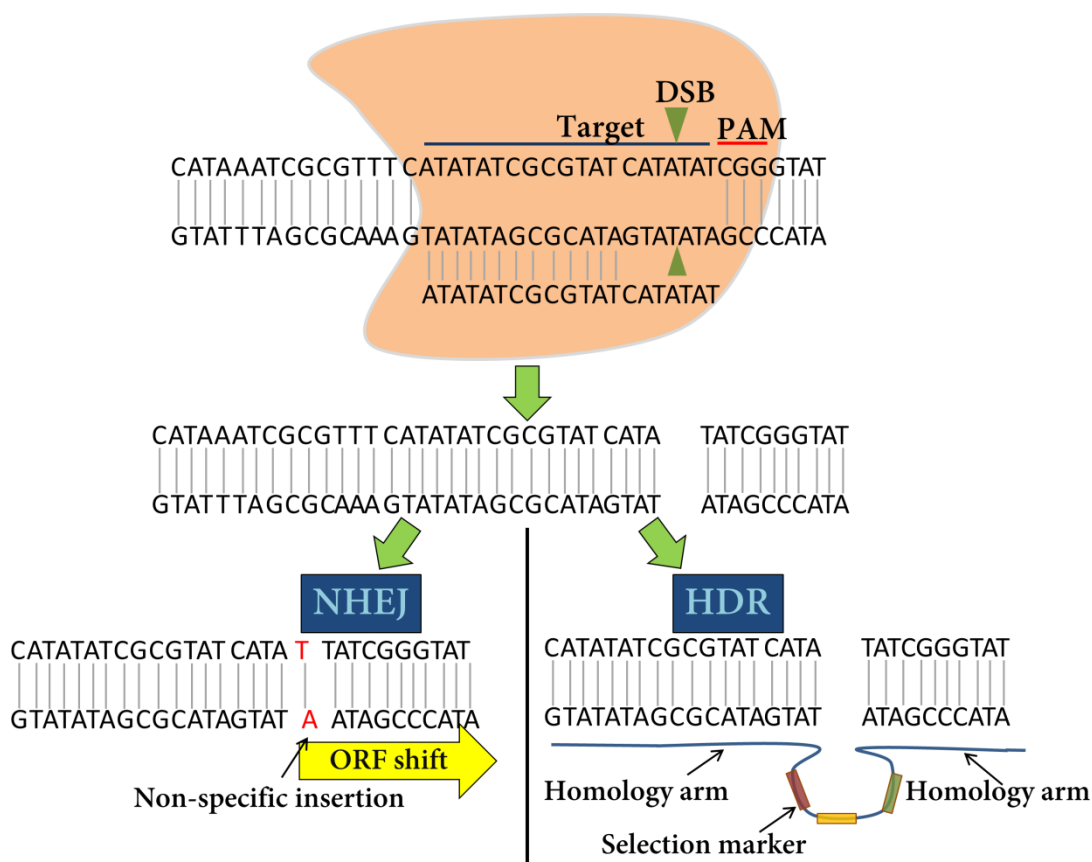


**Figure 6: Mechanism of CRISPR-Cas9, adapted from (37).** Cas9 protein is shown in orange. DSB: Double strand break; PAM: protospacer adjacent motif; NHEJ: Non-Homologous End Joining; HDR: Homology directed recombination

For the system to work, the PAM sequence needs to be directly adjacent to the target gene sequence (Figure 6), which should not have any homologies outside the gene of interest in order to avoid off-target artifacts. The gRNA and Cas9 form a complex and will bind to any genomic sequence with a PAM, but the DSB is only introduced when the gRNA matches the target gene.

The big advantage of CRISPR-Cas9 over TALENs and ZFNs is the simplicity of designing the targeting gRNA and the higher efficiency, if a HDR plasmid is used.

### **3. Methods**

If not stated otherwise all chemicals were purchased from Sigma Aldrich (St. Louis, MO, USA) and ultrapure water and HPLC-grade solvents were used.

#### **3.1. Cell culture**

##### **3.1.1. B-cells**

BCR-ABL transfected premature B-lymphocytes from ATGL-KO and WT mice (BALB) were obtained from Veronika Sexl, Veterinary Medical University of Vienna, Austria, and will be hereafter referred to as ATGL-KO and WT B-cells.

Three WT and three ATGL-KO B-cell lines were obtained (originated from six different mice). Cells were cultured in Roswell Park Memorial Institute (RPMI) medium supplied with 10 % fetal bovine serum (FBS) (ThermoFisher Scientific, Waltham, MA, USA), 4 mM glutamine, 2 g/L glucose (if not contained in the original formulation of the medium), 1 % penicillin/streptomycin and 3.5  $\mu$ L/L  $\beta$ -mercaptoethanol.

The cell number was determined every day using CASY<sup>®</sup> (Roche, Basel, Switzerland) and cell suspension was diluted to  $0.4 \times 10^6$  cells/mL.

##### **3.1.2. A549 cells**

A549 cells, human epithelial lung carcinoma cells, were obtained from American Type Culture Collection (ATCC) via the in house cell bank. Cells were cultured in Kaighn's Modification of Ham's F-12 Medium (F12K) growth medium and was supplied with penicillin/streptomycin and 10 % FBS.

#### **3.2. Uptake of glucose and glutamine in B-cells**

<sup>14</sup>C-glucose and <sup>14</sup>C-glutamine were obtained from Hartmann Analytics (Braunschweig, Germany). For uptake assays  $3 \times 10^6$  B-cells were washed in phosphate buffered saline (PBS), 1 % bovine serum albumin (BSA) in PBS and again PBS. B-cells were then incubated for different times in serum free medium containing 0.2  $\mu$ Ci/mL of <sup>14</sup>C-glucose or <sup>14</sup>C-glutamine. Cells were immediately put on ice after the incubation, centrifuged at 300 x g at 4 °C and then washed thrice with ice cold PBS. The cell pellet was resuspended in 500  $\mu$ L PBS and transferred

to a scintillation vial containing Rotiszint eco plus (0016.3, Roth, Karlsruhe, Germany) scintillation cocktail, incubated for two hours and then counted by liquid scintillation (LS 6500 Scintillation System, Beckmann Coulter, Brea, CA, USA).

### **3.3. Stable isotope resolved metabolomics (SIRM) of B-cells**

#### **3.3.1. Cell labeling and harvesting**

$1.5 \times 10^7$  B-cells were washed in cell culture medium without any supplements and then resuspended in 10 mL of tracer medium (including 2 g/L of  $^{13}\text{C}_6$ -glucose or 2 mM  $^{15}\text{N}_2$ - $^{13}\text{C}_5$ -glutamine). After 17 h of incubation at 37 °C B-cells were washed twice with ice cold PBS. After removing the second wash, B-cells were hard pelleted at 1700 x *g* at 4 °C for 5 min and all PBS was removed using a 200  $\mu\text{L}$  pipette. The cell pellet was then flash frozen in liquid nitrogen.

#### **3.3.2. SIRM in vivo**

All experiments in mice (mouse husbandry, injection of tumor cells, euthanization and harvest of tissues) were done in cooperation by Prof. Gerald Höfler's laboratory at the Medical University of Graz (Austria).

ATGL-KO and WT B-cell suspensions ( $1.5 \times 10^5$  cells) were injected subcutaneously into 12-13 weeks old, female C57BL/6 mice. Solid tumors formed and were grown for 9-16 days. 40 and 20 min before sacrificing the mice were injected with a 20 %  $^{13}\text{C}$ -glucose solution into the tail vein. After sacrificing the mice blood samples were taken (a first blood sample was taken from each mouse just before the injection of the  $^{13}\text{C}$ -glucose solution). Tumors were excised and flash frozen. Furthermore liver, WAT, heart, quadriceps were excised and flash frozen.

All animal experiments were approved by the BMWFW.

#### **3.3.3. Liquid-nitrogen grinding of frozen tissue samples**

Frozen tissues were ground in liquid nitrogen in a 6750 Freezer/Mill (Retsch, Inc., Newton, PA, USA). Around 10 mg of the tissue powder was then weighed and used for the extraction of polar compounds, lipids and proteins.

#### 3.3.4. Extraction of polar compounds, lipids and protein

Extraction was performed with acetonitrile:chloroform:water (2:1:1.5). The lipid layer was collected into glass vials and polar compounds into Eppendorf tubes. Extraction was then repeated and extracts were combined. Protein from the interphase was kept for concentration determination and normalization on protein levels. After the second extraction combined polar compounds were lyophilized overnight. Lipids were dried in a vacuum centrifuge. Dried extracts were stored at -80 °C.

#### 3.3.5. Acidification and derivatization of polar compounds for GC-MS analysis

Acidification was performed with 20 µL of 10 % trichloroacetic acid (TCA) on ice. For internal calibration 5 nmol of norleucine was added to each sample together with the TCA and then the samples were immediately flash frozen in liquid nitrogen, in order to minimize acid hydrolysis. Samples were lyophilized and dried samples were derivatized with 1:1; (v/v) acetonitrile:MTBSTFA (*N*-methyl-*N*-[*tert*-butyl-dimethylsilyl]trifluoroacetamide) (Regis Chemical, Morton Grove, IL, USA). After adding the derivatizing agent vials were sealed with crimp caps, sonicated for three hours and left in the water bath overnight at room temperature. The derivatized extract was transferred to autosampler vials and spun for 10 min to remove insoluble material. Along with the samples a blank and amino acid standards were acidified and derivatized.

#### 3.3.6. Gas chromatography-Mass spectrometry (GC-MS) analysis

Analysis of polar metabolites was performed on a GC-Ion Trap System ITQ 1100 (Thermo, Waltham, MA, USA). Of each sample and standard 1 µL was injected. GC-MS conditions were as follows: injector temperature was 280 °C, temperature of the column was 60 °C for first two minutes, followed by a 20 °C/min ramp up to 150 °C and then 6 °C/min to 300 °C, splitless vent held for 1.5 min, He carrier gas velocity 30 cm/s at 60 °C, transfer line temperature was 280 °C. Electron energy was at 70 eV, the source was heated to 220 °C, automatic gain control target value was set to 50, maximum inject time to 50 ms, helium damping gas flow was set to 1.5 mL/min, full scan acquisition from 140 to 650 m/z at a rate of 5 spectra

per second which were averaged into one. Mass calibration performed by perfluorotributylamine and a mass defect of 1.0 mmu/amu was applied to all spectra.

### **3.3.7. GC-MS data processing**

Polar metabolites were identified based on their GC retention times and mass fragmentation pattern matched against external standards which were run the same day (after every ten samples one standard was run in order to ensure stable performance of the GC-MS). Identification and quantitation was done in Xcalibur Quan Browser (ThermoFisher Scientific, Waltham, MA, USA) using a processing method which was set up beforehand, including the retention times and fragment masses of all standards. As GC-retention times may shift over time identifications were validated manually. Quantitation of metabolites was achieved by comparing ion response for each metabolite and each isotopologue in the samples with that for the corresponding standard of known concentration. It was assumed that isotopologues of each metabolite have the same molar response as the mono-isotopic pseudomolecular ion, as there are no authentic standards available. Obtained concentrations were then normalized on the protein content for each sample which was determined using BCA Protein Assay Kit (ThermoFisher Scientific, Waltham, MA, USA).

## **3.4. Quantitative proteomics using isobaric labeling**

Cell pellets of all six B-cell lines (WT7a, WT74, WT75, KO4, KO84, KO85) were resuspended in 4 % sodium dodecyl sulfate (SDS), 10 mM dithiothreitol (DTT) in 100 mM triethylammonium bicarbonate (TEAB) pH 8 and cells were disrupted by in probe sonication and heated to 95 °C for 5 min. Protein concentration was determined according to Lowry protein assay (38). Of each sample 100 µg protein was used for digestion according to the filter aided digestion protocol published by Wisniewski et al (39), with the modification that Tris buffers were exchanged for TEAB buffers. Peptides were dried and resuspended in 100 mM TEAB pH 8 and subjected to isobaric labeling with tandem mass tags (TMT) (ThermoFisher Scientific, Waltham, MA, USA) according to the manufacturer's protocol. 1 µg of each sample was then combined into one vial and analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS) analysis.

Chromatography was performed on a nano ultra-performance liquid chromatography (UPLC) reversed phase (RP) column in a five hour gradient. The solvents used were the following solvent A: 0.5 % formic acid in water, solvent B: 0.5 % formic acid in 80 % acetonitrile. The performed LC-gradient was as follows: 0-2 min 4 % solvent B, 2.01-180 min 4-28 % solvent B, 180.01-255 min 28-50 % solvent B, 255.01-260 min 50-95 % solvent B, 260.01-279 min 95 % solvent B, 279.01-300 min 4% solvent B. Fragmentation and detection was performed on an Orbitrap Velos Pro (ThermoFisher Scientific, Waltham, MA, USA). The mass spectrometer was operated in data-dependent mode where the ten most intense peaks were subjected to higher energy collision dissociation (HCD) fragmentation with a collision energy of 40 eV. Fragment masses were acquired in the orbitrap mass analyzer. Data analysis was performed using MaxQuant (40) with the default settings for an orbitrap. Two missed cleavages were allowed, LysC and Trypsin were set as proteases, carbamidomethylation of cysteines was set a fixed modification and oxidation of methionine was set as variable modification. Statistical analysis of identified and quantified proteins was done using Perseus (<http://www.perseus-framework.org/>).

### **3.5. Activity based proteomics of serine hydrolases**

#### **3.5.1. Activity based probes**

As ABP for targeting serine hydrolases 1-[3-azidopropyl(hexoxy)phosphoryl]oxy-4-nitro-benzene was used, from now on called C6-probe due its binding group. The structure of the C6- probe is shown in Figure 7. The synthesis was performed by Matthias Schittmayer as described before (41). As alcohol hexanol was used in the last step in order to obtain the ABP with the hexyl-binding group.

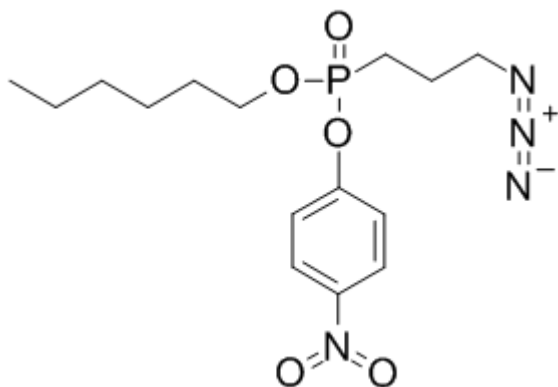


Figure 7: C6-probe used for targeting serine hydrolases.

### 3.5.2. Labeling in vivo

200 nmol of C6-probe were dissolved in 30  $\mu$ L of DMSO and added to 3 mL of serum-free medium. B-cells were incubated with the medium-probe-mix for 1 h at 37 °C. Cells were then harvested, washed and cell pellets were frozen at -20 °C until further analysis.

### 3.5.3. Synthesis of DIBAC-Fluorophore

For the strain promoted click chemistry reaction first an alkyne had to be generated that is bound to a fluorophore. The synthesis was performed by Matthias Schittmayer. A solution of 10 mM Azadibenzylcyclooctyne (DIBAC) Amine (Jena Bioscience, Jena, Germany) in tetrahydrofuran (THF) was prepared. 50  $\mu$ L of this DIBAC solution were mixed with 50  $\mu$ L of 50 mM sodium bicarbonate buffer (pH 8.3). 250 nmol of dry ATTO-Dye N-Hydroxysuccinimid (NHS)-ester (ATTO Rho6G NHS-Ester, ATTO 633 NHS-Ester, ATTO-TEC, Siegen, Germany) were incubated with the DIBAC/sodium bicarbonate solution over night at 37 °C under constant agitation. Then the dye was purified by high performance liquid chromatography (HPLC) (Agilent Technologies, Santa Clara, CA, USA) on a RP-column to remove free acid and excess unbound DIBAC. Solvent A consisted of 0.1 % acetic acid in water, solvent B consisted of 0.1 % acetic acid in acetonitrile. The HPLC gradient used was as follows: 0-10 min 20-95 % B, 10.01 min-13 min 95 % B, 13.01-16 min 20 % B.

### 3.5.4. Strain-promoted click chemistry

After labeling the cells in vivo with the C6-probe, cells were harvested and lysed in 50 mM TrisHCl pH 7.5 by sonication. 30  $\mu$ g of protein per sample were reduced in

50 mM DTT and subsequently alkylated with 500 mM iodoacetamide (in 1 M sodium chloride and 8 M urea). Samples were then incubated with either the DIBAC-633-ATTO or DIBAC-Rho6G-ATTO for 1 h at 37 °C in the dark.

#### 3.5.5. Protein precipitation and Two-dimensional gel electrophoresis

After labeling proteins WT and ATGL-KO B-cells, labeled with different fluorophores were mixed. Then proteins were precipitated with 10 % TCA, washed twice with acetone and the protein pellet was resuspended in 200 µL 2D gel rehydration buffer (7 M urea, 2 M thiourea, 2 % CHAPS (3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate), 0.002 % bromophenol blue, 0.5 % pharmalyte (GE Healthcare, Little Chalfont, UK), 50 mM DTT). An 11 cm immobilized pH gradient (IPG) strip (pH 3-10) (Bio-Rad, Hercules, CA, USA) was then rehydrated in the protein suspension overnight. The isoelectric focusing was performed in a Protean IEF-cell (Bio-Rad, Hercules, CA, USA) with the following program: step 1: 500 V for 1000 Vh, step 2: linear gradient up to 1000 V for 1000 Vh, step 3: linear gradient to 8000 V for a total of 12000 Vh and then 500 V were hold till the program was stopped. The IPG strip was then put on top of a precast 4-12 % polyacrylamide gel (Bio-Rad, Hercules, CA, USA) and sealed with hot 0.5 % agarose solution. The gel was run at 4 W for approximately two hours.

#### 3.5.6. Visualization of labeled proteins and quantitation

Gels were visualized by using a Molecular Imager FX (Bio-Rad, Hercules, CA, USA). Analysis and quantitation of the different channels was done in Delta 2 D (Decodon, Greifswald, Germany). Wilcoxon-Mann-Whitney Test was used for statistical testing and the p-value cutoff was set to 0.05. Eleven spots were identified to be significantly different between WT and ATGL-KO B-cells and were chosen for identification.

#### 3.5.7. Spot picking and protein identification

Spot picking was performed with an EXQuest Spot Cutter (Bio-Rad, Hercules, CA, USA). Proteins were digested in-gel overnight with trypsin; peptides were extracted and analyzed with LC-MS/MS.

### 3.5.8. Overexpression of PLBD2 in cos7 cells

Expression vectors for PLBD2 and His-tagged PLBD2 were kindly provided by Juliane Bogner-Strauß (Technical University of Graz). The sequence for PLBD2 (Q3TCN2) was cloned in the pcDNA4 HismaxC vector using the cloning sites KpnI and EcoRI (vector map: Figure S 8) and in the pMSCV puro vector using the cloning sites HpaI and EcoRI (vector map: Figure S 9). Cos7 cells were transfected with the different vectors using nanofectin (GE Healthcare Biosciences, Pittsburgh, PA, USA) according to the supplier's manual. LacZ, also cloned in a pcDNA4Hismax vector, was used as transfection control.

### 3.5.9. Transfection control using Western Blot

Western Blots were performed in order to confirm successful transfection of cos7 cells with PLBD2, PLBD2-His and LacZ.

After SDS-polyacryl gel electrophoresis (SDS-PAGE) proteins were blotted onto a polyvinylidene difluoride (PVDF) membrane using a semi dry blotting system. During blotting a maximum voltage of 25 V was set as well as an electric current maximum of 180 mA. After blotting the membrane was washed thrice in 0.9 % NaCl, in order to verify the protein transfer on the membrane, the membrane was then stained with PonceauS. After staining, the membrane was extensively washed in water and tris-buffered saline containing 1% Tween20 (Bio-Rad, Hercules, CA, USA) (TBS-T) until the red stain disappeared. Free binding sites on the membrane were then blocked with 5 % BSA in TBS-T for 1 h at room temperature. The membrane was incubated with the primary antibody (1:1000 in 5 % BSA in TBS-T; mouse anti-His (QIAGEN, Hilden, Germany) or rabbit anti-PLBD2 (AP16210C, Abgent, WuXi AppTec, Shanghai, China)) overnight, then washed three times for 5 minutes in TBS-T and incubated with the secondary antibody (1:3000 in 5 % skim milk in TBS-T; anti-rabbit or anti-mouse) for 1 h at room temperature. Finally the membrane was washed three times in TBS-T and antibody-bound proteins were visualized by enhanced chemiluminescence (ECL) (GE Healthcare, Little Chalfont, UK) and the light formation was detected by exposure to an x-ray film. The anti-mouse secondary antibody had a fluorescent tag and was thus imaged using the Molecular Imager FX (BioRad, Hercules, CA, USA).

### **3.5.10. Phospholipase-assay**

Phospholipase A<sub>1</sub>/A<sub>2</sub> activity was assayed using a glycerophosphocholine with BODIPY<sup>®</sup> dye-labeled sn-1 and sn-2 acyl chains which upon cleavage by phospholipase results in an increase in fluorescence intensity. Bis-BODIPY<sup>®</sup> FL C<sub>11</sub>-PC (B7701, Molecular Probes, Eugene, OR, USA) was dissolved in ethanol and stored protected from light at -20°C. The assay was performed according to the supplier's manual. Fluorescence was monitored over 40 min, with fluorescence measurements every 30 seconds (Excitation=485 nm, Emission=520 nm) on a FLUOstar Omega (BMG Labtech, Ortenberg, Germany). The increase in fluorescence was determined for the first six measurement point, as the graph followed a linear increase in that area. Statistical analysis was done in R using one-way ANOVA.

### **3.6. Oxygen consumption rate measurements**

Measurements of oxygen consumption rate were performed in cooperation by Prof. Wolfgang Graier's group at the Medical University of Graz.

ATGL-KO and WT B-cells had to be immobilized on the assay plate using Cell-Tak<sup>™</sup> (Corning, Corning, NY, USA). Per well 10<sup>5</sup> cells were seeded. After immobilizing, cells were incubated with XF assay medium (Seahorse Bioscience, North Billerica, MA, USA) supplied with 34 µM BSA and either no palmitate or 200 µM palmitate for 1 h at 37 °C. Then the oxygen consumption rate was measured every 7 min using an XF96 extracellular flux analyzer (Seahorse Bioscience, North Billerica, MA, USA). Basal measurement was performed for 20 min followed by the addition of 2 µM oligomycin, after another 15 min 0.4 µM carbonyl cyanide *p*-trifluoromethoxyphenylhydrazone (FCCP) was added and finally after a total of 70 min 2.5 µM antimycin A was added. Oxygen consumption rate was normalized on the protein content. Basal respiration was calculated from the difference in oxygen consumption at the first measurement (0 min) and the last measurement after the addition of antimycin A (84 min).

### **3.7. mRNA expression of PPAR $\alpha$ targets**

The analysis of mRNA expression was done by real-time polymerase chain reaction (PCR) in cooperation by Prof. Juliane Bogner-Strauß's group at the Technical University of Graz.

ATGL-KO and WT B-cells were preincubated with PPAR $\alpha$  agonist (WY 14643, 200  $\mu$ M) and PPAR $\alpha$  antagonist (GW6471, Tocris Bioscience, 10  $\mu$ M) for 24 h. Total RNA was isolated using the PeqGOLD total RNA isolation kit (Peqlab, Erlangen, Germany). cDNA was generated using Qiagen QuantiTect RT kit. mRNA expression was assessed using SYBR green real-time PCR on a ABI 7000 instrument. mRNA expression of the PPAR $\alpha$  target carnitine palmitoyltransferase 1a (CPT1a), acyl-CoA oxidase 1 (Acox1) and acyl-CoA dehydrogenase 1 (Acad1) was analyzed. Following primers were used:

CPT1a\_forward: TGAGTGGCGTCCTCTTTGG

CPT1a\_reverse: CAGCGAGTAGCGCATAGTCA

Acox1\_forward: GGGAGTGCTACGGGTACATG

Acox1\_reverse: CCGATATCCCCAACAGTGATG

Acad1\_forward: TTTCCGGGAGAGTGTAAGGA

Acad1\_reverse: ACTTCTCCAGCTTTCTCCCA.

Expression values were calculated with an in-house tool (42), which considers the PCR efficiency.

### **3.8. Incorporation of palmitic acid**

4x10<sup>6</sup> B-cells were incubated with 1 mL of serum-free medium including 200  $\mu$ M palmitate conjugated to BSA and 1  $\mu$ Ci <sup>14</sup>C-palmitate for 15 min at 37 °C. Cells were washed with ice cold 0.5 % BSA in PBS and then in PBS. Lipids were extracted with chloroform:methanol:2 % phosphoric acid (2:1:1). Lipids were dried under a nitrogen stream and resuspended in 20  $\mu$ L chloroform. Thin-layer chromatography (TLC) was performed according to Ruiz and Ochoa (43). Briefly a

five-solvent-system was used as follows: Chloroform:methanol:water (60:40:10) 2 cm, Ethylacetate:2-propanol:ethanol:Chloroform:methanol:0.25%KCl (35:5:20:22:15:9) 5 cm, Toluene:diethylether:ethanol (60:40:3) 7.5 cm, Hexane:diethylether (94:8) 10.5 cm, hexane 12.5 cm. After each solvent the plate was first dried completely and then redeveloped in the new solvent until the running front reached the stated height. After the last development plate was dried and incubated on a phosphor screen (Biorad, Hercules, CA, USA) overnight. The phosphor screen was analyzed on a Molecular Imager (Biorad, Hercules, CA, USA).

### **3.9. Oxidation of palmitic acid and serine**

The  $\beta$ -oxidation assay was performed in 50 ml falcon tubes.  $10^7$  cells were incubated with serum free medium containing 1  $\mu$ Ci  $^{14}$ C-palmitic acid or 1  $\mu$ Ci  $^{14}$ C-serine for 2 h at 37 °C. A piece of Whatman<sup>®</sup> paper was pre-wetted with 1 M sodium hydroxide and placed into the lid before incubation of the cells. After 2 h the tubes were removed from the incubator and the suspension was acidified with 3 M perchloric acid (added with a syringe through the lid) in order to release trapped  $^{14}$ CO<sub>2</sub> which was then collected on the prewetted filter paper. Filter papers were put into scintillation vials and covered with Rotiszint eco plus (0016.3 Roth, Karlsruhe, Germany) scintillation cocktail, incubated for two hours and then counted by liquid scintillation (LS 6500 Scintillation System, Beckmann Coulter, Brea, CA, USA).

### **3.10. Diacylglycerol acyltransferase (DGAT) assay**

DGAT assay was performed according to the protocol from McFie and Stone (44) with the following changes. After extraction dried lipids were resuspended in 20  $\mu$ L of chloroform and then spotted on a TLC plate (Millipore, Billerica, MA, USA). The TLC plate was developed in a solvent system containing of hexane/acetyl acetate/acetic acid (80:20:1).

### **3.11. Generating a stable ATGL-KO cell line using CRISPR-Cas9 in A549 cells**

The CRISPR-Cas9 plasmid including the gRNA targeting ATGL was obtained from Santa Cruz (sc-401711, Santa Cruz, Dallas, TX, USA). In order to support the

HDR repair mechanism for DSBs created by the Cas9, an HDR plasmid was exogenously provided (sc-401711-HDR, Santa Cruz, Dallas, TX, USA). The HDR plasmid contained a puromycin resistance and red fluorescent protein (RFP). Transfection of A549 cells was performed using Lipofectamine<sup>®</sup> (Thermo Fisher Scientific L3000-015) according to the manufacturer's manual in serum-free and antibiotics-free growth medium. After 5 h, medium containing 20% FBS was added to reach a final concentration of 10 % FBS. 24 h post-transfection the medium was exchanged for normal growth medium, including FBS and penicillin/streptomycin. Cells from a 6-well plate were then either selected with puromycin or expanded. Upon reaching a cell number of approximately  $10^6$  cells; a suspension of  $10^6$  cells/mL was subjected to fluorescence activated cell sorting (FACS). Before FACS a 96-well plate was filled with 50 % preconditioned medium. Preconditioned medium was obtained by incubating non-transfected A549 cells at 40 % confluency for 24 h with fresh growth medium, medium was then filtered (0.22  $\mu$ m filter) in order to remove floating cells. During FACS RFP positive cells were sorted into the 96-well plate filled with 50 % preconditioned medium, one cell per well, in order to obtain single cell colonies. Cells were then expanded, tested for protein expression using Western Blot and checked for insertion of HDR plasmid using PCR.

### **3.11.1. Western Blotting**

After SDS-polyacrylamide gel electrophoresis (SDS-PAGE) proteins were blotted onto a PVDF membrane using a semi dry blotting system. During blotting a maximum voltage of 25 V was set as well as an electric current maximum of 180 mA. After blotting the membrane was washed thrice in 0.9 % NaCl. In order to control the successful protein transfer on the membrane, the membrane was then stained with PonceauS. After staining the membrane was extensively washed in water and TBS-T until the red stain disappeared. Free binding sites on the membrane were then blocked with 5 % skim milk powder in TBS-T for 1 h at room temperature. Membrane was incubated with the primary antibody (1:1000 in 5 % skim milk in TBS-T; rabbit anti-ATGL or rabbit anti-GLDC (2138S and 12794S, respectively, Cell Signaling Technology, Danvers, MA, USA)) overnight, then washed three times for 5 minutes in TBS-T and incubated with the anti-rabbit secondary antibody (7074 S, Cell Signaling Technology, Danvers, MA, USA),

1:3000 in 5 % skim milk in TBS-T) for 1 h at room temperature. Finally the membrane was washed three times in TBS-T and antibody-bound proteins were visualized by enhanced chemiluminescence (ECL) (GE Healthcare, Little Chalfont, UK) and the light formation was detected by exposure to an x-ray film.

### 3.11.2. DNA extraction of A549 cells

$2-3 \times 10^6$  cells were collected and washed with PBS before DNA was extracted using the mammalian DNA extraction kit from Sigma (G1N70-1KT) according to the manufacturer's protocol. Resulting DNA concentrations were around 200 ng/ $\mu$ L.

### 3.11.3. PCR conditions and primer

Forward primer: CCTCTTCCTCTGAACTTTGTCC

Reverse primer: CTCCTCTCTCTCTTTCCCTCCT

LongAmp® Taq PCR Kit (E5200S, New England Biolabs, Ipswich, MA, USA) was used for the control of CRISPR clones.

The reaction buffer for each 25  $\mu$ L reaction was composed as follows:

|                                 |              |
|---------------------------------|--------------|
| 5X LongAmp Tag Reaction buffer: | 5 $\mu$ L    |
| 10 mM dNTPs                     | 0.75 $\mu$ L |
| 10 $\mu$ M Forward Primer       | 1 $\mu$ L    |
| 10 $\mu$ M Reverse Primer       | 1 $\mu$ L    |
| Template DNA                    | 2 $\mu$ L    |
| LongAmp Taq DNA Polymerase      | 1 $\mu$ L    |
| DMSO                            | 0.75 $\mu$ L |
| Nuclease-free water             | 13.5 $\mu$ L |

The PCR program was adjusted for amplification products of up to 10 kb and was performed as follows:

**Initial denaturation**

94 °C for 30 sec

**30 cycles:**

94 °C for 30 sec

63 °C for 45 sec

65 °C for 9 min

**Final extension**

65 °C for 10 min

**Hold at 4 °C**

The PCR product was then mixed with 5 µL of gel loading dye (B7021S, New England Biolabs, Ipswich, MA, USA) and 8 µL were loaded on a 0.7 % agarose gel, including 0.01 % GelRed™ (730-2957, VWR, Radnor, PA, USA), Quick-load 1 kb DNA ladder (N0468S, New England Biolabs, Ipswich, MA, USA) was used as a DNA marker. The gel was run at constant at 90 V for approximately 1 h. DNA bands were made visible under UV light and documented by a Chemidoc system (Bio-Rad, Hercules, CA, USA).

### **3.12. Growth curve of A549 cells**

10<sup>5</sup> cells were seeded in each well of a 6-well plate. Every 24 h cells from a fresh well were trypsinized and counted with CASY® (Schärfe System GmbH, Reutlingen, Germany).

### **3.13. Lipid droplet and nuclei staining**

The day before staining, 7.5x10<sup>4</sup> A549 cells were seeded in each well of a 24-well plate. Just before staining cells were washed once with PBS and fixed with 4 %

formaldehyde for 10 min at room temperature. Cells were washed 4 times with H<sub>2</sub>O and then incubated with 300 nM DAPI in PBS for 20 min in the dark at room temperature. After DAPI staining, cells were washed 5 times with H<sub>2</sub>O and then incubated with 1 µg/mL BODIPY<sup>®</sup> 493/503 (D3922, ThermoFisher Scientific, Waltham, MA, USA) in H<sub>2</sub>O. BODIPY staining was performed for 45 min. Then cells were washed 5 times in H<sub>2</sub>O and covered with 200 µL PBS before microscopy.

### **3.14. Quantitation of lipid droplets**

Quantitation of lipid droplets was done in ImageJ. The number of lipid droplets was estimated in ImageJ using the particle analysis. Particle settings for lipid droplets were as follows: size 15-200 pixels<sup>2</sup>; circularity 0.6-1.0.

The number of cells was estimated on pictures of cells stained with DAPI, also in ImageJ using the particle analysis. Particle settings for nuclei were as follows: size 2000-20000; circularity 0.2-0.9.

For every clone the numbers of lipid droplets and cells were calculated.

### **3.15. Statistical analysis**

Unless stated otherwise statistical analysis was performed using a Student's t-test. Error bars show standard deviation.

## 4. Results

### 4.1. Growth advantage of ATGL-KO B-cells over WT B-cells

Three different cell lines for the two genotypes were available. The influence of the absence of ATGL in those cells was tested in growth experiments. After 4 days it was obvious that ATGL-KO cells grew significantly faster ( $p=0.02$ ) than WT cell lines (Figure 8).

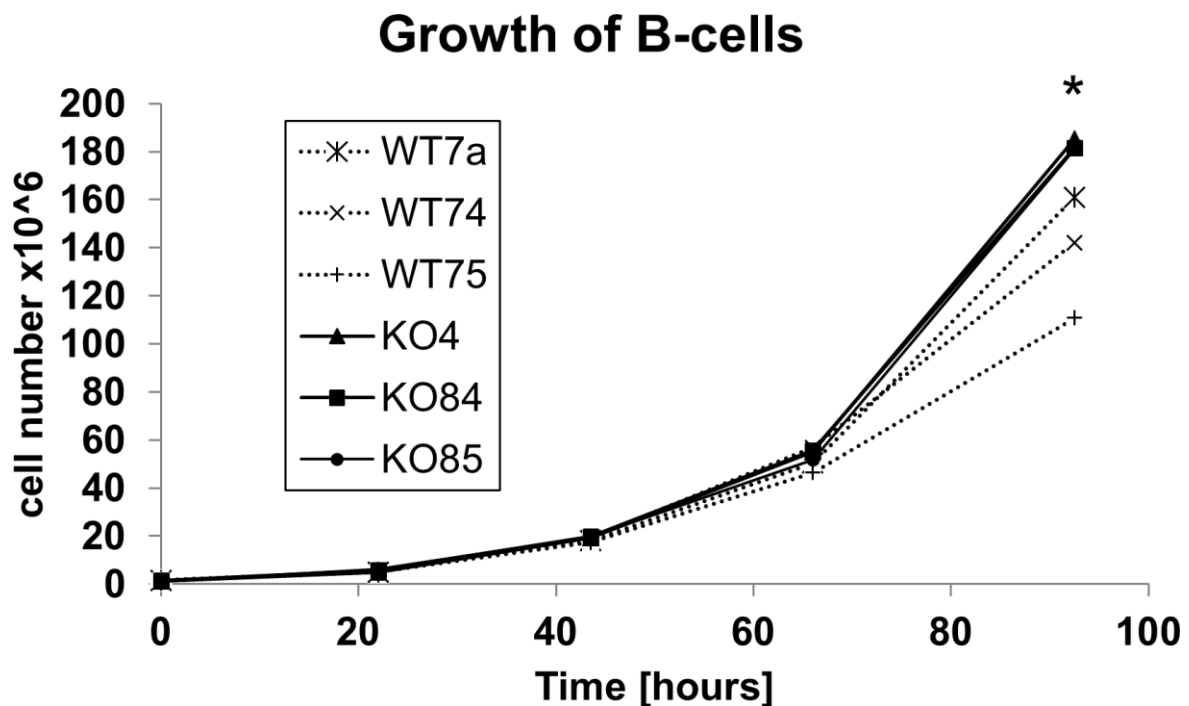


Figure 8: Growth curves for ATGL-KO and WT B-cells. Cells were seeded at a density of  $0.4 \times 10^6$  cells/mL, counted after 24 h, diluted to  $0.4 \times 10^6$  cells/mL and counted again in order to obtain the exact number of seeded cells. This procedure was repeated every 24 h. This experiment was repeated 3 times and always showed similar results. \*:  $p < 0.05$

### 4.2. Uptake of glucose and glutamine is unaltered in ATGL-KO B-cells

Enhanced uptake of glucose and increased dependency on glutamine is a common phenomenon in cancer cells. Hence the first assumption was that the growth advantage of ATGL-KO cells might be based on enhanced uptake of either glucose or glutamine, in order to compensate for a lack of available fatty acids for energy production. Figure 9 shows that the uptake for both, glucose and glutamine is unaltered ( $p=0.9$  and  $p=0.4$ , respectively) in ATGL-KO B-cells.

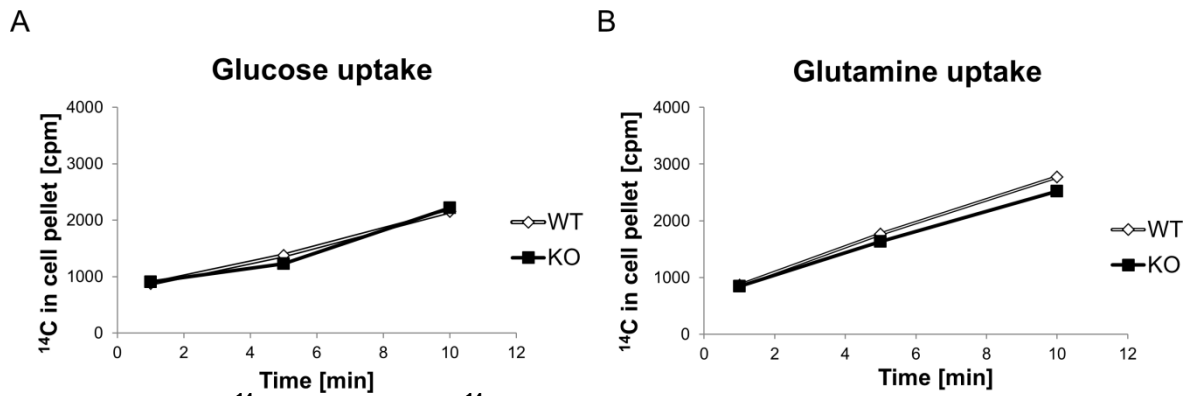


Figure 9: Uptake of  $^{14}\text{C}$ -glucose (A) and  $^{14}\text{C}$ -glutamine (B) by ATGL-KO and WT B-cells.

#### 4.3. Stable isotope resolved metabolomics (SIRM) using $^{13}\text{C}_6$ -glucose reveals no difference in central carbon metabolism

As the uptake of glucose and glutamine was unaltered in ATGL-KO cells, metabolomics was used in order to follow the fate of glucose and glutamine through cellular metabolism. Even if glucose uptake is identical, it can still be used in different ways which could lead to a growth advantage.

SIRM enables the analysis of the flux of glucose through different metabolic pathways. Using targeted GC-MS, the metabolites listed in Table S 1 were identified and quantified. In Figure 10 the comparison of selected metabolites and their isotopologues is shown for ATGL-KO and WT B-cells.

The only significant differences between ATGL-KO and WT B-cells could be observed for the m0 ( $p=0.04$ ), m2 ( $p=0.03$ ) and m4 ( $p=0.03$ ) isotopologues of succinate. For these isotopologues ATGL-KO B-cells exhibited higher concentrations. This might be solely due to a slightly increased level of succinate, as the fractional distribution of the isotopologues of succinate is unchanged between ATGL-KO and WT B-cells and thus the incorporation of  $^{13}\text{C}$ -glucose is unchanged.

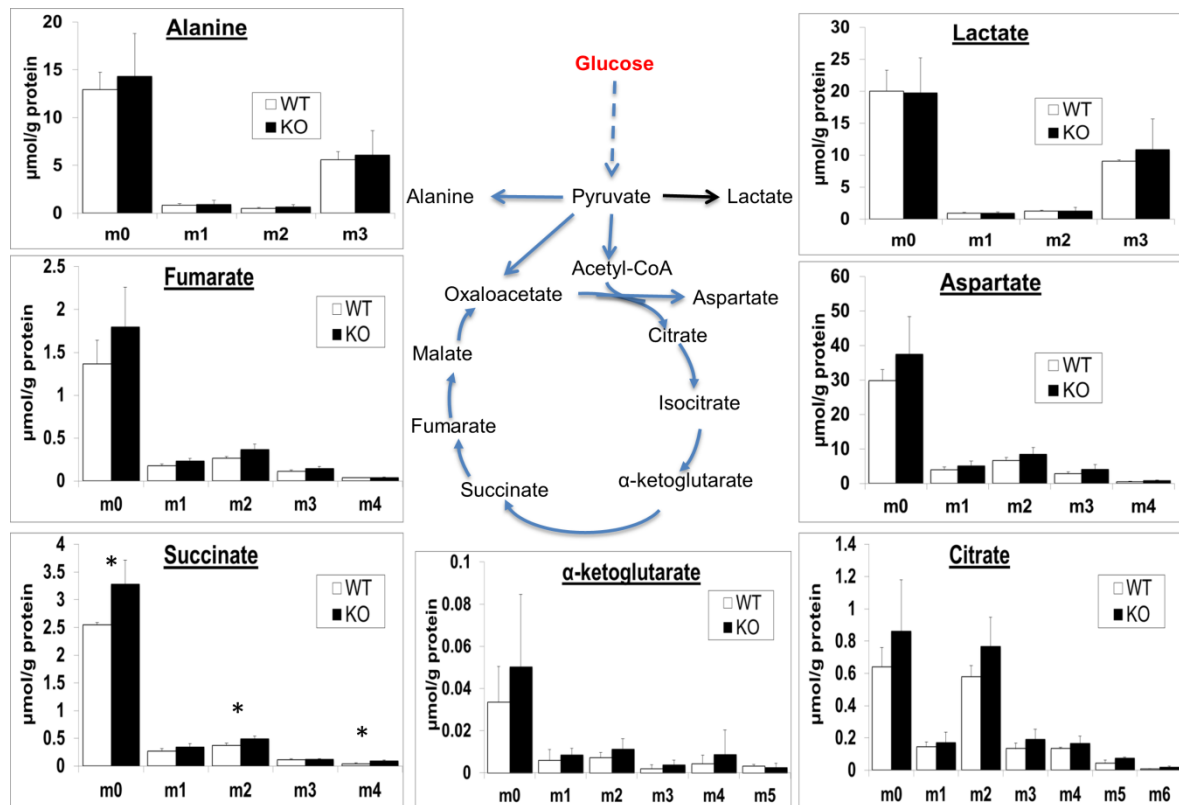


Figure 10: SIRM comparing polar metabolites of ATGL-KO and WT B-cells after metabolic labeling with  $^{13}\text{C}$ -glucose. Displayed is a selection of the metabolites analyzed. The isotopologue patterns of all analytes can be found in the supplementary Figure S 1 \*:  $p < 0.05$

#### 4.4. Incorporation of $^{15}\text{N}_2$ , $^{13}\text{C}_5$ -glutamine is similar in ATGL-KO and WT B-cells

Besides glucose, most cancer cells are also highly dependent on glutamine. Hence, the metabolic labeling experiment was repeated using stable isotope enriched glutamine. Except for the medium preparation the workflow for the extraction and analysis of polar metabolites was identical as for the glucose experiment. The comparison of selected metabolites is shown in Figure 11.

Glutamine has five carbon atoms and two nitrogen atoms. Here, a heavy glutamine with all carbon and nitrogen atoms labeled was used. Hence, the  $^{15}\text{N}_2$ ,  $^{13}\text{C}_5$ -glutamine is 7 Da heavier than unlabeled glutamine. However, due to the low resolution of the ion trap, which was used for targeted analysis of the polar metabolites, the increase in mass from  $^{12}\text{C}$  to  $^{13}\text{C}$  cannot be differentiated from the increase in mass from  $^{14}\text{N}$  to  $^{15}\text{N}$ . Hence in Figure 11 the glutamate isotopologue m5 could consist of four  $^{13}\text{C}$ -atoms and one  $^{15}\text{N}$ -atom or five  $^{13}\text{C}$ -atoms. The other metabolites, with the exception of alanine, do not contain any nitrogen; hence the isotopologues represent the number of labeled carbons only.

Again only small significant difference could be observed (m3 of lactate:  $p=0.02$ ; m3 of succinate:  $p=0.02$ ) which cannot explain the growth difference and might be rather due to artefacts in the analysis. But even though no explanation for the growth advantage of ATGL-KO cells could be found by metabolic tracking of glutamine, the stable isotope labeling experiments gave some insights about the metabolism of these cancerous B-cells.

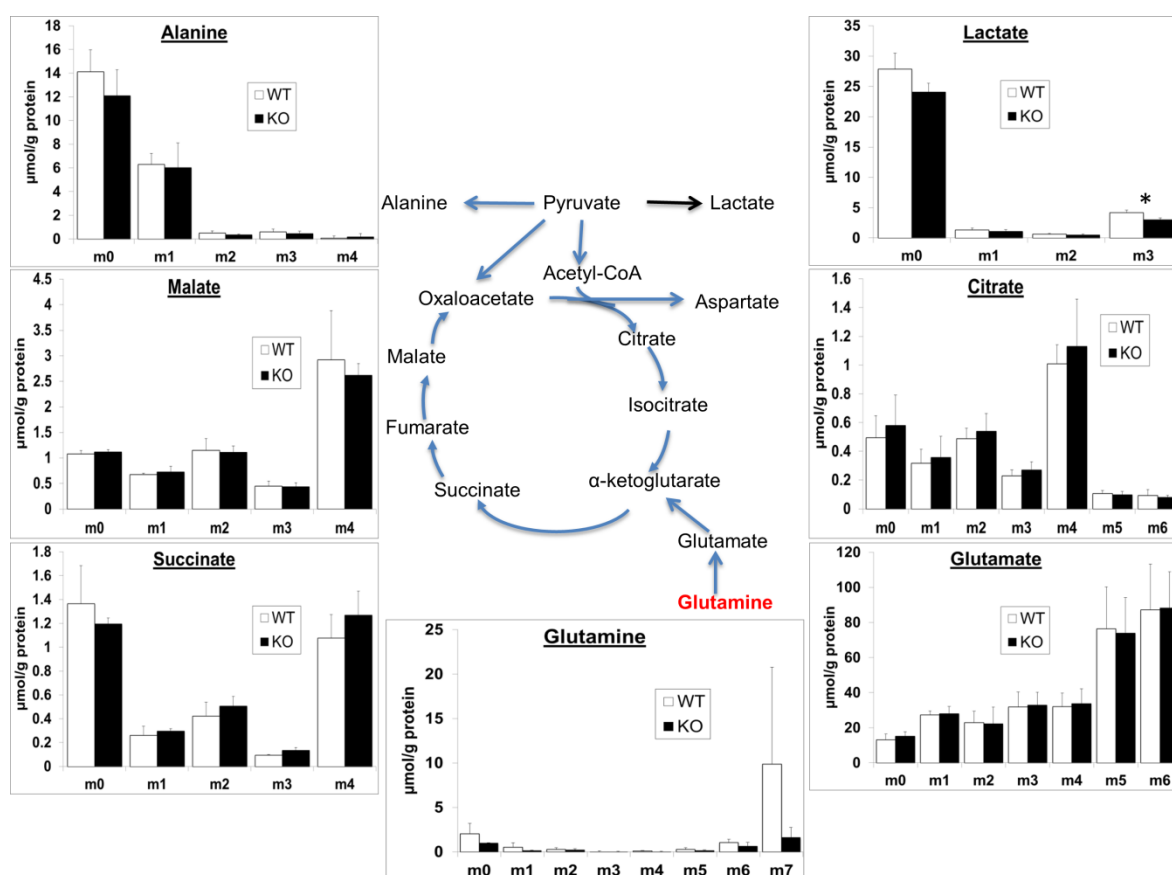


**Figure 11: SIRM comparing polar metabolites of ATGL-KO and WT B-cells after metabolic labeling with  $^{15}\text{N}_2$ ,  $^{13}\text{C}_5$ -glutamine. Displayed is a selection of the metabolites analyzed. The isotopologue patterns of all analytes can be found in the supplementary Figure S 2. \*:  $p<0.05$**

Glutamine is used in the forward reaction of the TCA cycle and not in the reverse direction. Reductive glutamine metabolism has been shown to be highly abundant in brown adipocytes (45) and also in various hypoxic cancer cells in order to support lipid synthesis (46). Here reductive glutamine metabolism is not very prominent which becomes obvious from the isotopologue pattern of citrate. The occurrence of four labeled carbons in citrate can only be explained by the conversion of glutamine to glutamate, the entry in the TCA cycle via alpha-ketoglutarate and the loss of  $\text{CO}_2$  when succinate is formed, resulting in four labeled carbons (forward reaction of the citrate cycle). The reversed reaction on

the other hand would result in five heavy carbons in the citrate molecule, which is observed only to a low percentage.

#### 4.5. SIRM with $^{13}\text{C}$ -glucose in mice showed no differences in central carbon metabolism of ATGL-KO and WT B-cell tumors

The observed growth difference of ATGL-KO B-cells was more pronounced when the cells were injected in mice (data not shown). Therefore an SIRM experiment was performed in mice using  $^{13}\text{C}$ -glucose.

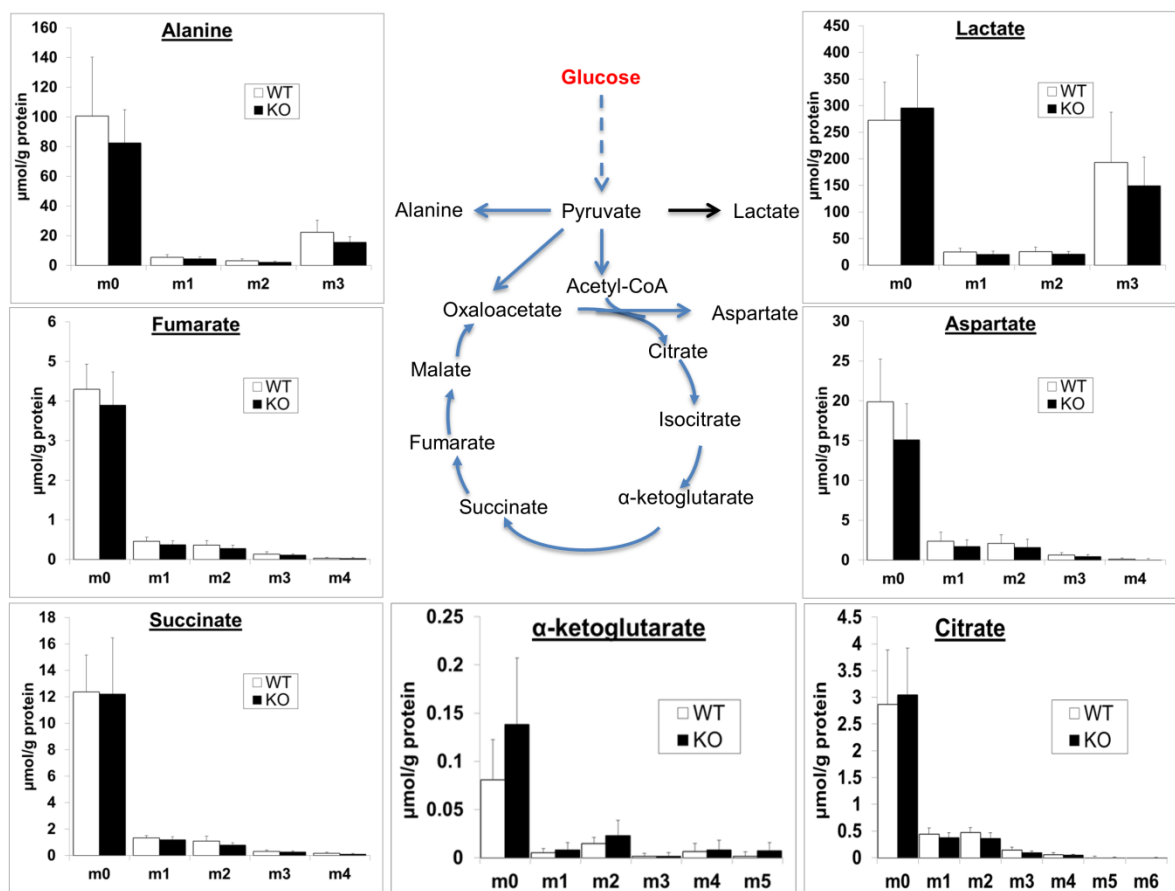


**Figure 12:** Incorporation of  $^{13}\text{C}$ -glucose into tumor metabolites. Tumors in mice were grown till tumor sizes for the different genotypes were approximately equal. Just before sacrificing the mice, mice were injected twice with  $^{13}\text{C}$ -glucose solution. Tumors were then harvested, flash frozen and ground in liquid nitrogen. The isotopologue patterns of all analytes can be found in the supplementary Figure S 3.

Figure 12 shows that no differences could be detected between WT and ATGL-KO tumors. Furthermore it can be seen that the time for incorporation might have been too short as labeling of metabolites is not very prominent. However, 30 % of lactate is completely labeled (m3). This shows that the method itself worked and

reveals the typical phenomenon that cancer cells convert most of the glucose taken up into lactate.

The analysis of plasma samples (Figure S 4 and Figure S 5) and liver (Figure S 6) from the same mice showed similar isotopic pattern of metabolites as in the tumors with no significant differences.

#### 4.6. Quantitative proteomics reveal down regulation of enzymes involved in one-carbon metabolism

To identify dysregulated proteins in ATGL-KO cells a quantitative screening of the proteome of WT and ATGL-KO B-cells was performed using TMT-labeling. The volcano plot in Figure 13 shows the distribution of  $-\log(p\text{-values})$  of identified proteins relative to their difference between the two groups (WT and ATGL-KO). Three proteins were found to be significantly (the black lines in the volcano plot, Figure 13, signify the borders of significance) (Table 1; the complete list of identified and quantified proteins can be found in Table S 2). Among the most interesting proteins identified was glycine dehydrogenase (GLDC). The enzyme is involved in glycine degradation which in turn is important in purine synthesis.

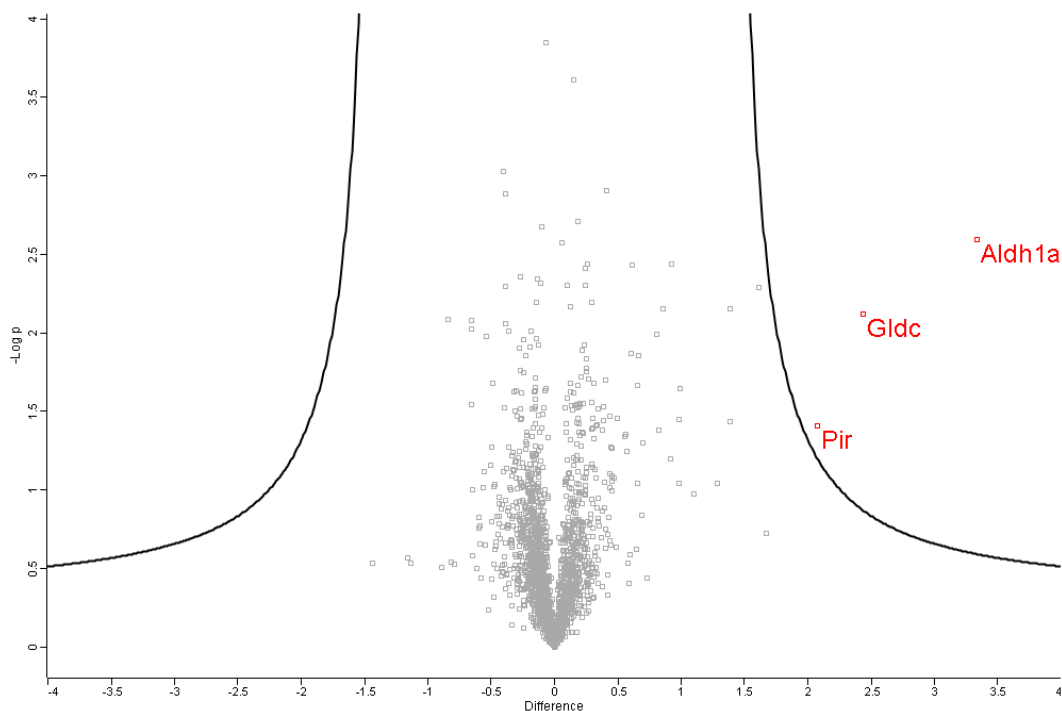


Figure 13: Volcano plot for all identified and quantified proteins from the quantitative proteomics analysis using TMT. Difference displays the difference between the mean log2 values of ATGL-KO and WT.

**Table 1: Significantly regulated proteins from the quantitative proteomics analysis using TMT.**

| p-value | Difference (WT-KO) | Protein names                                               | Protein IDs           | Gene names      |
|---------|--------------------|-------------------------------------------------------------|-----------------------|-----------------|
| 0,0026  | 3,33               | Retinal dehydrogenase 1;Aldehyde dehydrogenase, cytosolic 1 | B2RTL5;P24549; O35945 | Aldh1a7;Aldh1a1 |
| 0,0076  | 2,44               | Glycine dehydrogenase (decarboxylating), mitochondrial      | E9PXH3;Q91W43         | Gldc            |
| 0,0389  | 2,07               | Pirin                                                       | A2AIH8;Q9D711         | Pir             |

The downregulation of glycine dehydrogenase in ATGL-KO B-cells was confirmed by Western Blotting (Figure 14). The specific protein band can be seen at approximately 110 kDa which matches the expected size of 113 kDa.

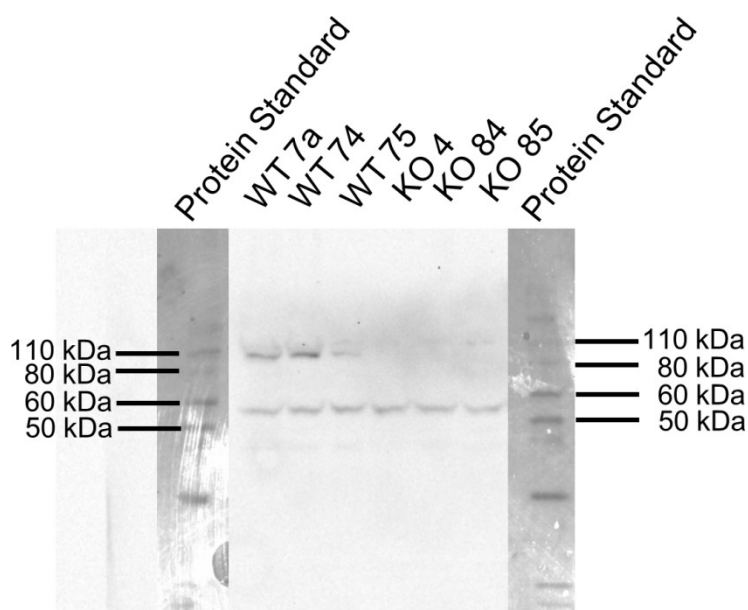


**Figure 14: Western Blot for glycine dehydrogenase (GLDC).**

#### 4.7. Serine oxidation

As the protein levels of glycine dehydrogenase were downregulated, a change in glycine metabolism was expected. Glycine dehydrogenase catalyzes the degradation of glycine which results in the release of carbon dioxide. Glycine in turn, together with methylene-tetrahydrofolate, is a product from the reaction of tetrahydrofolate and serine, catalyzed by serine hydroxymethyltransferases (SHMT1/2). It was assumed that the decarboxylation of glycine is downregulated in ATGL-KO cells as the protein level of GLDC was found to be down regulated. As cells have been reported to be dependent on external serine rather than glycine, 1-<sup>14</sup>C-serine was used as a labeled substrate and the resulting <sup>14</sup>CO<sub>2</sub> was

measured. Due to the lack of GLDC in ATGL-KO cells it was assumed that the contribution to folate metabolism from this pathway is decreased and that this might be compensated for by the conversion of serine into folate metabolites. In order to distinguish between the two different pathways 3-<sup>14</sup>C-serine was also used as labeled substrate and the production of <sup>14</sup>CO<sub>2</sub> was monitored. Both assays led to a higher <sup>14</sup>CO<sub>2</sub> release in the WT B-cells (Figure 15 A). However, this difference was not statistically significant. Furthermore it can be seen that 1-<sup>14</sup>C-serine led to a significantly higher release of <sup>14</sup>CO<sub>2</sub> than 3-<sup>14</sup>C-serine, in both the WT and ATGL-KO cells (p=0.005 and p=0.003, respectively). The higher levels of <sup>14</sup>CO<sub>2</sub> release from 1-<sup>14</sup>C-serine can be explained by the conversion of serine to phosphatidylserine (PS) and the subsequent release of <sup>14</sup>CO<sub>2</sub> when PS is decarboxylated in order to form phosphatidylethanolamine (PE) as shown in Figure 15 B.

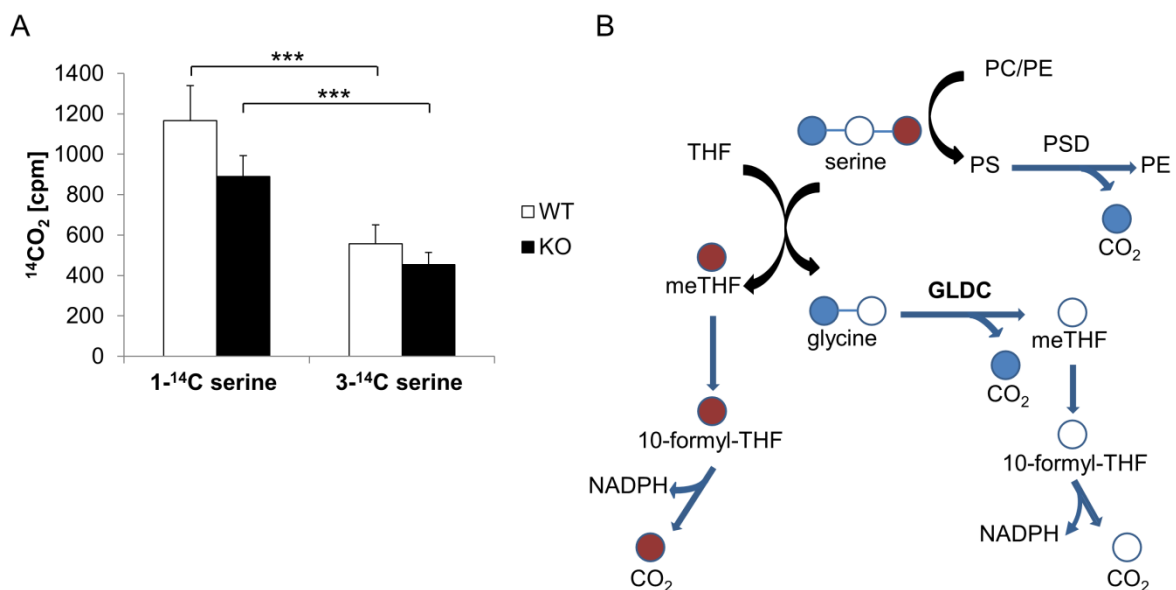


Figure 15: A: production of <sup>14</sup>CO<sub>2</sub> after the incubation with 1-<sup>14</sup>C- or 3-<sup>14</sup>C-serine. B: Schematic overview of the different possibilities of serine metabolism. \*\*\*: p≤0.005

## 4.8. Changes in lipid metabolism related to loss of ATGL

### 4.8.1. Oxygen consumption rate

The oxygen consumption rate (OCR) was determined using an XF96-analyzer (Seahorse Bioscience). The results in Figure 16 show a reduced basal OCR for the ATGL-KO B-cells, however this difference is not significant. The OCR was then determined after addition of assay medium containing 200 μM palmitate

(complexed with BSA) and incubation of cells for one hour, which led to a significant increase in the basal OCR of ATGL-KO cells, but no change in WT B-cells.

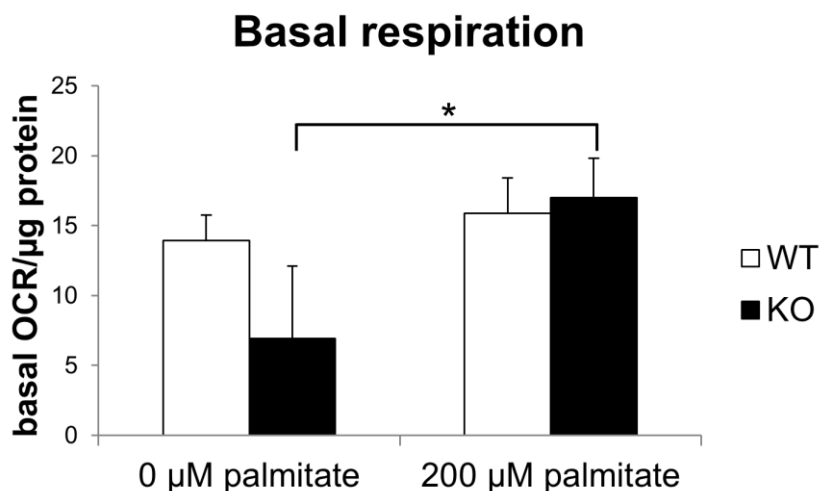


Figure 16: Basal oxygen consumption rate in ATGL-KO and WT B-cells. \*:  $p < 0.05$

#### 4.8.2. Palmitic acid uptake is unaltered but its incorporation into lipids appears to be lower in ATGL-KO B-cells

As there was a different response to palmitic acid in the oxygen consumption rate, the uptake of palmitic acid was investigated. In Figure 17 A it can be seen that the uptake of  $^{14}\text{C}$ -palmitic acid does not differ between ATGL-KO and WT B-cells. However, even though the uptake might be the same, the use of palmitic acid might differ between ATGL-KO and WT B-cells. Hence the incorporation of palmitic acid into different lipids was determined. In order to separate not only different lipid categories (phospholipids, neutral lipids, free fatty acids) but also their classes (e.g. phosphatidylcholine (PC), phosphatidylserine (PS) and phosphatidylethanolamine (PE)) a multi-one-dimensional thin-layer chromatography was performed. From the TLC (Figure 17 B) it became apparent that the ATGL-KO B-cells incorporate less palmitic acid into lipids (Figure 17 C), but especially incorporation into triacylglycerides was decreased, whereas diacylglycerides seemed to show similar incorporation of palmitic acid (Figure 17 D); however, these differences were not statistically significant.

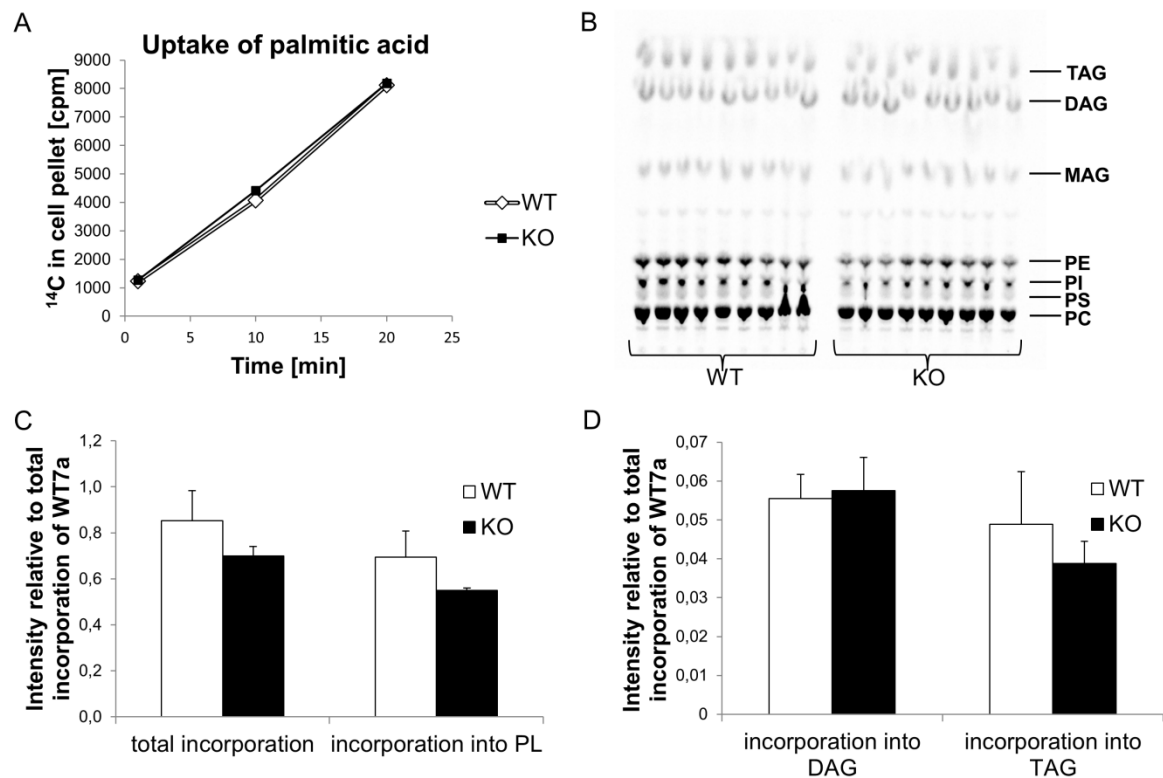


**Figure 17: A: Palmitic acid uptake is unaltered in ATGL-KO B-cells. B: TLC of lipid extracts of B-cells after incorporation of  $^{14}\text{C}$ -palmitic acid. For quantitation a volume analysis of TLC spots was performed. C: Intensities for total incorporation and incorporation into phospholipids (PL), all values are relative to the total lane intensity of WT7a. D Relative intensities for incorporation into DAG and TAG, all values are relative to the total lane intensity of WT7a. TAG: Triacylglycerol; DAG: Diacylglycerol; MAG: Monoacylglycerol; PE: Phosphatidylethanolamine; PI: Phosphatidylinositol; PS: Phosphatidylserine; PC: Phosphatidylcholine**

#### 4.8.3. PPAR $\alpha$ target expression is independent of ATGL in B-cells

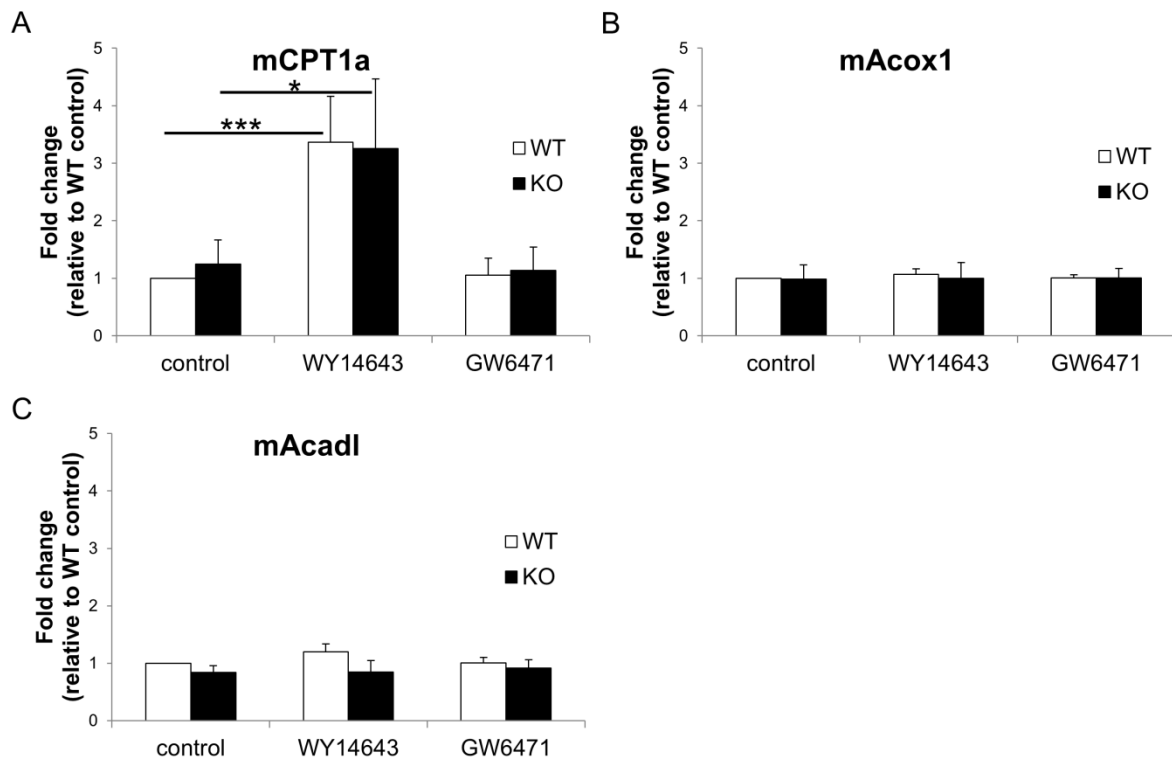


**Figure 18: mRNA expression of PPAR $\alpha$  target genes. A: mRNA expression of mitochondrial carnitine palmitoyltransferase (mCPT1a); B: mRNA expression of acyl-CoA oxidase (mAcox1); C: mRNA expression of: long-chain acyl-CoA dehydrogenase (mAcadl). Cycle times were normalized on the WT control. \*\*\*:  $p < 0.001$ ; \*:  $p < 0.05$**

PPAR $\alpha$  is a transcription factor that regulates the expression of genes affecting fatty acid  $\beta$ -oxidation. In cardiac mitochondria, the expression of PPAR $\alpha$  targets has been shown to be highly dependent on the presence of ATGL (47). Free fatty acids generated by ATGL were assumed to act as ligands for PPAR $\alpha$ . Figure 18 shows that in the B-cell model ATGL is not necessary for the expression of PPAR $\alpha$  targets. However, the addition of the PPAR-agonist WY14643 showed only a significant (approximately 3-fold increase: WT:  $p = 0.0001$ ; KO:  $p = 0.02$ ) effect for CPT1a (Figure 18 A) and overall mRNA levels were low. Also the antagonist GW6471 did not show any effects on mRNA levels. This might have been due to too low concentrations of the antagonist.

#### 4.8.4. ATGL-KO B-cells show tendency towards increased $\beta$ -oxidation of oleic acid and palmitic acid

As PPAR $\alpha$  target genes seemed unaffected by the lack of ATGL,  $\beta$ -oxidation of oleic acid and palmitic acid was investigated. For both fatty acids,  $\beta$ -oxidation seemed slightly increased in ATGL-KO B-cells; however this difference was not

statistically significant (oleic acid:  $p=0.13$  (Figure 19 A); palmitic acid:  $p=0.06$  (Figure 19 B)).

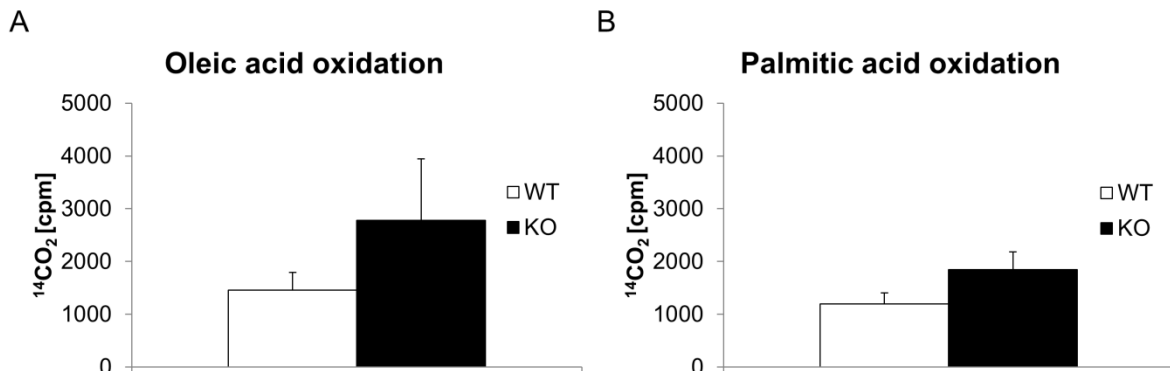


Figure 19:  $\beta$ -oxidation seems increased in ATGL-KO cells for oleic acid (A) as well as palmitic acid (B); however, the difference is not statistically significant

#### 4.8.5. ATGL-KO B-cells show no difference in diacylglycerol acyltransferase (DGAT) activity

As it appeared that TAG production was decreased while DAG synthesis appeared to be similar in ATGL-KO cells (Figure 17 D), it was hypothesized that this might be due to reduced DGAT activity. The DGAT activity assay used here is based on the reaction of the fluorescent acyl-CoA (NBD-FA-CoA) with exogenous diacylglycerol (DAG), catalyzed by DGAT. Two different concentrations of magnesium chloride were used in the assay as it is known that magnesium chloride inhibits DGAT-2 activity but not DGAT-1 activity (48). Figure 20 shows that contrary to expectations DGAT activity was not changed in ATGL-KO B-cells under either of the two magnesium chloride concentrations. Furthermore at concentrations of 100 mM  $\text{MgCl}_2$  DGAT activity was higher for both genotypes. This is contradictory to the findings of Cases et al (48), who reported that only DGAT-1 is active at 100 mM, whereas at 20 mM  $\text{MgCl}_2$  both enzymes should be active.

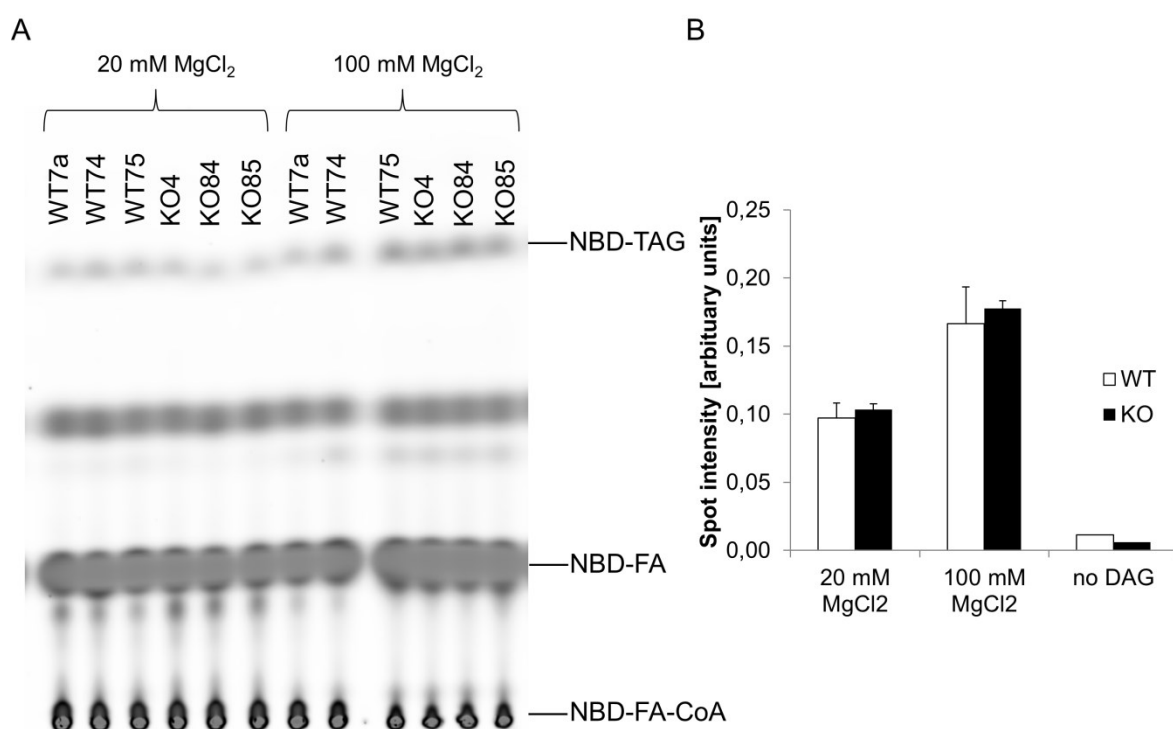


Figure 20: A: Fluorescence image of TLC of NBD-labeled lipids, shown here is one technical replicate. The entire TLC with all three technical replicates, including the no DAG control, can be found in the supplementary Figure S 7. NBD-TAG is derived from the transfer of NBD-FA-CoA onto exogenous DAG. B: Volume analysis of all technical replicates. Error bars represent standard deviation of means of biological replicates.

#### 4.9. Activity based proteomics reveal differential serine hydrolase profiles

It was hypothesized that the lack of ATGL may be compensated by other serine hydrolases. DABGE was thus used to visualize differences in the serine hydrolase activity profile of ATGL-KO B-cells. In Figure 21 a representative gel is shown. In order to avoid fluorophore based differences a dye swap was performed, i.e. ATGL-KO B-cell serine hydrolases were labeled with ATTO-633 and ATTO-Rho6G and mixed with WT serine hydrolases labeled with the respective other fluorophore. In total 4 gels were run and analyzed, however DABGE was only performed on one cell line each (KO4 and WT7a).

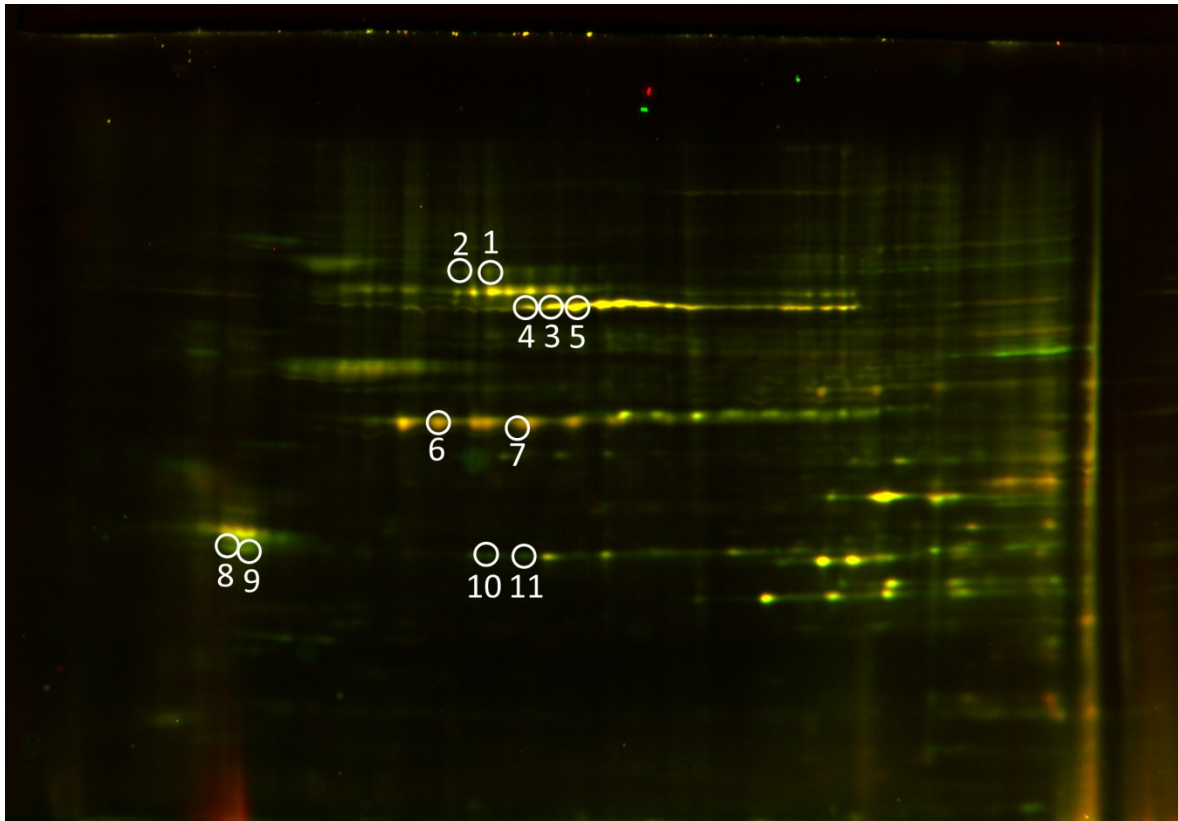


Figure 21: DABGE showing differential serine hydrolase profile in ATGL-KO B-cells. ATGL-KO activity profile is depicted in green, WT in red. Overlaps in activity are shown in yellow. The white circles show the approximate position of the picked spots. The actual gel spots were smaller

The analysis in Delta 2 D revealed 11 spots to be significantly differentially expressed ( $p\text{-value} < 0.05$ ). Those 11 spots were picked from the gel. The analysis of peptides by LC-MS/MS led to several identifications per gel spot (all identified proteins per gel spot are shown in Table S 3 to Table S 13). In Table 2 the intensity ratios and identified proteins are shown. Proteins shown here were chosen based on their probable serine hydrolase activity.

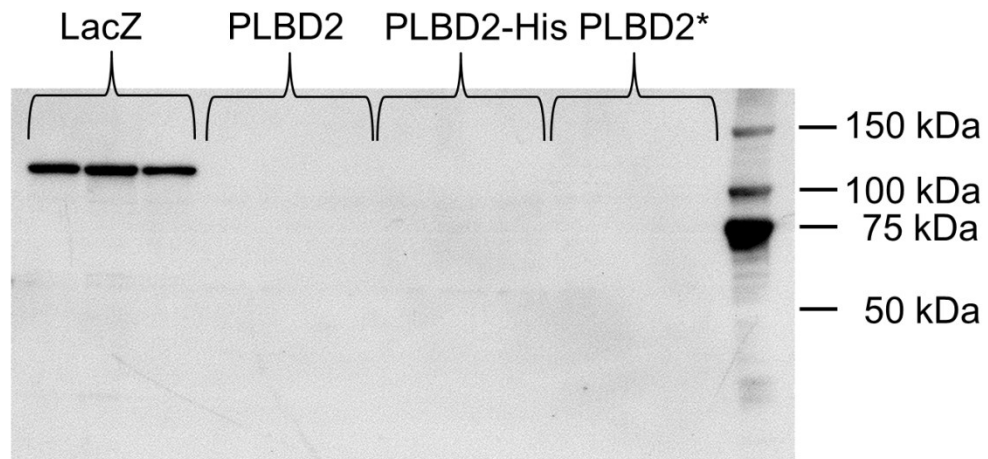
**Table 2: Selected Identified proteins from in-gel digest of 2D gel spots.**

| spot | WT/KO intensity | Identified proteins                                                                    |
|------|-----------------|----------------------------------------------------------------------------------------|
| 1    | 0.557           | Acylamino-acid-releasing enzyme                                                        |
| 2    | 0.752           | Prolyl endopeptidase                                                                   |
| 3    | 1.798           | Prolyl endopeptidase                                                                   |
| 4    | 2.014           | Xaa-Pro aminopeptidase                                                                 |
| 5    | 1.865           | Peroxiredoxin-2                                                                        |
| 6    | 1.150           | Protein arginine N-methyltransferase, SUMO-activating enzyme subunit 1, Glutaredoxin-3 |
| 7    | 1.33            | Cathepsin D                                                                            |
| 8    | 0.253           | Putative phospholipase B-like 2                                                        |
| 9    | 0.322           | Ubiquitin-like-conjugating enzyme ATG3                                                 |
| 10   | 0.725           | Platelet-activating factor acetylhydrolase IB subunit beta                             |
| 11   | 0.574           | Platelet-activating factor acetylhydrolase IB subunit beta                             |

#### 4.9.1. Putative phospholipase B-like 2

In spot 8 (Table 2) putative phospholipase B-like 2 (PLBD2) was identified. According to the Delta 2 D analysis the activity of this enzyme was upregulated in ATGL-KO B-cells. The protein is assumed to have phospholipase activity, but so far this has not been confirmed yet. To determine if PLBD2 has phospholipase activity, the protein was cloned and Cos7 cells were transfected with two different PLBD2 vectors (one with a His-tag, the other one untagged). Even though there is no positive signal in the anti-His Western Blot (Figure 22 A), it can be assumed that the overexpression using the pcDNA4 HismaxC vector worked. Figure 22 B shows an additional band for the cells treated with the His-PLBD2 plasmids. This protein band corresponds to a molecular weight of approximately 65-70 kDa, murine PLBD2 has been reported to have a size of 66.3 kDa (49). PLBD2 in *Cercopithecus* has a size of 55.2 kDa, so the lower band in Figure 22 B is most likely the endogenously expressed PLBD2 of Cos7 cells.

A



B

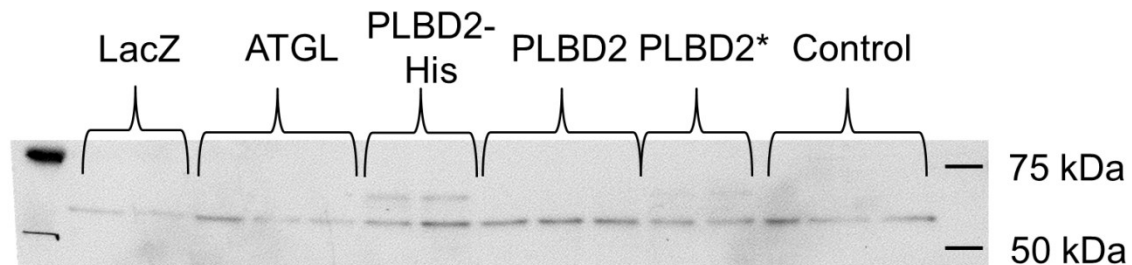


Figure 22: Western Blot for A: His-tagged proteins and B: His-PLBD2; \*: plasmid preparation from Juliane Bogner-Strauß' laboratory

#### 4.9.2. Overexpression of PLBD2 did not result in increased phospholipase activity

A phospholipase assay was performed in order to determine if the overexpression of PLBD2 leads to an increase in phospholipase activity. Phospholipase B can cleave both sn1- and sn2 acyl chains from phospholipids (lysophospholipids). Thus the assay used here is sensitive to both the loss of sn1- and sn2-acyl chains and leads to an increase in fluorescence.

In Figure 23 A the increase of fluorescence in the linear phase of the assay can be seen for the different cell lysates. The mean relative fluorescence increase/min is not significantly different ( $p=0.19$ ) for the cell lysates transfected with either His-PLBD2, PLBD2, LacZ, or the non-transfected control (Figure 23 B).

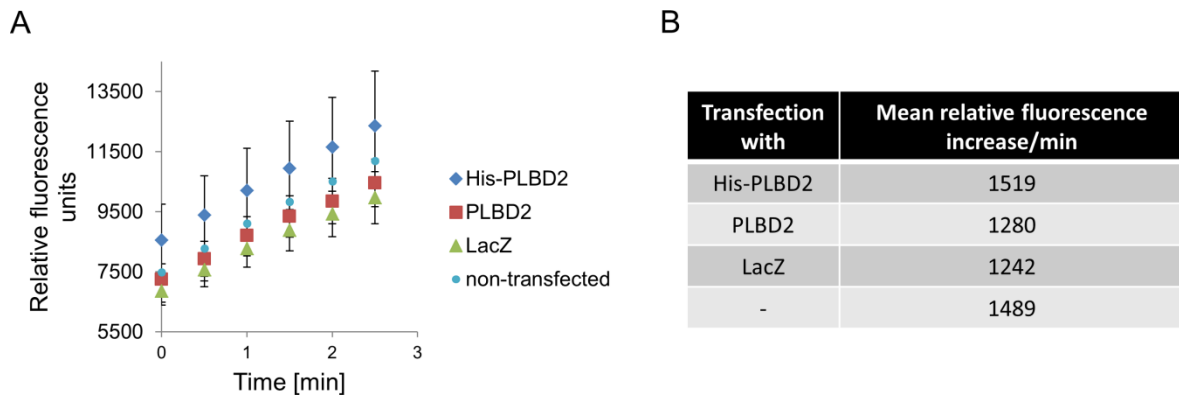


**Figure 23: Phospholipase assay. A: Linear phase of enzyme activity. B: Mean linear increase calculated for first six measurement points. One-way ANOVA showed no significant differences for the increase in fluorescence of differently transfected cell lysates ( $p=0.19$ ).**

In this approach an increase in phospholipase B activity upon the overexpression of PLBD2 could not be observed.

#### 4.10. Generation of stable ATGL-KO A549 cell lines

In order to obtain an additional model cell line, CRISPR-Cas9 was used to generate a stable protein-KO of ATGL in A549 cells.

A549 cells are human lung carcinoma cells which express moderate levels of ATGL. The CRISPR-Cas9 plasmid obtained from Santa Cruz included a mix of 3 plasmids which only differed in the sequence of the gRNA targeting a sequence in the third exon, at the intron-exon junction of the fifth exon or within the fifth exon of *ATGL*. The HDR plasmid also consisted of a pool of three different plasmids corresponding to the sites of the DSBs induced by the CRISPR-Cas9 plasmid. Co-transfection of both plasmids enabled the selection of positive cells with puromycin and FACS. After transfection of the cells with the plasmids two different strategies were applied in order to obtain KO clones. In a 6-well plate, three wells were subjected to puromycin selection followed by FACS while one well was directly expanded and used for FACS. During FACS RFP positive cells were sorted into single wells of a 96-well plate, filled with 200  $\mu$ L of conditioned and fresh medium (1:1). This procedure was intended to achieve the generation of cell lines originating from individual clones. 96-well plates were visually checked for the presence of only one cell per well and after one week, wells were inspected for red fluorescence. Aliquots of each clonal cell line were frozen, protein extracted for Western Blot analysis and DNA extracted for PCR. In Figure 24 the DNA gel of the PCR products is shown. The primers for the PCR were chosen to enclose the

entire region where the gRNAs can introduce double breaks and the reverse primer was put in a region that is not covered by the homology arms of either of the plasmids. The expected size in WT cells was 3.2 kb which can be found in samples B9, D9 and Ctrl (Ctrl being the parental non transfected A549 cells, B9 and D9 were transfected with the control plasmid with a scrambled gRNA which should not induce any DSBs). The numbered samples were transfected with the KO plasmid (the prefix 6 (Figure 24 A) is used for the clones which were not puromycin selected prior to FACS; prefix 3 (Figure 24 B) marks the clones which underwent puromycin selection).

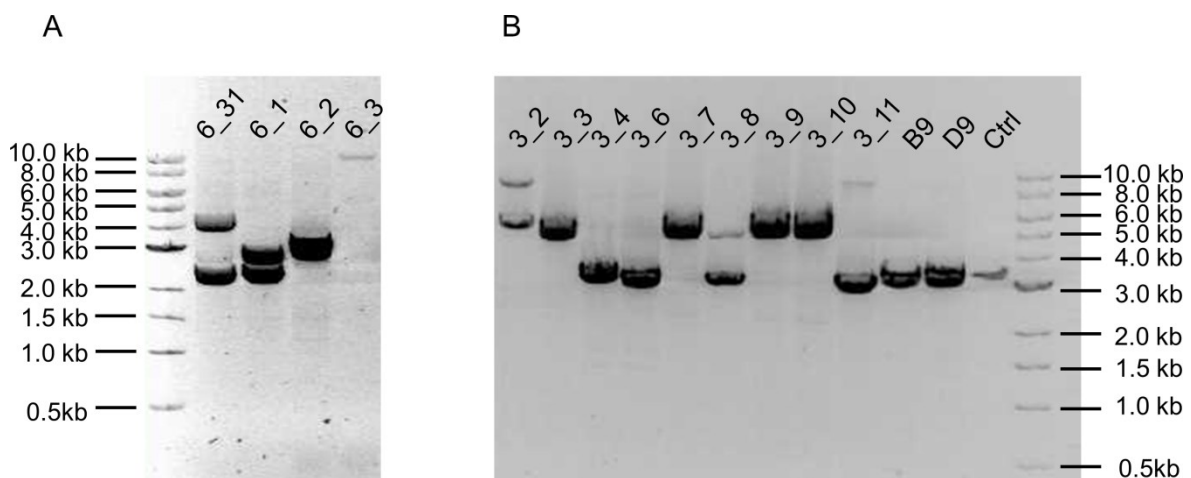


**Figure 24: PCR analysis for selected CRISPR-Cas9 clones.** The amplified WT fragment has a size of 3.2 kb. Panel A and B show excerpts from two different DNA gels. Ctrl: non transfected A549 cells. B9, D9: transfected with control plasmid, which should not induce DSBs. 6\_31-6\_3: no puromycin selection was performed prior to FACS. 3\_2-3\_11: puromycin selection. PCR for all clones is shown in supplementary figures (Figure S 11, Figure S 12, Figure S 13 and Figure S 14).

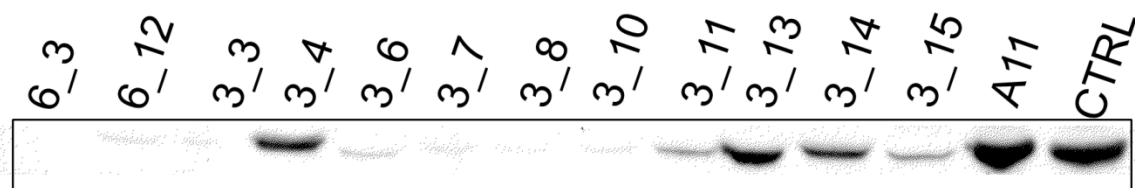


**Figure 25: Western Blot analysis for selected CRISPR-Cas9 transfected clones.** Western Blot was performed using an anti-ATGL primary and anti-rabbit secondary antibody. A11: transfected with control plasmid. Western Blots of all clones is shown in supplementary Figure S 10.

The band just above 3 kb is considered as the WT band where no HDR plasmid was integrated into that gene sequence. However, a DSB might have occurred but the HDR plasmid had failed to integrate. In that case, if the break was repaired by NHEJ an insertion or a deletion could have shifted the ORF leading to a premature stop codon or erroneous translation of the gene. This could be the case for sample 3\_6 where the Western Blot (Figure 25) shows only a very faint band for ATGL but the PCR indicates an amplicon at WT size. As this would have to be further

investigated, clones were considered as total KO when the Western Blot showed no protein and if there was no product in the PCR at a size of 3.2 kb and a larger product was present. Among others, the cell lines 6\_3, 3\_3, 3\_7 and 3\_10 met these criteria.

The smaller PCR products at about 2.2-2.4 kb were unexpected and only appeared in clones treated with the KO plasmid. An explanation for this band might be that two DSBs had been made by Cas9 and the cuts had been religated omitting the middle part. With the selected gRNAs this would have led to a reduction of 600 or 670 bp fitting the observed smaller PCR products.

#### 4.11. Impaired growth of A549 ATGL-KO clones

After obtaining the ATGL-KO clones the first question was if there was a growth advantage of ATGL-KO versus wildtype as it had been observed for the B-cells. Thus the cell number was monitored for 6 days. After 4 days, however, the curve flattened out as the cells reached 100 % confluency in the well. Figure 26 shows, that there is no growth advantage for ATGL-KO cells. In contrast, when looking at the slope of the last three time points, the increase in cell number of the WT clones was significantly ( $p=0.04$ ) faster than the increase in cell number of the ATGL-KO clones.

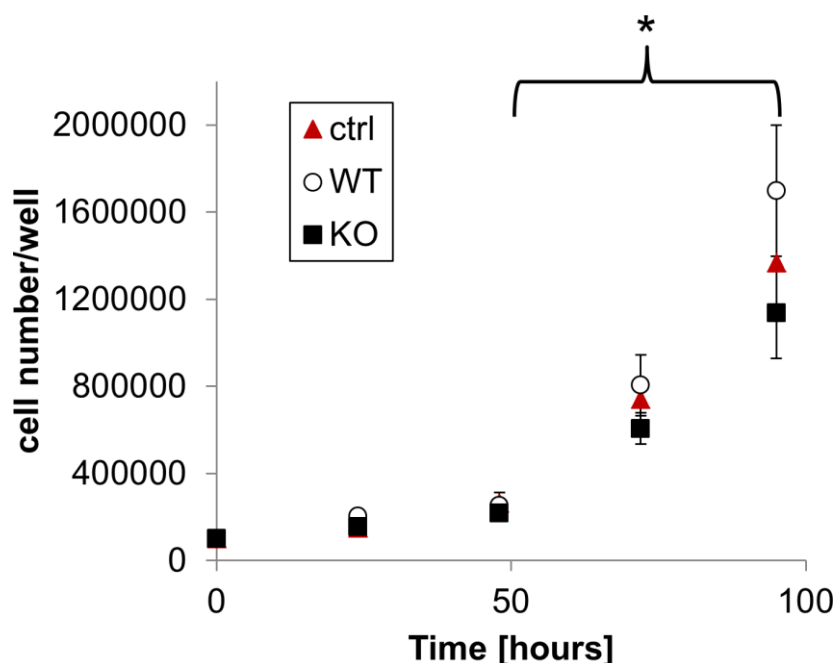


Figure 26: Impaired growth of ATGL-KO A549 cells. Linear growth was observed over the last three time points, after that the growth curve flattened out (not shown). \*:  $p<0.05$

#### 4.12. Lipid droplet formation in ATGL-KO clones

The lack of ATGL is presumed to lead to an accumulation of triacylglycerol. This accumulation is expected to be seen in cells as lipid droplets. Most cell types have lipid droplets or are able to produce them. In Figure 27 is shown that control transfected A549 cells only have very few lipid droplets, whereas the ATGL-KO cells have a significantly ( $p=0.0003$ ) 7-fold increased number of lipid droplets (Figure 28). This is most likely due to the lack of ATGL as triacylglycerols cannot be degraded but have to be stored.

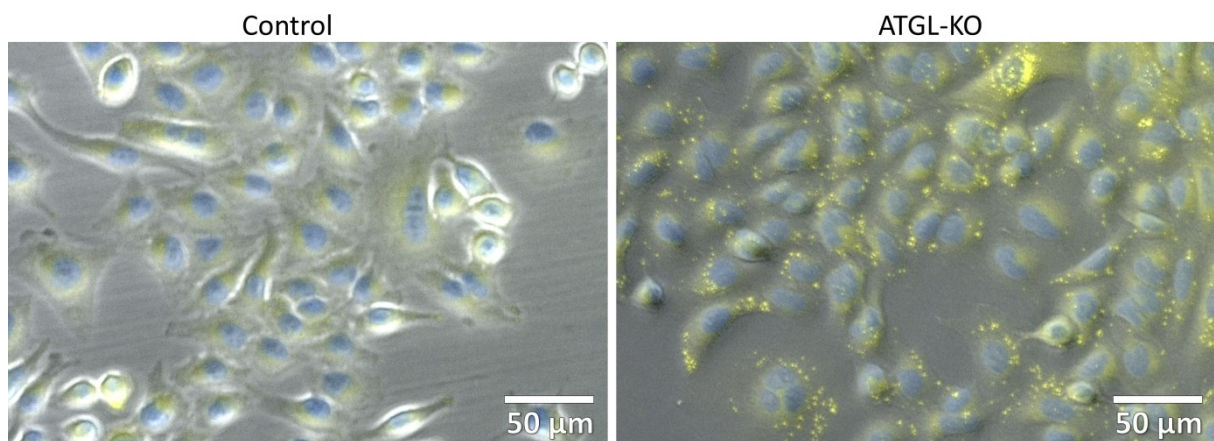


Figure 27: Lipid droplets accumulate in ATGL-KO A549 cells. Bodipy® staining is shown in yellow, DAPI staining in blue. Shown here are two representative pictures, all ATGL-KO clones displayed a similar accumulation of lipid droplets. Lipid staining of all clones is shown in the supplementary figures (Figure S 15 and Figure S 16).

The numbers of lipid droplets in Figure 28 might be underrepresented, as the software failed to recognize very small lipid droplets. However, as this applies for both ATGL-KO and control clones, the difference between the different cell types should be reflected quite well.

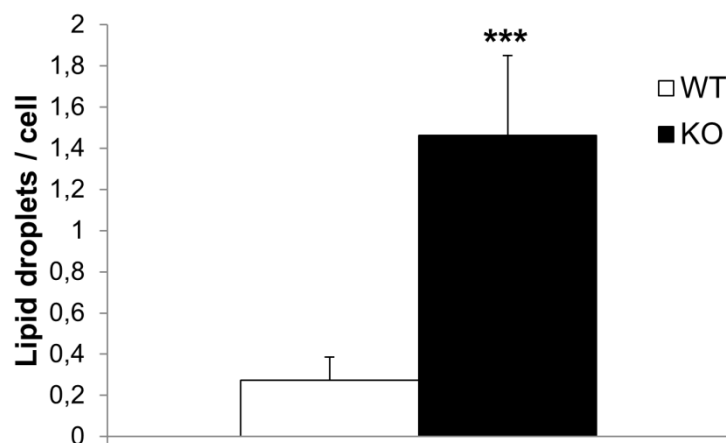


Figure 28: Number of lipid droplets in ATGL-KO A549 cells is 7-times increased. Quantitation of lipid droplets was done by ImageJ from 200-350 cells. \*\*\*:  $p<0.005$

## **5. Discussion**

### **5.1. Unaltered lipid metabolism in ATGL-KO B-cells**

To determine the mechanisms behind the growth advantage of ATGL-KO B-cells many aspects of their metabolism were investigated. Naturally, one would assume that fatty acid metabolism in these cells is changed as the first enzyme in lipid degradation is missing. Hence the first experiments presented here were directed at the uptake, incorporation and  $\beta$ -oxidation of free fatty acids (oleic acid and palmitic acid). However, no significant differences could be observed; although there was a tendency of decreased incorporation of fatty acids into lipids and increased fatty acid oxidation, as well as a higher dependency on fatty acids for basal oxygen consumption in ATGL-KO B-cells.

In cardiomyocytes ATGL is crucial for providing ligands for PPAR $\alpha$ . PPAR $\alpha$  in turn is an important transcription factor involved in the regulation of fatty acid oxidation. The lack of ATGL in cardiomyocytes led to impaired fatty acid oxidation and increased lipid accumulation (47). Here, ATGL-KO B-cells rather showed the opposite effect, i.e. a tendency towards increased  $\beta$ -oxidation and no effect on PPAR $\alpha$  target gene expression. The B-cells used in this work are characterized by a very low expression of ATGL and ATGL-KO B-cells do not accumulate lipid droplets (personal correspondence with Prof. Gerald Höfler at the Medical University of Graz). Thus they might not need the lipase function of the enzyme. Another explanation would be that the B-cells have a completely altered metabolism due to the cancerous nature of the cells. For example, they could rely on exogenous fatty acids, independent of the presence of ATGL, for incorporation into structural lipids as has been reported by Louie et al (15). However, the question of the reason for the growth advantage of ATGL-KO B-cells is still unresolved.

### **5.2. Unaltered central carbon metabolism of ATGL-KO B-cells**

As there were no changes in lipid metabolism that could explain the growth advantage of ATGL-KO cells, central carbon metabolism was analyzed more in detail using stable isotope resolved metabolomics (SIRM). As there was no difference in the uptake of either glucose or glutamine, it was hypothesized that

incorporation of these fuels might differ and ATGL-KO B-cells would channel these molecules into the production of building blocks in order to accommodate their increased growth rate. But neither in vitro nor in vivo differences of glucose or glutamine incorporation into metabolites of the central carbon metabolism could be observed. What remains to be investigated, however, is the incorporation of glucose and glutamine into lipids. Even though there was no difference in citrate, which is a precursor in lipid synthesis, there could be a preferred synthesis of signaling lipids, such as LPA which drives tumorigenesis (21). This could happen even though overall channeling of glucose and glutamine into lipids is unaltered.

Further investigations might also include alternative fuels such as acetate which has been reported before to be used by cancer cells and facilitates cell growth (50, 51).

### **5.3. Potential role of one carbon metabolism in ATGL-KO B-cells**

Quantitative proteomics revealed the downregulation of glycine dehydrogenase (GLDC) in ATGL-KO B-cells. This finding was confirmed in a Western Blot where the GLDC protein seems absent in ATGL-KO B-cells. GLDC has been reported to be involved in tumorigenesis, but the results are contradictory. Zhang et al found elevated levels of GLDC in tumor initiating cells in non-small cell lung cancer and showed increased expression of the enzyme after oncogenic transformation with MYC, KRAS and PIK3CA (52). However, Labuschagne et al reported that the knockdown of GLDC in human colon cancer cells did not have any effects on proliferation or glycine flux into purines (10). And Min et al reported a tumor suppressive role of GLDC in HEK293 cells and SNU484 cells (53). These results might suggest a tissue specific role for GLDC. In this work, it still cannot be told if the lack of GLDC is responsible for the growth advantage of ATGL-KO B-cells. Further investigations are needed to answer this question such as the analysis of purine synthesis and growth rate of a knockdown or knockout of GLDC. Also the relationship, if there is any, between GLDC and ATGL is unclear and requires further research.

#### **5.4. Increased activity of putative phospholipase B-like 2 in ATGL-KO cells**

According to the DABGE results, the activity of putative phospholipase B-like 2 was increased in ATGL-KO B-cells. ATGL has been shown to have phospholipase A2 activity (24), hence it was hypothesized that the lack of ATGL might lead to the upregulation of another phospholipase (here PLBD2). PLBD2 is a lysosomal protein (49) with predicted phospholipase activity based on sequence similarity. If the protein does exhibit phospholipase activity it might compensate for the lack of ATGL in ATGL-KO B-cells. In order to test for this hypothesis the overexpression of PLBD2 in Cos7 cells was attempted with the final aim to examine the protein for phospholipase activity. An overexpression of PLBD2 could only be observed using the pcDNA4/HisMaxC construct. The N-terminal His-tag was most likely cleaved off together with the signal peptide required for transport into the ER prior to further transport into the golgi and lysosome along the secretory pathway, as only untagged PLBD2 could be observed. However the overexpression of PLBD2 did not result in any increased phospholipase activity. This could have many reasons. For one the overexpression might not have been high enough and thus was masked by endogenous phospholipase A and B activities. Another reason could be that the investigated protein actually does not possess any phospholipase activity or that the protein is not active under the tested conditions. As the enzyme has been reported to be found in lysosomes, phospholipase activity should be assayed at acidic pH, as can be found in lysosomes. However this might require a different assay as the fluorescent assay used here was optimized for secreted phospholipases.

In future investigations the overexpression of PLBD2 should be optimized in order to yield higher concentration of the protein. Furthermore the cloning of PLBD2 could be repeated using a C-terminal His-tag, to purify the enzyme and test it for phospholipase activity this would omit problems of endogenous phospholipase expression.

#### **5.5. ATGL-KO A549 cells as an additional model cell line**

As opposed to the results in B-cells presented here, Zagani et al indicated that the inhibition or knockdown of ATGL would decrease cancer cell growth (27). Hence

CRISPR-Cas9 was employed in order to knockout ATGL in A549 cells. Unlike the B-cells, A549 cells have an intermediate level of ATGL expression. The knockout with CRISPR-Cas9 was successful and four different clones of each genotype (control transfected and ATGL-KO cells) were chosen for further analysis.

Comparable to the results reported by Zagani et al (27) it was shown here that ATGL-KO A549 cells grow slower than the control cells. Furthermore it was found that ATGL-KO cells accumulate lipid droplets. This contradicts the results in the B-cells, but might be due to the different tissue origin of the cells.

Also, the B-cells, purified from the bone marrow of ATGL-KO or WT mice, were transfected with BCR-ABL in order to turn them oncogenic. And even though all three B-cell ATGL-KO cell lines showed a similar phenotype this might be due to the transfection with BCR-ABL. BCR-ABL is a fusion protein often observed in leukemias and is characterized by the hyper-phosphorylation of tyrosines in downstream targets but also in BCR-ABL itself. The result is an activation of several oncogenic pathways, including the Ras-MAPK pathway leading to increased proliferation (54).

The generation of those oncogenic B-cell lines was repeated. That is, pre/pro B-cells were isolated from WT and ATGL-KO mice and then transfected with BCR-ABL. However, these new B-cells proliferated very slowly or not at all and did not show the same phenotype (ATGL-KO B-cells growing faster than WT cells) as the first generation of B-cells (Prof. Dr. Gerald Höfler, personal communication). This could indicate that the growth difference might be due to differences in BCR-ABL transfection or differences in the mice used as bone marrow donors.

## **5.6. Conclusion**

The observed growth advantage in ATGL-KO BCR-ABL transformed pre/pro B-cells could not be explained by the experiments performed. In general no significant changes could be observed in the metabolism of ATGL-KO B-cells. This suggests that the role of ATGL in B-cell metabolism is minor. Still, ATGL deficiency might in some way lead to the downregulation of GLDC, which was observed in the ATGL-KO B-cells. However, whether this is true and if this downregulation is related to the growth advantage requires further investigations.

The knockout of ATGL in A549 cells did not lead to a growth advantage in these cells, as previously reported in the literature (27). This indicates that the observed growth advantage of ATGL-KO B-cells might be tissue specific or not related to ATGL at all.

This in turn can be interpreted as ATGL playing an important role in cancer progression and the inhibition of the enzyme could be a potential target in cancer therapy.

## **Chapter Two – Impact of Trypsin Artefacts in Proteomic Database Searches**

## **6. Introduction**

### **6.1. Proteomics**

As one of the omics technologies, proteomics investigates the entirety of proteins of a cell, tissue or whole organism at a given state. In contrast to genomics which is not dependent on external influences, i.e. the genome of a fly is not changing whether it is cold or warm outside, proteomics can lead to vastly different results under different circumstances. The proteome, e.g. of a cell, changes with time/age and under certain conditions such as stress. On the one hand this enables analyses of processes in detail on the other hand one has to be very careful in sample preparation and handling in order to obtain reproducible results. Proteomics gives information about protein abundances, their variation within different samples or different cell states and modifications including post-translational modifications (PTMs) such as phosphorylation or acetylation. These PTMs can define the activation state of a protein. AMP-activated protein kinase (AMPK), for example, is activated through phosphorylation by LKB1 and then in turn phosphorylates other proteins involved in energy metabolism (55). However, phosphorylation can also lead to an inactivation of a protein, e.g. in the case of glycogen synthase kinase 3, which is phosphorylated and inactivated by protein kinase A (56). Thus the analysis of PTMs can give insights into pathway regulation.

One of the most important tools in proteomics is mass spectrometry. Mass spectrometry can determine the mass of either an intact protein (top down proteomics) or peptides derived from the digest of a protein (bottom up proteomics). Due to challenges of top down proteomics like the solubility of an intact protein, detection of large proteins, and lack of data analysis tools the most commonly used technique is bottom up proteomics. Bottom up proteomics enables the analysis of thousands of different proteins at a time in an untargeted manner. The basic proteomics workflow is depicted in Figure 29.

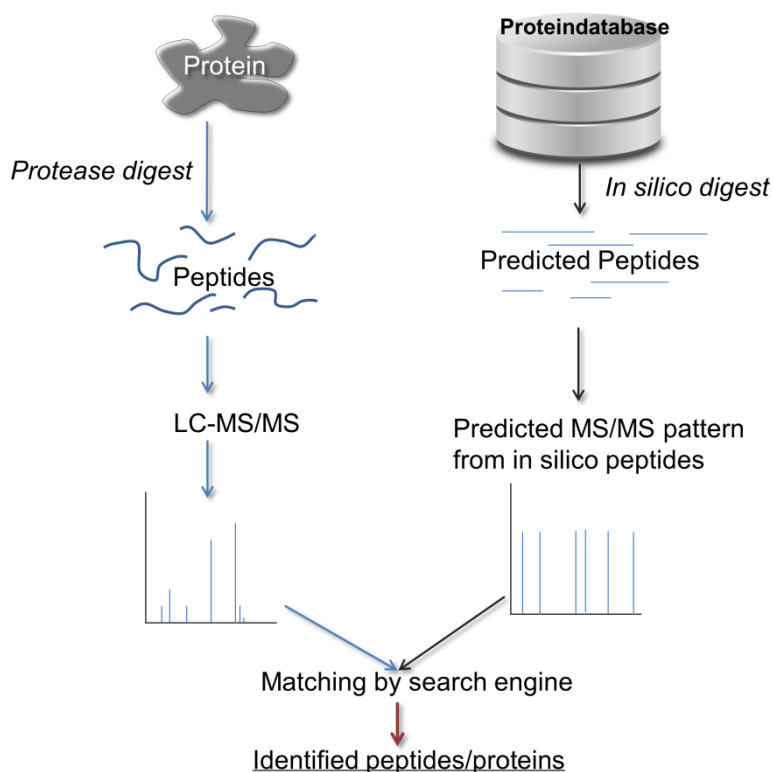


**Figure 29: Basic proteomics workflow**

## 6.2. Tandem Mass spectrometry coupled to liquid chromatography

Unravelling the proteome of a cell requires some kind of fractionation before the analysis in the mass spectrometer as otherwise only the most abundant peptides would be identified. About a decade ago proteins were separated using one- or two-dimensional electrophoresis (1-DE or 2-DE, respectively) and proteins were then either directly identified by mass spectrometry or analysis of the tryptic peptides derived from the in-gel digest was performed (57). Even though this technique separates and visualizes hundreds of proteins it has severe drawbacks. 1-DE provides only low resolution of proteins and the required staining of proteins might decrease the sensitivity of the mass spectrometer. Both labour intensive, 2-DE in addition is limited to small proteins (< 500kDa) with low hydrophobicity and furthermore cannot detect highly basic or acidic proteins.

Tandem mass spectrometry coupled to liquid chromatography (LC-MS/MS) can overcome many of the limitations of gel-based separations (reviewed in (58)). Peptides derived from protein digests are separated during chromatography based on specific properties (e.g. reversed phase liquid chromatography separates peptides based on their hydrophobicity, the higher the hydrophobicity of a peptide

the longer it is retained on the column). After elution from the column the peptide mass to charge ratio is analyzed in a mass spectrometer. Dependent on the method settings, the most abundant peptide masses are then chosen for fragmentation in a second mass spectrometer.

Today, gel-based fractionation is sometimes coupled to LC-MS/MS, but has been mostly outdated by chromatography-based methods such as strong cation exchange chromatography (SCX) (59). However, with new advancements in top-down applications 2-DE came back into focus as a prefractionation (60).

Recent advances in quantitative proteomics, including the use of stable isotopes for labeling, facilitate the comparison of up to 10 samples in one analysis (61). The untargeted way of comparison can give rise to differentially regulated proteins that otherwise would have been thought to be unrelated to the original question or hypothesis. Performing a similar analysis using Western Blotting is plainly impossible. First of all Western Blotting requires the knowledge about targets to obtain suitable antibodies, secondly not all antibodies are readily available and most importantly they are not always reliable, showing plenty of unspecific binding sites.

### **6.3. Protein digest with trypsin**

In order to generate peptides for bottom up proteomics, typically digestion enzymes are used for cleaving of proteins. Despite the existence of many different digestion enzymes with different cleavage sites, trypsin is the most commonly used enzyme in bottom up proteomics. The popularity of trypsin is based on its specificity, efficiency, availability and relatively low cost. Tryptic cleavage of amino acid sequences C-terminal to lysine and arginine residues (except for the occurrence of N-terminal proline) results in peptides of suitable length and charge for liquid chromatography analysis coupled to a mass spectrometer (62). As porcine trypsin contains 11 lysine and 4 arginine residues, it is subject to autolysis (63). Autolysis of trypsin not only leads the inactivation of the enzyme but also to high amounts of tryptic peptides in bottom up proteomics. As the usual enzyme to protein ratio ranges between 1:20 and 1:100, high quality spectra during MS/MS analysis are subsequently identified if the enzyme is self-digested.

## 6.4. Database identification of proteins

After the enzymatic digest of proteins peptide and peptide fragment masses are measured by tandem mass spectrometry after online separation by reverse phase liquid chromatography. The derived spectra are assigned to peptides with the help of search engines such as Mascot (64), SEQUEST (65), X!Tandem (66) or MS Amanda (67). As peptides fragment in a predictable manner, the fragmentation patterns that peptides in the database produce can be foreseen. Furthermore the user can set expected modifications introduced during the workflow. For example, reduction and alkylation of cysteines results in carbamidomethylation of cysteines which prevents refolding of proteins. This modification leads to a higher mass of the peptide and hence, if not considered, prevents identification of cysteine containing peptides. As all cysteines are modified, this modification can be set as static, so the expected mass of cysteine is raised by 57.02 Da. However, PTMs, such as phosphorylation do not occur on every serine, threonine and tyrosine. If these modifications are expected, e.g. after enrichment of phosphopeptides, they can be set as variable modification. Taking these modifications into account search engines then compare observed masses to theoretical peptide and fragment masses obtained by the in silico digest of the database (Figure 29). The in silico generated spectra and modified versions thereof constitute the so called search space. Then the matches are statistically scored according to the calculated probability that these matches resemble false positives. For evaluation of statistical significance of peptide matches false discovery rates (FDR) are generally applied. In proteomic approaches FDRs are often determined with the help of decoy databases (i.e. reversed or randomized databases) and are defined as the ratio of false positive matches to the total number of assignments (false positives/(false positives + true positives)). In order to minimize the number of false positive hits the database in use should be as precise as possible, meaning that all proteins present in the sample are represented in the database. This includes also contaminants that are introduced during sample handling. These can be introduced either by accident or as a reagent during sample preparation. Among the best know examples for the former group is human keratin. The degree of contamination with this group can be reduced by proper sample handling. The second group of contaminants includes proteases added in proteomics workflow to

digest proteins in the sample, or e.g. deglycosidases or phosphatases to deglycosidate or dephosphorylate proteins in the sample. Although the database should contain all possible components of the sample, it is not recommended to use the entire UniProt TrEMBL database as large databases not only increase the search time but also increase the number of random peptide matches (68).

## **6.5. Importance of appropriate databases**

The necessity of using appropriate databases was shown by Knudsen and Chalkey (69) who reanalyzed a dataset that identified various viral proteins in a honey bee-derived protein sample. The original publication (70) concluded that the occurrence of these viruses might be responsible for colony collapse disorder, which is the traceless disappearance of bees from the beehive. The database used for this publication only included viral and bacterial protein sequences. The reanalysis with a database including the reported proteome of honey bees, however, could not identify any of these viral proteins. This example clearly depicts that all expected proteins of the sample have to be included in the database search; otherwise misassignments to completely unrelated proteins can occur.

In a cluster analysis of the PRIDE repository Griss et al (71) identified several thousand peptides of trypsin, emphasizing the importance of adding the protease to the database.

## **6.6. Modification of trypsin**

To prevent autolysis of trypsin and the associated loss of activity (72), the enzyme can be modified which would also omit the presence of peptides of trypsin in subsequent LC-MS/MS analysis. Modification of trypsin can be either done by dimethylation (Promega, Sigma) or acetylation (New England Biolabs) of lysine residues. Both modifications yield a trypsin that is more resistant to autolysis while retaining its catalytic function.

Acetylation of lysine can be performed with a selection of anhydrides, e.g. acetic, succinic and maleic, the latter one being only temporary and hence not useful for trypsin acetylation (73). New England Biolabs modifies their bovine trypsin by acetylation using acetic anhydride which should target lysines specifically. It has

been reported that also tyrosine residues are acetylated. However this can be circumvented by working at low pH (74).

Reductive methylation, the most common form of modification of trypsin, also applied to improve protein crystallization (75) and for isotopic labeling in quantitative proteomics (76), acts on primary amines. The  $\epsilon$ -amino group of lysine reacts with formaldehyde to form a Schiff base and is then reduced to a secondary amine. The secondary amine being more reactive than the primary amine, reacts with another formaldehyde unit and forms a dimethylamino group (77). Thus all primary amines are converted to dimethylamines. This includes all lysine side chains and the N-terminus.

In this chapter it will be shown that the modification of trypsin does not completely prevent autolysis of the protease and that subsequently peptides of modified trypsin can be identified in several tryptic digests. These modified peptides of trypsin, since they are not considered in the database search, have led to misassignments in various datasets, even if trypsin was considered as a contaminant in the database search. Modified trypsin can only be identified if the search settings are changed appropriately. Here it will be shown how this is achieved without impairing search statistics. The presented alternative search strategy should be integrated into standard proteomic workflows if modified trypsin is used.

## **7. Material and methods**

Experiments were carried out according to the descriptions in the publication “Cleaning out the Litterbox of Proteomic Scientists’ Favourite Pet: Optimizing Data Analysis Avoiding Trypsin Artifacts” (78) which this work is based on.

### **7.1. Databases**

Swiss-Prot\_Yeast database was downloaded on June 10<sup>th</sup> 2015. Swiss-Prot\_Human database was downloaded on August 11<sup>th</sup> 2015. Swiss-Prot\_Mouse database was downloaded on April 17<sup>th</sup> 2015. The list of common Repository of Adventitious Proteins (cRAP) was downloaded from <ftp://ftp.thegpm.org/fasta/cRAP> (Version Jan 30 2015). The protein identifiers were then uploaded to UniProt Retrieve/ID mapping tool to generate a FASTA file in UniProtKB format (2015/02/02).

### **7.2. Search strategies**

Search strategy A: As database Swiss-Prot\_Human or Swiss-Prot\_Yeast was used, carbamidomethylation of cysteines was set as fixed modification. Oxidation of methionine and protein N-terminal acetylation were set as variable modifications.

Search strategy B: As database Swiss-Prot\_Human or Swiss-Prot\_Yeast was used, cRAP database was concatenated. Carbamidomethylation of cysteines was set as fixed modification. Oxidation of methionine and protein N-terminal acetylation were set as variable modifications.

Search strategy C: As database Swiss-Prot\_Human or Swiss-Prot\_Yeast was used, cRAP database was concatenated. Carbamidomethylation of cysteines was set as fixed modification. Oxidation of methionine and protein N-terminal acetylation were set as variable modifications. For dataset 2 acetylation of lysine was allowed as additional variable modification, for all other datasets monomethylation and dimethylation of lysine were allowed as additional variable modification.

Search strategy D: As database Swiss-Prot\_Human or Swiss-Prot\_Yeast was used, cRAP database was concatenated. Furthermore modified trypsin was added

to the database (where all lysines were replaced by dimethylated lysines). Carbamidomethylation of cysteines was set as fixed modification. Oxidation of methionine, protein N-terminal acetylation and loss of monomethylation and dimethylation of dimethylated lysines (J) were set as variable modification.

### 7.3. Datasets

Dataset 1: Human Breast Cancer Study, [PXD000246](#)(79); Dimethylated Trypsin

Dataset 2: Mitochondrial preparation from murine ATGL-KO B-cells

(KO\_mito\_digest.raw); dimethylated trypsin

Dataset 3: Murine tumor lysate; Dimethylated trypsin

Dataset 4: *S. cerevisiae*; Dimethylated Trypsin, PXD002726

Dataset 5: Phosphorylation sites of Numb, human cell line with mouse recombinant protein Numb, [PXD000997](#) (80); Acetylated Trypsin

Dataset 6: Human Brain 6-11 reference map, [PRD000151](#)(81); Dimethylated trypsin

Dataset 7: Identified spectra from 209 public human datasets from the PRIDE repository (see Supplementary Table S1)

### 7.4. Data analysis

Database search: Database search was performed using Mascot Ver. 2.4.1 or MS Amanda Standalone\_Windows\_1.0.0.3948 customized to contain J = 156.125710 and O = 144.0641770 (kindly provided by Viktoria Dorfer). Data were searched against human and *S. cerevisiae* Swiss-Prot (Swiss-Prot\_Yeast) database as specified in database section. For false discovery rate estimation a target / decoy database search was used. Peptides were matched using trypsin as a digestion enzyme. Peptides mass tolerance was set to 10 ppm (or 100 ppm for dataset 6) and fragment mass tolerance to 0.8 Da. A maximum of two missed

cleavages was allowed. Carbamidomethylation of cysteine was set as a fixed modification and oxidation of methionine was set as variable modification. In order to detect peptides containing the artificial amino acid J, the cleavage specificity for trypsin was changed to J, K and R, not after P. Furthermore to detect mixed peptides (i.e. peptides including dimethylated and unmodified lysine) the loss of dimethylation of lysines (i.e. only J) was added as a variable modification.

Dataset 4 was searched using X!Tandem (66) (version 'Piledriver (2015.04.01.1)') in cooperation by Johannes Griss (Medical University of Vienna). As X!Tandem restricts the amino acids that may be redefined, 'O' was used to represent dimethylated lysine. The mass of O was set to 156.12571 using the 'protein, modified residue mass file' option. Carbamidomethylation of cysteine was set as fixed modification and oxidation of methionine, N-terminal acetylation and a loss of 28.0307517 Da on 'O' representing dedimethylation as variable modifications. Parent mass error was set to 2 Da and fragment mass error to 0.4 Da. 2 missed cleavages were allowed, the specificity of trypsin adapted as described before and refinement mode was disabled. All results were filtered to reach an FDR of 1 %.

## **7.5. Statistical analysis**

Statistical analysis for Figure 31 was done in R using a repeated measures ANOVA. Pairwise comparison of different groups (i.e. search strategies A-D (see above) for 5 biological replicates taken from dataset 1) was performed using Tukey post-hoc test in R.

## **7.6. Experimental details dataset 2, 3 and 4**

### **7.6.1. Dataset 2 and 3**

Mitochondrial preparations or tumor-lysates were digested according to Wisniewski et al (39). Peptides were dried and resuspended in 5 % acetonitrile and 0.1 % trifluoroacetic acid and peptides were separated on a Acclaim PepMap RSLC C18, 2  $\mu$ m, 100 Å, 75  $\mu$ m i.d. x 50 cm column employing a Dionex Ultimate 3000 RSLC coupled to a LTQ-Orbitrap Velos (Thermo Fisher Scientific, Waltham, MA, USA). The LC-method consisted of a 120 min gradient. Data dependent Top 10 CID MS and MS/MS data were acquired in the Orbitrap analyzer at a resolution of 60000 and in the ion trap employing normal scan rate settings,

respectively. Software Version of XCalibur (Thermo Fisher Scientific, Waltham, MA, USA) was 3.0.

#### 7.6.2. Dataset 4

Proteins from *S. cerevisiae* lysates were separated with SDS-PAGE. Proteins were stained using Coomassie brilliant blue. Gel bands were cut out and destained using 50 % acetonitrile in 100 mM ammonium bicarbonate. After dehydration with 100 % acetonitrile, gel pieces were dried and then reduced with 10 mM dithiothreitol for 30 min at 56 °C and subsequently alkylated with 55 mM iodoacetamide for 20 min at 37 °C in the dark. Gel pieces were dehydrated and dried again and incubated with 0.19 µg of sequencing grade modified trypsin (V5111, Promega, Madison, WI, USA) overnight. Peptides were extracted in four sequential steps: 15 µL of 25 mM ammonium bicarbonate, 150 µL of acetonitrile, 40 µL of 5 % formic acid and 150 µL of acetonitrile. Supernatants were combined and dried under vacuum. The dried peptide extracts were resuspended in 5 % acetonitrile and 0.1 % trifluoroacetic acid. The LC-MS/MS conditions were as described above except the LC gradient was only 70 min.

The mass spectrometry proteomics data was deposited to the ProteomeXchange Consortium (82) (<http://proteomecentral.proteomexchange.org>) via the PRIDE partner repository with the dataset identifier PXD002726 and 10.6019/PXD002726.

## 8. Results

### 8.1. Use of contaminant databases

Even though guidelines for proteomics experiments urge scientists to include common contaminants in their database searches, to date there are no publications showing the necessity of it. Hence different datasets 1-3 were analyzed in a mascot search using two different search strategies. Search strategy A used the appropriate database (i.e. Swiss-Prot\_Mouse or Swiss-Prot\_Human) but excluded common contaminants. Search strategy B represents the community standard of database search which includes a list of common contaminants additional to the appropriate database. For both search strategies carbamidomethylation of cysteines was set as fixed modification; and oxidation of methionine and protein N-terminal acetylation were set as variable modifications. Table 3 shows some examples for misassignments of spectra due to a missing contaminant database.

**Table 3: Misassignments due to a lack of contaminant list during database search**

| Search strategy | query | peptide sequence         | Peptide Score | protein                   | file                                                                |
|-----------------|-------|--------------------------|---------------|---------------------------|---------------------------------------------------------------------|
| A               | 18683 | K.AGADTHGRLLQGNCNDAVTK.A | 37            | CASPC_HUMAN               | Site1_Cell_line_ERneg_H<br>ER2neg_Pool1_1D_Rep4.<br>raw (Dataset 1) |
| B               | 18683 | R.LGEHNIDVLEGNEQFINAAK.I | 114           | TRYP_PIG                  |                                                                     |
| A               | 18641 | K.AGADTHGRLLQGNCNDAVTK.A | 33            | CASPC_HUMAN               | Site1_Cell_line_ERneg_H<br>ER2neg_Pool1_1D_Rep3.<br>raw (Dataset 1) |
| B               | 18641 | R.LGEHNIDVLEGNEQFINAAK.I | 110           | TRYP_PIG                  |                                                                     |
| A               | 21558 | R.FLEQQNQVLQTK.W         | 40            | K2C73_MOUSE               | KO_mito_digest.raw<br>(Dataset 2)                                   |
| B               | 21558 | R.FLEQQNQVLQTK.W         | 40            | K2C1_HUMAN/K2<br>2E_HUMAN |                                                                     |
| A               | 706   | R.SLDLDSIIAEVK.A         | 91            | K2C6B_MOUSE               | 1496_trypsin.RAW<br>(Dataset 3)                                     |
| B               | 706   | R.SLDLDSIIAEVK.A         | 91            | K2C1_HUMAN                |                                                                     |

These are just a few examples from four different raw files. The first two files originated from human samples, the last two from murine samples. In the first two examples it can be assumed that porcine trypsin (TRYP\_PIG) is the more likely hit, but using search strategy A the same spectrum was assigned to human inactive caspase-12 (CASPC\_HUMAN).

For the two murine files the misassignments are confined to keratin. K2C1\_HUMAN has 54% sequence identity with K2C73\_MOUSE, hence peptides can be identical for both species, which is the case in these examples (Figure 30). However, a contamination with human keratin is more likely in this case as additional human keratin peptides but no murine keratin peptides were identified.

```

1  MSRQFSSRSGYRSGGGFSSGSGAGIINYQRRTSSSTRSSGGGGGRFSSCGGGGSGFAGGGFGSRLVNLGGSKSISISV 80
1  MNRFQFTCKPGV-ANRGFSGCSAVL-----SGGSSSSYRAAGKG-----LSGGFSSRSLYSLRSPRSISFINV 60

81  ARGGGRGSGFGGGYGGGFGGGGFGGGGIAGGGFGGFGSGGGGFGGGGFGGGYGGGYGPVCPGGIQEVITINQS 160
61  ASSSGRT----GGYGFGRNRRASGFAGSMFGSGALGPSN-----PSLCLPGGIHQVTVNKS 111

161  LLQPLNVEIDPEIQKVKSREREQIKSLNNQFASFIDKVFLEQQNQVLQTKIELLQQVDTSTRTHNLEPYFESFINNLR 240
112  LLAPLNVEIDPEIQKVRQEREQIKALNNKFASFIDKVFLEQQNQVLQTKIELLQQLDLSNCRRLNLEPVYEAHISSLQK 191

241  RVDQLKSDQSRLDSELKNMQDMVEDYRNKYEDEINKRTNAENEFVTIKDQVDGAYMTKVDLQAKLDNLQQEIDFLTALYQ 320
192  QLDSLSGDRVRLDSELRGMRDAVEDCKKRYEEIEINKRTTAENEFVVLKQDVAAYMSKVELQAKVDALDGEIKFLKCLYE 271

321  AELSQMOTQISETNVILSMDNNRSLDLSIIAEVKAQYEDIAQKSKAEAEELYQSKYEELQITAGRHGDSVRNSKIEISE 400
272  GEITQMQSHISDTSVVLSDNNRNLDLDSIIAEVRAQYEDIAKSKAEAEVYQTKFQELQLAAGRHGDDLKHTRWIEISE 351

401  LNRVIQRLRSEIDNVKKQISNLQSSISDAEQRGENALKDAKNKLNLDLEDALQQAKEDLARLLRDYQELMNTKLALDLEIA 480
352  LTRLIQRLRSEIESVKKQCSNLETAIADAEQRGDCALKDARAKLDELERALHQAKEELARMLREHQELMSMKLALDIEIA 431

481  TYRTLLEGEESRMSGECAPNVSVSYSTHTTISGGGSRGGGGGGYSGGSSYSGGGGSGGGGGGGGSGY--SGGSS 558
432  TYRKLLEGEECRMSGHEHTSAVSISVISS-----SAPGTVGAGTSFGFSSAGTYGYRQSSVAGG-----YGILSGGCV 498

559  YSGGGGSGYSGGGGGGGHSGYSGSSSSGGYRGSGGGGGSSGGRSGGGSSGGSSIGGRGSSGGVKSSGGSSSVKVFSTT 638
499  TSGGNCS-----PRGDTKNR-LGSASEFKEYSGKTLALG-----SPSKTMR-- 539

639  YSGVTR 644
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**Figure 30: Sequence alignment of human (upper sequence) and murine (lower sequence) keratin (K2C1\_HUMAN and K2C73\_MOUSE, respectively). The black frame highlights the identified peptide, which is identical in the two proteins. Sequence identity of human compared to murine keratin is 54 %.**

Table 4 shows how abundant these contaminants can be. This example originates from an in-gel-digest from *Saccharomyces cerevisiae* samples from our laboratory (dataset 4). Although spectra were not misassigned they were nevertheless not considered because the database did not include the matching peptides (search A). Human keratin appears as the third and sixth highest scoring protein (K2C1\_HUMAN, K22E\_HUMAN) and porcine trypsin (TRYP\_PIG) as fifth highest scoring protein when the list of common contaminants was included into the database search (search B).

**Table 4: Influence of inclusion of contaminant databases on protein identification results using Mascot**

|     | Search strategy |       |             |       |
|-----|-----------------|-------|-------------|-------|
|     | A               |       | B           |       |
| Hit | Protein         | Score | Protein     | Score |
| 1   | HSP72_YEAST     | 5952  | HSP72_YEAST | 5542  |
| 2   | HSP71_YEAST     | 5764  | HSP71_YEAST | 5349  |
| 3   | HSP74_YEAST     | 3063  | K2C1_HUMAN  | 3610  |
| 4   | HSP76_YEAST     | 1330  | HSP74_YEAST | 2896  |
| 5   | HSP75_YEAST     | 1276  | TRYP_PIG    | 1932  |
| 6   | VATA_YEAST      | 1062  | K22E_HUMAN  | 1899  |

While the inclusion of common contaminant lists in the database search is accepted as standard procedure, even if not always performed, the modification of trypsin has not been considered so far.

## 8.2. Completeness of protease modification and inhibition of proteolytic activity

Modified trypsin is most commonly used as protease in proteomics workflows. But despite the frequently employed modification to avoid self-digestion Griss et al identified thousands of spectra representing peptides of trypsin (71). However, these identifications only represented the unmodified fraction of peptides of trypsin. Even though the reductive methylation of lysines is considered complete on peptide level (76), unmodified peptides might occur due to the native state of trypsin during reductive dimethylation.

Given that unmodified peptides of trypsin can be found, the completeness of the inhibition of self-digestion is highly questionable. Hence it was assumed that also modified peptides can be identified and the search was optimized to find both mono- and dimethylated trypsin peptides. The first approach included methylation as variable modification (search strategy C) and shows that indeed both modifications in trypsin peptides can be found in dataset 4 (Table 5).

Interestingly, the modification could also be found at the C-terminus which indicates that self-digestion cannot be completely inhibited by dimethylation.

The number of methylated peptides derived from trypsin varied in different datasets, so does the ratio of methylated to dimethylated peptides (Table 6), ranging from 18 % to 67 % of mono-methylated peptides.

**Table 5: Occurrence of methylated peptides in trypsin. Methylation and dimethylation of lysines was allowed as variable modification in Mascot database search. Shown are selected peptides for trypsin. The modified amino acid is depicted in bold letters.**

| peptide | score | Expect  | Sequence                                            | PSM |
|---------|-------|---------|-----------------------------------------------------|-----|
| 1       | 47    | 1.0E-04 | R.VATVSLPR.S                                        | 30  |
| 2       | 62    | 8.9E-06 | K.LSSPATLNSR.V                                      | 7   |
| 3       | 45    | 3.1E-04 | K.SSGSSYPSSLQCLK.A                                  | 2   |
| 4       | 43    | 5.1E-04 | K.VCNYVNWIIQQTIAAN.-                                | 1   |
| 5       | 105   | 6.7E-11 | R.SCAAAGTECLISGWGNTK.S                              | 2   |
| 6       | 85    | 9.3E-09 | R.SCAAAGTECLISGWGNT <b>K</b> .S + Methyl (K)        | 1   |
| 7       | 118   | 4.9E-12 | R.SCAAAGTECLISGWGNT <b>K</b> .S + Dimethyl (K)      | 7   |
| 8       | 110   | 1.2E-10 | R.LGEHNIDVLEGNEQFINAAK.I                            | 30  |
| 9       | 110   | 1.4E-10 | R.LGEHNIDVLEGNEQFINAA <b>K</b> .I + Methyl (K)      | 3   |
| 10      | 92    | 4.9E-09 | R.LGEHNIDVLEGNEQFINAA <b>K</b> .I + Dimethyl (K)    | 15  |
| 11      | 79    | 1.9E-07 | K.IITHPNFNGNTLDNDIMLIK.L                            | 2   |
| 12      | 48    | 2.2E-04 | K.IITHPNFNGNTLDNDIML <b>I</b> K.L + Methyl (K)      | 1   |
| 13      | 79    | 1.3E-07 | K.IITHPNFNGNTLDNDIM <b>L</b> IK.L + Oxidation (M)   | 2   |
| 14      | 43    | 4.8E-04 | K.SSGSSYPSSLQCL <b>K</b> APVLSDSCK.S + Dimethyl (K) | 1   |

**Table 6: Number of methylated and dimethylated peptides from trypsin exemplified in dataset 1 and dataset 4.**

| Dataset (file #)   | # mono-methylated peptides from trypsin | # dimethylated peptides from trypsin | Mono-methylated/dimethylated [%] |
|--------------------|-----------------------------------------|--------------------------------------|----------------------------------|
| Dataset 1 (file 1) | 6                                       | 4                                    | <b>60/40</b>                     |
| Dataset 1 (file 2) | 5                                       | 6                                    | 45/ <b>55</b>                    |
| Dataset 1 (file 3) | 5                                       | 5                                    | 50/50                            |
| Dataset 1 (file 4) | 6                                       | 3                                    | <b>67/33</b>                     |
| Dataset 1 (file 5) | 5                                       | 5                                    | 50/50                            |
| Dataset 4 (file 1) | 4                                       | 17                                   | 19/ <b>81</b>                    |
| Dataset 4 (file 2) | 5                                       | 23                                   | 18/ <b>82</b>                    |
| Dataset 4 (file 3) | 7                                       | 11                                   | 39/ <b>61</b>                    |

Using a similar approach, acetylated peptides from trypsin could be identified in a human epithelial cell dataset (dataset 5), for which acetylated trypsin was used as a protease (80) (Table 7). Interestingly, acetylated peptides could only be found as missed cleavages, not C-terminal.

**Table 7: Peptides identified from acetylated trypsin in dataset 5. Unmodified and acetylated peptides could be identified when allowing acetylation of lysine as a variable modification**

| peptide | score | Expect  | Sequence                                 |
|---------|-------|---------|------------------------------------------|
| 1       | 49    | 1.4E-05 | K.SAASLNSR.V                             |
| 2       | 15    | 3.2E-02 | K.LKSAASLNSR.V                           |
| 3       | 29    | 1.3E-03 | K.LKSAASLNSR.V + Acetyl (K)              |
| 4       | 70    | 9.6E-08 | K.SSGTSYPDLK.C                           |
| 5       | 42    | 6.8E-05 | K.VCNYVSWIK.Q                            |
| 6       | 128   | 1.7E-13 | K.LQGIVSWGSGCAQK.N                       |
| 7       | 33    | 5.4E-04 | K.VCNYVSWIKQTIASN.- + Acetyl (K)         |
| 8       | 153   | 4.7E-16 | R.LGEDNINVEGNEQFISASK.S                  |
| 9       | 77    | 1.8E-08 | K.SIVHPSYNSNTLNNDIMLIK.L + Oxidation (M) |

With this search strategy (C) the score of trypsin increases, as more peptides can be identified (Table 8).

However, each added variable modification in a database search increases the search space. With the increase in search space come several disadvantageous effects, the most severe being the increase of random matches and the associated

impact on result statistics. Adding a variable modification multiplies the search space, thus increasing the score threshold for positive spectrum matches. Furthermore the larger the search space the more time takes the search.

In order to avoid these negative effects, a new search strategy (D) was devised that considers modification of trypsin without significantly increasing the search space. Dimethylated lysine was introduced as an artificial amino acid. In Mascot this is easy to perform by changing the unimod.xml file where the two letters J and O are available for user-defined amino acids. Hence J was chosen to be dimethylated lysine with a monoisotopic mass of 156.125710 Da ( $J = K + \text{dimethyl} (+C_2H_4/28.0313)$ ). In the protein database a copy of porcine trypsin with all lysines replaced by J was then added (this trypsin form was called TRYP\_ART with the fictional accession number 012345). To also detect mixed peptides, i.e. peptides with both methylated and unmodified lysines, the loss of methylation and dimethylation on lysines was set as a variable modification. As this variable modification only concerns Js, the increase in search space is minimal (there are 11 Js in porcine trypsin). Using the database including artificial trypsin and setting the modifications explained above, led to the identification of methylated and unmodified as well as mixed peptides of trypsin in the *S. cerevisiae* dataset (Table 8).

**Table 8: The effect of different search strategies on the proteins identified.**

| Hit | Search strategy |       |             |       |             |       |             |       |
|-----|-----------------|-------|-------------|-------|-------------|-------|-------------|-------|
|     | A               |       | B           |       | C           |       | D           |       |
|     | Protein         | Score | Protein     | Score | Protein     | Score | Protein     | Score |
| 1   | HSP72_YEAST     | 5952  | HSP72_YEAST | 5542  | HSP72_YEAST | 4276  | HSP72_YEAST | 5542  |
| 2   | HSP71_YEAST     | 5764  | HSP71_YEAST | 5349  | HSP71_YEAST | 4048  | HSP71_YEAST | 5349  |
| 3   | HSP74_YEAST     | 3063  | K2C1_HUMAN  | 3610  | K2C1_HUMAN  | 2972  | K2C1_HUMAN  | 3610  |
| 4   | HSP76_YEAST     | 1330  | HSP74_YEAST | 2896  | HSP74_YEAST | 2264  | TRYP_ART    | 2953  |
| 5   | HSP75_YEAST     | 1276  | TRYP_PIG    | 1932  | TRYP_PIG    | 2147  | HSP74_YEAST | 2896  |
| 6   | VATA_YEAST      | 1062  | K22E_HUMAN  | 1899  | K1C9_HUMAN  | 1550  | K22E_HUMAN  | 1899  |

### 8.3. Deleterious impact of increasing the search space in database searches

Using the new search strategy should not have any negative effects compared to standard workflows but still be able to identify modified peptides of trypsin. Hence

the influence of the different search strategies on peptide spectrum matches, peptide scores and average protein scores was investigated. As examples five raw files from a human breast cancer data set (dataset 1) were used. These files were chosen due to their complexity and human origin. For all searches the FDR was kept at 1 %. Naturally, search strategy A identified fewer peptides as it was unable to assign spectra to common contaminants. Search strategy B, which is supposed to be the standard procedure in the proteomics community, included the list of common contaminants. Hence this search assigned more spectra and also yielded more PSMs after applying the 1 % FDR cutoff (Figure 31 A). Search strategy C, including both dimethylation and monomethylation of lysines, results in a higher number of assigned spectra, however at the cost of PSMs after applying 1 % FDR. This effect of variable modifications is also reflected in the lower average protein score (Figure 31 B). Lastly, search strategy D could identify methylated trypsin, however, proves to have no negative effects on result statistics compared to the community standard (i.e. search strategy B). Total PSMs, PSMs after applying 1 % FDR and average protein score are not altered. Only search strategy C significantly impaired the outcome of the database search.

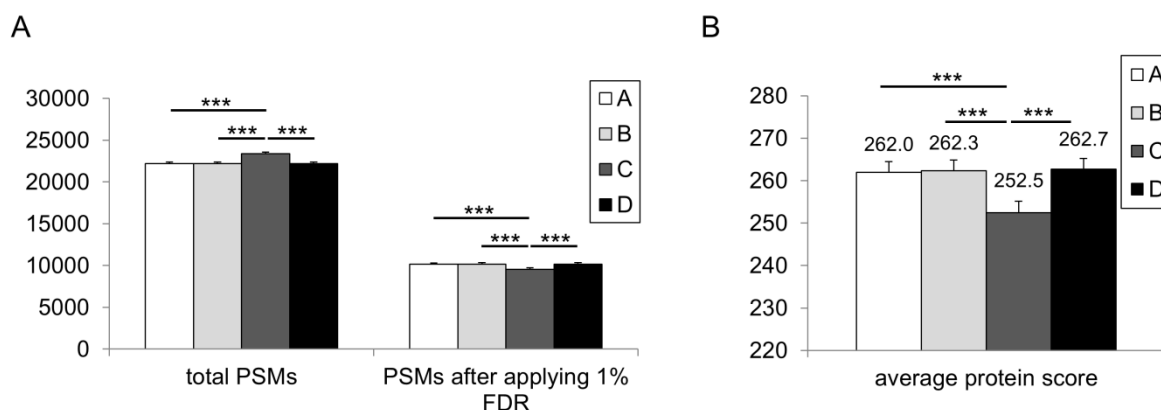


**Figure 31: Impact of different search strategies on search output. A: Total PSMs and PSMs after applying 1 % FDR are only significantly altered for search C. B: Adding variable modification influences the score threshold for peptides at 1 % FDR. This is also reflected in the lower average protein score. Statistical analysis was done using a repeated measures one-way-ANOVA in R. \*\*\* indicates p-value of  $< 10^{-10}$**

#### 8.4. False positive assignments due to omitting modified trypsin from database searches

The advantage of search strategy D is the ability of correctly assigning spectra derived from modified trypsin to modified trypsin. This is very important in order to avoid false positive results. Trypsin is highly abundant; so is its modification.

Hence a large number of high quality spectra are present that, when not included into the database, can be assigned to completely unrelated proteins. One example for this is shown in Figure 32 where one file from dataset 1 was searched using search strategy B (Figure 32, right panel) and again using search strategy D (Figure 32, left panel). Search strategy D led to the identification of methylated trypsin with a very high score. Search strategy B on the other hand led to the identification of an entirely unrelated protein (Ras-related protein Rab-32) with a lower score; however, the score was still high enough to pass the score threshold.

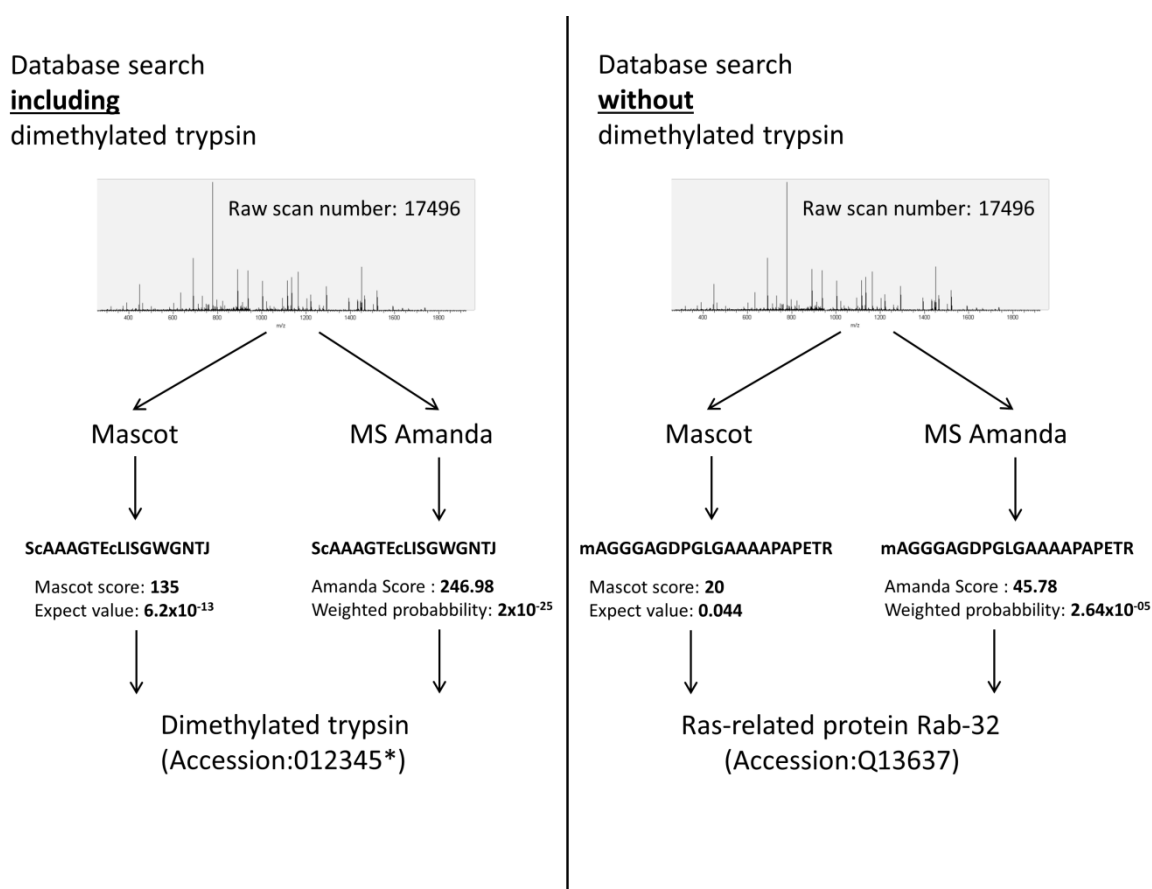


**Figure 32: Comparison of database searches including methylated trypsin or omitting methylated trypsin. In this example a dimethylated trypsin peptide was identified if this was included in the database using either Mascot or MS Amanda as search engines, respectively. Otherwise Ras-related protein Rab-32 was matched on that spectrum yielding a false positive identification.**

In order to exclude search engine specific effects, the same search was run using a customized version of MS Amanda (83) (where the amino acid J was defined as dimethylated lysine) which led to the same misassignment (Figure 32). It has to be emphasized that the database search without dimethylated trypsin (Figure 32, right panel) meets the requirements of database searches drafted by the proteomics community.

Another interesting example occurred when reprocessing a file from human brain tissue (dataset 6). After first reanalyzing the samples with search strategy B it was impossible to reproduce the originally reported results. Comparing the search settings revealed that for the original publication a higher parent-mass tolerance (100 ppm) was used. Employing this parent-mass tolerance it was possible to reproduce the identification of human trypsin isoform 2 with a  $\delta$  parent mass of approximately 25 mmu. Employing search strategy D identified, on the other hand, a peptide from dimethylated porcine trypsin and from human trypsin isoform 2, both displaying almost identical Mascot and MS Amanda scores (Figure 33).

P07478|TRY2\_HUMAN QGDSGGPVVSNGLQGI V S W G Y G C A Q K **NRPGVYTK** VYNYVDWIKDTIAANS  
P00761|TRYP\_PIG QGDSGGPVVCNGQLQGI V S W G Y G C A Q K **NKPGVYTK** VCNYYVNWIIQQTIAAN  
012345|TRY\_ART QGDSGGPVVCNGQLQGI V S W G Y G C A Q J **NJPGVYTJ** VCNYYVNWIIQQTIAAN

| Search               | B          | D        | D        |
|----------------------|------------|----------|----------|
| Precursor tol.       | 100ppm     | 100ppm   | 10ppm    |
| Peptide              | NRPGVYTK   | NJPGVYTJ | NJPGVYTJ |
| Accession Number     | P07478     | 012345   | 012345   |
| Protein              | TRY2_HUMAN | TRY_ART  | TRY_ART  |
| Mascot score         | 31.5       | 29.9     | 29.9     |
| Mascot Expect        | 0.023      | 0.032    | 0.013    |
| Amanda Score         | 88.1057    | 88.1057  | 88.1057  |
| Weighted Probability | 1.55E-09   | 1.55E-09 | 1.55E-09 |
| Calculated           | 933.5032   | 933.5273 | 933.5273 |
| Measured mass        | 933.5283   | 933.5283 | 933.5283 |
| Delta mass [mmu]     | 25.1       | 1        | 1        |

| Amino acid | Monoisotopic mass (Da) |
|------------|------------------------|
| R          | 156.10111              |
| J          | 156.12571              |

**Figure 33: Misassignment of dimethylated trypsin to human trypsin isoform 2 (dataset 6) due to pseudoisobaric amino acids arginine and dimethyl lysine. Even though the score for dimethylated trypsin is slightly lower in the Mascot search, the mass difference and biological origin of the sample implicate that dimethylated trypsin is the correct hit**

Comparing the sequences of the two peptides identified with search strategy D revealed that the sequences were almost identical; only the human isoform contains an arginine instead of a lysine in the porcine isoform. The mass difference between dimethylated lysine and arginine, intriguingly, is 24.6 mmu, almost identical to the difference of the observed versus the expected mass in the original publication. Due to the expected accuracy of the orbitrap instrument and the biological origin of the tissue (brain) it can be assumed that this is most likely a case of misassignment of dimethylated trypsin spectra.

## 8.5. Prevalence of misassignments in reported proteomic experiments

When reanalyzing all publically available human proteomic data sets (dataset 7; PRIDE database), hundreds of statistically significant wrong assignments in more than 18 % of the data sets were identified because of methylated peptides originating from trypsin, corresponding to up to 66 % of all false positive hits (Table 9). For the remaining 80 % of the projects it is not clear if trypsin was used or if an enzyme preparation was used which does not utilize reductive methylation to modify trypsin.

**Table 9: Summary of PRIDE cluster search results. Result of the PRIDE cluster analysis of all current human datasets (209) (dataset 7) for wrongly assigned spectra originating from modified trypsin**

| Accession | Submitted identified Spectra (1% FDR) | Modified Trypsin Peptides (PSM) | Unmodified | Monomethylated | Dimethyl | false positives | % of false positives modified |
|-----------|---------------------------------------|---------------------------------|------------|----------------|----------|-----------------|-------------------------------|
| PRD000032 | 597628                                | 27                              | 7          | 18             | 9        | 5976            | 0.5                           |
| PRD000073 | 340831                                | 1                               | 2          | 0              | 1        | 3408            | 0.0                           |
| PRD000108 | 106944                                | 44                              | 14         | 39             | 5        | 1069            | 4.1                           |
| PRD000212 | 7448                                  | 1                               | 0          | 1              | 0        | 74              | 1.3                           |
| PRD000234 | 16051                                 | 19                              | 3          | 7              | 12       | 161             | 11.8                          |
| PRD000242 | 4241                                  | 28                              | 2          | 10             | 18       | 42              | 66.0                          |
| PRD000269 | 374835                                | 120                             | 0          | 23             | 97       | 3748            | 3.2                           |
| PRD000354 | 75978                                 | 56                              | 0          | 40             | 16       | 760             | 7.4                           |
| PRD000416 | 184963                                | 21                              | 0          | 4              | 17       | 1850            | 1.1                           |
| PRD000417 | 168397                                | 13                              | 0          | 1              | 12       | 1684            | 0.8                           |
| PRD000511 | 268582                                | 14                              | 0          | 10             | 4        | 2686            | 0.5                           |
| PRD000523 | 64590                                 | 3                               | 0          | 1              | 2        | 646             | 0.5                           |
| PRD000544 | 86350                                 | 1                               | 0          | 1              | 0        | 864             | 0.1                           |
| PRD000594 | 1056205                               | 555                             | 2          | 148            | 407      | 10562           | 5.3                           |
| PRD000607 | 2499                                  | 1                               | 0          | 1              | 0        | 25              | 4.0                           |
| PRD000711 | 868975                                | 1                               | 0          | 1              | 0        | 8690            | 0.0                           |
| PXD000004 | 310300                                | 122                             | 448        | 99             | 23       | 3103            | 3.9                           |
| PXD000197 | 203725                                | 600                             | 56         | 323            | 277      | 2037            | 29.5                          |
| PXD000226 | 62807                                 | 284                             | 15         | 90             | 194      | 628             | 45.2                          |
| PXD000263 | 57838                                 | 62                              | 79         | 22             | 40       | 578             | 10.7                          |
| PXD000383 | 417771                                | 1                               | 0          | 0              | 1        | 4178            | 0.0                           |
| PXD000412 | 16925                                 | 34                              | 0          | 1              | 33       | 169             | 20.1                          |
| PXD000426 | 85224                                 | 1                               | 0          | 1              | 0        | 852             | 0.1                           |
| PXD000447 | 61930                                 | 1                               | 0          | 1              | 0        | 619             | 0.2                           |
| PXD000457 | 96978                                 | 2                               | 4          | 2              | 0        | 970             | 0.2                           |
| PXD000536 | 23432                                 | 2                               | 0          | 2              | 0        | 234             | 0.9                           |
| PXD000651 | 320917                                | 116                             | 57         | 73             | 43       | 3209            | 3.6                           |
| PXD000652 | 457445                                | 199                             | 145        | 114            | 85       | 4574            | 4.4                           |
| PXD000653 | 117078                                | 2                               | 0          | 1              | 1        | 1171            | 0.2                           |
| PXD000654 | 569466                                | 28                              | 24         | 9              | 19       | 5695            | 0.5                           |
| PXD000655 | 76853                                 | 22                              | 0          | 7              | 15       | 769             | 2.9                           |
| PXD000656 | 100946                                | 89                              | 10         | 26             | 63       | 1009            | 8.8                           |
| PXD000657 | 418475                                | 28                              | 16         | 13             | 15       | 4185            | 0.7                           |
| PXD000682 | 676569                                | 359                             | 63         | 232            | 127      | 6766            | 5.3                           |
| PXD000765 | 21530                                 | 3                               | 0          | 2              | 1        | 215             | 1.4                           |
| PXD001174 | 54990                                 | 6                               | 0          | 0              | 6        | 550             | 1.1                           |
| PXD001390 | 205869                                | 85                              | 60         | 44             | 41       | 2059            | 4.1                           |
| PXD001403 | 31146                                 | 2                               | 0          | 2              | 0        | 311             | 0.6                           |

## **9. Discussion**

Trypsin is the most common protease used in proteomics workflows. The modification of trypsin, usually performed by dimethylation or acetylation, is supposed to protect the enzyme from autolysis.

Here it was shown that the modification on the one hand is not complete and on the other hand, even if dimethylated the protein is not entirely protected from autolysis. On peptide level reductive methylation was shown to be complete and did not yield any incompletely modified products, such as methylation (77). Hence it was surprising that peptides of trypsin were found that are partly unmodified but also the relative abundance of mono-methylation (methylation accounted for 20-60% of methylated peptides). This is probably due to the native state of trypsin during reductive methylation. Reductive methylation can only take place at lysine residues that are accessible to the reagent in the natively folded state of the protease. The different percentages of mono-methylated peptides might be due to different trypsin preparations. However, more interesting is the fact that even if modified, the protein is not completely protected from self-digestion. In fact, many peptides were identified that carried the modified lysine at the cleavage site.

The self-digestion leads to a decrease in activity; which is usually not a problem considering that the protease is used in excess. Problems arise due to the presence of modified peptides of trypsin that are not accounted for in the database.

In proteomics using the appropriate databases is pivotal for the accurate identification of peptides but also (and maybe more importantly) to avoid false positive peptide hits (69). But even if contaminant databases are used as suggested by the proteomics community, peptides derived from methylated trypsin are not being considered. This leads to an avoidable risk of increasing numbers of false-positive identifications. However, the most intuitive solution of adding methylation as a variable modification during the database search leads to impaired result statistics due the increased number of permutations.

Here a method is reported to circumvent these problems while still avoiding false-positive peptide identifications originated from modified trypsin. Introducing an

artificial amino acid, defined as dimethylated lysine (here called J), enables the specific search for methylated trypsin without increasing the search space. Several search engines allow for the introduction of non-natural amino acids, such as Mascot, X!Tandem and COMET; for others, however, the amino acid letters and masses are hard-coded. Once the amino acid is integrated into the search engines it is an easy task to add a copy of trypsin that contains dimethylated lysines. Care must be taken, though, that the letter of choice is not used in the database, e.g. J is used in NCBI nr for isoleucine/leucine. In the future it might be worth considering increasing the namespace for amino acids. Right now, one is limited to the 26 letters of the alphabet to encode for 20 naturally occurring amino acids. In Mascot four of the remaining six letters are hard-coded, leaving only two letters for the user to define. Besides dimethyllysine, there are selenocysteine and pyrrolysine which naturally occur in proteins and in specific cases might be worth considering.

Another option would be to use multiple databases within one search; this would be needed to be implemented in search engines, though. Then the user could use trypsin in a separate database and apply modification only for that database. This would avoid the inflation of the search space, just like the method presented here.

In conclusion, methylated trypsin peptides are highly abundant and can be assigned to completely unrelated proteins if modified trypsin is not included in the database. At the moment the method presented here is probably the easiest way to avoid false positive matches that derive from modified trypsin.

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## Appendix

### **Published manuscript**

Schittmayer M, **Fritz K** (co-first author), Liesinger L, Griss J, Birner-Gruenberger R. **Cleaning out the Litterbox of Proteomic Scientists' Favorite Pet: Optimized Data Analysis Avoiding Trypsin Artifacts**. Journal of proteome research. 2016;15(4):1222-9

## **Supplementary figures and tables**

### **List of metabolites identified by GC-MS**

**Table S 1: List of metabolites identified by GC-MS**

| <b>Metabolite</b>         | <b>Comments</b>                                                                                   |
|---------------------------|---------------------------------------------------------------------------------------------------|
| Lactate                   |                                                                                                   |
| Alanine                   |                                                                                                   |
| Glycine                   |                                                                                                   |
| Valine                    |                                                                                                   |
| Leucine                   |                                                                                                   |
| Isoleucine                |                                                                                                   |
| Norleucine                | Not a natural amino acid, Norleucine was added just before acidification as an internal reference |
| Succinate                 |                                                                                                   |
| $\gamma$ -amino butyrate  |                                                                                                   |
| Proline                   |                                                                                                   |
| Fumarate                  |                                                                                                   |
| Phosphate                 |                                                                                                   |
| Serine                    |                                                                                                   |
| Methionine                | Methionine levels cannot be measured reliably with the method presented                           |
| Threonine                 |                                                                                                   |
| Malate                    |                                                                                                   |
| Phenylalanine             |                                                                                                   |
| Aspartate                 |                                                                                                   |
| Hydroxy-proline           |                                                                                                   |
| Cysteine                  |                                                                                                   |
| Glutamate                 |                                                                                                   |
| Ornithine                 |                                                                                                   |
| Asparagine                |                                                                                                   |
| Lysine                    |                                                                                                   |
| cis-aconitate             |                                                                                                   |
| $\beta$ -hydroxy butyrate |                                                                                                   |
| Glutamine                 |                                                                                                   |
| Arginine                  |                                                                                                   |
| Glycerol-3-Phosphate      |                                                                                                   |
| Citrate                   |                                                                                                   |
| Histidine                 | Histidine levels cannot be measured reliably with the method presented                            |
| Tyrosine                  |                                                                                                   |
| $\alpha$ -ketoglutarate   |                                                                                                   |
| Tryptophane               |                                                                                                   |
| Ascorbate                 |                                                                                                   |

# <sup>13</sup>C-Glucose labeling in cell culture – cell extracts

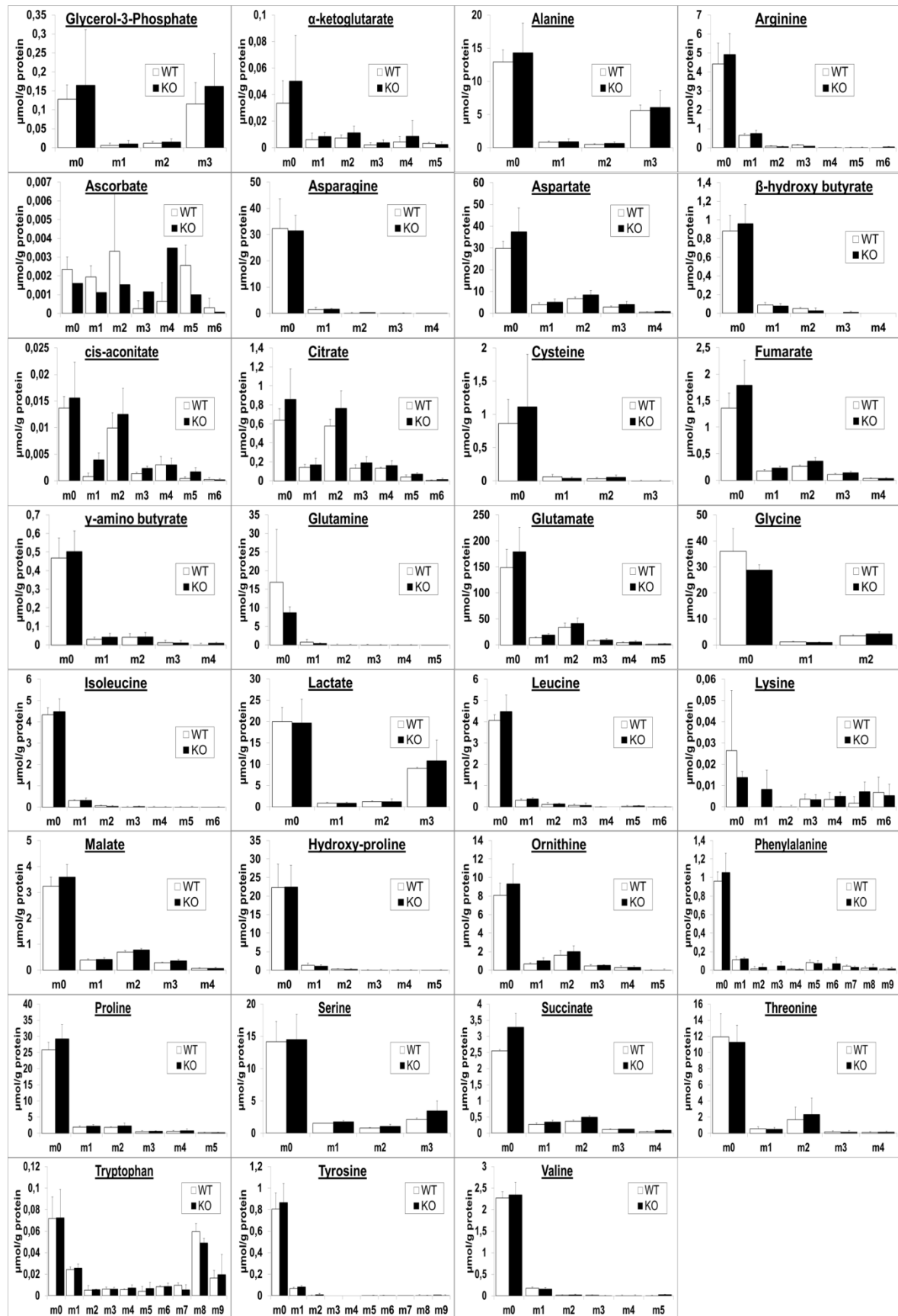


Figure S 1: <sup>13</sup>C-Glucose labeling in ATGL-KO and WT B-cells

## $^{13}\text{C}$ - $^{15}\text{N}$ -glutamine labeling in cell culture – cell extracts

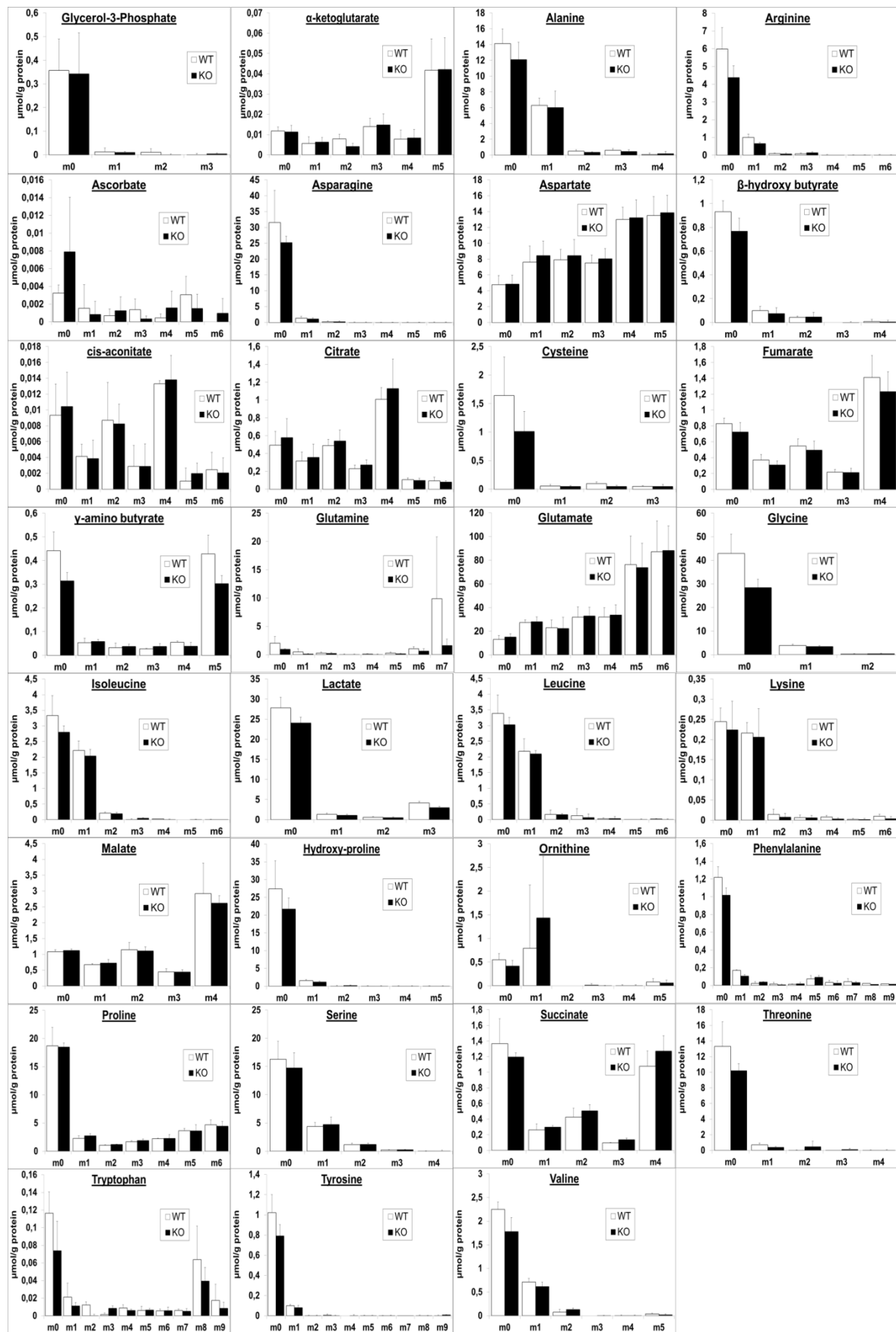


Figure S 2:  $^{13}\text{C}$ - $^{15}\text{N}$ -glutamine labeling in ATGL-KO and WT B-cells

# <sup>13</sup>C-glucose labeling in vivo – tumor extract

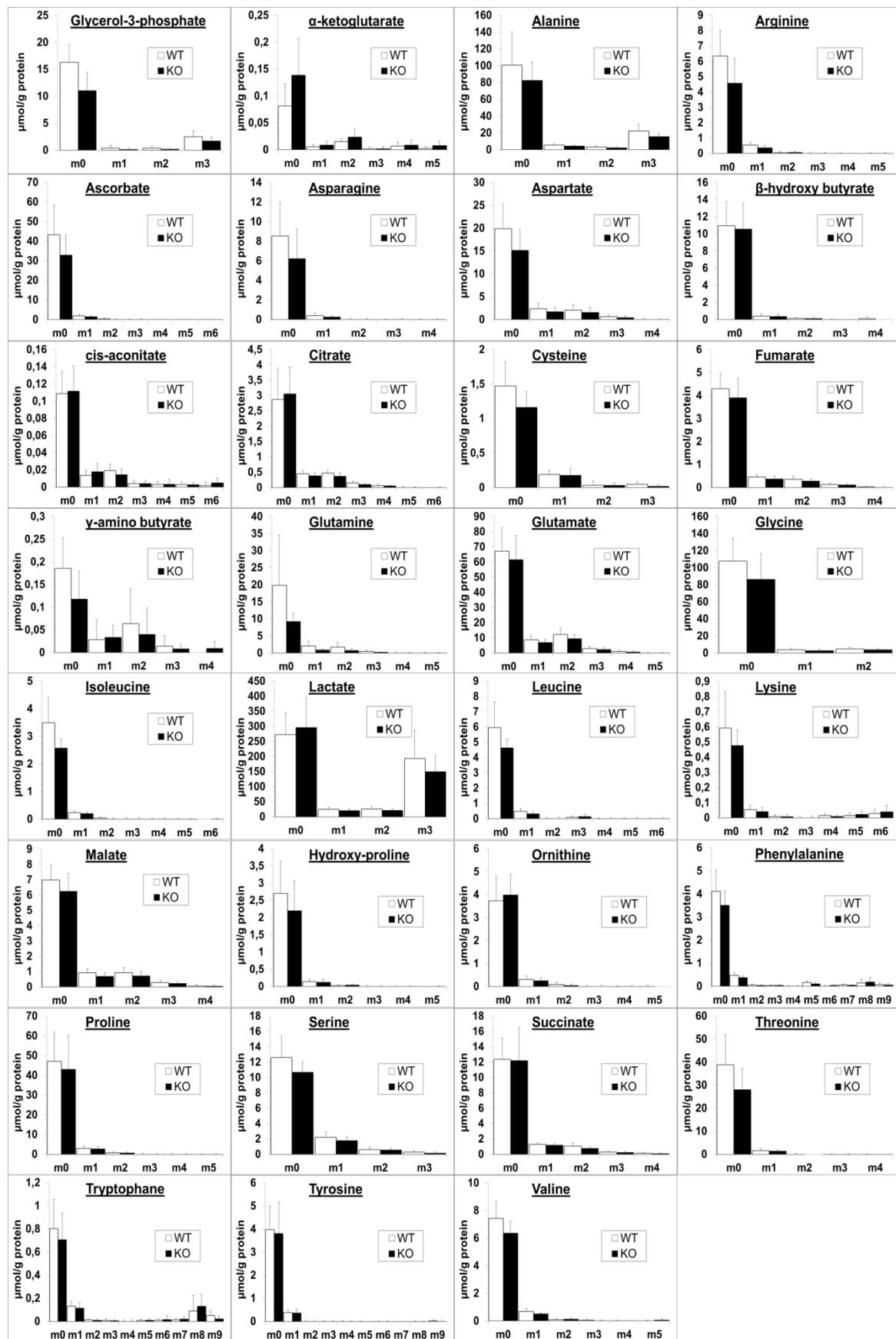


Figure S 3: <sup>13</sup>C-glucose labeling in vivo in tumor bearing mice. Tumors were excised, ground in liquid nitrogen and polar metabolites were extracted and analyzed by GC-MS.

## <sup>13</sup>C-glucose labeling in vivo – plasma extract

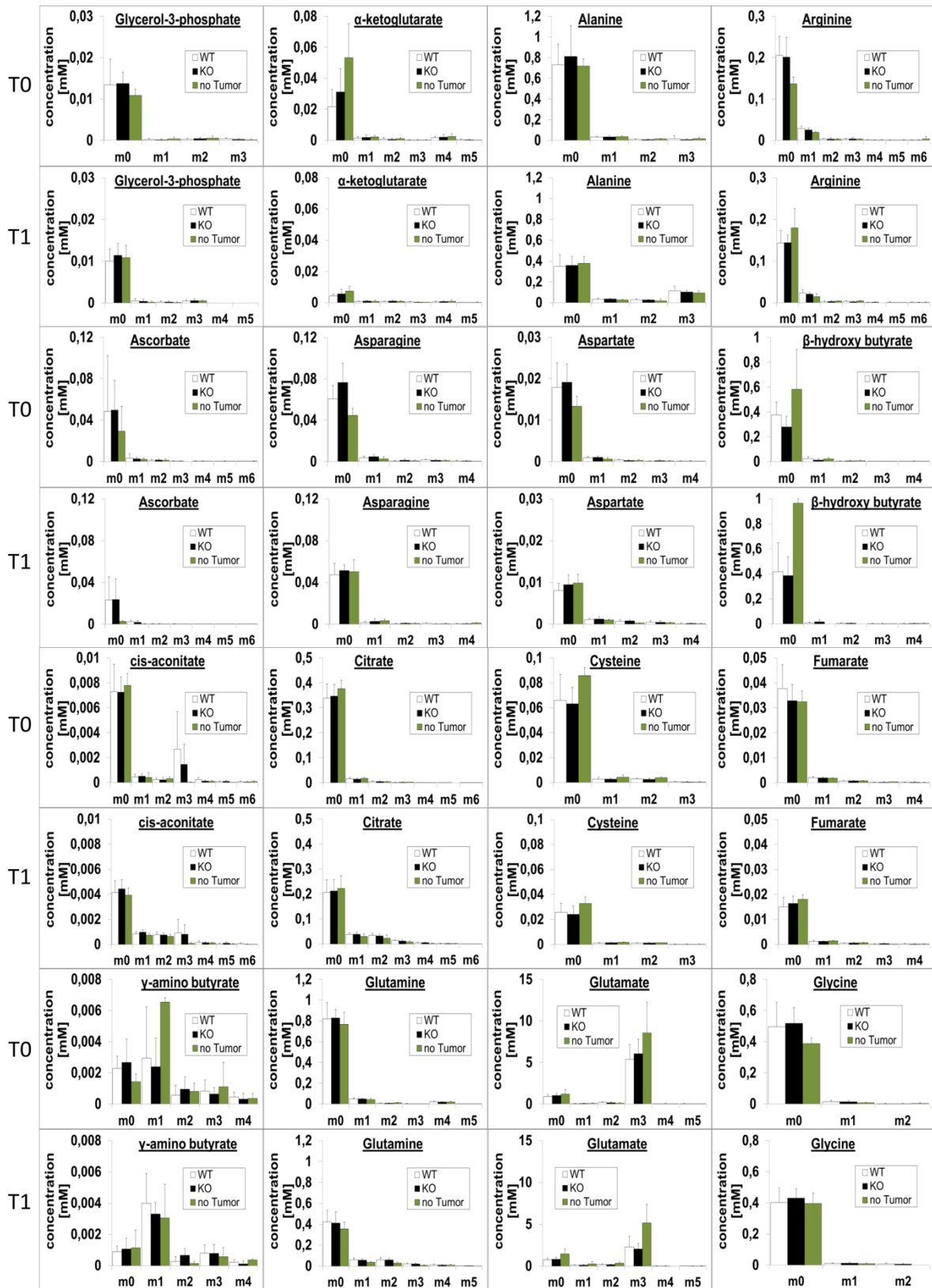


Figure S 4: Plasma extracts from mice; blood was taken just before the first injection of <sup>13</sup>C-glucose (T0) and after euthanizing together with the removal of other organs (T1). Polar metabolites were extracted from 30 µL of plasma and analyzed by GC-MS. No Tumor: No tumor-bearing mice were used as control (labeling with <sup>13</sup>C-glucose was performed the same way as in tumor-bearing mice).

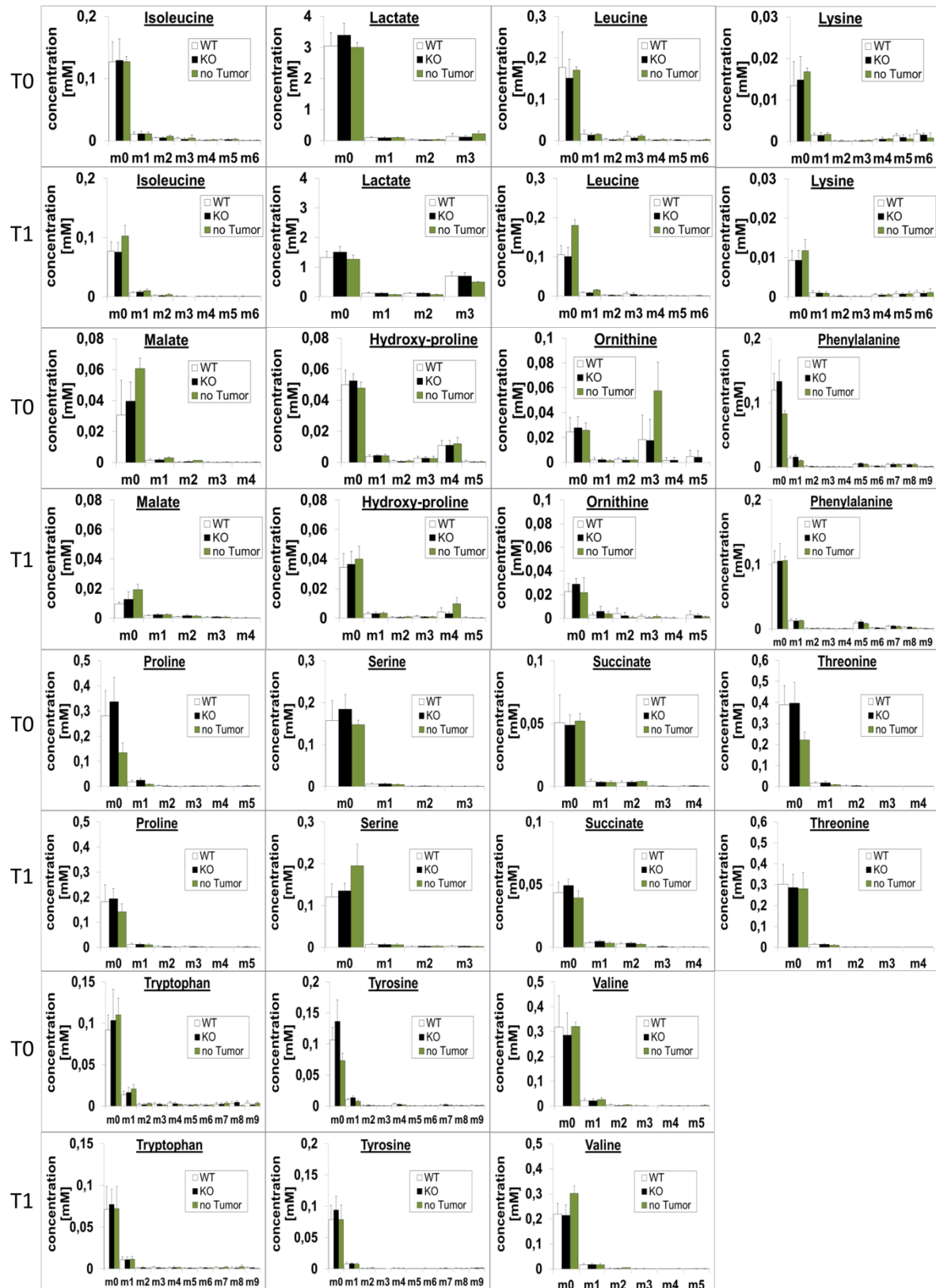


**Figure S 5: Plasma extracts from mice continued; blood was taken just before the first injection of  $^{13}\text{C}$ -glucose (T0) and after euthanizing together with the removal of other organs (T1). Polar metabolites were extracted from 30  $\mu\text{L}$  of plasma and analyzed by GC-MS. No Tumor: No tumor-bearing mice were used as control (labeling with  $^{13}\text{C}$ -glucose was performed the same way as in tumor-bearing mice).**

## <sup>13</sup>C-glucose labeling in vivo – liver extract

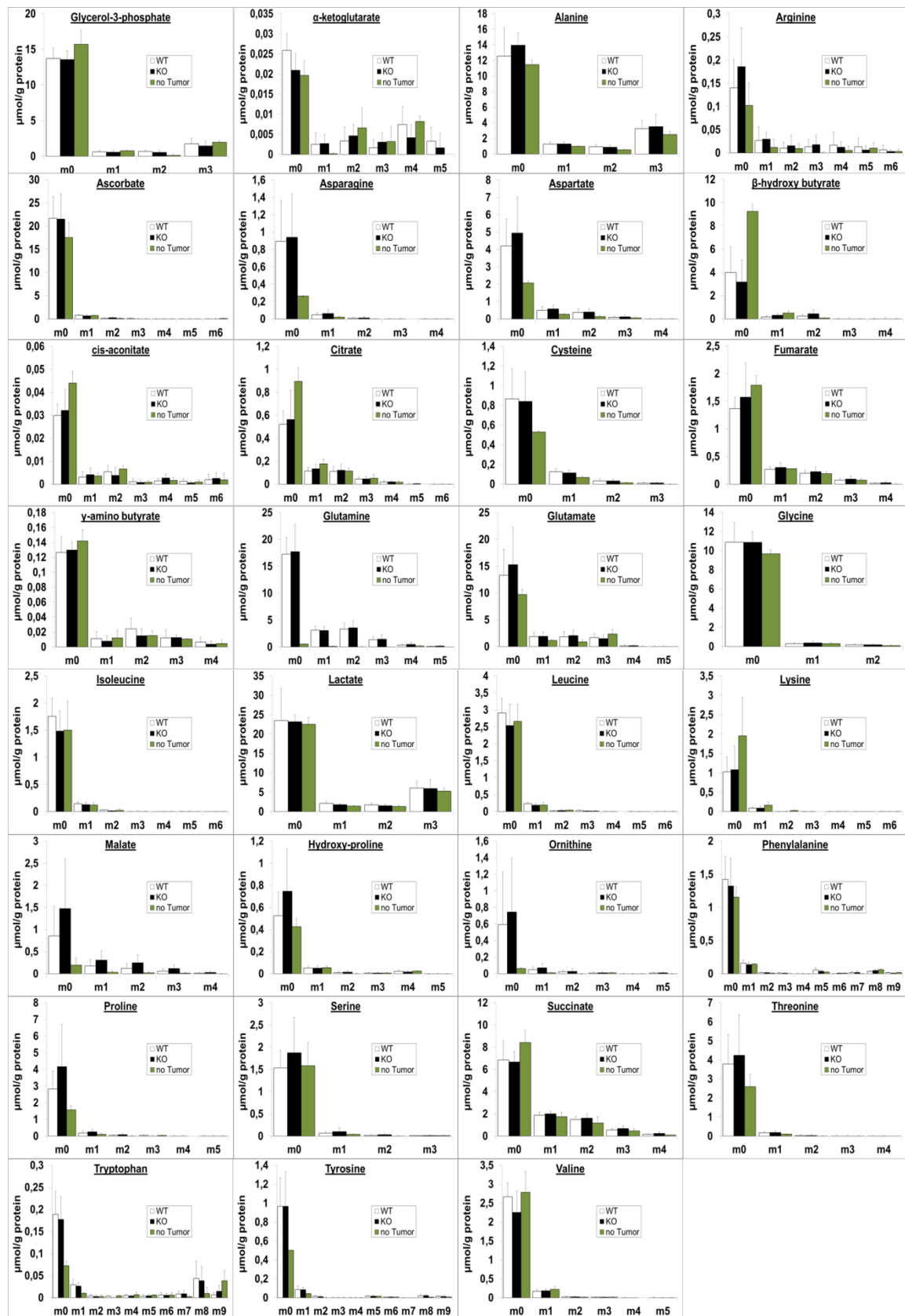


Figure S 6: <sup>13</sup>C-glucose labeling patterns in liver in tumor bearing mice. Livers were excised, ground in liquid nitrogen and polar metabolites were extracted and analyzed by GC-MS. No Tumor: No tumor-bearing mice were used as control (labeling with <sup>13</sup>C-glucose was performed the same way as in tumor-bearing mice).

## Quantitative Proteomics using TMT labeling - List of identified and quantified protein

**Table S 2: Complete list of proteins identified and quantified with quantitative proteomics using TMT labeling comparing ATGL-KO and WT B-cells.**

| -LOG(P-value) | Difference | Gene names      | Protein names                                                                                                                                         |
|---------------|------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3,85          | -0,07      | Eif2b5          | Translation initiation factor eIF-2B subunit epsilon                                                                                                  |
| 3,61          | 0,15       | Bola1           | BolA-like protein 1                                                                                                                                   |
| 3,03          | -0,41      | Snrpd2;Gm5449   | Small nuclear ribonucleoprotein Sm D2                                                                                                                 |
| 2,91          | 0,41       | Znrf2           | E3 ubiquitin-protein ligase ZNRF2                                                                                                                     |
| 2,88          | -0,38      | Rpl23a;Gm6096   | 60S ribosomal protein L23a                                                                                                                            |
| 2,71          | 0,18       | Rps6ka5         | Ribosomal protein S6 kinase alpha-5                                                                                                                   |
| 2,67          | -0,10      | Rrp9            | U3 small nucleolar RNA-interacting protein 2                                                                                                          |
| 2,59          | 3,33       | Aldh1a7;Aldh1a1 | Retinal dehydrogenase 1;Aldehyde dehydrogenase, cytosolic 1                                                                                           |
| 2,57          | 0,06       | Golga2          | Golgin subfamily A member 2                                                                                                                           |
| 2,44          | 0,26       | Ogt             | UDP-N-acetylglucosamine--peptide N-acetylglucosaminyltransferase 110 kDa subunit                                                                      |
| 2,44          | 0,93       | Ckap5           | Cytoskeleton-associated protein 5                                                                                                                     |
| 2,43          | 0,61       | Ppt1            | Palmitoyl-protein thioesterase 1                                                                                                                      |
| 2,41          | 0,24       | Ppp2r2d         | Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit B delta isoform;Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit B |
| 2,36          | -0,27      | Ddx21           | Nucleolar RNA helicase 2                                                                                                                              |
| 2,34          | -0,14      | Ddx24           | ATP-dependent RNA helicase DDX24                                                                                                                      |
| 2,31          | -0,11      |                 | UPF0449 protein C19orf25 homolog                                                                                                                      |
| 2,30          | 0,25       | Uggt1           | UDP-glucose:glycoprotein glucosyltransferase 1                                                                                                        |
| 2,30          | 0,10       | Sec24c          |                                                                                                                                                       |
| 2,30          | -0,38      | Gnas            | Guanine nucleotide-binding protein G(s) subunit alpha isoforms short;Guanine nucleotide-binding protein G(s) subunit alpha isoforms XLas              |
| 2,29          | 1,61       | Aldh1b1;Aldh1a2 | Aldehyde dehydrogenase X, mitochondrial;Retinal dehydrogenase 2                                                                                       |
| 2,19          | 0,29       | Gns             | N-acetylglucosamine-6-sulfatase                                                                                                                       |
| 2,19          | -0,15      | Psm10           | 26S proteasome non-ATPase regulatory subunit 10                                                                                                       |
| 2,17          | 0,13       | Dock2           | Dedicator of cytokinesis protein 2                                                                                                                    |
| 2,15          | 1,39       | B2m             | Beta-2-microglobulin                                                                                                                                  |
| 2,15          | 0,86       | Tap2            | Antigen peptide transporter 2                                                                                                                         |
| 2,12          | 2,44       | Gldc            | Glycine dehydrogenase (decarboxylating), mitochondrial                                                                                                |
| 2,08          | -0,84      | Bzw2            | Basic leucine zipper and W2 domain-containing protein 2                                                                                               |
| 2,08          | -0,66      | Ca2             | Carbonic anhydrase 2                                                                                                                                  |
| 2,06          | -0,39      | Mical1          | Protein-methionine sulfoxide oxidase MICAL1                                                                                                           |
| 2,02          | -0,65      | Galk1           | Galactokinase                                                                                                                                         |
| 2,01          | -0,18      | Hspa4l          | Heat shock 70 kDa protein 4L                                                                                                                          |
| 2,01          | -0,36      | Glg1            | Golgi apparatus protein 1                                                                                                                             |
| 1,99          | 0,81       | Pepd            | Xaa-Pro dipeptidase                                                                                                                                   |
| 1,98          | -0,54      | Ndufb3          | NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 3                                                                                           |
| 1,96          | -0,14      | Ndufb10         | NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 10                                                                                          |
| 1,96          | -0,25      | Cpsf1           | Cleavage and polyadenylation specificity factor subunit 1                                                                                             |
| 1,92          | -0,13      | Ttc1            | Tetratricopeptide repeat protein 1                                                                                                                    |
| 1,92          | 0,24       | Atp6v0d1        | V-type proton ATPase subunit d 1                                                                                                                      |
| 1,91          | -0,20      | Uhrf1           | E3 ubiquitin-protein ligase UHRF1                                                                                                                     |
| 1,90          | -0,28      | Eif2s3x         | Eukaryotic translation initiation factor 2 subunit 3, X-linked                                                                                        |
| 1,89          | 0,22       | Erap1           | Endoplasmic reticulum aminopeptidase 1                                                                                                                |
| 1,87          | 0,61       | Osbpl8          | Oxysterol-binding protein                                                                                                                             |
| 1,86          | 0,66       | Tmem173         | Stimulator of interferon genes protein                                                                                                                |
| 1,85          | -0,23      | Rrp1            | Ribosomal RNA processing protein 1 homolog A                                                                                                          |

|      |       |                  |                                                                                      |
|------|-------|------------------|--------------------------------------------------------------------------------------|
| 1,84 | 0,25  | Usp47            | Ubiquitin carboxyl-terminal hydrolase 47                                             |
| 1,78 | 0,25  | Aars             | Alanine--tRNA ligase, cytoplasmic                                                    |
| 1,76 | -0,27 | Ndufv1           | NADH dehydrogenase [ubiquinone] flavoprotein 1, mitochondrial                        |
| 1,75 | 0,25  | Il16             | Pro-interleukin-16;Interleukin-16                                                    |
| 1,75 | -0,24 | Set              | Protein SET                                                                          |
| 1,72 | 0,21  | Taldo1           | Transaldolase                                                                        |
| 1,71 | -0,16 | Pi4ka            |                                                                                      |
| 1,70 | 0,27  | Gdi1             | Rab GDP dissociation inhibitor alpha                                                 |
| 1,70 | 0,41  | Sqstm1           | Sequestosome-1                                                                       |
| 1,68 | 0,31  | Asns             | Asparagine synthetase [glutamine-hydrolyzing]                                        |
| 1,68 | -0,49 | Msto1            | Protein misato homolog 1                                                             |
| 1,68 | 0,12  | Gtf2b            | Transcription initiation factor IIB                                                  |
| 1,67 | 0,66  | Them6            | Protein THEM6                                                                        |
| 1,66 | 0,18  | Ywhaq            | 14-3-3 protein theta                                                                 |
| 1,65 | -0,15 | Safb             | Scaffold attachment factor B1                                                        |
| 1,64 | -0,06 | Crkl             | Crk-like protein                                                                     |
| 1,64 | 0,99  | Actn1            | Alpha-actinin-1                                                                      |
| 1,63 | -0,30 | Rbm28            | RNA-binding protein 28                                                               |
| 1,63 | -0,08 | Ebna1bp2         | Probable rRNA-processing protein EBP2                                                |
| 1,63 | -0,15 | Sfxn1            | Sideroflexin-1                                                                       |
| 1,63 | 0,13  | Stx12            | Syntaxin-12                                                                          |
| 1,62 | -0,32 | Ndufs1           | NADH-ubiquinone oxidoreductase 75 kDa subunit, mitochondrial                         |
| 1,62 | -0,16 | EG433182;Eno1    | Alpha-enolase                                                                        |
| 1,62 | -0,26 | Mphosph10        | U3 small nucleolar ribonucleoprotein protein MPP10                                   |
| 1,62 | 0,15  | Dpm3             | Dolichol-phosphate mannosyltransferase subunit 3                                     |
| 1,58 | 0,10  | Nono             | Non-POU domain-containing octamer-binding protein                                    |
| 1,58 | -0,16 | Skiv2l2          | Superkiller viralicidal activity 2-like 2                                            |
| 1,56 | 0,29  | Map4k4;Tnik      | Mitogen-activated protein kinase kinase kinase kinase 4                              |
| 1,55 | 0,23  | Anxa5            | Annexin A5                                                                           |
| 1,55 | 0,20  | Gmppa            | Mannose-1-phosphate guanylttransferase alpha                                         |
| 1,55 | -0,66 | Lsp1             | Lymphocyte-specific protein 1                                                        |
| 1,54 | 0,20  | Epb4.1l2;Epb41l2 | Band 4.1-like protein 2                                                              |
| 1,54 | 0,18  | Blvra            | Biliverdin reductase A                                                               |
| 1,54 | 0,16  | Tbca             | Tubulin-specific chaperone A                                                         |
| 1,54 | 0,14  | Nudcd1           | NudC domain-containing protein 1                                                     |
| 1,53 | 0,19  | Ndel1;Nde1       | Nuclear distribution protein nudE-like 1;Nuclear distribution protein nudE homolog 1 |
| 1,53 | -0,15 | Icam1            | Intercellular adhesion molecule 1                                                    |
| 1,53 | 0,39  | Esd              | S-formylglutathione hydrolase                                                        |
| 1,53 | -0,09 | Bicd2            | Protein bicaudal D homolog 2                                                         |
| 1,52 | -0,39 | Ptp3;Ptp1        | Polypyrimidine tract-binding protein 3;Polypyrimidine tract-binding protein 1        |
| 1,52 | 0,09  | Gorasp2          | Golgi reassembly-stacking protein 2                                                  |
| 1,52 | 0,18  | Dock8            | Dedicator of cytokinesis protein 8                                                   |
| 1,52 | -0,18 | Sdhd             | Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial              |
| 1,52 | -0,16 | Ndufs3           | NADH dehydrogenase [ubiquinone] iron-sulfur protein 3, mitochondrial                 |
| 1,52 | -0,27 | Cacybp           | Calcyclin-binding protein                                                            |
| 1,51 | 0,35  | Lamp2            | Lysosome-associated membrane glycoprotein 2                                          |
| 1,51 | 0,14  | Msn              | Moesin                                                                               |
| 1,50 | -0,31 | Snrpb2           | U2 small nuclear ribonucleoprotein B                                                 |
| 1,49 | -0,09 | Cstf3            | Cleavage stimulation factor subunit 3                                                |
| 1,48 | -0,13 | Elp2             | Elongator complex protein 2                                                          |
| 1,47 | -0,29 | Rrm1             | Ribonucleoside-diphosphate reductase large subunit                                   |
| 1,47 | 0,44  | Snrpa1           | U2 small nuclear ribonucleoprotein A                                                 |

|      |       |                                                        |                                                                                                                                                                                                                                                                                                                                              |
|------|-------|--------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1,46 | 0,31  | Cap1                                                   | Adenylyl cyclase-associated protein 1                                                                                                                                                                                                                                                                                                        |
| 1,46 | 0,49  | Psmb10                                                 | Proteasome subunit beta type-10                                                                                                                                                                                                                                                                                                              |
| 1,46 | 0,18  | Ptpn1                                                  | Tyrosine-protein phosphatase non-receptor type;Tyrosine-protein phosphatase non-receptor type 1                                                                                                                                                                                                                                              |
| 1,46 | -0,26 | Gm8300;Gm2016;Gm5662;Gm2046                            |                                                                                                                                                                                                                                                                                                                                              |
| 1,45 | -0,27 | Aprt                                                   | Adenine phosphoribosyltransferase                                                                                                                                                                                                                                                                                                            |
| 1,45 | 0,99  | Psap                                                   | Prosaposin                                                                                                                                                                                                                                                                                                                                   |
| 1,44 | 0,38  | Dok3                                                   | Docking protein 3                                                                                                                                                                                                                                                                                                                            |
| 1,44 | 1,39  | H2-Q4;H2-Q7;H2-D1;H2-T3;H2-Q6;H2-Q9;H2-Q10;H2-Q8;H2-K1 | H-2 class I histocompatibility antigen, D-B alpha chain;H-2 class I histocompatibility antigen, Q9 alpha chain;H-2 class I histocompatibility antigen, Q10 alpha chain;H-2 class I histocompatibility antigen, Q8 alpha chain;H-2 class I histocompatibility antigen, Q7 alpha chain;H-2 class I histocompatibility antigen, K-D alpha chain |
| 1,43 | 0,18  | Rdh11                                                  | Retinol dehydrogenase 11                                                                                                                                                                                                                                                                                                                     |
| 1,42 | -0,15 | Khsrp                                                  | Far upstream element-binding protein 2                                                                                                                                                                                                                                                                                                       |
| 1,42 | 0,09  | Myo1c                                                  | Unconventional myosin-Ic                                                                                                                                                                                                                                                                                                                     |
| 1,42 | 0,19  | Sart3                                                  | Squamous cell carcinoma antigen recognized by T-cells 3                                                                                                                                                                                                                                                                                      |
| 1,41 | 0,34  | Sh3bgrl                                                | SH3 domain-binding glutamic acid-rich-like protein                                                                                                                                                                                                                                                                                           |
| 1,41 | 2,07  | Pir                                                    | Pirin                                                                                                                                                                                                                                                                                                                                        |
| 1,41 | 0,32  | Pspc1                                                  | Paraspeckle component 1                                                                                                                                                                                                                                                                                                                      |
| 1,39 | -0,10 | Mthfd1l                                                | Monofunctional C1-tetrahydrofolate synthase, mitochondrial                                                                                                                                                                                                                                                                                   |
| 1,39 | 0,30  | Fkbp5                                                  | Peptidyl-prolyl cis-trans isomerase FKBP5;Peptidyl-prolyl cis-trans isomerase FKBP5, N-terminally processed                                                                                                                                                                                                                                  |
| 1,39 | -0,17 | Fto                                                    | Alpha-ketoglutarate-dependent dioxygenase FTO                                                                                                                                                                                                                                                                                                |
| 1,39 | 0,29  | Dpf2                                                   | Zinc finger protein ubi-d4                                                                                                                                                                                                                                                                                                                   |
| 1,38 | 0,83  | Plscr1                                                 | Phospholipid scramblase 1                                                                                                                                                                                                                                                                                                                    |
| 1,38 | 0,38  | Pyhin1                                                 | Pyrin and HIN domain-containing protein 1                                                                                                                                                                                                                                                                                                    |
| 1,37 | -0,11 | Dkc1                                                   | H/ACA ribonucleoprotein complex subunit 4                                                                                                                                                                                                                                                                                                    |
| 1,37 | -0,22 | Nudt21                                                 | Cleavage and polyadenylation specificity factor subunit 5                                                                                                                                                                                                                                                                                    |
| 1,37 | 0,22  | Habp2                                                  | Hyaluronan-binding protein 2;Hyaluronan-binding protein 2 50 kDa heavy chain;Hyaluronan-binding protein 2 50 kDa heavy chain alternate form;Hyaluronan-binding protein 2 27 kDa light chain;Hyaluronan-binding protein 2 27 kDa light chain alternate form                                                                                   |
| 1,37 | 0,20  | Vcp                                                    | Transitional endoplasmic reticulum ATPase                                                                                                                                                                                                                                                                                                    |
| 1,37 | 0,09  | Ddx17                                                  | Probable ATP-dependent RNA helicase DDX17                                                                                                                                                                                                                                                                                                    |
| 1,36 | 0,23  | Hadh                                                   | Hydroxyacyl-coenzyme A dehydrogenase, mitochondrial                                                                                                                                                                                                                                                                                          |
| 1,35 | 0,56  | Mvp                                                    | Major vault protein                                                                                                                                                                                                                                                                                                                          |
| 1,35 | -0,22 | Rpl12;Gm16519                                          | 60S ribosomal protein L12                                                                                                                                                                                                                                                                                                                    |
| 1,35 | 0,21  | Flna                                                   | Filamin-A                                                                                                                                                                                                                                                                                                                                    |
| 1,34 | -0,18 | Ndufc2                                                 | NADH dehydrogenase [ubiquinone] 1 subunit C2                                                                                                                                                                                                                                                                                                 |
| 1,34 | 0,55  | Sec11c                                                 | Signal peptidase complex catalytic subunit SEC11C                                                                                                                                                                                                                                                                                            |
| 1,33 | -0,05 | Lrrc47                                                 | Leucine-rich repeat-containing protein 47                                                                                                                                                                                                                                                                                                    |
| 1,33 | 0,31  | Sun2                                                   | SUN domain-containing protein 2                                                                                                                                                                                                                                                                                                              |
| 1,32 | 0,13  | Scarb2                                                 | Lysosome membrane protein 2                                                                                                                                                                                                                                                                                                                  |
| 1,30 | -0,22 | Cbx3                                                   | Chromobox protein homolog 3                                                                                                                                                                                                                                                                                                                  |
| 1,30 | 0,70  | N4bp2                                                  |                                                                                                                                                                                                                                                                                                                                              |
| 1,29 | -0,22 | Cdc5l                                                  | Cell division cycle 5-like protein                                                                                                                                                                                                                                                                                                           |
| 1,29 | 0,18  | Mrpl1                                                  | 39S ribosomal protein L1, mitochondrial                                                                                                                                                                                                                                                                                                      |
| 1,28 | 0,21  | Brd3                                                   | Bromodomain-containing protein 3                                                                                                                                                                                                                                                                                                             |
| 1,28 | -0,15 | Rrs1                                                   | Ribosome biogenesis regulatory protein homolog                                                                                                                                                                                                                                                                                               |
| 1,27 | -0,36 | Ndufs2                                                 | NADH dehydrogenase [ubiquinone] iron-sulfur protein 2, mitochondrial                                                                                                                                                                                                                                                                         |
| 1,27 | 0,45  | Ndufb6                                                 | NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 6                                                                                                                                                                                                                                                                                  |
| 1,27 | -0,11 | Esf1                                                   | ESF1 homolog                                                                                                                                                                                                                                                                                                                                 |
| 1,27 | -0,50 | Acaa2                                                  | 3-ketoacyl-CoA thiolase, mitochondrial                                                                                                                                                                                                                                                                                                       |
| 1,26 | 0,46  | Atpif1                                                 | ATPase inhibitor, mitochondrial                                                                                                                                                                                                                                                                                                              |
| 1,26 | -0,22 | Nop58                                                  | Nucleolar protein 58                                                                                                                                                                                                                                                                                                                         |
| 1,25 | -0,13 | Kti12                                                  | Protein KTI12 homolog                                                                                                                                                                                                                                                                                                                        |

|      |       |                  |                                                                                                 |
|------|-------|------------------|-------------------------------------------------------------------------------------------------|
| 1,25 | 0,57  | Tpm1             | Tropomyosin alpha-1 chain                                                                       |
| 1,24 | -0,28 | Ptpn6            | Tyrosine-protein phosphatase non-receptor type;Tyrosine-protein phosphatase non-receptor type 6 |
| 1,24 | -0,33 | Vimp             | Selenoprotein S                                                                                 |
| 1,23 | -0,17 | Pes1             | Pescadillo homolog                                                                              |
| 1,23 | -0,15 | Far1             | Fatty acyl-CoA reductase 1                                                                      |
| 1,23 | -0,17 | Tardbp           | TAR DNA-binding protein 43                                                                      |
| 1,23 | -0,17 | Prpf40a          | Pre-mRNA-processing factor 40 homolog A                                                         |
| 1,23 | -0,14 | Ap1m1;Ap1m2      | AP-1 complex subunit mu-2;AP-1 complex subunit mu-1                                             |
| 1,22 | -0,17 | Dido1            | Death-inducer obliterator 1                                                                     |
| 1,22 | 0,18  | Phgdh            | D-3-phosphoglycerate dehydrogenase                                                              |
| 1,22 | -0,15 | Rps3a1;Rps3a     | 40S ribosomal protein S3a                                                                       |
| 1,22 | -0,17 | Ppil4            | Peptidyl-prolyl cis-trans isomerase-like 4                                                      |
| 1,22 | -0,33 | Ehd1             | EH domain-containing protein 1                                                                  |
| 1,21 | -0,17 | Armc6            | Armadillo repeat-containing protein 6                                                           |
| 1,21 | -0,29 | Rpl30            | 60S ribosomal protein L30                                                                       |
| 1,21 | 0,15  | Fam49b;Fam49a    | Protein FAM49B;Protein FAM49A                                                                   |
| 1,20 | 0,92  | Psmb9            | Proteasome subunit beta type-9                                                                  |
| 1,20 | -0,16 | Aatf             | Protein AATF                                                                                    |
| 1,19 | 0,17  | Rhoa;Rhoc        | Transforming protein RhoA;Rho-related GTP-binding protein RhoC                                  |
| 1,19 | 0,10  | Lman2            | Vesicular integral-membrane protein VIP36                                                       |
| 1,19 | 0,21  | Mina             | Bifunctional lysine-specific demethylase and histidyl-hydroxylase MINA                          |
| 1,19 | 0,18  | Commd3           | COMM domain-containing protein 3                                                                |
| 1,18 | -0,30 | Hnmpd            | Heterogeneous nuclear ribonucleoprotein D0                                                      |
| 1,18 | -0,11 | Chordc1          | Cysteine and histidine-rich domain-containing protein 1                                         |
| 1,18 | -0,31 | Rcor1            | REST corepressor 1                                                                              |
| 1,17 | -0,25 | Exosc9           | Exosome complex component RRP45                                                                 |
| 1,17 | 0,30  | Flii             | Protein flightless-1 homolog                                                                    |
| 1,17 | -0,19 | Trim28           | Transcription intermediary factor 1-beta                                                        |
| 1,16 | -0,15 | Nup107           | Nuclear pore complex protein Nup107                                                             |
| 1,16 | -0,51 |                  |                                                                                                 |
| 1,16 | 0,15  | Nmt1             | Glycylpeptide N-tetradecanoyltransferase;Glycylpeptide N-tetradecanoyltransferase 1             |
| 1,15 | 0,30  |                  | UPF0428 protein CXorf56 homolog                                                                 |
| 1,15 | -0,09 | Adrbk1;Adrbk2    | Beta-adrenergic receptor kinase 1;Beta-adrenergic receptor kinase 2                             |
| 1,15 | -0,28 | Mre11a           | Double-strand break repair protein MRE11A                                                       |
| 1,15 | 0,25  | Pstpip1          | Proline-serine-threonine phosphatase-interacting protein 1                                      |
| 1,14 | -0,24 | Tcof1            | Treacle protein                                                                                 |
| 1,14 | -0,22 | Rps21            | 40S ribosomal protein S21                                                                       |
| 1,13 | -0,38 | Cyp51a1          | Lanosterol 14-alpha demethylase                                                                 |
| 1,13 | 0,32  | Zbed3            | Zinc finger BED domain-containing protein 3                                                     |
| 1,13 | -0,33 | Alad             | Delta-aminolevulinic acid dehydratase                                                           |
| 1,13 | -0,13 | Usp7             | Ubiquitin carboxyl-terminal hydrolase;Ubiquitin carboxyl-terminal hydrolase 7                   |
| 1,13 | -0,19 | Ddx6             | Probable ATP-dependent RNA helicase DDX6                                                        |
| 1,13 | -0,32 | Cnbp             | Cellular nucleic acid-binding protein                                                           |
| 1,12 | -0,13 | mt-Co2;Mtco2     | Cytochrome c oxidase subunit 2                                                                  |
| 1,12 | -0,55 | Kpna4            | Importin subunit alpha;Importin subunit alpha-3                                                 |
| 1,12 | -0,12 | Dcps             | m7GpppX diphosphatase                                                                           |
| 1,12 | -0,20 | Trp53bp1;Tp53bp1 | Tumor suppressor p53-binding protein 1                                                          |
| 1,11 | -0,40 | Hk2              | Hexokinase;Hexokinase-2                                                                         |
| 1,11 | 0,18  | Crif3            | Cytokine receptor-like factor 3                                                                 |
| 1,11 | 0,12  | Cux1             | Homeobox protein cut-like;Homeobox protein cut-like 1                                           |
| 1,11 | 0,25  | Itgb2            | Integrin beta;Integrin beta-2                                                                   |

|      |       |                                                                           |                                                                                                                                                                                                                                                                                                                                 |
|------|-------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1,11 | -0,15 | Mybbp1a                                                                   | Myb-binding protein 1A                                                                                                                                                                                                                                                                                                          |
| 1,10 | 0,43  | Rnh1                                                                      | Ribonuclease inhibitor                                                                                                                                                                                                                                                                                                          |
| 1,10 | -0,15 | Dhx9                                                                      | ATP-dependent RNA helicase A                                                                                                                                                                                                                                                                                                    |
| 1,10 | 0,11  | Ppp6r1                                                                    | Serine/threonine-protein phosphatase 6 regulatory subunit 1                                                                                                                                                                                                                                                                     |
| 1,10 | -0,21 | Fasn                                                                      | Fatty acid synthase;[Acyl-carrier-protein] S-acetyltransferase;[Acyl-carrier-protein] S-malonyltransferase;3-oxoacyl-[acyl-carrier-protein] synthase;3-oxoacyl-[acyl-carrier-protein] reductase;3-hydroxyacyl-[acyl-carrier-protein] dehydratase;Enoyl-[acyl-carrier-protein] reductase;Oleoal-[acyl-carrier-protein] hydrolase |
| 1,09 | 0,46  | Bcr                                                                       | Breakpoint cluster region protein                                                                                                                                                                                                                                                                                               |
| 1,09 | -0,19 | Rps13                                                                     | 40S ribosomal protein S13                                                                                                                                                                                                                                                                                                       |
| 1,09 | -0,33 | Nxf1                                                                      | Nuclear RNA export factor 1                                                                                                                                                                                                                                                                                                     |
| 1,09 | -0,13 | Kif5b                                                                     | Kinesin-1 heavy chain;Kinesin-like protein                                                                                                                                                                                                                                                                                      |
| 1,08 | 0,22  | Aldh18a1                                                                  | Delta-1-pyrroline-5-carboxylate synthase;Glutamate 5-kinase;Gamma-glutamyl phosphate reductase                                                                                                                                                                                                                                  |
| 1,08 | -0,20 | Ubfd1                                                                     | Ubiquitin domain-containing protein UBFD1                                                                                                                                                                                                                                                                                       |
| 1,08 | 0,33  | Uhrf2                                                                     | E3 ubiquitin-protein ligase UHRF2                                                                                                                                                                                                                                                                                               |
| 1,08 | 0,24  | Smarcc2                                                                   | SWI/SNF complex subunit SMARCC2                                                                                                                                                                                                                                                                                                 |
| 1,08 | 0,47  | Acadl                                                                     | Long-chain specific acyl-CoA dehydrogenase, mitochondrial                                                                                                                                                                                                                                                                       |
| 1,08 | 0,14  | Sema4a                                                                    | Semaphorin-4A                                                                                                                                                                                                                                                                                                                   |
| 1,08 | -0,19 | Slc7a6os                                                                  | Probable RNA polymerase II nuclear localization protein SLC7A6OS                                                                                                                                                                                                                                                                |
| 1,08 | -0,30 | Krt76                                                                     | Keratin, type II cytoskeletal 2 oral                                                                                                                                                                                                                                                                                            |
| 1,07 | 0,09  | Mars                                                                      | Methionine--tRNA ligase, cytoplasmic                                                                                                                                                                                                                                                                                            |
| 1,07 | -0,28 | Pcm1                                                                      | Pericentriolar material 1 protein                                                                                                                                                                                                                                                                                               |
| 1,07 | -0,18 | Ppp1r7                                                                    | Protein phosphatase 1 regulatory subunit 7                                                                                                                                                                                                                                                                                      |
| 1,06 | -0,21 | Kiaa0020                                                                  | Pumilio domain-containing protein KIAA0020                                                                                                                                                                                                                                                                                      |
| 1,06 | 0,46  | Efh1                                                                      | EF-hand domain-containing protein D1                                                                                                                                                                                                                                                                                            |
| 1,05 | 0,09  | Spag5                                                                     | Sperm-associated antigen 5                                                                                                                                                                                                                                                                                                      |
| 1,05 | 0,39  | Paccin2                                                                   | Protein kinase C and casein kinase substrate in neurons protein 2                                                                                                                                                                                                                                                               |
| 1,05 | 0,09  | Pkn2                                                                      | Serine/threonine-protein kinase N2                                                                                                                                                                                                                                                                                              |
| 1,05 | -0,26 | Thop1                                                                     | Thimet oligopeptidase                                                                                                                                                                                                                                                                                                           |
| 1,04 | -0,27 | Dynll1                                                                    | Dynein light chain 1, cytoplasmic                                                                                                                                                                                                                                                                                               |
| 1,04 | 0,99  | Tubb3                                                                     | Tubulin beta-3 chain                                                                                                                                                                                                                                                                                                            |
| 1,04 | 1,28  | Cdkn2a                                                                    | Cyclin-dependent kinase inhibitor 2A                                                                                                                                                                                                                                                                                            |
| 1,04 | -0,12 | Rras2                                                                     | Ras-related protein R-Ras2                                                                                                                                                                                                                                                                                                      |
| 1,04 | 0,66  | Gbp7                                                                      |                                                                                                                                                                                                                                                                                                                                 |
| 1,04 | -0,17 | Tfam                                                                      | Transcription factor A, mitochondrial                                                                                                                                                                                                                                                                                           |
| 1,04 | 0,17  | Rock1                                                                     | Rho-associated protein kinase 1                                                                                                                                                                                                                                                                                                 |
| 1,04 | -0,47 | Rpa2                                                                      | Replication protein A 32 kDa subunit                                                                                                                                                                                                                                                                                            |
| 1,04 | -0,17 | Mdh1                                                                      | Malate dehydrogenase, cytoplasmic                                                                                                                                                                                                                                                                                               |
| 1,04 | 0,08  | Dnajb11                                                                   | DnaJ homolog subfamily B member 11                                                                                                                                                                                                                                                                                              |
| 1,04 | -0,21 | Caprin1                                                                   | Caprin-1                                                                                                                                                                                                                                                                                                                        |
| 1,03 | 0,19  | Tcf4;Tcf12                                                                | Transcription factor 4;Transcription factor 12                                                                                                                                                                                                                                                                                  |
| 1,03 | 0,24  | Ugt1a7c;Ugt1a6a;Ugt1a10;Ugt1a5;Ugt1a8;Ugt1a6b;Ugt1a9;Ugt1a6;Ugt1a2;Ugt1a1 | UDP-glucuronosyltransferase 1-9;UDP-glucuronosyltransferase 1-7C;UDP-glucuronosyltransferase 1-6;UDP-glucuronosyltransferase 1-2;UDP-glucuronosyltransferase 1-1                                                                                                                                                                |
| 1,03 | -0,25 | Eps15                                                                     | Epidermal growth factor receptor substrate 15                                                                                                                                                                                                                                                                                   |
| 1,02 | -0,24 | Zc3h18                                                                    | Zinc finger CCCH domain-containing protein 18                                                                                                                                                                                                                                                                                   |
| 1,02 | -0,48 | Cwf19l1                                                                   | CWF19-like protein 1                                                                                                                                                                                                                                                                                                            |
| 1,02 | -0,16 | Rpl37                                                                     | 60S ribosomal protein L37                                                                                                                                                                                                                                                                                                       |
| 1,02 | -0,13 | Ints1                                                                     | Integrator complex subunit 1                                                                                                                                                                                                                                                                                                    |
| 1,02 | 0,12  | Stx8                                                                      | Syntaxin-8                                                                                                                                                                                                                                                                                                                      |
| 1,02 | 0,43  | Sit1                                                                      | Signaling threshold-regulating transmembrane adapter 1                                                                                                                                                                                                                                                                          |
| 1,02 | -0,56 | Apex1                                                                     | DNA-(apurinic or apyrimidinic site) lyase;DNA-(apurinic or apyrimidinic site) lyase, mitochondrial                                                                                                                                                                                                                              |
| 1,01 | -0,26 | Strap                                                                     | Serine-threonine kinase receptor-associated protein                                                                                                                                                                                                                                                                             |

|      |       |                                                                                                      |                                                                                                                                                                                                                                 |
|------|-------|------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1,01 | -0,36 | Sart1                                                                                                | U4/U6.U5 tri-snRNP-associated protein 1                                                                                                                                                                                         |
| 1,01 | -0,14 | Nvl                                                                                                  | Nuclear valosin-containing protein-like                                                                                                                                                                                         |
| 1,01 | -0,19 | Gsk3a                                                                                                | Glycogen synthase kinase-3 alpha                                                                                                                                                                                                |
| 1,01 | -0,20 | H2afx                                                                                                | Histone H2AX                                                                                                                                                                                                                    |
| 1,01 | -0,14 | Nampt                                                                                                | Nicotinamide phosphoribosyltransferase                                                                                                                                                                                          |
| 1,01 | -0,29 | Ap1g2                                                                                                | AP-1 complex subunit gamma-like 2                                                                                                                                                                                               |
| 1,01 | -0,13 | Atp5i                                                                                                | ATP synthase subunit e, mitochondrial                                                                                                                                                                                           |
| 1,01 | 0,13  | Smc2                                                                                                 | Structural maintenance of chromosomes protein 2                                                                                                                                                                                 |
| 1,01 | -0,13 | Rps6                                                                                                 | 40S ribosomal protein S6                                                                                                                                                                                                        |
| 1,00 | -0,34 | Lig1                                                                                                 | DNA ligase;DNA ligase 1                                                                                                                                                                                                         |
| 1,00 | -0,64 | Psmb5                                                                                                | Proteasome subunit beta type-5                                                                                                                                                                                                  |
| 1,00 | -0,08 | Mthfd1                                                                                               | C-1-tetrahydrofolate synthase, cytoplasmic;Methylenetetrahydrofolate dehydrogenase;Methenyltetrahydrofolate cyclohydrolase;Formyltetrahydrofolate synthetase;C-1-tetrahydrofolate synthase, cytoplasmic, N-terminally processed |
| 1,00 | 0,45  | Ccnd3                                                                                                | G1/S-specific cyclin-D3                                                                                                                                                                                                         |
| 1,00 | -0,11 | Nudc                                                                                                 | Nuclear migration protein nudC                                                                                                                                                                                                  |
| 0,99 | 0,24  | Cep192                                                                                               |                                                                                                                                                                                                                                 |
| 0,99 | -0,18 | Gnl1                                                                                                 | Guanine nucleotide-binding protein-like 1                                                                                                                                                                                       |
| 0,99 | -0,19 | Srsf1                                                                                                | Serine/arginine-rich splicing factor 1                                                                                                                                                                                          |
| 0,99 | -0,21 | Naa15                                                                                                | N-alpha-acetyltransferase 15, NatA auxiliary subunit                                                                                                                                                                            |
| 0,99 | 0,21  | Pafah1b3                                                                                             | Platelet-activating factor acetylhydrolase IB subunit gamma                                                                                                                                                                     |
| 0,99 | -0,14 | Nmd3                                                                                                 | 60S ribosomal export protein NMD3                                                                                                                                                                                               |
| 0,99 | -0,13 | Nsa2                                                                                                 | Ribosome biogenesis protein NSA2 homolog                                                                                                                                                                                        |
| 0,99 | -0,16 | Prim2                                                                                                | DNA primase large subunit                                                                                                                                                                                                       |
| 0,99 | 0,17  | Qtrt1                                                                                                | Queuine tRNA-ribosyltransferase                                                                                                                                                                                                 |
| 0,99 | 0,21  | Pdim1                                                                                                | PDZ and LIM domain protein 1                                                                                                                                                                                                    |
| 0,98 | 0,19  | Sod1                                                                                                 | Superoxide dismutase [Cu-Zn]                                                                                                                                                                                                    |
| 0,98 | -0,21 | Pgls                                                                                                 | 6-phosphogluconolactonase                                                                                                                                                                                                       |
| 0,98 | 0,20  | Dus4l                                                                                                | tRNA-dihydrouridine(20a/20b) synthase [NAD(P)+]-like                                                                                                                                                                            |
| 0,98 | -0,15 | D2Wsu81e                                                                                             | Putative methyltransferase C9orf114 homolog                                                                                                                                                                                     |
| 0,98 | -0,08 | Akap8                                                                                                | A-kinase anchor protein 8                                                                                                                                                                                                       |
| 0,98 | 1,10  | Cobl1                                                                                                | Cordon-bleu protein-like 1                                                                                                                                                                                                      |
| 0,97 | 0,23  | Snf8                                                                                                 | Vacuolar-sorting protein SNF8                                                                                                                                                                                                   |
| 0,97 | -0,19 | Dvl2                                                                                                 | Segment polarity protein dishevelled homolog DVL-2                                                                                                                                                                              |
| 0,97 | -0,09 | Cct4                                                                                                 | T-complex protein 1 subunit delta                                                                                                                                                                                               |
| 0,97 | -0,18 | Hist1h2bk;Hist1h2br;LO C665622;Hist1h2bf;Hist1h2bb;Hist1h2bp;Hist3h2bb;Hist1h2ba;Hist2h2be;Hist3h2ba | Histone H2B;Histone H2B type 1-K;Histone H2B type 1-F/J/L;Histone H2B type 1-B;Histone H2B type 1-P;Histone H2B type 3-B;Histone H2B type 1-A;Histone H2B type 2-E;Histone H2B type 3-A                                         |
| 0,97 | 0,24  | Irak4                                                                                                | Interleukin-1 receptor-associated kinase 4                                                                                                                                                                                      |
| 0,97 | -0,19 | Timm8a1                                                                                              | Mitochondrial import inner membrane translocase subunit Tim8 A                                                                                                                                                                  |
| 0,96 | -0,05 | Gltscr2                                                                                              |                                                                                                                                                                                                                                 |
| 0,96 | 0,09  | Cops3                                                                                                | COP9 signalosome complex subunit 3                                                                                                                                                                                              |
| 0,95 | -0,44 |                                                                                                      | Uncharacterized protein C19orf43 homolog                                                                                                                                                                                        |
| 0,95 | -0,15 | Adi1                                                                                                 | 1,2-dihydroxy-3-keto-5-methylthiopentene dioxygenase                                                                                                                                                                            |
| 0,95 | -0,17 | Rpl18a                                                                                               | 60S ribosomal protein L18a                                                                                                                                                                                                      |
| 0,95 | -0,05 | Ddx46                                                                                                | Probable ATP-dependent RNA helicase DDX46                                                                                                                                                                                       |
| 0,95 | 0,14  | Tagln2                                                                                               | Transgelin-2                                                                                                                                                                                                                    |
| 0,95 | -0,15 | Phb                                                                                                  | Prohibitin                                                                                                                                                                                                                      |
| 0,94 | 0,13  | Slc7a5                                                                                               | Large neutral amino acids transporter small subunit 1                                                                                                                                                                           |
| 0,94 | 0,34  | Rbm42                                                                                                | RNA-binding protein 42                                                                                                                                                                                                          |
| 0,94 | 0,19  | Fpgs                                                                                                 | Folylpolyglutamate synthase, mitochondrial                                                                                                                                                                                      |
| 0,94 | -0,17 | Rcc1                                                                                                 | Regulator of chromosome condensation                                                                                                                                                                                            |
| 0,94 | -0,19 | Qars                                                                                                 |                                                                                                                                                                                                                                 |

|      |       |                                 |                                                                                                                                                                                                                                                                                                                          |
|------|-------|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0,94 | 0,30  | Smtn                            | Smoothelin                                                                                                                                                                                                                                                                                                               |
| 0,94 | -0,10 | Abcf1                           | ATP-binding cassette sub-family F member 1                                                                                                                                                                                                                                                                               |
| 0,94 | -0,19 | Chd4                            | Chromodomain-helicase-DNA-binding protein 4                                                                                                                                                                                                                                                                              |
| 0,93 | -0,38 | Supt16;Supt16h                  | FACT complex subunit SPT16                                                                                                                                                                                                                                                                                               |
| 0,93 | -0,25 | Snx2                            | Sorting nexin-2                                                                                                                                                                                                                                                                                                          |
| 0,93 | -0,27 | Prpf38b                         | Pre-mRNA-splicing factor 38B                                                                                                                                                                                                                                                                                             |
| 0,93 | -0,14 | Huwe1                           | E3 ubiquitin-protein ligase HUWE1                                                                                                                                                                                                                                                                                        |
| 0,93 | -0,16 | Pcyt2                           | Ethanolamine-phosphate cytidyltransferase                                                                                                                                                                                                                                                                                |
| 0,93 | 0,19  | Sec23b                          | Protein transport protein Sec23B                                                                                                                                                                                                                                                                                         |
| 0,92 | 0,14  | Myh9                            | Myosin-9                                                                                                                                                                                                                                                                                                                 |
| 0,92 | -0,24 | Heatr3                          | HEAT repeat-containing protein 3                                                                                                                                                                                                                                                                                         |
| 0,92 | -0,30 | P4ha1                           | Prolyl 4-hydroxylase subunit alpha-1                                                                                                                                                                                                                                                                                     |
| 0,92 | -0,10 | Ints2                           | Integrator complex subunit 2                                                                                                                                                                                                                                                                                             |
| 0,92 | 0,30  | Noc3l                           | Nucleolar complex protein 3 homolog                                                                                                                                                                                                                                                                                      |
| 0,92 | -0,10 | Mcm6                            | DNA helicase;DNA replication licensing factor MCM6                                                                                                                                                                                                                                                                       |
| 0,92 | 0,11  | Ppp2r2a;Ppp2r2c;Ppp2r2d;Ppp2r2b | Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit B;Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit B gamma isoform;Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit B alpha isoform;Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit B beta isoform |
| 0,91 | 0,13  | Pank3;Pank1;Pank2               | Pantothenate kinase 3;Pantothenate kinase 1                                                                                                                                                                                                                                                                              |
| 0,91 | -0,19 | Ube3a                           | Ubiquitin-protein ligase E3A                                                                                                                                                                                                                                                                                             |
| 0,91 | 0,22  | Nup210                          | Nuclear pore membrane glycoprotein 210                                                                                                                                                                                                                                                                                   |
| 0,91 | -0,43 | Lgals1                          | Galectin-1                                                                                                                                                                                                                                                                                                               |
| 0,91 | -0,41 | Nucks1                          | Nuclear ubiquitous casein and cyclin-dependent kinase substrate 1                                                                                                                                                                                                                                                        |
| 0,91 | -0,16 | Ftsj3                           | pre-rRNA processing protein FTSJ3                                                                                                                                                                                                                                                                                        |
| 0,90 | 0,15  | Vps16                           |                                                                                                                                                                                                                                                                                                                          |
| 0,90 | -0,11 | Tcea1                           | Transcription elongation factor A protein 1                                                                                                                                                                                                                                                                              |
| 0,90 | -0,23 | Padi2                           | Protein-arginine deiminase type-2                                                                                                                                                                                                                                                                                        |
| 0,90 | -0,19 | Hdac2                           | Histone deacetylase 2                                                                                                                                                                                                                                                                                                    |
| 0,90 | -0,33 | Drp2                            | Developmentally-regulated GTP-binding protein 2                                                                                                                                                                                                                                                                          |
| 0,90 | 0,17  | Irf8                            | Interferon regulatory factor 8                                                                                                                                                                                                                                                                                           |
| 0,89 | -0,23 | Anapc2                          | Anaphase-promoting complex subunit 2                                                                                                                                                                                                                                                                                     |
| 0,89 | -0,13 | Usmg5                           | Up-regulated during skeletal muscle growth protein 5                                                                                                                                                                                                                                                                     |
| 0,89 | -0,36 | Rtn4rl2                         | Reticulon-4 receptor-like 2                                                                                                                                                                                                                                                                                              |
| 0,89 | -0,23 | Gm8991;Hnmpa3;Gm6793            | Heterogeneous nuclear ribonucleoprotein A3                                                                                                                                                                                                                                                                               |
| 0,89 | 0,34  | Sec11a                          | Signal peptidase complex catalytic subunit SEC11;Signal peptidase complex catalytic subunit SEC11A                                                                                                                                                                                                                       |
| 0,89 | -0,29 | Rpl32;Rpl32-ps                  | 60S ribosomal protein L32;Putative 60S ribosomal protein L32                                                                                                                                                                                                                                                             |
| 0,88 | 0,10  | Rab11b;Rab11a                   | Ras-related protein Rab-11A;Ras-related protein Rab-11B                                                                                                                                                                                                                                                                  |
| 0,88 | 0,39  | Myl6                            | Myosin light polypeptide 6                                                                                                                                                                                                                                                                                               |
| 0,88 | -0,42 | Fkbp3                           | Peptidyl-prolyl cis-trans isomerase;Peptidyl-prolyl cis-trans isomerase FKBP3                                                                                                                                                                                                                                            |
| 0,88 | -0,17 | Ranbp1                          | Ran-specific GTPase-activating protein                                                                                                                                                                                                                                                                                   |
| 0,88 | -0,19 | Polr2h                          | DNA-directed RNA polymerases I, II, and III subunit RPABC3                                                                                                                                                                                                                                                               |
| 0,87 | 0,12  | Clint1                          | Clathrin interactor 1                                                                                                                                                                                                                                                                                                    |
| 0,87 | -0,18 | Arf6                            | ADP-ribosylation factor 6                                                                                                                                                                                                                                                                                                |
| 0,87 | 0,38  | Cnp                             | 2,3-cyclic-nucleotide 3-phosphodiesterase                                                                                                                                                                                                                                                                                |
| 0,87 | -0,08 | Smu1                            | WD40 repeat-containing protein SMU1;WD40 repeat-containing protein SMU1, N-terminally processed                                                                                                                                                                                                                          |
| 0,87 | -0,12 | Sf3b3                           | Splicing factor 3B subunit 3                                                                                                                                                                                                                                                                                             |
| 0,87 | -0,19 | Slc25a4;Slc25a5;Slc25a31        | ADP/ATP translocase 1;ADP/ATP translocase 2;ADP/ATP translocase 2, N-terminally processed;ADP/ATP translocase 4;ADP/ATP translocase 4, N-terminally processed                                                                                                                                                            |
| 0,86 | -0,19 | Dus3l                           | tRNA-dihydrouridine(47) synthase [NAD(P)(+)]-like                                                                                                                                                                                                                                                                        |
| 0,86 | -0,37 | Lgals9                          | Galectin;Galectin-9                                                                                                                                                                                                                                                                                                      |
| 0,86 | -0,17 | Ube2s                           | Ubiquitin-conjugating enzyme E2 S                                                                                                                                                                                                                                                                                        |

|      |       |                |                                                                                                                 |
|------|-------|----------------|-----------------------------------------------------------------------------------------------------------------|
| 0,86 | -0,16 | Rad18          | E3 ubiquitin-protein ligase RAD18                                                                               |
| 0,86 | -0,21 | Wdr75          |                                                                                                                 |
| 0,86 | 0,15  | Rab18          | Ras-related protein Rab-18                                                                                      |
| 0,85 | 0,17  | Osbp           | Oxysterol-binding protein 1                                                                                     |
| 0,85 | -0,16 | Nans           |                                                                                                                 |
| 0,85 | -0,23 | Igf2bp3        | Insulin-like growth factor 2 mRNA-binding protein 3                                                             |
| 0,85 | 0,17  | Slc9a3r1       | Na(+)/H(+) exchange regulatory cofactor NHE-RF;Na(+)/H(+) exchange regulatory cofactor NHE-RF1                  |
| 0,85 | 0,29  | Rcsd1          | CapZ-interacting protein                                                                                        |
| 0,85 | -0,28 | Suc1g2         | Succinyl-CoA ligase [GDP-forming] subunit beta, mitochondrial                                                   |
| 0,84 | -0,26 | Ybx1           | Nuclease-sensitive element-binding protein 1                                                                    |
| 0,84 | -0,16 | Fgd2           | FYVE, RhoGEF and PH domain-containing protein 2                                                                 |
| 0,84 | -0,35 | Pgk1           | Phosphoglycerate kinase 1                                                                                       |
| 0,84 | -0,11 | Txn1           | Thioredoxin-like protein 1                                                                                      |
| 0,84 | -0,21 | Rps9           | 40S ribosomal protein S9                                                                                        |
| 0,84 | -0,09 | Glr5           | Glutaredoxin-related protein 5, mitochondrial                                                                   |
| 0,84 | 0,69  | Ankrd11        |                                                                                                                 |
| 0,84 | -0,17 | Ube2v1;Gm20431 | Ubiquitin-conjugating enzyme E2 variant 1                                                                       |
| 0,84 | -0,14 | Gtf2a2         | Transcription initiation factor IIA subunit 2                                                                   |
| 0,83 | -0,30 | Tpm3           |                                                                                                                 |
| 0,83 | -0,33 | Ppie           | Peptidyl-prolyl cis-trans isomerase E                                                                           |
| 0,83 | -0,45 | Akr1c13        | Aldo-keto reductase family 1 member C13                                                                         |
| 0,83 | -0,43 | Rps19          | 40S ribosomal protein S19                                                                                       |
| 0,83 | -0,10 | Cluh           | Clustered mitochondria protein homolog                                                                          |
| 0,83 | -0,16 | Btf3           | Transcription factor BTF3                                                                                       |
| 0,83 | 0,42  |                |                                                                                                                 |
| 0,83 | -0,15 | Elav1          | ELAV-like protein 1                                                                                             |
| 0,82 | 0,11  | Noc2l          | Nucleolar complex protein 2 homolog                                                                             |
| 0,82 | -0,59 | Cyb5a          | Cytochrome b5                                                                                                   |
| 0,82 | -0,16 | Mcm7           | DNA helicase;DNA replication licensing factor MCM7                                                              |
| 0,82 | -0,16 | Sec13          | Protein SEC13 homolog                                                                                           |
| 0,82 | -0,34 | Idi1           | Isopentenyl-diphosphate Delta-isomerase 1                                                                       |
| 0,82 | 0,35  | Pitpnb         |                                                                                                                 |
| 0,82 | -0,25 | Ilf2           | Interleukin enhancer-binding factor 2                                                                           |
| 0,82 | 0,29  | Psma4          | Proteasome subunit alpha type-4                                                                                 |
| 0,81 | -0,09 | Nup160         | Nuclear pore complex protein Nup160                                                                             |
| 0,81 | -0,14 | Ncl            | Nucleolin                                                                                                       |
| 0,81 | 0,16  | Arhgdib        | Rho GDP-dissociation inhibitor 2                                                                                |
| 0,81 | -0,14 | Eif3m          | Eukaryotic translation initiation factor 3 subunit M                                                            |
| 0,81 | -0,10 | Tbl3           | Transducin beta-like protein 3                                                                                  |
| 0,81 | -0,18 | Rpsa           | 40S ribosomal protein SA                                                                                        |
| 0,81 | -0,16 | Etf1           | Eukaryotic peptide chain release factor subunit 1                                                               |
| 0,81 | -0,27 | Phf6           | PHD finger protein 6                                                                                            |
| 0,81 | 0,20  | Xab2           | Pre-mRNA-splicing factor SYF1                                                                                   |
| 0,81 | -0,20 | Psip1          | PC4 and SFRS1-interacting protein                                                                               |
| 0,80 | -0,24 | Erp29          | Endoplasmic reticulum resident protein 29                                                                       |
| 0,80 | 0,18  | Ythdc1         | YTH domain-containing protein 1                                                                                 |
| 0,80 | -0,20 | Gramd4         | GRAM domain-containing protein 4                                                                                |
| 0,80 | 0,20  | Mia3           | Melanoma inhibitory activity protein 3                                                                          |
| 0,80 | 0,21  | Gabpb1         | GA-binding protein subunit beta-1                                                                               |
| 0,80 | 0,35  | Ctps2          | CTP synthase 2                                                                                                  |
| 0,80 | -0,20 | Eif2a          | Eukaryotic translation initiation factor 2A;Eukaryotic translation initiation factor 2A, N-terminally processed |

|      |       |                      |                                                                                                                                 |
|------|-------|----------------------|---------------------------------------------------------------------------------------------------------------------------------|
| 0,80 | 0,26  | Zfand6               | AN1-type zinc finger protein 6                                                                                                  |
| 0,80 | 0,20  | Plekhh1              | Pleckstrin homology domain-containing family H member 1                                                                         |
| 0,80 | -0,21 | Hspd1                | 60 kDa heat shock protein, mitochondrial                                                                                        |
| 0,80 | 0,12  | Smarca4              | Transcription activator BRG1                                                                                                    |
| 0,80 | 0,17  | Npc2                 | Epididymal secretory protein E1                                                                                                 |
| 0,80 | -0,07 | Mrps16               | 28S ribosomal protein S16, mitochondrial                                                                                        |
| 0,80 | -0,27 | Bax                  | Apoptosis regulator BAX                                                                                                         |
| 0,79 | -0,15 | Arl8b                | ADP-ribosylation factor-like protein 8B                                                                                         |
| 0,79 | -0,49 | Ak2                  | Adenylate kinase 2, mitochondrial;Adenylate kinase 2, mitochondrial, N-terminally processed                                     |
| 0,79 | -0,09 | Rps3                 | 40S ribosomal protein S3                                                                                                        |
| 0,79 | -0,20 | Usp10                | Ubiquitin carboxyl-terminal hydrolase 10                                                                                        |
| 0,79 | 0,22  | Tfg                  |                                                                                                                                 |
| 0,79 | 0,14  | Cstf1                | Cleavage stimulation factor subunit 1                                                                                           |
| 0,79 | -0,08 | Srp19                |                                                                                                                                 |
| 0,79 | -0,16 | Adrm1;Gm9774         | Proteasomal ubiquitin receptor ADRM1                                                                                            |
| 0,79 | -0,23 | Pabpc1;Pabpc6        | Polyadenylate-binding protein 1;Polyadenylate-binding protein                                                                   |
| 0,79 | -0,11 | Ddx19a;Ddx19b        | ATP-dependent RNA helicase DDX19A                                                                                               |
| 0,78 | 0,16  | Ddrgk1               | DDRCK domain-containing protein 1                                                                                               |
| 0,78 | 0,07  | Pak2                 | Serine/threonine-protein kinase PAK 2;PAK-2p27;PAK-2p34                                                                         |
| 0,78 | 0,16  | Ube2e1;Ube2e3;Ube2e2 | Ubiquitin-conjugating enzyme E2 E1;Ubiquitin-conjugating enzyme E2 E2;Ubiquitin-conjugating enzyme E2 E3                        |
| 0,78 | -0,13 | Sfpq                 | Splicing factor, proline- and glutamine-rich                                                                                    |
| 0,78 | 0,28  | Grap2                | GRB2-related adaptor protein 2                                                                                                  |
| 0,78 | -0,44 | Sep.09               | Septin-9                                                                                                                        |
| 0,78 | 0,11  | Pdcd6ip              | Programmed cell death 6-interacting protein                                                                                     |
| 0,78 | 0,15  | Acot9;Acot10         | Acyl-coenzyme A thioesterase 9, mitochondrial;Acyl-coenzyme A thioesterase 10, mitochondrial                                    |
| 0,78 | -0,13 | Phb2                 | Prohibitin-2                                                                                                                    |
| 0,78 | 0,28  | Vamp8                | Vesicle-associated membrane protein 8                                                                                           |
| 0,78 | -0,23 | Imp3                 | U3 small nucleolar ribonucleoprotein protein IMP3                                                                               |
| 0,78 | 0,16  | Dbr1                 | Lariat debranching enzyme                                                                                                       |
| 0,78 | 0,28  | Hgs                  | Hepatocyte growth factor-regulated tyrosine kinase substrate                                                                    |
| 0,78 | 0,18  | Bccip                | BRCA2 and CDKN1A-interacting protein                                                                                            |
| 0,78 | 0,08  | Dync1h1              | Cytoplasmic dynein 1 heavy chain 1                                                                                              |
| 0,78 | -0,37 | Snrpe                | Small nuclear ribonucleoprotein E                                                                                               |
| 0,78 | -0,26 | Mri1                 | Methylthioribose-1-phosphate isomerase                                                                                          |
| 0,77 | -0,27 | Slc25a1              | Tricarboxylate transport protein, mitochondrial                                                                                 |
| 0,77 | 0,15  | Nob1                 | RNA-binding protein NOB1                                                                                                        |
| 0,77 | -0,33 | Ccs                  | Copper chaperone for superoxide dismutase                                                                                       |
| 0,77 | 0,36  | Ifi47                |                                                                                                                                 |
| 0,77 | 0,22  | Ago2                 | Protein argonaute-2                                                                                                             |
| 0,77 | -0,13 | Cwc27                | Peptidyl-prolyl cis-trans isomerase CWC27 homolog                                                                               |
| 0,77 | -0,25 | Prrc2a               | Protein PRRC2A                                                                                                                  |
| 0,77 | -0,36 | Nedd4                | E3 ubiquitin-protein ligase NEDD4                                                                                               |
| 0,77 | -0,59 | Nap1l1               | Nucleosome assembly protein 1-like 1                                                                                            |
| 0,77 | 0,21  | Faim                 | Fas apoptotic inhibitory molecule 1                                                                                             |
| 0,76 | -0,41 | Zmpste24             | CAAX prenyl protease 1 homolog                                                                                                  |
| 0,76 | -0,06 | Bag5                 | BAG family molecular chaperone regulator 5                                                                                      |
| 0,76 | -0,15 | Aamp                 |                                                                                                                                 |
| 0,76 | -0,14 | Utp20                | Small subunit processome component 20 homolog                                                                                   |
| 0,76 | -0,15 | Serbp1               | Plasminogen activator inhibitor 1 RNA-binding protein                                                                           |
| 0,76 | -0,09 | Naca                 | Nascent polypeptide-associated complex subunit alpha;Nascent polypeptide-associated complex subunit alpha, muscle-specific form |
| 0,76 | -0,21 | Acaca                | Acetyl-CoA carboxylase 1;Biotin carboxylase                                                                                     |

|      |       |                    |                                                                                                                                                                     |
|------|-------|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0,76 | -0,13 | Pnn                | Pinin                                                                                                                                                               |
| 0,76 | -0,37 | Polr1c             | DNA-directed RNA polymerases I and III subunit RPAC1                                                                                                                |
| 0,76 | -0,21 | Wdfy4              |                                                                                                                                                                     |
| 0,76 | 0,08  | Uri1               | Unconventional prefoldin RPB5 interactor                                                                                                                            |
| 0,76 | -0,27 | Cox6b1             | Cytochrome c oxidase subunit 6B1                                                                                                                                    |
| 0,75 | -0,60 | Slc2a1             | Solute carrier family 2, facilitated glucose transporter member 1                                                                                                   |
| 0,75 | 0,30  | Selh               | Selenoprotein H                                                                                                                                                     |
| 0,75 | -0,16 | Carm1              | Histone-arginine methyltransferase CARM1                                                                                                                            |
| 0,75 | 0,11  | Cars               | Cysteine--tRNA ligase, cytoplasmic                                                                                                                                  |
| 0,75 | -0,17 | Rplp2              | 60S acidic ribosomal protein P2                                                                                                                                     |
| 0,75 | -0,30 | Kiaa1671           | Uncharacterized protein KIAA1671                                                                                                                                    |
| 0,75 | -0,15 | Psmb6              | Proteasome subunit beta type-6                                                                                                                                      |
| 0,75 | 0,10  | Lrrfp1             | Leucine-rich repeat flightless-interacting protein 1                                                                                                                |
| 0,75 | 0,12  | Pfas               | Phosphoribosylformylglycinamide synthase                                                                                                                            |
| 0,75 | 0,22  | Nudcd3             | NudC domain-containing protein 3                                                                                                                                    |
| 0,75 | 0,16  | Sep.01             | Septin-1                                                                                                                                                            |
| 0,75 | 0,40  | Yaf2               | YY1-associated factor 2                                                                                                                                             |
| 0,75 | 0,19  | Sec22b             | Vesicle-trafficking protein SEC22b                                                                                                                                  |
| 0,75 | -0,18 | Prpf19             | Pre-mRNA-processing factor 19                                                                                                                                       |
| 0,75 | -0,09 | Pcbp1              | Poly(rC)-binding protein 1                                                                                                                                          |
| 0,75 | 0,21  | Plbd2              | Putative phospholipase B-like 2;Putative phospholipase B-like 2 28 kDa form;Putative phospholipase B-like 2 40 kDa form;Putative phospholipase B-like 2 15 kDa form |
| 0,75 | -0,19 | Xrn2               | 5-3 exoribonuclease 2                                                                                                                                               |
| 0,75 | -0,25 | Ppil1              | Peptidyl-prolyl cis-trans isomerase;Peptidyl-prolyl cis-trans isomerase-like 1                                                                                      |
| 0,75 | -0,24 | Acat2;Acat3        | Acetyl-CoA acetyltransferase, cytosolic                                                                                                                             |
| 0,74 | 0,13  | Elmo1              | Engulfment and cell motility protein 1                                                                                                                              |
| 0,74 | 0,10  | Yars               | Tyrosine--tRNA ligase;Tyrosine--tRNA ligase, cytoplasmic;Tyrosine--tRNA ligase, cytoplasmic, N-terminally processed                                                 |
| 0,74 | -0,10 | Ppp1r10            | Serine/threonine-protein phosphatase 1 regulatory subunit 10                                                                                                        |
| 0,74 | -0,16 | Rps14              | 40S ribosomal protein S14                                                                                                                                           |
| 0,74 | -0,22 | Tsn                | Translin                                                                                                                                                            |
| 0,74 | 0,22  | Cd79b              | B-cell antigen receptor complex-associated protein beta chain                                                                                                       |
| 0,74 | -0,18 | Srsf2              | Serine/arginine-rich splicing factor 2                                                                                                                              |
| 0,73 | -0,06 | Rbmx1;Rbmx         | RNA binding motif protein, X-linked-like-1;RNA-binding motif protein, X chromosome;RNA-binding motif protein, X chromosome, N-terminally processed                  |
| 0,73 | -0,27 | Apoo               | Apolipoprotein O                                                                                                                                                    |
| 0,73 | -0,24 | Psmb7              | Proteasome subunit beta type-7                                                                                                                                      |
| 0,73 | 0,14  | Actn4              | Alpha-actinin-4                                                                                                                                                     |
| 0,73 | -0,11 | Rpl3               | 60S ribosomal protein L3                                                                                                                                            |
| 0,73 | -0,12 | Rpl36              | 60S ribosomal protein L36                                                                                                                                           |
| 0,73 | 1,68  | Taf15              |                                                                                                                                                                     |
| 0,73 | -0,19 | Gtf2i              | General transcription factor II-I                                                                                                                                   |
| 0,73 | -0,10 | Drg1               | Developmentally-regulated GTP-binding protein 1                                                                                                                     |
| 0,72 | -0,16 | Ctdspl2            | CTD small phosphatase-like protein 2                                                                                                                                |
| 0,72 | -0,14 | Map3k19            | Mitogen-activated protein kinase kinase kinase 19                                                                                                                   |
| 0,72 | -0,26 | 1110004F10Rik;Smap | Small acidic protein                                                                                                                                                |
| 0,72 | -0,26 | Mrps6              | 28S ribosomal protein S6, mitochondrial                                                                                                                             |
| 0,72 | -0,18 | Fcf1               | rRNA-processing protein FCF1 homolog                                                                                                                                |
| 0,72 | 0,11  | Ahctf1             | Protein ELYS                                                                                                                                                        |
| 0,72 | -0,29 | Eif4a1             | Eukaryotic initiation factor 4A-I                                                                                                                                   |
| 0,72 | -0,19 | Hnmpc              | Heterogeneous nuclear ribonucleoproteins C1/C2                                                                                                                      |
| 0,72 | 0,10  | Trmt5              | tRNA (guanine(37)-N1)-methyltransferase                                                                                                                             |
| 0,72 | -0,15 | Larp4b             | La-related protein 4B                                                                                                                                               |

|      |       |                |                                                                                                                                                          |
|------|-------|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0,72 | 0,12  | Helb           | DNA helicase B                                                                                                                                           |
| 0,71 | -0,12 | Kars           | Lysine--tRNA ligase                                                                                                                                      |
| 0,71 | 0,42  | Stat5a;Stat5b  | Signal transducer and activator of transcription;Signal transducer and activator of transcription 5B;Signal transducer and activator of transcription 5A |
| 0,71 | -0,45 | Polr2e         | DNA-directed RNA polymerases I, II, and III subunit RPABC1                                                                                               |
| 0,71 | 0,21  | Ripk1          | Receptor-interacting serine/threonine-protein kinase 1                                                                                                   |
| 0,71 | -0,14 | Prpf8          | Pre-mRNA-processing-splicing factor 8                                                                                                                    |
| 0,71 | -0,21 | Anp32b         | Acidic leucine-rich nuclear phosphoprotein 32 family member B                                                                                            |
| 0,71 | -0,07 | Plcg1          | Phosphoinositide phospholipase C;1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-1                                                       |
| 0,71 | 0,08  | Ube2j1         | Ubiquitin-conjugating enzyme E2 J1                                                                                                                       |
| 0,71 | -0,08 | Mrps35         | 28S ribosomal protein S35, mitochondrial                                                                                                                 |
| 0,71 | -0,27 | Elf5a          | Eukaryotic translation initiation factor 5A-1                                                                                                            |
| 0,71 | -0,18 | Polr2b         | DNA-directed RNA polymerase II subunit RPB2                                                                                                              |
| 0,71 | 0,16  | Usp8           | Ubiquitin carboxyl-terminal hydrolase;Ubiquitin carboxyl-terminal hydrolase 8                                                                            |
| 0,71 | -0,12 | Zbtb8os        | Protein archease                                                                                                                                         |
| 0,71 | 0,23  | Lcp1           | Plastin-2                                                                                                                                                |
| 0,70 | 0,13  | Wibg           | Partner of Y14 and mago                                                                                                                                  |
| 0,70 | 0,20  | Slc4a7         | Anion exchange protein;Sodium bicarbonate cotransporter 3                                                                                                |
| 0,70 | 0,30  | Ikzf1          | DNA-binding protein Ikaros                                                                                                                               |
| 0,70 | -0,14 | Nol6           | Nucleolar protein 6                                                                                                                                      |
| 0,70 | -0,07 | Elf5           | Eukaryotic translation initiation factor 5                                                                                                               |
| 0,70 | 0,18  | Purb           | Transcriptional activator protein Pur-beta                                                                                                               |
| 0,70 | 0,27  | Srp54;Srp54c   | Signal recognition particle 54 kDa protein                                                                                                               |
| 0,70 | -0,26 | Col14a1        | Collagen alpha-1(XIV) chain                                                                                                                              |
| 0,70 | 0,11  | Gars           | Glycine--tRNA ligase                                                                                                                                     |
| 0,70 | 0,37  | Psm14          | 26S proteasome non-ATPase regulatory subunit 14                                                                                                          |
| 0,70 | 0,10  | Pfdn2          | Prefoldin subunit 2                                                                                                                                      |
| 0,70 | -0,21 | Rlim           | E3 ubiquitin-protein ligase RLIM                                                                                                                         |
| 0,69 | 0,03  | Dctn1          | Dynactin subunit 1                                                                                                                                       |
| 0,69 | 0,08  | Kcmf1          | E3 ubiquitin-protein ligase KCMF1                                                                                                                        |
| 0,69 | -0,26 | Pccb           | Propionyl-CoA carboxylase beta chain, mitochondrial                                                                                                      |
| 0,69 | -0,19 | Rif1           | Telomere-associated protein RIF1                                                                                                                         |
| 0,69 | 0,22  | Sema4d         | Semaphorin-4D                                                                                                                                            |
| 0,69 | -0,17 | Ylpm1          |                                                                                                                                                          |
| 0,69 | -0,43 | Hat1           | Histone acetyltransferase type B catalytic subunit                                                                                                       |
| 0,69 | 0,24  | Smarcc1        | SWI/SNF complex subunit SMARCC1                                                                                                                          |
| 0,69 | -0,23 | Arf3;Arf1;Arf2 | ADP-ribosylation factor 1;ADP-ribosylation factor 3;ADP-ribosylation factor 2                                                                            |
| 0,69 | 0,12  | Fhl3           | Four and a half LIM domains protein 3                                                                                                                    |
| 0,69 | -0,18 |                | Uncharacterized protein C11orf98 homolog                                                                                                                 |
| 0,69 | -0,28 | Vdac2          | Voltage-dependent anion-selective channel protein 2                                                                                                      |
| 0,69 | 0,09  | Tubb5          | Tubulin beta-5 chain                                                                                                                                     |
| 0,69 | -0,09 | Polr1e         | DNA-directed RNA polymerase I subunit RPA49                                                                                                              |
| 0,69 | -0,34 | Rfc1           | Replication factor C subunit 1                                                                                                                           |
| 0,68 | 0,07  | Dynlrb1        | Dynein light chain roadblock-type 1                                                                                                                      |
| 0,68 | -0,08 | Gtpbp4         | Nucleolar GTP-binding protein 1                                                                                                                          |
| 0,68 | -0,20 | Rpl18          | 60S ribosomal protein L18                                                                                                                                |
| 0,68 | 0,10  | Cnot1          | CCR4-NOT transcription complex subunit 1                                                                                                                 |
| 0,68 | -0,26 | Pgam1          | Phosphoglycerate mutase 1                                                                                                                                |
| 0,68 | -0,34 | Ide            | Insulin-degrading enzyme                                                                                                                                 |
| 0,68 | 0,44  | P2ry10         | Putative P2Y purinoceptor 10                                                                                                                             |
| 0,68 | -0,10 | Ubap2l         | Ubiquitin-associated protein 2-like                                                                                                                      |
| 0,67 | -0,21 | Cdca7          | Cell division cycle-associated protein 7                                                                                                                 |

|      |       |                    |                                                                                                                                                                                                                                                                                           |
|------|-------|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0,67 | -0,14 | Rps28              | 40S ribosomal protein S28                                                                                                                                                                                                                                                                 |
| 0,67 | -0,07 | Snrnp200           | U5 small nuclear ribonucleoprotein 200 kDa helicase                                                                                                                                                                                                                                       |
| 0,67 | -0,14 | Uqcc2              | Ubiquinol-cytochrome-c reductase complex assembly factor 2                                                                                                                                                                                                                                |
| 0,67 | -0,21 | Hirip3             | HIRA-interacting protein 3                                                                                                                                                                                                                                                                |
| 0,67 | 0,14  | Gmfg               | Glia maturation factor gamma                                                                                                                                                                                                                                                              |
| 0,67 | 0,18  | Tuba4a             | Tubulin alpha-4A chain                                                                                                                                                                                                                                                                    |
| 0,67 | -0,27 | Limd2              | LIM domain-containing protein 2                                                                                                                                                                                                                                                           |
| 0,67 | -0,46 | Ptgs1              | Prostaglandin G/H synthase 1                                                                                                                                                                                                                                                              |
| 0,67 | -0,12 | Synrg              | Synergina gamma                                                                                                                                                                                                                                                                           |
| 0,67 | -0,27 | Timm17b            | Mitochondrial import inner membrane translocase subunit Tim17-B                                                                                                                                                                                                                           |
| 0,67 | -0,04 | Mcm2               | DNA replication licensing factor MCM2                                                                                                                                                                                                                                                     |
| 0,67 | 0,21  | Rock2              | Rho-associated protein kinase;Rho-associated protein kinase 2                                                                                                                                                                                                                             |
| 0,67 | -0,19 | Spn                | Leukosialin                                                                                                                                                                                                                                                                               |
| 0,67 | -0,16 | Ciao1              | Probable cytosolic iron-sulfur protein assembly protein CIAO1                                                                                                                                                                                                                             |
| 0,67 | -0,23 | Gfer               | FAD-linked sulfhydryl oxidase ALR                                                                                                                                                                                                                                                         |
| 0,67 | 0,17  | Prdx3              | Thioredoxin-dependent peroxide reductase, mitochondrial                                                                                                                                                                                                                                   |
| 0,67 | -0,21 | Eif2s2             | Eukaryotic translation initiation factor 2 subunit 2                                                                                                                                                                                                                                      |
| 0,67 | 0,07  | Gm28036;Rbm12      | RNA-binding protein 12                                                                                                                                                                                                                                                                    |
| 0,66 | 0,17  | Slu7               | Pre-mRNA-splicing factor SLU7                                                                                                                                                                                                                                                             |
| 0,66 | -0,34 | Hnrnpa1            | Heterogeneous nuclear ribonucleoprotein A1;Heterogeneous nuclear ribonucleoprotein A1, N-terminally processed                                                                                                                                                                             |
| 0,66 | -0,18 | Hist1h1a           | Histone H1.1                                                                                                                                                                                                                                                                              |
| 0,66 | 0,25  | Copg2              | Coatomer subunit gamma-2                                                                                                                                                                                                                                                                  |
| 0,66 | 0,08  | Dnaja1             | DnaJ homolog subfamily A member 1                                                                                                                                                                                                                                                         |
| 0,66 | -0,38 | Ppm1f              | Protein phosphatase 1F                                                                                                                                                                                                                                                                    |
| 0,66 | -0,04 | Shank3             | SH3 and multiple ankyrin repeat domains protein 3                                                                                                                                                                                                                                         |
| 0,66 | 0,20  | Glrx3              | Glutaredoxin-3                                                                                                                                                                                                                                                                            |
| 0,66 | 0,22  | Arhgap9;Arhgap15   | Rho GTPase-activating protein 15                                                                                                                                                                                                                                                          |
| 0,66 | 0,23  | Rnaseh2a           | Ribonuclease H2 subunit A;Ribonuclease                                                                                                                                                                                                                                                    |
| 0,66 | 0,14  | Dnaja3             | DnaJ homolog subfamily A member 3, mitochondrial                                                                                                                                                                                                                                          |
| 0,66 | -0,07 | Gemin5             | Gem-associated protein 5                                                                                                                                                                                                                                                                  |
| 0,66 | 0,05  | Cfl1               | Cofilin-1                                                                                                                                                                                                                                                                                 |
| 0,66 | -0,18 | Ccdc12             | Coiled-coil domain-containing protein 12                                                                                                                                                                                                                                                  |
| 0,66 | -0,10 | Sep.02             | Septin-2                                                                                                                                                                                                                                                                                  |
| 0,66 | 0,19  | Smrce1             | SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1                                                                                                                                                                                             |
| 0,65 | -0,59 | Pnp                | Purine nucleoside phosphorylase                                                                                                                                                                                                                                                           |
| 0,65 | -0,23 | Fbl1               | rRNA/tRNA 2-O-methyltransferase fibrillarin-like protein 1                                                                                                                                                                                                                                |
| 0,65 | -0,17 | Hnmpf              | Heterogeneous nuclear ribonucleoprotein F;Heterogeneous nuclear ribonucleoprotein F, N-terminally processed                                                                                                                                                                               |
| 0,65 | 0,44  | Gm7030;H2-K1;H2-D1 | H-2 class I histocompatibility antigen, K-Q alpha chain;H-2 class I histocompatibility antigen, K-K alpha chain;H-2 class I histocompatibility antigen, K-W28 alpha chain;H-2 class I histocompatibility antigen, K-B alpha chain;H-2 class I histocompatibility antigen, D-D alpha chain |
| 0,65 | 0,14  | Tsg101             | Tumor susceptibility gene 101 protein                                                                                                                                                                                                                                                     |
| 0,65 | -0,13 | Fam133b            | Protein FAM133B                                                                                                                                                                                                                                                                           |
| 0,65 | -0,11 | Ints7              | Integrator complex subunit 7                                                                                                                                                                                                                                                              |
| 0,65 | -0,34 | Rpl10;Rpl10l       | 60S ribosomal protein L10;60S ribosomal protein L10-like                                                                                                                                                                                                                                  |
| 0,65 | -0,55 | Nup85              | Nuclear pore complex protein Nup85                                                                                                                                                                                                                                                        |
| 0,65 | 0,15  | Bop1               | Ribosome biogenesis protein BOP1                                                                                                                                                                                                                                                          |
| 0,65 | -0,28 | Dbi                | Acyl-CoA-binding protein                                                                                                                                                                                                                                                                  |
| 0,65 | -0,46 | Trip12             | E3 ubiquitin-protein ligase TRIP12                                                                                                                                                                                                                                                        |
| 0,64 | 0,18  | Acy1               | Aminoacylase-1                                                                                                                                                                                                                                                                            |
| 0,64 | -0,22 | Rps24              | 40S ribosomal protein S24                                                                                                                                                                                                                                                                 |
| 0,64 | -0,08 | Gart               | Trifunctional purine biosynthetic protein adenosine-3;Phosphoribosylamine-glycine                                                                                                                                                                                                         |

|      |       |                                |                                                                                                                 |                                        |
|------|-------|--------------------------------|-----------------------------------------------------------------------------------------------------------------|----------------------------------------|
|      |       |                                | ligase;Phosphoribosylformylglycinamide<br>formyltransferase                                                     | cyclo-ligase;Phosphoribosylglycinamide |
| 0,64 | -0,08 | Lsm14a                         | Protein LSM14 homolog A                                                                                         |                                        |
| 0,64 | -0,12 | Mrps30                         | 28S ribosomal protein S30, mitochondrial                                                                        |                                        |
| 0,64 | -0,18 | Nat10                          | N-acetyltransferase 10                                                                                          |                                        |
| 0,64 | -0,10 | Sipa1                          | Signal-induced proliferation-associated protein 1                                                               |                                        |
| 0,64 | 0,20  | Wwp2                           | NEDD4-like E3 ubiquitin-protein ligase WWP2                                                                     |                                        |
| 0,64 | -0,10 | Ppif                           | Peptidyl-prolyl cis-trans isomerase F, mitochondrial                                                            |                                        |
| 0,64 | -0,33 | Rab4b                          | Ras-related protein Rab-4B                                                                                      |                                        |
| 0,64 | -0,07 | Tmx1                           | Thioredoxin-related transmembrane protein 1                                                                     |                                        |
| 0,63 | -0,21 | Dnttip2                        | Deoxynucleotidyltransferase terminal-interacting protein 2                                                      |                                        |
| 0,63 | 0,49  | Cog1                           | Conserved oligomeric Golgi complex subunit 1                                                                    |                                        |
| 0,63 | 0,34  | Coro7                          | Coronin-7                                                                                                       |                                        |
| 0,63 | -0,16 | Diablo                         | Diablo homolog, mitochondrial                                                                                   |                                        |
| 0,63 | 0,17  | Zpr1                           | Zinc finger protein ZPR1                                                                                        |                                        |
| 0,63 | -0,08 | Heatr1                         |                                                                                                                 |                                        |
| 0,63 | 0,17  | Setd3                          | Histone-lysine N-methyltransferase setd3                                                                        |                                        |
| 0,63 | 0,12  | Ppp1r21                        | Protein phosphatase 1 regulatory subunit 21                                                                     |                                        |
| 0,63 | -0,06 | Hspa4                          | Heat shock 70 kDa protein 4                                                                                     |                                        |
| 0,63 | -0,08 | Srsf10                         | Serine/arginine-rich splicing factor 10                                                                         |                                        |
| 0,63 | 0,40  | Morc3                          |                                                                                                                 |                                        |
| 0,63 | -0,22 | Xpo5                           | Exportin-5                                                                                                      |                                        |
| 0,63 | -0,17 | Cnot11                         | CCR4-NOT transcription complex subunit 11                                                                       |                                        |
| 0,63 | 0,25  | Sep.11                         | Septin-11                                                                                                       |                                        |
| 0,63 | -0,07 | Chaf1a                         | Chromatin assembly factor 1 subunit A                                                                           |                                        |
| 0,62 | 0,23  | Vwa5a;AW551984                 | von Willebrand factor A domain-containing protein 5A                                                            |                                        |
| 0,62 | -0,10 | Gm18025;Rps2;Gm6576<br>;Gm8225 | 40S ribosomal protein S2                                                                                        |                                        |
| 0,62 | -0,14 | Nasp                           | Nuclear autoantigenic sperm protein                                                                             |                                        |
| 0,62 | 0,15  | Slmap                          | Sarcolemmal membrane-associated protein                                                                         |                                        |
| 0,62 | -0,19 | Utp3                           | Something about silencing protein 10                                                                            |                                        |
| 0,62 | 0,26  | Uso1                           | General vesicular transport factor p115                                                                         |                                        |
| 0,62 | -0,15 | Snrpb;Snrpn                    | Small nuclear ribonucleoprotein-associated protein B;Small nuclear ribonucleoprotein-associated protein N       |                                        |
| 0,62 | -0,47 | Vps18                          | Vacuolar protein sorting-associated protein 18 homolog                                                          |                                        |
| 0,62 | 0,64  | Xrn1                           | 5-3 exoribonuclease 1                                                                                           |                                        |
| 0,62 | 0,09  | Arpc3                          | Actin-related protein 2/3 complex subunit 3                                                                     |                                        |
| 0,62 | -0,13 | Apbb1ip                        | Amyloid beta A4 precursor protein-binding family B member 1-interacting protein                                 |                                        |
| 0,62 | -0,10 | Fmnl1                          | Formin-like protein 1                                                                                           |                                        |
| 0,61 | -0,08 | Lemd3                          | Inner nuclear membrane protein Man1                                                                             |                                        |
| 0,61 | -0,14 | Hist1h1e                       | Histone H1.4                                                                                                    |                                        |
| 0,61 | 0,15  | Sar1b                          | GTP-binding protein SAR1b                                                                                       |                                        |
| 0,61 | 0,07  | Acot7                          | Cytosolic acyl coenzyme A thioester hydrolase                                                                   |                                        |
| 0,61 | -0,11 | Upf3b                          |                                                                                                                 |                                        |
| 0,61 | 0,09  | Comt                           | Catechol O-methyltransferase                                                                                    |                                        |
| 0,61 | -0,18 | Dlst                           | Dihydrolipoylysine-residue succinyltransferase component of 2-oxoglutarate dehydrogenase complex, mitochondrial |                                        |
| 0,61 | 0,16  | Por                            | NADPH--cytochrome P450 reductase                                                                                |                                        |
| 0,61 | 0,13  | Numa1                          |                                                                                                                 |                                        |
| 0,61 | 0,08  | Grcc10                         | Protein C10                                                                                                     |                                        |
| 0,61 | -0,15 | Eef2k                          | Eukaryotic elongation factor 2 kinase                                                                           |                                        |
| 0,60 | -0,13 | Pum2                           | Pumilio homolog 2                                                                                               |                                        |
| 0,60 | 0,32  | Urod                           | Uroporphyrinogen decarboxylase                                                                                  |                                        |
| 0,60 | -0,18 | Rbm39                          | RNA-binding protein 39                                                                                          |                                        |

|      |       |              |                                                                                                                                            |
|------|-------|--------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| 0,60 | 0,23  | Tra2a        | Transformer-2 protein homolog alpha                                                                                                        |
| 0,60 | -0,18 | Gimap4       | GTPase IMAP family member 4                                                                                                                |
| 0,60 | 0,18  | Mad2l1       | Mitotic spindle assembly checkpoint protein MAD2A                                                                                          |
| 0,60 | -0,19 | Psmc5        | 26S proteasome non-ATPase regulatory subunit 5                                                                                             |
| 0,60 | -0,14 | Srsf6        | Serine/arginine-rich splicing factor 6                                                                                                     |
| 0,60 | -0,10 |              |                                                                                                                                            |
| 0,60 | -0,11 | Nfkbib       | NF-kappa-B inhibitor beta                                                                                                                  |
| 0,60 | -0,15 | Dhx15        | Pre-mRNA-splicing factor ATP-dependent RNA helicase DHX15                                                                                  |
| 0,59 | -0,27 | Gcom1;Polr2m | DNA-directed RNA polymerase II subunit GRINL1A                                                                                             |
| 0,59 | -0,13 | Eif3b        | Eukaryotic translation initiation factor 3 subunit B                                                                                       |
| 0,59 | -0,12 | Eif3l        | Eukaryotic translation initiation factor 3 subunit L                                                                                       |
| 0,59 | -0,12 | Rpl6;Gm5428  | 60S ribosomal protein L6                                                                                                                   |
| 0,59 | 0,17  | Igsf8        | Immunoglobulin superfamily member 8                                                                                                        |
| 0,59 | -0,10 | Cstf2        |                                                                                                                                            |
| 0,59 | -0,12 | Isy1         | Pre-mRNA-splicing factor ISY1 homolog                                                                                                      |
| 0,59 | 0,60  | Eny2         | Transcription and mRNA export factor ENY2                                                                                                  |
| 0,59 | -0,31 | Arhgap1      | Rho GTPase-activating protein 1                                                                                                            |
| 0,59 | -0,18 | Cd81         | CD81 antigen                                                                                                                               |
| 0,59 | -0,07 | Rpl31        | 60S ribosomal protein L31                                                                                                                  |
| 0,59 | 0,14  | Ddx39b       | Spliceosome RNA helicase Ddx39b                                                                                                            |
| 0,59 | 0,19  | Pcnt         | Pericentrin                                                                                                                                |
| 0,59 | -0,19 | Gm9493;Rps7  | 40S ribosomal protein S7                                                                                                                   |
| 0,58 | 0,10  | Zdhhc20      | Probable palmitoyltransferase ZDHHC20                                                                                                      |
| 0,58 | -0,21 | Ptma         | Prothymosin alpha;Prothymosin alpha, N-terminally processed;Thymosin alpha                                                                 |
| 0,58 | -0,65 | Sppl2a       | Signal peptide peptidase-like 2A                                                                                                           |
| 0,58 | 0,19  | Luc7l        | Putative RNA-binding protein Luc7-like 1                                                                                                   |
| 0,58 | -0,28 | Psat1        | Phosphoserine aminotransferase                                                                                                             |
| 0,58 | 0,08  | Mtor         | Serine/threonine-protein kinase mTOR                                                                                                       |
| 0,58 | -0,20 | Itga4        | Integrin alpha-4                                                                                                                           |
| 0,58 | -0,10 | Klhdc4       | Kelch domain-containing protein 4                                                                                                          |
| 0,58 | 0,32  | Pgm2l1       | Glucose 1,6-bisphosphate synthase                                                                                                          |
| 0,58 | -0,11 | Uchl5        | Ubiquitin carboxyl-terminal hydrolase isozyme L5                                                                                           |
| 0,58 | -0,30 |              | Uncharacterized protein KIAA1143 homolog                                                                                                   |
| 0,58 | -0,39 | Wdhd1        | WD repeat and HMG-box DNA-binding protein 1                                                                                                |
| 0,58 | 0,21  | Ctsc         | Dipeptidyl peptidase 1;Dipeptidyl peptidase 1 exclusion domain chain;Dipeptidyl peptidase 1 heavy chain;Dipeptidyl peptidase 1 light chain |
| 0,58 | 0,15  | Dpp4         | Dipeptidyl peptidase 4;Dipeptidyl peptidase 4 membrane form;Dipeptidyl peptidase 4 soluble form                                            |
| 0,57 | 0,23  | Akap12       | A-kinase anchor protein 12                                                                                                                 |
| 0,57 | -0,26 | Chrac1       | Chromatin accessibility complex protein 1                                                                                                  |
| 0,57 | 0,26  | Map4k2       | Mitogen-activated protein kinase kinase kinase kinase 2                                                                                    |
| 0,57 | -0,06 | Polr2i       | DNA-directed RNA polymerase subunit;DNA-directed RNA polymerase II subunit RPB9                                                            |
| 0,57 | -0,14 | Fkbp8        | Peptidyl-prolyl cis-trans isomerase FKBP8                                                                                                  |
| 0,57 | -0,07 | Luc7l2       | Putative RNA-binding protein Luc7-like 2                                                                                                   |
| 0,57 | -1,16 | Rpsd2        | RNA pseudouridylylase synthase domain-containing protein 2                                                                                 |
| 0,57 | -0,18 | Pola1        | DNA polymerase alpha catalytic subunit                                                                                                     |
| 0,57 | 0,14  | Bzw1         | Basic leucine zipper and W2 domain-containing protein 1                                                                                    |
| 0,57 | -0,14 | Thoc3        | THO complex subunit 3                                                                                                                      |
| 0,57 | -0,12 | Hdgfrp2      | Hepatoma-derived growth factor-related protein 2                                                                                           |
| 0,57 | 0,21  | Nmral1       | NmrA-like family domain-containing protein 1                                                                                               |
| 0,56 | -0,18 | Polr2c       | DNA-directed RNA polymerase II subunit RPB3                                                                                                |
| 0,56 | 0,07  | Emc4         | ER membrane protein complex subunit 4                                                                                                      |
| 0,56 | 0,12  | Ywhaz        | 14-3-3 protein zeta/delta                                                                                                                  |

|      |       |                  |                                                                               |
|------|-------|------------------|-------------------------------------------------------------------------------|
| 0,56 | -0,15 | Pip4k2c          | Phosphatidylinositol 5-phosphate 4-kinase type-2 gamma                        |
| 0,56 | -0,08 | Son              | Protein SON                                                                   |
| 0,56 | -0,14 | Pus7             |                                                                               |
| 0,56 | -0,18 | Hist2h4;Hist1h4a | Histone H4                                                                    |
| 0,56 | 0,35  | Pnp2             | Purine nucleoside phosphorylase                                               |
| 0,56 | -0,09 | Ttc37            |                                                                               |
| 0,56 | -0,19 | Ppa1             | Inorganic pyrophosphatase                                                     |
| 0,56 | 0,22  | Rnaseh2b         | Ribonuclease H2 subunit B                                                     |
| 0,55 | -0,10 | Hexim1           | Protein HEXIM1                                                                |
| 0,55 | -0,16 | Rraga;Rragb      | Ras-related GTP-binding protein A;Ras-related GTP-binding protein B           |
| 0,55 | 0,07  | Faf1             | FAS-associated factor 1                                                       |
| 0,55 | -0,12 | Hdgf             | Hepatoma-derived growth factor                                                |
| 0,55 | 0,11  | Ccdc88b          | Coiled-coil domain-containing protein 88B                                     |
| 0,55 | 0,07  | Fgfr1op2         | FGFR1 oncogene partner 2 homolog                                              |
| 0,55 | 0,17  | Zbtb7a           | Zinc finger and BTB domain-containing protein 7A                              |
| 0,55 | 0,06  | Fen1             | Flap endonuclease 1                                                           |
| 0,55 | -0,21 | Aldoa;Aldoat1    | Fructose-bisphosphate aldolase;Fructose-bisphosphate aldolase A               |
| 0,55 | -0,11 | Edc4             | Enhancer of mRNA-decapping protein 4                                          |
| 0,55 | -0,08 | Impdh2           | Inosine-5-monophosphate dehydrogenase;Inosine-5-monophosphate dehydrogenase 2 |
| 0,55 | -0,06 | Psm8             | 26S proteasome non-ATPase regulatory subunit 8                                |
| 0,55 | -0,17 | Hmgb2            | High mobility group protein B2                                                |
| 0,55 | 0,07  | Ddx41            | Probable ATP-dependent RNA helicase DDX41                                     |
| 0,55 | -0,16 | Fbl              | rRNA 2-O-methyltransferase fibrillarin                                        |
| 0,55 | 0,11  | Ndc1             | Nucleoporin NDC1                                                              |
| 0,55 | -0,10 | Chek1            | Serine/threonine-protein kinase Chk1                                          |
| 0,55 | 0,05  | Hax1             | HCLS1-associated protein X-1                                                  |
| 0,55 | -0,25 | Gnl3             | Guanine nucleotide-binding protein-like 3                                     |
| 0,54 | -0,14 | Yrdc             | YrdC domain-containing protein, mitochondrial                                 |
| 0,54 | -0,17 | Ssrp1            | FACT complex subunit SSRP1                                                    |
| 0,54 | 0,28  | Blnk             | B-cell linker protein                                                         |
| 0,54 | 0,15  | Arhgef2          | Rho guanine nucleotide exchange factor 2                                      |
| 0,54 | -0,19 | Irf2bp1          | Interferon regulatory factor 2-binding protein 1                              |
| 0,54 | 0,10  | Cmtm7            | CKLF-like MARVEL transmembrane domain-containing protein 7                    |
| 0,54 | -0,22 | Ppid             | Peptidyl-prolyl cis-trans isomerase D                                         |
| 0,54 | -0,82 | Kctd12           | BTB/POZ domain-containing protein KCTD12                                      |
| 0,54 | -0,10 | Rps18;Gm10260    | 40S ribosomal protein S18                                                     |
| 0,54 | 0,17  | Ilf3             | Interleukin enhancer-binding factor 3                                         |
| 0,54 | -0,11 | Lrriq1           | Leucine-rich repeat and IQ domain-containing protein 1                        |
| 0,54 | 0,12  | Mrps15           | 28S ribosomal protein S15, mitochondrial                                      |
| 0,54 | 0,20  | Strn             | Striatin                                                                      |
| 0,54 | -0,16 | Rpl13a           | 60S ribosomal protein L13a                                                    |
| 0,54 | -0,14 | Ube4b            | Ubiquitin conjugation factor E4 B                                             |
| 0,54 | -0,20 | Ccdc86           | Coiled-coil domain-containing protein 86                                      |
| 0,54 | -1,13 | S100a6           | Protein S100;Protein S100-A6                                                  |
| 0,53 | -1,44 | Ccdc115          | Coiled-coil domain-containing protein 115                                     |
| 0,53 | -0,12 | Prrc2c           | Protein PRRC2C                                                                |
| 0,53 | 0,27  | Foxp1            | Forkhead box protein P1                                                       |
| 0,53 | -0,19 | Gna13            | Guanine nucleotide-binding protein subunit alpha-13                           |
| 0,53 | -0,13 | Eef1b;Eef1b2     | Elongation factor 1-beta                                                      |
| 0,53 | -0,09 | Ate1             | Arginyl-tRNA--protein transferase 1                                           |
| 0,53 | 0,58  | Ikzf3            | Zinc finger protein Aiolos                                                    |
| 0,53 | 0,13  | Lars             | Leucine--tRNA ligase, cytoplasmic                                             |

|      |       |                         |                                                                                                                                         |
|------|-------|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| 0,53 | -0,08 | Fermt3                  | Fermitin family homolog 3                                                                                                               |
| 0,53 | -0,79 | Ckb                     | Creatine kinase B-type                                                                                                                  |
| 0,53 | -0,14 | Atic                    | Bifunctional purine biosynthesis protein PURH;Phosphoribosylaminoimidazolecarboxamide formyltransferase;IMP cyclohydrolase              |
| 0,53 | 0,29  | Atp6v1h                 | V-type proton ATPase subunit H                                                                                                          |
| 0,53 | -0,14 | Rbbp7;Rbbp4             | Histone-binding protein RBBP7;Histone-binding protein RBBP4                                                                             |
| 0,53 | -0,18 | Qdpr                    | Dihydropteridine reductase                                                                                                              |
| 0,53 | -0,15 | Nosip                   | Nitric oxide synthase-interacting protein                                                                                               |
| 0,53 | -0,14 | Smarcb1                 | SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1                                           |
| 0,53 | -0,39 | Vapa                    | Vesicle-associated membrane protein-associated protein A                                                                                |
| 0,53 | 0,16  | Akr1a1                  | Alcohol dehydrogenase [NADP(+)]                                                                                                         |
| 0,53 | -0,23 | Actl6a                  | Actin-like protein 6A                                                                                                                   |
| 0,52 | 0,09  | Grb2                    | Growth factor receptor-bound protein 2                                                                                                  |
| 0,52 | -0,48 | Psmc7                   | 26S proteasome non-ATPase regulatory subunit 7                                                                                          |
| 0,52 | -0,12 | Lonp1                   | Lon protease homolog, mitochondrial                                                                                                     |
| 0,52 | 0,14  | Rps10                   | 40S ribosomal protein S10                                                                                                               |
| 0,52 | -0,12 | Zc3h15                  | Zinc finger CCCH domain-containing protein 15                                                                                           |
| 0,52 | -0,11 | Ubxn7                   | UBX domain-containing protein 7                                                                                                         |
| 0,52 | -0,14 | Cul3;mKIAA0617          | Cullin-3                                                                                                                                |
| 0,52 | -0,27 | Rbm7                    | RNA-binding protein 7                                                                                                                   |
| 0,52 | 0,25  | Arid1a                  | AT-rich interactive domain-containing protein 1A                                                                                        |
| 0,52 | 0,12  | Hccs                    | Cytochrome c-type heme lyase                                                                                                            |
| 0,52 | -0,09 | Hmgn5                   | High mobility group nucleosome-binding domain-containing protein 5                                                                      |
| 0,52 | -0,41 | Xpnpep1                 | Xaa-Pro aminopeptidase 1                                                                                                                |
| 0,52 | -0,31 | Uchl3;Uchl4             | Ubiquitin carboxyl-terminal hydrolase isozyme L3;Ubiquitin carboxyl-terminal hydrolase;Ubiquitin carboxyl-terminal hydrolase isozyme L4 |
| 0,52 | -0,20 | Med27                   | Mediator of RNA polymerase II transcription subunit 27                                                                                  |
| 0,52 | 0,13  | Rnf40                   | E3 ubiquitin-protein ligase BRE1B                                                                                                       |
| 0,52 | 0,11  | Fh                      | Fumarate hydratase, mitochondrial                                                                                                       |
| 0,51 | -0,05 | Cct7                    | T-complex protein 1 subunit eta                                                                                                         |
| 0,51 | 0,23  |                         | Uncharacterized protein C9orf78 homolog                                                                                                 |
| 0,51 | -0,08 | Ywhae                   | 14-3-3 protein epsilon                                                                                                                  |
| 0,51 | -0,17 | Arhgdia                 | Rho GDP-dissociation inhibitor 1                                                                                                        |
| 0,51 | -0,27 | Acdb6                   | Acyl-CoA-binding domain-containing protein 6                                                                                            |
| 0,51 | -0,22 | Cd3eap                  | DNA-directed RNA polymerase I subunit RPA34                                                                                             |
| 0,51 | 0,13  | Tmem168                 | Transmembrane protein 168                                                                                                               |
| 0,51 | -0,89 | Actg2;Actc1;Acta1;Acta2 | Actin, gamma-enteric smooth muscle;Actin, alpha skeletal muscle;Actin, alpha cardiac muscle 1;Actin, aortic smooth muscle               |
| 0,51 | 0,14  | Prep                    | Prolyl endopeptidase                                                                                                                    |
| 0,51 | -0,06 | Smc1a                   | Structural maintenance of chromosomes protein 1A                                                                                        |
| 0,51 | 0,32  | Ska3                    | Spindle and kinetochore-associated protein 3                                                                                            |
| 0,51 | 0,05  | Rsf1                    |                                                                                                                                         |
| 0,51 | 0,30  | Nit2                    | Omega-amidase NIT2                                                                                                                      |
| 0,51 | 0,22  | Hdac7                   | Histone deacetylase 7                                                                                                                   |
| 0,51 | -0,11 | Ezh2                    | Histone-lysine N-methyltransferase EZH2                                                                                                 |
| 0,51 | -0,07 | Top1                    | DNA topoisomerase 1                                                                                                                     |
| 0,50 | 0,18  | Gbp4                    | Guanylate-binding protein 4                                                                                                             |
| 0,50 | 0,09  | Elac2                   | Zinc phosphodiesterase ELAC protein 2                                                                                                   |
| 0,50 | -0,14 | Ncbp2                   | Nuclear cap-binding protein subunit 2                                                                                                   |
| 0,50 | 0,11  | Anxa7                   | Annexin A7                                                                                                                              |
| 0,50 | -0,13 | Exosc6                  | Exosome complex component MTR3                                                                                                          |
| 0,50 | -0,29 | Serf2                   | Small EDRK-rich factor 2                                                                                                                |
| 0,50 | -0,29 | Vbp1                    | Prefoldin subunit 3                                                                                                                     |

|      |       |                        |                                                                                                                                                |
|------|-------|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| 0,50 | -0,10 | Polr2d                 | DNA-directed RNA polymerase II subunit RPB4                                                                                                    |
| 0,50 | -0,10 | 1110037F02Rik;Kiaa1429 | Protein virilizer homolog                                                                                                                      |
| 0,50 | 0,30  | Pml                    | Protein PML                                                                                                                                    |
| 0,50 | -0,16 | Sf1                    | Splicing factor 1                                                                                                                              |
| 0,50 | 0,31  | Acbd3                  | Golgi resident protein GCP60                                                                                                                   |
| 0,50 | -0,32 | Fam21                  | WASH complex subunit FAM21                                                                                                                     |
| 0,50 | 0,15  | Tsfm                   | Elongation factor Ts, mitochondrial                                                                                                            |
| 0,50 | 0,08  | Sdc4                   | Syndecan;Syndecan-4                                                                                                                            |
| 0,50 | -0,11 | Trappc5                | Trafficking protein particle complex subunit 5                                                                                                 |
| 0,50 | -0,61 | GAPDH;Gapdh;Gm7293     | Glyceraldehyde-3-phosphate dehydrogenase                                                                                                       |
| 0,50 | 0,08  | Swap70                 | Switch-associated protein 70                                                                                                                   |
| 0,50 | -0,46 | Prex1                  | Phosphatidylinositol 3,4,5-trisphosphate-dependent Rac exchanger 1 protein                                                                     |
| 0,50 | 0,26  | Aip                    | AH receptor-interacting protein                                                                                                                |
| 0,50 | -0,15 | Ncbp1                  | Nuclear cap-binding protein subunit 1                                                                                                          |
| 0,50 | -0,11 | Itgb1                  | Integrin beta-1                                                                                                                                |
| 0,50 | -0,15 | Cltb                   | Clathrin light chain B                                                                                                                         |
| 0,50 | -0,13 | Fam98b                 | Protein FAM98B                                                                                                                                 |
| 0,49 | -0,14 | Lzic                   | Protein LZIC                                                                                                                                   |
| 0,49 | -0,16 | Ppp2ca;Ppp2cb          | Serine/threonine-protein phosphatase 2A catalytic subunit alpha isoform;Serine/threonine-protein phosphatase 2A catalytic subunit beta isoform |
| 0,49 | 0,19  | Vps4b                  | Vacuolar protein sorting-associated protein 4B                                                                                                 |
| 0,49 | 0,10  | Eif3g                  | Eukaryotic translation initiation factor 3 subunit G                                                                                           |
| 0,49 | -0,17 | Gtf2f1                 | General transcription factor IIF subunit 1                                                                                                     |
| 0,49 | -0,08 | Atp5a1                 | ATP synthase subunit alpha, mitochondrial;ATP synthase subunit alpha                                                                           |
| 0,49 | -0,35 | Add1                   | Alpha-adducin                                                                                                                                  |
| 0,49 | -0,15 | Gpn1                   | GPN-loop GTPase 1                                                                                                                              |
| 0,49 | -0,27 | Tpi1                   | Triosephosphate isomerase                                                                                                                      |
| 0,49 | -0,23 | Sf3b4                  | Splicing factor 3B subunit 4                                                                                                                   |
| 0,49 | 0,11  | Ppp5c                  | Serine/threonine-protein phosphatase;Serine/threonine-protein phosphatase 5                                                                    |
| 0,49 | -0,23 | Apeh                   | Acylamino-acid-releasing enzyme                                                                                                                |
| 0,49 | -0,09 | Mdn1                   |                                                                                                                                                |
| 0,49 | -0,12 | Pds5b                  | Sister chromatid cohesion protein PDS5 homolog B                                                                                               |
| 0,48 | -0,13 | Agps                   | Alkylidihydroxyacetonephosphate synthase, peroxisomal                                                                                          |
| 0,48 | 0,10  | Rps12                  | 40S ribosomal protein S12                                                                                                                      |
| 0,48 | -0,12 | Ncapg                  |                                                                                                                                                |
| 0,48 | -0,41 | Cds2                   | Phosphatidate cytidylyltransferase;Phosphatidate cytidylyltransferase 2                                                                        |
| 0,48 | -0,10 | Prmt1                  | Protein arginine N-methyltransferase 1                                                                                                         |
| 0,48 | -0,16 | Ndufb7                 | NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 7                                                                                    |
| 0,48 | 0,08  | Rbm4;Rbm4b             | RNA-binding protein 4;RNA-binding protein 4B                                                                                                   |
| 0,48 | 0,15  | Sdha                   | Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial                                                                       |
| 0,48 | -0,12 | Paics                  | Multifunctional protein ADE2;Phosphoribosylaminoimidazole-succinocarboxamide synthase;Phosphoribosylaminoimidazole carboxylase                 |
| 0,48 | -0,13 | Tra2b                  | Transformer-2 protein homolog beta                                                                                                             |
| 0,48 | 0,23  | Suz12                  | Polycomb protein Suz12                                                                                                                         |
| 0,48 | -0,18 | Pin1                   | Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1                                                                                         |
| 0,48 | -0,12 | Dhx33                  | Putative ATP-dependent RNA helicase DHX33                                                                                                      |
| 0,48 | -0,09 | Eif1a;Eif1ax           | Eukaryotic translation initiation factor 1A, X-chromosomal;Eukaryotic translation initiation factor 1A                                         |
| 0,48 | -0,09 | Atp5f1                 | ATP synthase F(0) complex subunit B1, mitochondrial                                                                                            |
| 0,48 | -0,16 | Rpl10a                 | Ribosomal protein;60S ribosomal protein L10a                                                                                                   |
| 0,48 | -0,22 | U2af114                | Splicing factor U2AF 26 kDa subunit                                                                                                            |
| 0,48 | 0,22  | Ppib                   | Peptidyl-prolyl cis-trans isomerase;Peptidyl-prolyl cis-trans isomerase B                                                                      |
| 0,48 | -0,10 | Xrcc6                  | X-ray repair cross-complementing protein 6                                                                                                     |

|      |       |              |                                                                                                  |
|------|-------|--------------|--------------------------------------------------------------------------------------------------|
| 0,47 | 0,16  | Spag9        | C-Jun-amino-terminal kinase-interacting protein 4                                                |
| 0,47 | 0,26  | Ewsr1        | RNA-binding protein EWS                                                                          |
| 0,47 | 0,05  | Snd1         | Staphylococcal nuclease domain-containing protein 1                                              |
| 0,47 | 0,32  | Bcat1        | Branched-chain-amino-acid aminotransferase;Branched-chain-amino-acid aminotransferase, cytosolic |
| 0,47 | 0,19  | Hnmp3        |                                                                                                  |
| 0,47 | -0,12 | Eef1g        | Elongation factor 1-gamma                                                                        |
| 0,47 | -0,22 | BC035947     |                                                                                                  |
| 0,47 | -0,21 | Timm23       | Mitochondrial import inner membrane translocase subunit Tim23                                    |
| 0,47 | -0,18 | Rpl27        | 60S ribosomal protein L27                                                                        |
| 0,47 | 0,12  | Exosc10      | Exosome component 10                                                                             |
| 0,47 | 0,11  | Sars         | Serine--tRNA ligase, cytoplasmic                                                                 |
| 0,47 | -0,40 | Rps16        | 40S ribosomal protein S16                                                                        |
| 0,47 | -0,16 | Rpl17        | 60S ribosomal protein L17                                                                        |
| 0,47 | 0,10  | Uqcrrh       | Cytochrome b-c1 complex subunit 6, mitochondrial                                                 |
| 0,47 | -0,11 | Dek          | Protein DEK                                                                                      |
| 0,47 | -0,11 | Srrm2        | Serine/arginine repetitive matrix protein 2                                                      |
| 0,47 | 0,17  | Dock11       | Dedicator of cytokinesis protein 11                                                              |
| 0,47 | -0,26 | Eif4ebp2     | Eukaryotic translation initiation factor 4E-binding protein 2                                    |
| 0,47 | 0,13  | Actr3        | Actin-related protein 3                                                                          |
| 0,47 | -0,14 | Baz1b        | Tyrosine-protein kinase BAZ1B                                                                    |
| 0,47 | 0,16  | Cul5         | Cullin-5                                                                                         |
| 0,47 | 0,33  | Rpa3         | Replication protein A 14 kDa subunit                                                             |
| 0,47 | 0,09  | Prpf6        | Pre-mRNA-processing factor 6                                                                     |
| 0,47 | -0,19 | Pcca         | Propionyl-CoA carboxylase alpha chain, mitochondrial                                             |
| 0,47 | -0,08 | Hdh2;Ier3ip1 | Immediate early response 3-interacting protein 1                                                 |
| 0,47 | -0,13 | Ube2k        | Ubiquitin-conjugating enzyme E2 K                                                                |
| 0,47 | -0,16 | Nup35        | Nucleoporin NUP53                                                                                |
| 0,47 | -0,10 | Prorsd1      | Prolyl-tRNA synthetase associated domain-containing protein 1                                    |
| 0,47 | 0,14  | Dhx16        |                                                                                                  |
| 0,46 | 0,27  | Wasf2        | Wiskott-Aldrich syndrome protein family member 2                                                 |
| 0,46 | 0,14  | Psmg1        | Proteasome assembly chaperone 1                                                                  |
| 0,46 | 0,19  | Abcf2        | ATP-binding cassette sub-family F member 2                                                       |
| 0,46 | -0,38 | Mcm3ap       | Germinal-center associated nuclear protein                                                       |
| 0,46 | -0,08 | G3bp1        | Ras GTPase-activating protein-binding protein 1                                                  |
| 0,46 | 0,28  | Casc3        | Protein CASC3                                                                                    |
| 0,46 | -0,17 | Raly         | RNA-binding protein Raly                                                                         |
| 0,46 | 0,42  | Fth1         | Ferritin heavy chain;Ferritin heavy chain, N-terminally processed                                |
| 0,46 | -0,09 | Rpl7         | 60S ribosomal protein L7                                                                         |
| 0,46 | 0,18  | Tap1         | Antigen peptide transporter 1                                                                    |
| 0,46 | -0,09 | Atxn2l       | Ataxin-2-like protein                                                                            |
| 0,46 | -0,20 | Rbm15        |                                                                                                  |
| 0,46 | -0,29 | Unc119       | Protein unc-119 homolog A                                                                        |
| 0,46 | -0,14 | Hsbp1        | Heat shock factor-binding protein 1                                                              |
| 0,46 | 0,10  | Cltc         | Clathrin heavy chain;Clathrin heavy chain 1                                                      |
| 0,46 | -0,38 | Szrd1        | SUZ domain-containing protein 1                                                                  |
| 0,46 | -0,17 | Med25        | Mediator of RNA polymerase II transcription subunit 25                                           |
| 0,46 | 0,13  | Mapre2       | Microtubule-associated protein RP/EB family member 2                                             |
| 0,46 | -0,23 | Pom121       | Nuclear envelope pore membrane protein POM 121                                                   |
| 0,46 | -0,15 | Bcl11a       | B-cell lymphoma/leukemia 11A                                                                     |
| 0,46 | -0,15 | Dnajc7       | DnaJ homolog subfamily C member 7                                                                |
| 0,46 | 0,17  | Sf3b5        | Splicing factor 3B subunit 5                                                                     |

|      |       |                |                                                                              |
|------|-------|----------------|------------------------------------------------------------------------------|
| 0,46 | 0,17  | Hint1          | Histidine triad nucleotide-binding protein 1                                 |
| 0,46 | 0,10  | Dut            |                                                                              |
| 0,46 | 0,14  | Utp23          | rRNA-processing protein UTP23 homolog                                        |
| 0,46 | 0,28  | Cat            | Catalase                                                                     |
| 0,46 | -0,42 | Atxn10         | Ataxin-10                                                                    |
| 0,45 | -0,10 | Prpf31         | U4/U6 small nuclear ribonucleoprotein Prp31                                  |
| 0,45 | -0,16 | Rab2a;Rab2b    | Ras-related protein Rab-2A;Ras-related protein Rab-2B                        |
| 0,45 | 0,12  | Mtx1           | Metaxin-1                                                                    |
| 0,45 | -0,13 | Zcchc11        | Terminal uridylyltransferase 4                                               |
| 0,45 | -0,04 | Clns1a         | Methylosome subunit pCln                                                     |
| 0,45 | -0,06 | Toe1           | Target of EGR1 protein 1                                                     |
| 0,45 | 0,06  | Trnt1          | CCA tRNA nucleotidyltransferase 1, mitochondrial                             |
| 0,45 | 0,11  | Mrpl38         | 39S ribosomal protein L38, mitochondrial                                     |
| 0,45 | -0,07 | Ubr4           | E3 ubiquitin-protein ligase UBR4                                             |
| 0,45 | -0,12 | Nolc1          |                                                                              |
| 0,45 | -0,14 | Ldha           | L-lactate dehydrogenase;L-lactate dehydrogenase A chain                      |
| 0,45 | 0,11  | Incenp         | Inner centromere protein                                                     |
| 0,45 | 0,05  | Cct2           | T-complex protein 1 subunit beta                                             |
| 0,45 | -0,12 | Eif5b          | Eukaryotic translation initiation factor 5B                                  |
| 0,45 | -0,07 | Luc7l3         | Luc7-like protein 3                                                          |
| 0,45 | -0,05 | Gm28062;Hnrnpu | Heterogeneous nuclear ribonucleoprotein U                                    |
| 0,45 | 0,31  | Wdr76          | WD repeat-containing protein 76                                              |
| 0,45 | -0,21 | Hsd17b10       | 3-hydroxyacyl-CoA dehydrogenase type-2                                       |
| 0,45 | -0,09 | Upf1           | Regulator of nonsense transcripts 1                                          |
| 0,45 | -0,15 | Gm10126;Rps29  | 40S ribosomal protein S29                                                    |
| 0,44 | -0,15 | Glyr1          | Putative oxidoreductase GLYR1                                                |
| 0,44 | 0,20  | Ppard          | Peroxisome proliferator-activated receptor delta                             |
| 0,44 | -0,19 | Sbno1          | Protein strawberry notch homolog 1                                           |
| 0,44 | -0,10 | Ttn            | Titin                                                                        |
| 0,44 | -0,19 | Rbck1          | RanBP-type and C3HC4-type zinc finger-containing protein 1                   |
| 0,44 | -0,18 | Oat            | Ornithine aminotransferase, mitochondrial                                    |
| 0,44 | -0,21 | Napa           | Alpha-soluble NSF attachment protein                                         |
| 0,44 | -0,09 | Znf598         | Zinc finger protein 598                                                      |
| 0,44 | -0,18 | Hyou1          | Hypoxia up-regulated protein 1                                               |
| 0,44 | -0,03 | Eif3a          | Eukaryotic translation initiation factor 3 subunit A                         |
| 0,44 | 0,08  | Tfrc           | Transferrin receptor protein 1                                               |
| 0,44 | -0,15 | Nars           | Asparagine--tRNA ligase, cytoplasmic                                         |
| 0,44 | 0,11  | Ncapg2         | Condensin-2 complex subunit G2                                               |
| 0,44 | -0,09 | Timm50         | Mitochondrial import inner membrane translocase subunit TIM50                |
| 0,44 | -0,10 | Ssb            | Lupus La protein homolog                                                     |
| 0,44 | -0,11 | Aqr            | Intron-binding protein aquarius                                              |
| 0,44 | 0,73  | Gphn           | Gephyrin;Molybdopterin adenyltransferase;Molybdopterin molybdenumtransferase |
| 0,44 | -0,12 | Tial1          | Nucleolysin TIAR                                                             |
| 0,44 | -0,12 | Dnajb1         | DnaJ homolog subfamily B member 1                                            |
| 0,44 | -0,58 | Kctd16         | BTB/POZ domain-containing protein KCTD16                                     |
| 0,44 | -0,13 | Hsp90aa1       | Heat shock protein HSP 90-alpha                                              |
| 0,44 | -0,20 | Cyb5b          | Cytochrome b5 type B                                                         |
| 0,44 | -0,10 | C1qbp          | Complement component 1 Q subcomponent-binding protein, mitochondrial         |
| 0,44 | -0,08 | Trappc3        | Trafficking protein particle complex subunit 3                               |
| 0,44 | -0,32 | Cd47           | Leukocyte surface antigen CD47                                               |
| 0,44 | 0,11  | Lrch4          | Leucine-rich repeat and calponin homology domain-containing protein 4        |
| 0,44 | -0,29 | Abcf3          | ATP-binding cassette sub-family F member 3                                   |

|      |       |                         |                                                                                                                                         |
|------|-------|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| 0,43 | 0,06  |                         | UPF0609 protein C4orf27 homolog                                                                                                         |
| 0,43 | 0,09  | Gm11143                 |                                                                                                                                         |
| 0,43 | -0,17 | Dctpp1                  | dCTP pyrophosphatase 1                                                                                                                  |
| 0,43 | -0,13 | Cab39                   | Calcium-binding protein 39                                                                                                              |
| 0,43 | -0,13 | Mrps27                  | 28S ribosomal protein S27, mitochondrial                                                                                                |
| 0,43 | 0,14  | Hn1                     | Hematological and neurological expressed 1 protein;Hematological and neurological expressed 1 protein, N-terminally processed           |
| 0,43 | -0,08 | Rcl1                    | RNA 3-terminal phosphate cyclase-like protein                                                                                           |
| 0,43 | -0,49 | Nudt4                   | Diphosphoinositol polyphosphate phosphohydrolase 2                                                                                      |
| 0,43 | 0,15  | Rai1                    | Retinoic acid-induced protein 1                                                                                                         |
| 0,43 | -0,07 | Sfr1                    | Swi5-dependent recombination DNA repair protein 1 homolog                                                                               |
| 0,43 | -0,08 | Cwc15                   | Spliceosome-associated protein CWC15 homolog                                                                                            |
| 0,43 | -0,20 | Gak                     | Cyclin-G-associated kinase                                                                                                              |
| 0,43 | -0,15 | Atxn7l3b                | Putative ataxin-7-like protein 3B                                                                                                       |
| 0,43 | -0,11 | Api5                    | Apoptosis inhibitor 5                                                                                                                   |
| 0,43 | -0,10 | Rnpep                   | Aminopeptidase B                                                                                                                        |
| 0,43 | 0,15  | Cope                    | Coatomer subunit epsilon                                                                                                                |
| 0,43 | -0,21 | Cct5                    | T-complex protein 1 subunit epsilon                                                                                                     |
| 0,43 | -0,29 | Pgm2;Pgm1               | Phosphoglucomutase-1                                                                                                                    |
| 0,43 | -0,08 | Prpf4                   | U4/U6 small nuclear ribonucleoprotein Prp4                                                                                              |
| 0,43 | -0,12 | Cox4i1                  | Cytochrome c oxidase subunit 4 isoform 1, mitochondrial                                                                                 |
| 0,43 | -0,12 | Trmt1l                  | TRMT1-like protein                                                                                                                      |
| 0,43 | -0,10 | Mrpl37                  | 39S ribosomal protein L37, mitochondrial                                                                                                |
| 0,43 | 0,11  | Cpsf7                   | Cleavage and polyadenylation specificity factor subunit 7                                                                               |
| 0,43 | 0,11  | Kif4                    | Chromosome-associated kinesin KIF4                                                                                                      |
| 0,43 | 0,26  | Hmgn2                   | Non-histone chromosomal protein HMG-17                                                                                                  |
| 0,42 | 0,16  | Birc6                   | Baculoviral IAP repeat-containing protein 6                                                                                             |
| 0,42 | -0,29 | Metap1                  | Methionine aminopeptidase 1                                                                                                             |
| 0,42 | -0,17 | Ruvb1l                  | RuvB-like 1                                                                                                                             |
| 0,42 | -0,07 | Rps6ka3;Rps6ka1;Rps6ka2 | Ribosomal protein S6 kinase;Ribosomal protein S6 kinase alpha-1;Ribosomal protein S6 kinase alpha-2;Ribosomal protein S6 kinase alpha-3 |
| 0,42 | 0,20  | Sec23ip                 | SEC23-interacting protein                                                                                                               |
| 0,42 | 0,18  | Rela                    | Transcription factor p65                                                                                                                |
| 0,42 | -0,14 | Hmmr                    | Hyaluronan mediated motility receptor                                                                                                   |
| 0,42 | -0,28 | Ipo4                    | Importin-4                                                                                                                              |
| 0,42 | -0,08 | Mbd2                    | Methyl-CpG-binding domain protein 2                                                                                                     |
| 0,42 | 0,08  | Ncor1                   | Nuclear receptor corepressor 1                                                                                                          |
| 0,42 | -0,13 | Hnmpdl                  | Heterogeneous nuclear ribonucleoprotein D-like                                                                                          |
| 0,42 | 0,19  | Gbf1                    |                                                                                                                                         |
| 0,42 | -0,12 | Rcc2                    | Protein RCC2                                                                                                                            |
| 0,42 | 0,29  | Psmc4                   | 26S protease regulatory subunit 6B                                                                                                      |
| 0,42 | -0,09 | Ndufb11                 | NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 11, mitochondrial                                                             |
| 0,42 | -0,04 | Rbm3                    | RNA-binding protein 3                                                                                                                   |
| 0,42 | -0,10 | Gnl3l                   | Guanine nucleotide-binding protein-like 3-like protein                                                                                  |
| 0,42 | -0,05 | Usp9x                   | Ubiquitin carboxyl-terminal hydrolase;Probable ubiquitin carboxyl-terminal hydrolase FAF-X                                              |
| 0,42 | -0,15 | Colgalt1                | Procollagen galactosyltransferase 1                                                                                                     |
| 0,41 | -0,11 | Zdhhc5                  | Palmitoyltransferase ZDHHC5                                                                                                             |
| 0,41 | -0,18 | Chmp5                   | Charged multivesicular body protein 5                                                                                                   |
| 0,41 | 0,03  | Psm11                   | 26S proteasome non-ATPase regulatory subunit 11                                                                                         |
| 0,41 | -0,07 | Zcchc8                  | Zinc finger CCHC domain-containing protein 8                                                                                            |
| 0,41 | 0,25  | Cnot3                   | CCR4-NOT transcription complex subunit 3                                                                                                |
| 0,41 | -0,06 | Hspa9                   | Stress-70 protein, mitochondrial                                                                                                        |
| 0,41 | 0,06  | Fadd                    | FAS-associated death domain protein                                                                                                     |

|      |       |                |                                                                                                        |
|------|-------|----------------|--------------------------------------------------------------------------------------------------------|
| 0,41 | -0,12 | Elf3i          | Eukaryotic translation initiation factor 3 subunit I                                                   |
| 0,41 | -0,06 | Rad50          | DNA repair protein RAD50                                                                               |
| 0,41 | -0,21 | Twf2           | Twinfilin-2                                                                                            |
| 0,41 | -0,06 | Supt5h         | Transcription elongation factor SPT5                                                                   |
| 0,41 | -0,06 | Ipo7           | Importin-7                                                                                             |
| 0,41 | 0,17  | Rps5           | 40S ribosomal protein S5;40S ribosomal protein S5, N-terminally processed                              |
| 0,41 | -0,06 | Tpp2           | Tripeptidyl-peptidase 2                                                                                |
| 0,41 | -0,20 | Hddc2          | HD domain-containing protein 2                                                                         |
| 0,41 | -0,06 | Anp32a         | Acidic leucine-rich nuclear phosphoprotein 32 family member A                                          |
| 0,41 | -0,18 | Rpl28          | 60S ribosomal protein L28                                                                              |
| 0,41 | 0,15  | Nusap1         | Nucleolar and spindle-associated protein 1                                                             |
| 0,41 | 0,35  | Dync1i2        | Cytoplasmic dynein 1 intermediate chain 2                                                              |
| 0,41 | -0,16 | Cetn3          | Centrin-3                                                                                              |
| 0,41 | -0,18 | Arcn1          | Coatomer subunit delta                                                                                 |
| 0,41 | -0,37 | Srek1          | Splicing regulatory glutamine/lysine-rich protein 1                                                    |
| 0,41 | -0,13 | Memo1          | Protein MEMO1                                                                                          |
| 0,40 | 0,18  | Serinc3        | Serine incorporator 3                                                                                  |
| 0,40 | 0,14  | Txndc5         | Thioredoxin domain-containing protein 5                                                                |
| 0,40 | 0,26  | Cott1          | Coactosin-like protein                                                                                 |
| 0,40 | 0,06  | Casp8          | Caspase-8;Caspase-8 subunit p18;Caspase-8 subunit p10                                                  |
| 0,40 | 0,18  | G3bp2          | Ras GTPase-activating protein-binding protein 2                                                        |
| 0,40 | 0,16  | Pdia6          | Protein disulfide-isomerase A6                                                                         |
| 0,40 | 0,59  | Ccdc64b        | Bicaudal D-related protein 2                                                                           |
| 0,40 | -0,14 | Paf            | PCNA-associated factor                                                                                 |
| 0,40 | 0,17  | Fam185a        | Protein FAM185A                                                                                        |
| 0,40 | -0,30 | Add3           | Gamma-adducin                                                                                          |
| 0,40 | 0,27  | Trrap          |                                                                                                        |
| 0,40 | -0,06 | Atrx           | Transcriptional regulator ATRX                                                                         |
| 0,40 | 0,05  | Aldh9a1        | 4-trimethylaminobutyraldehyde dehydrogenase                                                            |
| 0,40 | 0,27  | Pid1           | PTB-containing, cubilin and LRP1-interacting protein                                                   |
| 0,40 | -0,16 | Rrp1b          | Ribosomal RNA processing protein 1 homolog B                                                           |
| 0,40 | -0,25 | Spc24          | Kinetochore protein Spc24                                                                              |
| 0,40 | -0,11 | Copb2          | Coatomer subunit beta                                                                                  |
| 0,40 | 0,04  | Rbbp6          | E3 ubiquitin-protein ligase RBBP6                                                                      |
| 0,40 | 0,15  | Bud31          |                                                                                                        |
| 0,40 | -0,07 | Csde1          | Cold shock domain-containing protein E1                                                                |
| 0,40 | -0,09 | Sf3a3          | Splicing factor 3A subunit 3                                                                           |
| 0,40 | -0,19 | Gm27029;Aarsd1 | Alanyl-tRNA editing protein Aarsd1                                                                     |
| 0,39 | -0,07 | Gm4799;Taf10   | Transcription initiation factor TFIID subunit 10                                                       |
| 0,39 | 0,16  | Tnpo1          | Transportin-1                                                                                          |
| 0,39 | 0,12  | Cutc           | Copper homeostasis protein cutC homolog                                                                |
| 0,39 | 0,06  | Prdx6          | Peroxiredoxin-6                                                                                        |
| 0,39 | -0,21 | Ppm1g          | Protein phosphatase 1G                                                                                 |
| 0,39 | 0,07  | Hmgcl;Hmgcl1   | Hydroxymethylglutaryl-CoA lyase, mitochondrial;3-hydroxymethyl-3-methylglutaryl-CoA lyase, cytoplasmic |
| 0,39 | 0,11  | Sord           | Sorbitol dehydrogenase                                                                                 |
| 0,39 | 0,14  | Sf1            |                                                                                                        |
| 0,39 | 0,09  | Slc3a2         | 4F2 cell-surface antigen heavy chain                                                                   |
| 0,39 | 0,03  | Hars           | Histidine--tRNA ligase, cytoplasmic                                                                    |
| 0,39 | 0,26  | H13;Hm13       | Minor histocompatibility antigen H13                                                                   |
| 0,39 | 0,18  | Pbrm1          | Protein polybromo-1                                                                                    |
| 0,39 | -0,15 | Srsf9          | Serine/arginine-rich splicing factor 9                                                                 |

|      |       |                                                            |                                                                                                                                           |
|------|-------|------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| 0,39 | -0,08 | Ube2m                                                      | NEDD8-conjugating enzyme Ubc12                                                                                                            |
| 0,39 | -0,08 | Idh3a                                                      | Isocitrate dehydrogenase [NAD] subunit alpha, mitochondrial                                                                               |
| 0,39 | -0,10 | Uqcrc1                                                     | Cytochrome b-c1 complex subunit 1, mitochondrial                                                                                          |
| 0,39 | -0,14 | Sar1a                                                      | GTP-binding protein SAR1a                                                                                                                 |
| 0,39 | -0,13 | Snx5                                                       | Sorting nexin-5                                                                                                                           |
| 0,39 | 0,12  | Rps25                                                      | 40S ribosomal protein S25                                                                                                                 |
| 0,39 | 0,04  | Nsf                                                        | Vesicle-fusing ATPase                                                                                                                     |
| 0,39 | -0,18 | Atp13a1                                                    | Manganese-transporting ATPase 13A1                                                                                                        |
| 0,39 | -0,13 | Mrto4                                                      | mRNA turnover protein 4 homolog                                                                                                           |
| 0,38 | 0,10  | Dbnl                                                       | Drebrin-like protein                                                                                                                      |
| 0,38 | -0,22 | Ddx54                                                      | ATP-dependent RNA helicase DDX54                                                                                                          |
| 0,38 | -0,12 | Utp15                                                      | U3 small nucleolar RNA-associated protein 15 homolog                                                                                      |
| 0,38 | 0,14  | Oxsr1                                                      | Serine/threonine-protein kinase OSR1                                                                                                      |
| 0,38 | 0,25  | Adnp                                                       | Activity-dependent neuroprotector homeobox protein                                                                                        |
| 0,38 | 0,08  | Isoc1                                                      | Isochorismatase domain-containing protein 1                                                                                               |
| 0,38 | 0,38  | Kin                                                        | DNA/RNA-binding protein KIN17                                                                                                             |
| 0,38 | 0,07  | Atp1a1                                                     | Sodium/potassium-transporting ATPase subunit alpha-1                                                                                      |
| 0,38 | 0,16  | Xrcc1                                                      | DNA repair protein XRCC1                                                                                                                  |
| 0,38 | 0,12  | Acbd5                                                      | Acyl-CoA-binding domain-containing protein 5                                                                                              |
| 0,38 | -0,07 | Gnb2l1                                                     | Guanine nucleotide-binding protein subunit beta-2-like 1;Guanine nucleotide-binding protein subunit beta-2-like 1, N-terminally processed |
| 0,38 | 0,21  | Vcl                                                        | Vinculin                                                                                                                                  |
| 0,38 | -0,29 | Cyp4f13;Cyp4f3                                             | Leukotriene-B(4) omega-hydroxylase 2                                                                                                      |
| 0,38 | -0,13 | Hnmpd                                                      | Heterogeneous nuclear ribonucleoprotein D0                                                                                                |
| 0,38 | 0,20  | Stmn2                                                      | Stathmin;Stathmin-2                                                                                                                       |
| 0,38 | 0,11  | Dync1li1                                                   | Cytoplasmic dynein 1 light intermediate chain 1                                                                                           |
| 0,38 | -0,23 | Hist1h2ah;Hist1h2ad;Hist1h2a;Hist1h2af;Hist1h2ab;Hist1h2aa | Histone H2A;Histone H2A type 1-H;Histone H2A type 1-F;Histone H2A type 3;Histone H2A type 1                                               |
| 0,38 | 0,12  | Tbc1d17                                                    | TBC1 domain family member 17                                                                                                              |
| 0,37 | 0,11  | Vcpi1                                                      | Deubiquitinating protein VCIP135                                                                                                          |
| 0,37 | -0,08 | Ywhah                                                      | 14-3-3 protein eta                                                                                                                        |
| 0,37 | -0,09 | Eef1a1                                                     | Elongation factor 1-alpha;Elongation factor 1-alpha 1                                                                                     |
| 0,37 | -0,06 | Alyref;Alyref2                                             | THO complex subunit 4;Aly/REF export factor 2                                                                                             |
| 0,37 | -0,27 | Hmgb1                                                      | High mobility group protein B1                                                                                                            |
| 0,37 | 0,14  | Psmb8                                                      | Proteasome subunit beta type-8                                                                                                            |
| 0,37 | -0,19 | Pbdc1                                                      | Protein PBDC1                                                                                                                             |
| 0,37 | -0,16 | Dnph1                                                      | 2-deoxynucleoside 5-phosphate N-hydrolase 1                                                                                               |
| 0,37 | 0,11  | Ap2a1                                                      | AP-2 complex subunit alpha-1                                                                                                              |
| 0,37 | -0,08 | Mrpl46                                                     | 39S ribosomal protein L46, mitochondrial                                                                                                  |
| 0,37 | -0,18 | Bclaf1                                                     | Bcl-2-associated transcription factor 1                                                                                                   |
| 0,37 | 0,07  | Hibadh                                                     | 3-hydroxyisobutyrate dehydrogenase, mitochondrial                                                                                         |
| 0,37 | 0,05  | Akt1                                                       | RAC-alpha serine/threonine-protein kinase                                                                                                 |
| 0,37 | -0,14 | Timm21                                                     |                                                                                                                                           |
| 0,37 | 0,16  | Inpp1                                                      | Phosphatidylinositol 3,4,5-trisphosphate 5-phosphatase 2                                                                                  |
| 0,37 | -0,39 |                                                            | Uncharacterized protein C12orf43 homolog                                                                                                  |
| 0,37 | -0,15 | Psmd2                                                      | 26S proteasome non-ATPase regulatory subunit 2                                                                                            |
| 0,37 | 0,08  | Rspo4                                                      | R-spondin-4                                                                                                                               |
| 0,37 | -0,11 | Rps4x;Rps4l                                                | 40S ribosomal protein S4;40S ribosomal protein S4, X isoform                                                                              |
| 0,37 | 0,10  | Ncapd2                                                     | Condensin complex subunit 1                                                                                                               |
| 0,37 | -0,22 | Ankrd44                                                    | Serine/threonine-protein phosphatase 6 regulatory ankyrin repeat subunit B                                                                |
| 0,37 | -0,16 | Idh1                                                       | Isocitrate dehydrogenase [NADP] cytoplasmic                                                                                               |
| 0,37 | -0,05 | Ccar2                                                      | Cell cycle and apoptosis regulator protein 2                                                                                              |

|      |       |                                  |                                                                                                                                                                                                                                               |
|------|-------|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0,37 | -0,11 | Cdk1                             | Cyclin-dependent kinase 1                                                                                                                                                                                                                     |
| 0,37 | -0,24 | Tfeb                             | Transcription factor EB                                                                                                                                                                                                                       |
| 0,37 | 0,13  | Ubl4;Ubl4a                       | Ubiquitin-like protein 4A                                                                                                                                                                                                                     |
| 0,36 | -0,09 | Ppp1r18                          | Phostensin                                                                                                                                                                                                                                    |
| 0,36 | -0,12 | Ap2m1                            | AP-2 complex subunit mu                                                                                                                                                                                                                       |
| 0,36 | -0,06 | Yme11                            | ATP-dependent zinc metalloprotease YME1L1                                                                                                                                                                                                     |
| 0,36 | -0,07 | Ranbp2                           | E3 SUMO-protein ligase RanBP2                                                                                                                                                                                                                 |
| 0,36 | 0,03  | Ascc2                            | Activating signal cointegrator 1 complex subunit 2                                                                                                                                                                                            |
| 0,36 | -0,27 | Ssca1                            | Sjogren syndrome/scleroderma autoantigen 1 homolog                                                                                                                                                                                            |
| 0,36 | 0,10  | Frmf8                            | FERM domain-containing protein 8                                                                                                                                                                                                              |
| 0,36 | -0,13 | Max                              | Protein max                                                                                                                                                                                                                                   |
| 0,36 | 0,15  | Crelf2                           | Cysteine-rich with EGF-like domain protein 2                                                                                                                                                                                                  |
| 0,36 | -0,12 | Rps8                             | 40S ribosomal protein S8                                                                                                                                                                                                                      |
| 0,36 | 0,10  | Dpp3                             | Dipeptidyl peptidase 3                                                                                                                                                                                                                        |
| 0,36 | 0,13  | Idh2                             | Isocitrate dehydrogenase [NADP], mitochondrial                                                                                                                                                                                                |
| 0,36 | -0,06 | Kif2c                            | Kinesin-like protein;Kinesin-like protein KIF2C                                                                                                                                                                                               |
| 0,36 | 0,23  | Tcirg1                           | V-type proton ATPase subunit a                                                                                                                                                                                                                |
| 0,36 | -0,12 | Snrpa;Gm5145                     | U1 small nuclear ribonucleoprotein A                                                                                                                                                                                                          |
| 0,36 | -0,11 | Hnmpul1                          | Heterogeneous nuclear ribonucleoprotein U-like protein 1                                                                                                                                                                                      |
| 0,36 | -0,03 | Sympk                            | Symplekin                                                                                                                                                                                                                                     |
| 0,36 | 0,28  | Phactr4                          | Phosphatase and actin regulator 4                                                                                                                                                                                                             |
| 0,36 | -0,19 | Skp1a;Skp1                       | S-phase kinase-associated protein 1                                                                                                                                                                                                           |
| 0,36 | 0,10  | Adss                             | Adenylosuccinate synthetase isozyme 2                                                                                                                                                                                                         |
| 0,36 | -0,18 | Crocc                            | Rootletin                                                                                                                                                                                                                                     |
| 0,36 | 0,14  | Tcf25                            | Transcription factor 25                                                                                                                                                                                                                       |
| 0,36 | -0,11 | Sh3glb1                          | Endophilin-B1                                                                                                                                                                                                                                 |
| 0,35 | 0,14  | Eif2ak2                          | Interferon-induced, double-stranded RNA-activated protein kinase                                                                                                                                                                              |
| 0,35 | -0,11 | Hnmp1                            | Heterogeneous nuclear ribonucleoprotein L                                                                                                                                                                                                     |
| 0,35 | 0,09  | Gfpt1                            | Glutamine--fructose-6-phosphate aminotransferase [isomerizing] 1                                                                                                                                                                              |
| 0,35 | 0,08  | Hnmpab                           | Heterogeneous nuclear ribonucleoprotein A/B                                                                                                                                                                                                   |
| 0,35 | -0,12 | Lrmp                             |                                                                                                                                                                                                                                               |
| 0,35 | 0,09  | Dak                              | Bifunctional ATP-dependent dihydroxyacetone kinase/FAD-AMP lyase (cyclizing);ATP-dependent dihydroxyacetone kinase;FAD-AMP lyase (cyclizing)                                                                                                  |
| 0,35 | -0,11 | Ppp4r2                           | Serine/threonine-protein phosphatase 4 regulatory subunit 2                                                                                                                                                                                   |
| 0,35 | 0,17  | Utp6                             | U3 small nucleolar RNA-associated protein 6 homolog                                                                                                                                                                                           |
| 0,35 | -0,06 | Vps26a                           | Vacuolar protein sorting-associated protein 26A                                                                                                                                                                                               |
| 0,35 | -0,09 | Srsf7                            | Serine/arginine-rich splicing factor 7                                                                                                                                                                                                        |
| 0,35 | -0,18 | Vasp                             | Vasodilator-stimulated phosphoprotein                                                                                                                                                                                                         |
| 0,35 | -0,05 | Kpna2                            | Importin subunit alpha;Importin subunit alpha-1                                                                                                                                                                                               |
| 0,35 | -0,09 | Bub3                             | Mitotic checkpoint protein BUB3                                                                                                                                                                                                               |
| 0,35 | 0,18  | Ablm1                            | Actin-binding LIM protein 1                                                                                                                                                                                                                   |
| 0,35 | 0,17  | Sp110                            | Sp110 nuclear body protein                                                                                                                                                                                                                    |
| 0,35 | 0,18  | Raver1                           | Ribonucleoprotein PTB-binding 1                                                                                                                                                                                                               |
| 0,35 | 0,05  | Tpm3                             |                                                                                                                                                                                                                                               |
| 0,35 | 0,19  | Snmp40                           | U5 small nuclear ribonucleoprotein 40 kDa protein                                                                                                                                                                                             |
| 0,35 | -0,11 | Tti2                             | TELO2-interacting protein 2                                                                                                                                                                                                                   |
| 0,35 | -0,07 | Clasp2                           | CLIP-associating protein 2                                                                                                                                                                                                                    |
| 0,35 | 0,04  | Dis3                             | Exosome complex exonuclease RRP44                                                                                                                                                                                                             |
| 0,34 | -0,10 | Ddx18                            | ATP-dependent RNA helicase DDX18                                                                                                                                                                                                              |
| 0,34 | -0,12 | Rps27a;Uba52;Kxd1;Ubc;Ubb;Gm5239 | Ubiquitin-40S ribosomal protein S27a;Ubiquitin;40S ribosomal protein S27a;Ubiquitin-60S ribosomal protein L40;Ubiquitin;60S ribosomal protein L40;Polyubiquitin-B;Ubiquitin;Polyubiquitin-C;Ubiquitin;Ubiquitin-related 1;Ubiquitin-related 2 |
| 0,34 | -0,16 | Pmpca                            | Mitochondrial-processing peptidase subunit alpha                                                                                                                                                                                              |

|      |       |                |                                                                                                                                                     |
|------|-------|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| 0,34 | -0,15 | Larp4          | La-related protein 4                                                                                                                                |
| 0,34 | -0,06 | Xpo7           | Exportin-7                                                                                                                                          |
| 0,34 | -0,06 | Nufip2         | Nuclear fragile X mental retardation-interacting protein 2                                                                                          |
| 0,34 | -0,15 | Kif23          | Kinesin-like protein KIF23                                                                                                                          |
| 0,34 | -0,12 | Parvg          | Gamma-parvin                                                                                                                                        |
| 0,34 | 0,06  | Hn11;AY358078  | Hematological and neurological expressed 1-like protein                                                                                             |
| 0,34 | -0,10 | Dpysl2         | Dihydropyrimidinase-related protein 2                                                                                                               |
| 0,34 | -0,08 | Vim            | Vimentin                                                                                                                                            |
| 0,34 | 0,07  | Snx6           | Sorting nexin-6;Sorting nexin-6, N-terminally processed                                                                                             |
| 0,34 | 0,17  | Tomm20         | Mitochondrial import receptor subunit TOM20 homolog                                                                                                 |
| 0,34 | -0,06 | Nsfl1c         | NSFL1 cofactor p47                                                                                                                                  |
| 0,34 | 0,10  | Al314180;Ecm29 | Proteasome-associated protein ECM29 homolog                                                                                                         |
| 0,34 | -0,29 | Psme1          | Proteasome activator complex subunit 1                                                                                                              |
| 0,34 | -0,16 | Impa1          | Inositol monophosphatase 1                                                                                                                          |
| 0,34 | -0,05 | Polr2a         | DNA-directed RNA polymerase II subunit RPB1                                                                                                         |
| 0,34 | 0,19  | Hip1r          | Huntingtin-interacting protein 1-related protein                                                                                                    |
| 0,34 | -0,08 | Rfc2           | Replication factor C subunit 2                                                                                                                      |
| 0,33 | 0,10  | Runx1          | Runt-related transcription factor 1                                                                                                                 |
| 0,33 | 0,09  | Dpy30          | Protein dpy-30 homolog                                                                                                                              |
| 0,33 | 0,18  | Stmn1          | Stathmin                                                                                                                                            |
| 0,33 | -0,17 | Hnmp1          | Heterogeneous nuclear ribonucleoprotein H;Heterogeneous nuclear ribonucleoprotein H, N-terminally processed                                         |
| 0,33 | -0,09 | Prkar1a        | cAMP-dependent protein kinase type I-alpha regulatory subunit;cAMP-dependent protein kinase type I-alpha regulatory subunit, N-terminally processed |
| 0,33 | -0,05 | Rpl7a          | 60S ribosomal protein L7a                                                                                                                           |
| 0,33 | -0,16 | Dstn           | Destrin                                                                                                                                             |
| 0,33 | 0,20  | Rp2            | Protein XRP2                                                                                                                                        |
| 0,33 | -0,15 | Psmc6          | 26S protease regulatory subunit 10B                                                                                                                 |
| 0,33 | 0,17  | Ttl12          | Tubulin--tyrosine ligase-like protein 12                                                                                                            |
| 0,33 | -0,04 | Hells          | Lymphocyte-specific helicase                                                                                                                        |
| 0,33 | -0,07 | Rmdn3          | Regulator of microtubule dynamics protein 3                                                                                                         |
| 0,33 | -0,14 | Pebp1          | Phosphatidylethanolamine-binding protein 1;Hippocampal cholinergic neurostimulating peptide                                                         |
| 0,33 | 0,11  | Rab5c          | Ras-related protein Rab-5C                                                                                                                          |
| 0,33 | -0,36 | Cstf2;Cstf2t   | Cleavage stimulation factor subunit 2;Cleavage stimulation factor subunit 2 tau variant                                                             |
| 0,33 | -0,17 | Ppme1          | Protein phosphatase methylesterase 1                                                                                                                |
| 0,33 | -0,18 | Zc3h6          | Zinc finger CCCH domain-containing protein 6                                                                                                        |
| 0,33 | -0,10 | Wdr33          | pre-mRNA 3 end processing protein WDR33                                                                                                             |
| 0,33 | -0,15 | Whsc1          | Histone-lysine N-methyltransferase NSD2                                                                                                             |
| 0,33 | 0,09  | Cops6          | COP9 signalosome complex subunit 6                                                                                                                  |
| 0,33 | 0,22  | Rsu1           | Ras suppressor protein 1                                                                                                                            |
| 0,33 | 0,42  | Marcks         | Myristoylated alanine-rich C-kinase substrate                                                                                                       |
| 0,33 | -0,05 | Park7          | Protein deglycase DJ-1                                                                                                                              |
| 0,33 | 0,08  | Pfdn6          | Prefoldin subunit 6                                                                                                                                 |
| 0,33 | -0,14 |                |                                                                                                                                                     |
| 0,33 | -0,15 | Adh5           | S-(hydroxymethyl)glutathione dehydrogenase;Alcohol dehydrogenase class-3                                                                            |
| 0,33 | 0,07  | Ybx3           | Y-box-binding protein 3                                                                                                                             |
| 0,33 | 0,08  | Vps29          | Vacuolar protein sorting-associated protein 29                                                                                                      |
| 0,33 | -0,10 | Ampd2          | AMP deaminase 2                                                                                                                                     |
| 0,33 | -0,12 | Rpl5           | 60S ribosomal protein L5                                                                                                                            |
| 0,33 | -0,07 | Wiz            | Protein Wiz                                                                                                                                         |
| 0,33 | 0,13  | Snrpf          | Small nuclear ribonucleoprotein F                                                                                                                   |
| 0,32 | 0,13  | Mavs           | Mitochondrial antiviral-signaling protein                                                                                                           |
| 0,32 | -0,17 | Ola1           | Obg-like ATPase 1                                                                                                                                   |

|      |       |           |                                                                                                                     |
|------|-------|-----------|---------------------------------------------------------------------------------------------------------------------|
| 0,32 | -0,20 | Naa30     | N-alpha-acetyltransferase 30                                                                                        |
| 0,32 | 0,10  | Tdp2      | Tyrosyl-DNA phosphodiesterase 2                                                                                     |
| 0,32 | 0,21  | Golga3    | Golgin subfamily A member 3                                                                                         |
| 0,32 | 0,26  | Marc2     | Mitochondrial amidoxime reducing component 2                                                                        |
| 0,32 | -0,08 | Elf3e     | Eukaryotic translation initiation factor 3 subunit E                                                                |
| 0,32 | 0,11  | Golph3    | Golgi phosphoprotein 3                                                                                              |
| 0,32 | -0,08 | Ppp6r3    | Serine/threonine-protein phosphatase 6 regulatory subunit 3                                                         |
| 0,32 | -0,11 | Nckap1l   |                                                                                                                     |
| 0,32 | 0,13  | FAM120A   | Constitutive coactivator of PPAR-gamma-like protein 1                                                               |
| 0,32 | 0,10  | Cmpk1     | UMP-CMP kinase                                                                                                      |
| 0,32 | -0,10 | Nup133    | Nuclear pore complex protein Nup133                                                                                 |
| 0,32 | -0,05 | Ruvbl2    | RuvB-like 2                                                                                                         |
| 0,32 | 0,07  | Atf1      | Cyclic AMP-dependent transcription factor ATF-1                                                                     |
| 0,32 | 0,12  | Cep170    | Centrosomal protein of 170 kDa                                                                                      |
| 0,32 | 0,12  | Fbxo3     | F-box only protein 3                                                                                                |
| 0,32 | -0,08 | Nrd1      | Nardilysin                                                                                                          |
| 0,32 | -0,08 | Scfd1     | Sec1 family domain-containing protein 1                                                                             |
| 0,32 | 0,10  | Hectd1    | E3 ubiquitin-protein ligase HECTD1                                                                                  |
| 0,32 | 0,32  | Ftl1      | Ferritin;Ferritin light chain 1                                                                                     |
| 0,32 | -0,06 | Rbm6      |                                                                                                                     |
| 0,32 | -0,12 | Slfn9     |                                                                                                                     |
| 0,31 | 0,15  | Mcmnbp    | Mini-chromosome maintenance complex-binding protein                                                                 |
| 0,31 | 0,14  | Scyl1     | N-terminal kinase-like protein                                                                                      |
| 0,31 | -0,48 | Ero1l     | ERO1-like protein alpha                                                                                             |
| 0,31 | 0,12  | Nop16     | Nucleolar protein 16                                                                                                |
| 0,31 | -0,15 | Unc93b1   | Protein unc-93 homolog B1                                                                                           |
| 0,31 | 0,09  | Tmpo      | Lamina-associated polypeptide 2, isoforms beta/delta/epsilon/gamma                                                  |
| 0,31 | -0,06 | Pgrmc1    | Membrane-associated progesterone receptor component 1                                                               |
| 0,31 | -0,05 | Nup205    |                                                                                                                     |
| 0,31 | 0,03  | Wars      | Tryptophan--tRNA ligase, cytoplasmic;T1-TrpRS;T2-TrpRS                                                              |
| 0,31 | 0,30  | Evl       | Ena/VASP-like protein                                                                                               |
| 0,31 | -0,10 | Aimp1     | Aminoacyl tRNA synthase complex-interacting multifunctional protein 1;Endothelial monocyte-activating polypeptide 2 |
| 0,31 | -0,06 | Ncaph     | Condensin complex subunit 2                                                                                         |
| 0,31 | -0,12 | Ipo5      | Importin-5                                                                                                          |
| 0,31 | -0,19 | Ywhag     | 14-3-3 protein gamma;14-3-3 protein gamma, N-terminally processed                                                   |
| 0,31 | -0,10 | Pygb      | Glycogen phosphorylase, brain form                                                                                  |
| 0,31 | 0,10  | Actr1a    | Alpha-centractin                                                                                                    |
| 0,31 | -0,08 | Hspbp1    | Hsp70-binding protein 1                                                                                             |
| 0,31 | -0,07 | Ddx49     | Probable ATP-dependent RNA helicase DDX49                                                                           |
| 0,31 | -0,06 | Sf3b2     |                                                                                                                     |
| 0,31 | -0,05 | Nop2      | Probable 28S rRNA (cytosine-C(5))-methyltransferase                                                                 |
| 0,31 | 0,13  | Vav1      | Proto-oncogene vav                                                                                                  |
| 0,31 | 0,13  | Gfm1      | Elongation factor G, mitochondrial                                                                                  |
| 0,31 | -0,20 | Srrm1     | Serine/arginine repetitive matrix protein 1                                                                         |
| 0,31 | -0,02 | Nap14     | Nucleosome assembly protein 1-like 4                                                                                |
| 0,31 | 0,11  | Helz      | Probable helicase with zinc finger domain                                                                           |
| 0,31 | 0,08  | Cdc37     | Hsp90 co-chaperone Cdc37;Hsp90 co-chaperone Cdc37, N-terminally processed                                           |
| 0,30 | -0,13 | Pqbp1     | Polyglutamine-binding protein 1                                                                                     |
| 0,30 | 0,11  | Rpl9      | 60S ribosomal protein L9                                                                                            |
| 0,30 | 0,27  | Hist1h2ak | Histone H2A type 1-K                                                                                                |
| 0,30 | -0,06 | Rps11     | 40S ribosomal protein S11                                                                                           |

|      |       |                      |                                                                                                                                     |
|------|-------|----------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| 0,30 | -0,11 | Hist1h1d             | Histone H1.3                                                                                                                        |
| 0,30 | 0,11  | Galns                | N-acetylgalactosamine-6-sulfatase                                                                                                   |
| 0,30 | -0,15 | Sri                  | Sorcin                                                                                                                              |
| 0,30 | -0,12 | Trp53i11             | Tumor protein p53-inducible protein 11                                                                                              |
| 0,30 | -0,14 | Psmc13               | 26S proteasome non-ATPase regulatory subunit 13                                                                                     |
| 0,30 | 0,07  | Acsf5                | Long-chain-fatty-acid--CoA ligase 5                                                                                                 |
| 0,30 | 0,20  | Wnt8a                | Protein Wnt-8a                                                                                                                      |
| 0,30 | -0,12 | Ube2l3               | Ubiquitin-conjugating enzyme E2 L3                                                                                                  |
| 0,30 | -0,07 | Abce1                | ATP-binding cassette sub-family E member 1                                                                                          |
| 0,30 | -0,05 | Cul4b;Cul4a          | Cullin-4B;Cullin-4A                                                                                                                 |
| 0,30 | -0,10 | Ivd                  | Isovaleryl-CoA dehydrogenase, mitochondrial                                                                                         |
| 0,30 | 0,04  | Glod4                | Glyoxalase domain-containing protein 4                                                                                              |
| 0,30 | 0,07  | Madd                 | MAP kinase-activating death domain protein                                                                                          |
| 0,30 | -0,06 | Smad5                | SMAD/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 5                                      |
| 0,30 | 0,07  | Usp48                | Ubiquitin carboxyl-terminal hydrolase 48                                                                                            |
| 0,30 | 0,14  | Ifi204;Mndal         | Myeloid cell nuclear differentiation antigen-like protein                                                                           |
| 0,30 | 0,12  | Erp44                | Endoplasmic reticulum resident protein 44                                                                                           |
| 0,30 | 0,08  | Gpko                 | G patch domain and KOW motifs-containing protein                                                                                    |
| 0,30 | -0,11 | Calm1;Calml3         | Calmodulin;Calmodulin-like protein 3                                                                                                |
| 0,30 | -0,17 | Nedd9                | Enhancer of filamentation 1                                                                                                         |
| 0,30 | -0,07 | Hsp90ab1             | Heat shock protein HSP 90-beta                                                                                                      |
| 0,30 | -0,24 | Trp53;Tp53           | Cellular tumor antigen p53                                                                                                          |
| 0,30 | -0,09 | Bcl7b                | B-cell CLL/lymphoma 7 protein family member B                                                                                       |
| 0,29 | -0,21 | Mbd3                 | Methyl-CpG-binding domain protein 3                                                                                                 |
| 0,29 | 0,07  | Ppih                 | Peptidyl-prolyl cis-trans isomerase;Peptidyl-prolyl cis-trans isomerase H                                                           |
| 0,29 | -0,07 | Acp1                 | Low molecular weight phosphotyrosine protein phosphatase                                                                            |
| 0,29 | 0,08  | Pmf1                 | Polyamine-modulated factor 1                                                                                                        |
| 0,29 | -0,03 | Top2a                | DNA topoisomerase 2-alpha                                                                                                           |
| 0,29 | -0,09 | Matr3                | Matrin-3                                                                                                                            |
| 0,29 | -0,08 | Rps15                | 40S ribosomal protein S15                                                                                                           |
| 0,29 | -0,15 | Rpl35a               | 60S ribosomal protein L35a                                                                                                          |
| 0,29 | -0,13 | Imp4                 | U3 small nucleolar ribonucleoprotein protein IMP4                                                                                   |
| 0,29 | 0,07  | Lman1                | Protein ERGIC-53                                                                                                                    |
| 0,29 | 0,04  | Cdca2                | Cell division cycle-associated protein 2                                                                                            |
| 0,29 | -0,05 | Ythdf1;Ythdf2;Ythdf3 | YTH domain-containing family protein 1;YTH domain-containing family protein 2;YTH domain-containing family protein 3                |
| 0,29 | 0,09  | Atp2a3               | Calcium-transporting ATPase;Sarcoplasmic/endoplasmic reticulum calcium ATPase 3                                                     |
| 0,29 | -0,04 | Ppp4r1               | Serine/threonine-protein phosphatase 4 regulatory subunit 1                                                                         |
| 0,29 | -0,07 | Ptpn2                | Tyrosine-protein phosphatase non-receptor type;Tyrosine-protein phosphatase non-receptor type 2                                     |
| 0,29 | -0,09 | Calr                 | Calreticulin                                                                                                                        |
| 0,29 | -0,11 | Cpsf3l               | Integrator complex subunit 11                                                                                                       |
| 0,29 | 0,11  | Copz1                | Coatomer subunit zeta-1                                                                                                             |
| 0,29 | -0,07 | Atp5o                | ATP synthase subunit O, mitochondrial                                                                                               |
| 0,29 | 0,09  | Ecd                  | Protein SGT1 homolog                                                                                                                |
| 0,29 | 0,09  | Nsmce1               | Non-structural maintenance of chromosomes element 1 homolog                                                                         |
| 0,29 | 0,06  | Pdha                 | Pyruvate dehydrogenase E1 component subunit beta, mitochondrial                                                                     |
| 0,29 | -0,07 | Pkm                  | Pyruvate kinase PKM                                                                                                                 |
| 0,29 | -0,08 | Pno1                 | RNA-binding protein PNO1                                                                                                            |
| 0,29 | 0,16  | Gm10269;Rpl35        | 60S ribosomal protein L35                                                                                                           |
| 0,28 | -0,05 | Actg1;Actb           | Actin, cytoplasmic 2;Actin, cytoplasmic 2, N-terminally processed;Actin, cytoplasmic 1;Actin, cytoplasmic 1, N-terminally processed |
| 0,28 | 0,07  | Txlna                | Alpha-taxilin                                                                                                                       |

|      |       |                              |                                                                                                                                                                                                                                                             |
|------|-------|------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0,28 | -0,04 | Sep.07                       | Septin-7                                                                                                                                                                                                                                                    |
| 0,28 | -0,08 | Hspe1                        | 10 kDa heat shock protein, mitochondrial                                                                                                                                                                                                                    |
| 0,28 | -0,08 | Gm20604                      | Uncharacterized protein C14orf142 homolog                                                                                                                                                                                                                   |
| 0,28 | 0,07  | Plec                         | Plectin                                                                                                                                                                                                                                                     |
| 0,28 | -0,12 | Ezr                          | Ezrin                                                                                                                                                                                                                                                       |
| 0,28 | -0,11 | Srfbp1                       | Serum response factor-binding protein 1                                                                                                                                                                                                                     |
| 0,28 | -0,13 | Ppig                         | Peptidyl-prolyl cis-trans isomerase G                                                                                                                                                                                                                       |
| 0,28 | -0,07 | Glmn                         | Glomulin                                                                                                                                                                                                                                                    |
| 0,28 | 0,13  | H2afv;H2afz                  | Histone H2A;Histone H2A.V;Histone H2A.Z                                                                                                                                                                                                                     |
| 0,28 | 0,07  | Rab6a;Rab6b;Rab39;Ra<br>b39a | Ras-related protein Rab-6A;Ras-related protein Rab-6B;Ras-related protein Rab-39A                                                                                                                                                                           |
| 0,28 | 0,09  | Parp1                        | Poly [ADP-ribose] polymerase 1                                                                                                                                                                                                                              |
| 0,28 | 0,08  | Gsto1                        | Glutathione S-transferase omega-1                                                                                                                                                                                                                           |
| 0,28 | -0,07 | Nup93                        | Nuclear pore complex protein Nup93                                                                                                                                                                                                                          |
| 0,28 | 0,07  | Prss12                       | Neurotrypsin                                                                                                                                                                                                                                                |
| 0,28 | -0,08 | Bag2                         | BAG family molecular chaperone regulator 2                                                                                                                                                                                                                  |
| 0,28 | 0,26  | Bak1                         | Bcl-2 homologous antagonist/killer                                                                                                                                                                                                                          |
| 0,28 | 0,03  | Mki67                        |                                                                                                                                                                                                                                                             |
| 0,28 | -0,09 | Bsg                          | Basigin                                                                                                                                                                                                                                                     |
| 0,28 | 0,10  | Atrn                         | Attractin                                                                                                                                                                                                                                                   |
| 0,28 | -0,03 | Wdr37                        | WD repeat-containing protein 37                                                                                                                                                                                                                             |
| 0,28 | 0,07  | Ssr1                         | Translocon-associated protein subunit alpha                                                                                                                                                                                                                 |
| 0,28 | 0,13  | Nploc4                       | Nuclear protein localization protein 4 homolog                                                                                                                                                                                                              |
| 0,28 | -0,08 | Abl1                         | Non-specific protein-tyrosine kinase;Tyrosine-protein kinase ABL1                                                                                                                                                                                           |
| 0,28 | -0,08 | Spag7                        | Sperm-associated antigen 7                                                                                                                                                                                                                                  |
| 0,28 | -0,06 | Ttc4                         | Tetratricopeptide repeat protein 4                                                                                                                                                                                                                          |
| 0,28 | -0,12 | Ap2s1                        | AP-2 complex subunit sigma                                                                                                                                                                                                                                  |
| 0,28 | -0,18 | Pold1                        | DNA polymerase delta catalytic subunit;DNA polymerase                                                                                                                                                                                                       |
| 0,28 | -0,05 | Uqcrc                        | Cytochrome b-c1 complex subunit 8                                                                                                                                                                                                                           |
| 0,28 | -0,18 | Mrpl43                       | 39S ribosomal protein L43, mitochondrial                                                                                                                                                                                                                    |
| 0,27 | -0,06 | Arnt                         | Aryl hydrocarbon receptor nuclear translocator                                                                                                                                                                                                              |
| 0,27 | -0,09 | Snw1                         | SNW domain-containing protein 1                                                                                                                                                                                                                             |
| 0,27 | -0,10 | Myef2                        | Myelin expression factor 2                                                                                                                                                                                                                                  |
| 0,27 | 0,14  | Sub1                         | Activated RNA polymerase II transcriptional coactivator p15                                                                                                                                                                                                 |
| 0,27 | 0,05  | Rpn1                         | Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 1                                                                                                                                                                                    |
| 0,27 | 0,14  | Ppp3cb;Ppp3cc;Ppp3ca         | Serine/threonine-protein phosphatase;Serine/threonine-protein phosphatase 2B catalytic subunit beta isoform;Serine/threonine-protein phosphatase 2B catalytic subunit alpha isoform;Serine/threonine-protein phosphatase 2B catalytic subunit gamma isoform |
| 0,27 | -0,08 | Dgkz                         | Diacylglycerol kinase;Diacylglycerol kinase zeta                                                                                                                                                                                                            |
| 0,27 | -0,16 | Dgcr14                       | Protein DGCR14                                                                                                                                                                                                                                              |
| 0,27 | -0,09 | Brd8                         | Bromodomain-containing protein 8                                                                                                                                                                                                                            |
| 0,27 | 0,10  | Trim11                       | E3 ubiquitin-protein ligase TRIM11                                                                                                                                                                                                                          |
| 0,27 | 0,07  | Atp6v1b2                     | V-type proton ATPase subunit B, brain isoform                                                                                                                                                                                                               |
| 0,27 | 0,08  | Rsrc2                        | Arginine/serine-rich coiled-coil protein 2                                                                                                                                                                                                                  |
| 0,27 | 0,06  | Tgfb1                        | Transforming growth factor beta-1;Latency-associated peptide                                                                                                                                                                                                |
| 0,27 | 0,10  | Akap10                       | A-kinase anchor protein 10, mitochondrial                                                                                                                                                                                                                   |
| 0,27 | -0,06 | H2afy                        | Core histone macro-H2A.1                                                                                                                                                                                                                                    |
| 0,27 | -0,06 | Vdac1                        | Voltage-dependent anion-selective channel protein 1                                                                                                                                                                                                         |
| 0,27 | 0,08  |                              | Uncharacterized protein CXorf23 homolog                                                                                                                                                                                                                     |
| 0,27 | 0,08  | Srp68                        | Signal recognition particle subunit SRP68                                                                                                                                                                                                                   |
| 0,27 | -0,17 | Psmb4                        | Proteasome subunit beta type-4                                                                                                                                                                                                                              |
| 0,27 | 0,07  | Tsr1                         | Pre-rRNA-processing protein TSR1 homolog                                                                                                                                                                                                                    |
| 0,27 | -0,09 | Psmb2                        | Proteasome subunit beta type-2                                                                                                                                                                                                                              |

|      |       |              |                                                                                                                                         |
|------|-------|--------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| 0,27 | -0,07 | Ppia;Gm5160  | Peptidyl-prolyl cis-trans isomerase;Peptidyl-prolyl cis-trans isomerase A;Peptidyl-prolyl cis-trans isomerase A, N-terminally processed |
| 0,27 | -0,11 | Atp2a2       | Sarcoplasmic/endoplasmic reticulum calcium ATPase 2                                                                                     |
| 0,27 | -0,06 | Erh          | Enhancer of rudimentary homolog                                                                                                         |
| 0,27 | -0,05 | Uimc1        | BRCA1-A complex subunit RAP80                                                                                                           |
| 0,27 | -0,13 | Il1r2        | Interleukin-1 receptor type 2;Interleukin-1 receptor type 2, membrane form;Interleukin-1 receptor type 2, soluble form                  |
| 0,27 | -0,08 | Csk          | Tyrosine-protein kinase CSK                                                                                                             |
| 0,27 | -0,08 | Pclo         | Protein piccolo                                                                                                                         |
| 0,27 | 0,08  | Sh2d3c       | SH2 domain-containing protein 3C                                                                                                        |
| 0,27 | -0,03 | Vars         | Valine--tRNA ligase                                                                                                                     |
| 0,27 | -0,25 | Cpsf6        | Cleavage and polyadenylation specificity factor subunit 6                                                                               |
| 0,27 | -0,05 | Arhgap18     | Rho GTPase-activating protein 18                                                                                                        |
| 0,26 | 0,08  | Fbxo38       | F-box only protein 38                                                                                                                   |
| 0,26 | -0,11 | Polr2g       | DNA-directed RNA polymerase II subunit RPB7                                                                                             |
| 0,26 | -0,23 | Cdkn2a       | Tumor suppressor ARF                                                                                                                    |
| 0,26 | 0,05  | Tln1         | Talin-1                                                                                                                                 |
| 0,26 | 0,13  | Fcgr2;Fcgr2b | Low affinity immunoglobulin gamma Fc region receptor II                                                                                 |
| 0,26 | 0,05  | Ovca2        | Ovarian cancer-associated gene 2 protein homolog                                                                                        |
| 0,26 | 0,21  | Cdkn2aip     | CDKN2A-interacting protein                                                                                                              |
| 0,26 | 0,19  | Hmgcs1       | Hydroxymethylglutaryl-CoA synthase, cytoplasmic                                                                                         |
| 0,26 | -0,07 | Ube2v2       | Ubiquitin-conjugating enzyme E2 variant 2                                                                                               |
| 0,26 | -0,14 | Dohh         | Deoxyhypusine hydroxylase                                                                                                               |
| 0,26 | -0,04 | Rbm5         | RNA-binding protein 5                                                                                                                   |
| 0,26 | 0,06  | Anxa1        | Annexin;Annexin A1                                                                                                                      |
| 0,26 | -0,06 | Rpl19        | Ribosomal protein L19;60S ribosomal protein L19                                                                                         |
| 0,26 | -0,34 | Ahnak        |                                                                                                                                         |
| 0,26 | 0,10  | Anks1;Anks1a | Ankyrin repeat and SAM domain-containing protein 1A                                                                                     |
| 0,26 | 0,06  | Kdm3b        |                                                                                                                                         |
| 0,26 | 0,24  | Ptgr1        | Prostaglandin reductase 1                                                                                                               |
| 0,26 | 0,06  | Ccnh         | Cyclin-H                                                                                                                                |
| 0,26 | 0,06  | Ddi2         | Protein DDI1 homolog 2                                                                                                                  |
| 0,26 | -0,12 | Trmt10a      | tRNA methyltransferase 10 homolog A                                                                                                     |
| 0,26 | -0,05 | Acad9        | Acyl-CoA dehydrogenase family member 9, mitochondrial                                                                                   |
| 0,26 | -0,08 | Marcks1      | MARCKS-related protein                                                                                                                  |
| 0,25 | 0,06  | Tceb2        | Transcription elongation factor B polypeptide 2                                                                                         |
| 0,25 | -0,12 | Acox3        | Acyl-coenzyme A oxidase;Peroxisomal acyl-coenzyme A oxidase 3                                                                           |
| 0,25 | -0,05 | Bcl2l1       | Bcl-2-like protein 1                                                                                                                    |
| 0,25 | -0,06 | Lamp1        | Lysosome-associated membrane glycoprotein 1                                                                                             |
| 0,25 | 0,06  | Clasp1       | CLIP-associating protein 1                                                                                                              |
| 0,25 | 0,14  | Btk          | Tyrosine-protein kinase BTK                                                                                                             |
| 0,25 | 0,05  | Capza1       | F-actin-capping protein subunit alpha-1                                                                                                 |
| 0,25 | -0,15 | Chtop        | Chromatin target of PRMT1 protein                                                                                                       |
| 0,25 | -0,13 | Lyar         | Cell growth-regulating nucleolar protein                                                                                                |
| 0,25 | -0,15 | Alpl         | Alkaline phosphatase, tissue-nonspecific isozyme;Alkaline phosphatase                                                                   |
| 0,25 | 0,07  | Stub1        | STIP1 homology and U box-containing protein 1                                                                                           |
| 0,25 | -0,14 | Cdk2         | Cyclin-dependent kinase 2                                                                                                               |
| 0,25 | -0,13 | Igpb1;Igbp1b | Immunoglobulin-binding protein 1;Immunoglobulin-binding protein 1b                                                                      |
| 0,25 | 0,11  | Ddx23        |                                                                                                                                         |
| 0,25 | 0,03  | Xiap         | E3 ubiquitin-protein ligase XIAP                                                                                                        |
| 0,25 | -0,09 | Ctdp1        | RNA polymerase II subunit A C-terminal domain phosphatase                                                                               |
| 0,25 | -0,11 | Nup50        | Nuclear pore complex protein Nup50                                                                                                      |
| 0,25 | 0,04  | Cpsf2        | Cleavage and polyadenylation specificity factor subunit 2                                                                               |

|      |       |                        |                                                                                                                           |
|------|-------|------------------------|---------------------------------------------------------------------------------------------------------------------------|
| 0,25 | 0,10  | Tars                   | Threonine--tRNA ligase, cytoplasmic                                                                                       |
| 0,25 | 0,07  | Ncoa5                  | Nuclear receptor coactivator 5                                                                                            |
| 0,24 | 0,08  | Stt3b                  | Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit STT3B                                              |
| 0,24 | 0,06  | Fam107b                | Protein FAM107B                                                                                                           |
| 0,24 | 0,14  | Stim1                  | Stromal interaction molecule 1                                                                                            |
| 0,24 | -0,10 | Ube2i                  | SUMO-conjugating enzyme UBC9                                                                                              |
| 0,24 | 0,05  | Pdcd11                 | Protein RRP5 homolog                                                                                                      |
| 0,24 | 0,08  | Hsp90b1                | Endoplasmic                                                                                                               |
| 0,24 | -0,11 | Wnk1;Wnk4;Wnk3         | Serine/threonine-protein kinase WNK1;Serine/threonine-protein kinase WNK4;Serine/threonine-protein kinase WNK3            |
| 0,24 | -0,08 | Eif3j1;Eif3j2          | Eukaryotic translation initiation factor 3 subunit J-A;Eukaryotic translation initiation factor 3 subunit J-B             |
| 0,24 | 0,06  | Frg1                   | Protein FRG1                                                                                                              |
| 0,24 | 0,07  | Exoc8                  | Exocyst complex component 8                                                                                               |
| 0,24 | -0,28 | Dcun1d5                | DCN1-like protein 5                                                                                                       |
| 0,24 | 0,04  | Rpa1                   | Replication protein A 70 kDa DNA-binding subunit;Replication protein A 70 kDa DNA-binding subunit, N-terminally processed |
| 0,24 | -0,07 | Tmx4                   | Thioredoxin-related transmembrane protein 4                                                                               |
| 0,24 | 0,15  | Ufd1l                  | Ubiquitin fusion degradation protein 1 homolog                                                                            |
| 0,24 | 0,06  | Stk26                  | Serine/threonine-protein kinase 26                                                                                        |
| 0,24 | -0,05 | Cdc40                  | Pre-mRNA-processing factor 17                                                                                             |
| 0,24 | -0,05 | Gar1                   | H/ACA ribonucleoprotein complex subunit 1                                                                                 |
| 0,24 | 0,05  | Nsun2                  | tRNA (cytosine(34)-C(5))-methyltransferase                                                                                |
| 0,24 | -0,09 | Tmed10                 | Transmembrane emp24 domain-containing protein 10                                                                          |
| 0,24 | 0,11  | Mogs                   | Mannosyl-oligosaccharide glucosidase                                                                                      |
| 0,24 | -0,15 | Hnrnpa0                | Heterogeneous nuclear ribonucleoprotein A0                                                                                |
| 0,24 | 0,06  | Pdpk1                  | 3-phosphoinositide-dependent protein kinase 1                                                                             |
| 0,24 | 0,08  | Iars                   | Isoleucine--tRNA ligase, cytoplasmic                                                                                      |
| 0,23 | -0,08 | Hsd17b12               | Very-long-chain 3-oxoacyl-CoA reductase                                                                                   |
| 0,23 | -0,05 | Rpl8                   | 60S ribosomal protein L8                                                                                                  |
| 0,23 | 0,12  | Prkaa1                 | 5-AMP-activated protein kinase catalytic subunit alpha-1                                                                  |
| 0,23 | 0,06  | Dennd4c                | DENN domain-containing protein 4C                                                                                         |
| 0,23 | 0,07  | Cnn3                   | Calponin-3                                                                                                                |
| 0,23 | -0,16 | Acp6                   | Lysophosphatidic acid phosphatase type 6                                                                                  |
| 0,23 | -0,10 | Psma5;Gm8394           | Proteasome subunit alpha type;Proteasome subunit alpha type-5                                                             |
| 0,23 | -0,52 | Ndrp3                  | Protein NDRG3                                                                                                             |
| 0,23 | -0,05 | Pex14                  | Peroxisomal membrane protein PEX14                                                                                        |
| 0,23 | -0,11 | Rab1b;Rab1;Rab1A;Rab8b | Ras-related protein Rab-1B;Ras-related protein Rab-1A;Ras-related protein Rab-8B                                          |
| 0,23 | 0,14  | Zfp428;Znf428          | Zinc finger protein 428                                                                                                   |
| 0,23 | 0,18  | Rrp12                  | RRP12-like protein                                                                                                        |
| 0,23 | -0,04 | Supt6h                 | Transcription elongation factor SPT6                                                                                      |
| 0,23 | -0,13 | Cad                    | CAD protein;Glutamine-dependent carbamoyl-phosphate synthase;Aspartate carbamoyltransferase;Dihydroorotase                |
| 0,23 | -0,06 | Gdi2                   | Rab GDP dissociation inhibitor beta                                                                                       |
| 0,23 | -0,07 | Immt                   | MICOS complex subunit Mic60                                                                                               |
| 0,23 | 0,09  | Tubb2b;Tubb2a          | Tubulin beta-2B chain;Tubulin beta-2A chain                                                                               |
| 0,23 | -0,10 | Rexo4                  | RNA exonuclease 4                                                                                                         |
| 0,23 | -0,09 | Txn                    | Thioredoxin                                                                                                               |
| 0,23 | 0,27  | Cdh17                  | Cadherin-17                                                                                                               |
| 0,23 | -0,12 | Prdx4                  | Peroxisome oxidoreductase-4                                                                                               |
| 0,23 | 0,08  | Tmed7                  |                                                                                                                           |
| 0,23 | 0,11  | Med4                   | Mediator of RNA polymerase II transcription subunit 4                                                                     |
| 0,23 | -0,03 | Cnbp                   | Cellular nucleic acid-binding protein                                                                                     |

|      |       |               |                                                                                                                                                 |
|------|-------|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| 0,23 | -0,04 | Ppp2r1a       | Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A alpha isoform                                                               |
| 0,23 | 0,06  | Akap13        |                                                                                                                                                 |
| 0,23 | -0,04 | Dhfr          | Dihydrofolate reductase                                                                                                                         |
| 0,23 | -0,07 | Hist1h1c      | Histone H1.2                                                                                                                                    |
| 0,23 | -0,05 | Fkbp4         | Peptidyl-prolyl cis-trans isomerase FKBP4;Peptidyl-prolyl cis-trans isomerase FKBP4, N-terminally processed;Peptidyl-prolyl cis-trans isomerase |
| 0,23 | 0,05  | Calu          | Calumenin                                                                                                                                       |
| 0,23 | -0,07 | Puf60         | Poly(U)-binding-splicing factor PUF60                                                                                                           |
| 0,22 | 0,15  | Gimap9        |                                                                                                                                                 |
| 0,22 | 0,17  | Zc3h11a       | Zinc finger CCCH domain-containing protein 11A                                                                                                  |
| 0,22 | -0,11 | Psmc3         | 26S protease regulatory subunit 6A                                                                                                              |
| 0,22 | 0,11  | Ipo9          | Importin-9                                                                                                                                      |
| 0,22 | 0,07  | Tomm34        | Mitochondrial import receptor subunit TOM34                                                                                                     |
| 0,22 | 0,07  | Rnps1         | RNA-binding protein with serine-rich domain 1                                                                                                   |
| 0,22 | -0,05 | Cct3          | T-complex protein 1 subunit gamma                                                                                                               |
| 0,22 | -0,11 | Arpc2         | Actin-related protein 2/3 complex subunit 2                                                                                                     |
| 0,22 | -0,02 | Pfdn4         | Prefoldin subunit 4                                                                                                                             |
| 0,22 | -0,04 | Setdb1        | Histone-lysine N-methyltransferase SETDB1                                                                                                       |
| 0,22 | -0,03 | Mrpl12        | 39S ribosomal protein L12, mitochondrial                                                                                                        |
| 0,22 | 0,07  | Anxa6         | Annexin;Annexin A6                                                                                                                              |
| 0,22 | -0,08 | Ddx5          | Probable ATP-dependent RNA helicase DDX5                                                                                                        |
| 0,22 | 0,13  | Eftud1        | Elongation factor Tu GTP-binding domain-containing protein 1                                                                                    |
| 0,22 | -0,09 | Naa25         | N-alpha-acetyltransferase 25, NatB auxiliary subunit                                                                                            |
| 0,22 | 0,05  | Eif4g2        | Eukaryotic translation initiation factor 4 gamma 2                                                                                              |
| 0,22 | -0,04 | Pgd           | 6-phosphogluconate dehydrogenase, decarboxylating                                                                                               |
| 0,22 | 0,14  | Kri1          | Protein KRI1 homolog                                                                                                                            |
| 0,22 | 0,07  | Cops8         | COP9 signalosome complex subunit 8                                                                                                              |
| 0,22 | 0,14  | Wbscr22       | Probable 18S rRNA (guanine-N(7))-methyltransferase                                                                                              |
| 0,22 | 0,05  | Rnf20         | E3 ubiquitin-protein ligase BRE1A                                                                                                               |
| 0,22 | 0,05  | Naa35         | N-alpha-acetyltransferase 35, NatC auxiliary subunit                                                                                            |
| 0,22 | -0,11 | Bcl7a         | B-cell CLL/lymphoma 7 protein family member A                                                                                                   |
| 0,22 | -0,05 |               |                                                                                                                                                 |
| 0,22 | -0,03 | Eif2s1        | Eukaryotic translation initiation factor 2 subunit 1                                                                                            |
| 0,22 | 0,19  | Zfp706;Znf706 | Zinc finger protein 706                                                                                                                         |
| 0,22 | 0,10  | Sh3bp1        | SH3 domain-binding protein 1                                                                                                                    |
| 0,22 | -0,05 | Usp14         | Ubiquitin carboxyl-terminal hydrolase;Ubiquitin carboxyl-terminal hydrolase 14                                                                  |
| 0,22 | -0,06 | Plcg2         | 1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-2                                                                               |
| 0,22 | -0,12 | Rad21         | Double-strand-break repair protein rad21 homolog                                                                                                |
| 0,22 | 0,06  | Dctn2         | Dynactin subunit 2                                                                                                                              |
| 0,22 | -0,12 | Psmd4         | 26S proteasome non-ATPase regulatory subunit 4                                                                                                  |
| 0,22 | 0,10  | Itpr1         | Inositol 1,4,5-trisphosphate receptor type 1                                                                                                    |
| 0,22 | 0,25  | Sptbn1        | Spectrin beta chain, non-erythrocytic 1                                                                                                         |
| 0,21 | 0,14  | Pde2a         | cGMP-dependent 3,5-cyclic phosphodiesterase                                                                                                     |
| 0,21 | -0,10 | Arl6ip4       | ADP-ribosylation factor-like protein 6-interacting protein 4                                                                                    |
| 0,21 | 0,19  | Actr5         | Actin-related protein 5                                                                                                                         |
| 0,21 | -0,08 | Etfa          | Electron transfer flavoprotein subunit alpha, mitochondrial                                                                                     |
| 0,21 | -0,12 | Rbm8a         | RNA-binding protein 8A                                                                                                                          |
| 0,21 | -0,13 | Hist1h1b      | Histone H1.5                                                                                                                                    |
| 0,21 | 0,05  | Hmg20a        | High mobility group protein 20A                                                                                                                 |
| 0,21 | 0,03  | Ywhab         | 14-3-3 protein beta/alpha;14-3-3 protein beta/alpha, N-terminally processed                                                                     |
| 0,21 | -0,06 | Cct6a         | T-complex protein 1 subunit zeta                                                                                                                |
| 0,21 | -0,14 | Chp1          | Calcineurin B homologous protein 1                                                                                                              |

|      |       |                      |                                                                                          |
|------|-------|----------------------|------------------------------------------------------------------------------------------|
| 0,21 | -0,06 | Diap1;Diaph1         | Protein diaphanous homolog 1                                                             |
| 0,21 | -0,07 | Tcp1                 | T-complex protein 1 subunit alpha                                                        |
| 0,21 | -0,03 | Kpnb1                | Importin subunit beta-1                                                                  |
| 0,21 | 0,03  | Anxa11               | Annexin;Annexin A11                                                                      |
| 0,21 | -0,06 | Ganab                | Neutral alpha-glucosidase AB                                                             |
| 0,21 | -0,10 | Eef1e1               | Eukaryotic translation elongation factor 1 epsilon-1                                     |
| 0,21 | 0,04  | Rbm10                | RNA-binding protein 10                                                                   |
| 0,21 | -0,02 | Eif3h                | Eukaryotic translation initiation factor 3 subunit H                                     |
| 0,21 | 0,03  | Lmnb2                | Lamin-B2                                                                                 |
| 0,21 | -0,10 | Pdcd5                | Programmed cell death protein 5                                                          |
| 0,21 | -0,05 | Nol11                | Nucleolar protein 11                                                                     |
| 0,20 | -0,12 | 1700009N14Rik;Ran    | GTP-binding nuclear protein Ran                                                          |
| 0,20 | -0,05 | Usp15                | Ubiquitin carboxyl-terminal hydrolase 15                                                 |
| 0,20 | -0,18 | Hmgn3                | High mobility group nucleosome-binding domain-containing protein 3                       |
| 0,20 | -0,04 | Dhx38                |                                                                                          |
| 0,20 | -0,09 | Espl1                | Separin                                                                                  |
| 0,20 | 0,06  | Ipo8                 | Importin-8                                                                               |
| 0,20 | 0,07  | Hspa5                | 78 kDa glucose-regulated protein                                                         |
| 0,20 | 0,07  | Eprs                 | Bifunctional glutamate--proline--tRNA ligase;Glutamate--tRNA ligase;Proline--tRNA ligase |
| 0,20 | 0,03  | Prdx2                | Peroxiredoxin-2                                                                          |
| 0,20 | -0,07 | Pola2                | DNA polymerase alpha subunit B                                                           |
| 0,20 | -0,07 | Nudcd2               | NudC domain-containing protein 2                                                         |
| 0,20 | 0,07  | Rab7;Rab7a           | Ras-related protein Rab-7a                                                               |
| 0,20 | 0,03  | U2surp               | U2 snRNP-associated SURP motif-containing protein                                        |
| 0,20 | -0,06 | Lasp1                | LIM and SH3 domain protein 1                                                             |
| 0,20 | -0,05 | Crnk1                | Crooked neck-like protein 1                                                              |
| 0,20 | -0,12 | Dph5                 | Diphthine synthase                                                                       |
| 0,20 | 0,06  | Tbcb                 | Tubulin-folding cofactor B                                                               |
| 0,20 | 0,07  | Napg                 | Gamma-soluble NSF attachment protein                                                     |
| 0,20 | 0,05  | Golgb1               |                                                                                          |
| 0,20 | 0,08  | Irgc1                |                                                                                          |
| 0,20 | -0,08 | Aaas                 | Aladin                                                                                   |
| 0,20 | 0,10  | Rasgrp2              | RAS guanyl-releasing protein 2                                                           |
| 0,20 | -0,08 | Map4                 | Microtubule-associated protein 4                                                         |
| 0,20 | 0,04  | Psma1                | Proteasome subunit alpha type;Proteasome subunit alpha type-1                            |
| 0,19 | -0,11 | Ptprc                | Receptor-type tyrosine-protein phosphatase C                                             |
| 0,19 | 0,09  | Gnb2                 | Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-2                         |
| 0,19 | -0,08 | Cbwd1                | COBW domain-containing protein 1                                                         |
| 0,19 | -0,11 | Grpel1               | GrpE protein homolog 1, mitochondrial                                                    |
| 0,19 | -0,04 | Mcm5                 | DNA helicase;DNA replication licensing factor MCM5                                       |
| 0,19 | -0,03 | Lbr                  | Lamin-B receptor                                                                         |
| 0,19 | -0,11 | mCG_120563;Hmga1     | High mobility group protein HMG-I/HMG-Y                                                  |
| 0,19 | 0,15  | Pusl1                | tRNA pseudouridine synthase-like 1                                                       |
| 0,19 | 0,04  | Nucb1                | Nucleobindin-1                                                                           |
| 0,19 | 0,05  | Rasal3               | RAS protein activator like-3                                                             |
| 0,19 | -0,04 | Tom70a               | Mitochondrial import receptor subunit TOM70                                              |
| 0,19 | 0,02  | Hdlbp                | Vigilin                                                                                  |
| 0,19 | 0,06  | Man1a;Man1a1         | alpha-1,2-Mannosidase;Mannosyl-oligosaccharide 1,2-alpha-mannosidase IA                  |
| 0,19 | -0,03 | Pgm3                 | Phosphoacetylglucosamine mutase                                                          |
| 0,19 | -0,03 | Ccdc132              | Coiled-coil domain-containing protein 132                                                |
| 0,19 | 0,07  | Papola;Papolg;Papalb | Poly(A) polymerase alpha;Poly(A) polymerase beta;Poly(A) polymerase gamma                |
| 0,19 | -0,07 | Sbds                 | Ribosome maturation protein SBDS                                                         |

|      |       |                 |                                                                                                                                                                       |
|------|-------|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0,19 | 0,08  | Atad3;Atad3a    | ATPase family AAA domain-containing protein 3                                                                                                                         |
| 0,19 | 0,02  | Ikbkap          | Elongator complex protein 1                                                                                                                                           |
| 0,19 | -0,07 | Otub1           | Ubiquitin thioesterase OTUB1                                                                                                                                          |
| 0,19 | 0,05  | Eif2b2          | Translation initiation factor eIF-2B subunit beta                                                                                                                     |
| 0,19 | 0,07  | Rbm17           | Splicing factor 45                                                                                                                                                    |
| 0,19 | -0,04 | Lrprrc          | Leucine-rich PPR motif-containing protein, mitochondrial                                                                                                              |
| 0,19 | -0,04 | Manf            | Mesencephalic astrocyte-derived neurotrophic factor                                                                                                                   |
| 0,19 | 0,10  | Arhgap12        | Rho GTPase-activating protein 12                                                                                                                                      |
| 0,19 | -0,11 | Rprd1b          | Regulation of nuclear pre-mRNA domain-containing protein 1B                                                                                                           |
| 0,19 | -0,19 | Rala            | Ras-related protein Ral-A                                                                                                                                             |
| 0,19 | -0,07 | Acin1           | Apoptotic chromatin condensation inducer in the nucleus                                                                                                               |
| 0,19 | 0,14  | Nop9            | Nucleolar protein 9                                                                                                                                                   |
| 0,19 | -0,06 | Fdps            | Farnesyl pyrophosphate synthase                                                                                                                                       |
| 0,19 | 0,22  | Pttg1ip         | Pituitary tumor-transforming gene 1 protein-interacting protein                                                                                                       |
| 0,18 | 0,05  | Wdr12           | Ribosome biogenesis protein WDR12                                                                                                                                     |
| 0,18 | -0,05 | Slc44a2         | Choline transporter-like protein 2                                                                                                                                    |
| 0,18 | -0,03 | Mtpap           | Poly(A) RNA polymerase, mitochondrial                                                                                                                                 |
| 0,18 | -0,11 | S100a13         | Protein S100-A13                                                                                                                                                      |
| 0,18 | -0,08 | Mlf2            | Myeloid leukemia factor 2                                                                                                                                             |
| 0,18 | -0,06 | Rpl26           | 60S ribosomal protein L26                                                                                                                                             |
| 0,18 | 0,05  | Ddost           | Dolichyl-diphosphooligosaccharide--protein glycosyltransferase 48 kDa subunit                                                                                         |
| 0,18 | 0,07  | Ankrd17         | Ankyrin repeat domain-containing protein 17                                                                                                                           |
| 0,18 | 0,08  | Metap2          | Methionine aminopeptidase 2                                                                                                                                           |
| 0,18 | -0,09 | Gls             | Glutaminase kidney isoform, mitochondrial                                                                                                                             |
| 0,18 | -0,17 | Khdrbs2;Khdrbs1 | KH domain-containing, RNA-binding, signal transduction-associated protein 2;KH domain-containing, RNA-binding, signal transduction-associated protein 1               |
| 0,18 | 0,02  | Eef2            | Elongation factor 2                                                                                                                                                   |
| 0,18 | 0,04  | Gatb            | Glutamyl-tRNA(Gln) amidotransferase subunit B, mitochondrial                                                                                                          |
| 0,18 | 0,05  | Usp39           | U4/U6.U5 tri-snRNP-associated protein 2                                                                                                                               |
| 0,18 | -0,05 | Copb1           | Coatomer subunit beta                                                                                                                                                 |
| 0,18 | 0,05  | Thoc5           | THO complex subunit 5 homolog                                                                                                                                         |
| 0,18 | 0,08  | 5031439G07Rik   |                                                                                                                                                                       |
| 0,18 | 0,05  | Amfr            | E3 ubiquitin-protein ligase AMFR                                                                                                                                      |
| 0,18 | 0,04  | Rars2           | Probable arginine--tRNA ligase, mitochondrial                                                                                                                         |
| 0,18 | 0,04  | Gm17430;Rpl24   | 60S ribosomal protein L24                                                                                                                                             |
| 0,18 | 0,08  | Ints3           | Integrator complex subunit 3                                                                                                                                          |
| 0,18 | 0,13  | N6amt2          | Protein-lysine N-methyltransferase N6amt2                                                                                                                             |
| 0,18 | 0,06  | Pfkfb           | ATP-dependent 6-phosphofructokinase;ATP-dependent 6-phosphofructokinase, platelet type                                                                                |
| 0,18 | -0,06 | Gm9755;Tufm     | Elongation factor Tu;Elongation factor Tu, mitochondrial                                                                                                              |
| 0,18 | 0,04  | Prkcd           | Protein kinase C delta type;Protein kinase C delta type;Protein kinase C delta type regulatory subunit;Protein kinase C delta type catalytic subunit;Protein kinase C |
| 0,18 | -0,08 | Pik3r6          | Phosphoinositide 3-kinase regulatory subunit 6                                                                                                                        |
| 0,18 | 0,10  | Zbed5;Chchd2    | Coiled-coil-helix-coiled-coil-helix domain-containing protein 2                                                                                                       |
| 0,18 | 0,04  | Exoc4           | Exocyst complex component 4                                                                                                                                           |
| 0,18 | -0,06 | Rprd2           | Regulation of nuclear pre-mRNA domain-containing protein 2                                                                                                            |
| 0,18 | 0,06  | Eftud2          | 116 kDa U5 small nuclear ribonucleoprotein component                                                                                                                  |
| 0,18 | 0,03  | Nrf1            | Nuclear respiratory factor 1                                                                                                                                          |
| 0,17 | 0,08  | Bin1            | Myc box-dependent-interacting protein 1                                                                                                                               |
| 0,17 | 0,06  | Tpx2            | Targeting protein for Xklp2                                                                                                                                           |
| 0,17 | -0,03 | Mta2            | Metastasis-associated protein MTA2                                                                                                                                    |
| 0,17 | -0,05 | Smim20          |                                                                                                                                                                       |
| 0,17 | -0,04 | Cct8            | T-complex protein 1 subunit theta                                                                                                                                     |
| 0,17 | -0,05 | Hook3           | Protein Hook homolog 3                                                                                                                                                |

|      |       |                     |                                                                                                                                   |
|------|-------|---------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| 0,17 | -0,05 | Nifk                | MKI67 FHA domain-interacting nucleolar phosphoprotein                                                                             |
| 0,17 | -0,11 | Mif                 | Macrophage migration inhibitory factor                                                                                            |
| 0,17 | -0,05 | Ttip11              | Tuftelin-interacting protein 11                                                                                                   |
| 0,17 | -0,04 | Clic1               | Chloride intracellular channel protein;Chloride intracellular channel protein 1                                                   |
| 0,17 | 0,08  | Actr2               | Actin-related protein 2                                                                                                           |
| 0,17 | -0,10 | Bri3bp              | BRI3-binding protein                                                                                                              |
| 0,17 | -0,11 | Hnmpr               |                                                                                                                                   |
| 0,17 | 0,04  | Pdxdp               | Pyridoxal phosphate phosphatase                                                                                                   |
| 0,17 | -0,05 | Bcap31              | B-cell receptor-associated protein 31                                                                                             |
| 0,17 | -0,06 | mKIAA0038;Eif4h     | Eukaryotic translation initiation factor 4H                                                                                       |
| 0,17 | -0,04 | Tkt                 | Transketolase                                                                                                                     |
| 0,17 | -0,07 | Bub1b               | Mitotic checkpoint serine/threonine-protein kinase BUB1 beta                                                                      |
| 0,17 | -0,03 | Nop56               | Nucleolar protein 56                                                                                                              |
| 0,17 | 0,10  | Anxa4               | Annexin;Annexin A4                                                                                                                |
| 0,17 | -0,11 | Jakmip1             | Janus kinase and microtubule-interacting protein 1                                                                                |
| 0,17 | 0,10  | Rpl15;Gm10020       | Ribosomal protein L15;60S ribosomal protein L15                                                                                   |
| 0,17 | 0,08  | Uck2                | Uridine-cytidine kinase;Uridine-cytidine kinase 2                                                                                 |
| 0,17 | -0,12 | Rps27               | 40S ribosomal protein S27                                                                                                         |
| 0,17 | 0,05  | Erg;Flt1            | Friend leukemia integration 1 transcription factor;Transcriptional regulator ERG                                                  |
| 0,17 | 0,04  | Cep250              | Centrosome-associated protein CEP250                                                                                              |
| 0,17 | -0,04 | Clpp                | ATP-dependent Clp protease proteolytic subunit, mitochondrial                                                                     |
| 0,17 | 0,06  | Trim56              | E3 ubiquitin-protein ligase TRIM56                                                                                                |
| 0,17 | -0,03 | Sap18;Gm10094       | Histone deacetylase complex subunit SAP18                                                                                         |
| 0,17 | -0,04 | Ik                  | Protein Red                                                                                                                       |
| 0,16 | -0,02 | Snap29              | Synaptosomal-associated protein 29                                                                                                |
| 0,16 | -0,09 | Tubb4b;Tubb6;Tubb4a | Tubulin beta-4B chain;Tubulin beta-4A chain;Tubulin beta-6 chain                                                                  |
| 0,16 | -0,08 | Ssbp1               | Single-stranded DNA-binding protein;Single-stranded DNA-binding protein, mitochondrial                                            |
| 0,16 | -0,05 | Fubp1               | Far upstream element-binding protein 1                                                                                            |
| 0,16 | 0,05  | Mesdc2              | LDLR chaperone MESD                                                                                                               |
| 0,16 | -0,03 | Ube2n               | Ubiquitin-conjugating enzyme E2 N                                                                                                 |
| 0,16 | -0,07 | Wdr61               | WD repeat-containing protein 61;WD repeat-containing protein 61, N-terminally processed                                           |
| 0,16 | -0,15 | Dtd1                | D-tyrosyl-tRNA(Tyr) deacylase 1                                                                                                   |
| 0,16 | 0,03  | P4hb                | Protein disulfide-isomerase                                                                                                       |
| 0,16 | -0,05 | Stk4                | Serine/threonine-protein kinase 4;Serine/threonine-protein kinase 4 37kDa subunit;Serine/threonine-protein kinase 4 18kDa subunit |
| 0,16 | -0,04 | Cand1               | Cullin-associated NEDD8-dissociated protein 1                                                                                     |
| 0,16 | 0,04  | Hprt1               | Hypoxanthine-guanine phosphoribosyltransferase                                                                                    |
| 0,16 | 0,04  | Phf3                |                                                                                                                                   |
| 0,16 | -0,05 | Slc39a7             | Zinc transporter SLC39A7                                                                                                          |
| 0,16 | 0,04  | Trip13              | Pachytene checkpoint protein 2 homolog                                                                                            |
| 0,16 | -0,04 | Psmc1               | 26S protease regulatory subunit 4                                                                                                 |
| 0,16 | -0,06 | Gigyf2              | PERQ amino acid-rich with GYF domain-containing protein 2                                                                         |
| 0,16 | 0,08  | Rpl34               | 60S ribosomal protein L34                                                                                                         |
| 0,16 | -0,11 | Hsph1               | Heat shock protein 105 kDa                                                                                                        |
| 0,16 | -0,02 | Rdx                 | Radixin                                                                                                                           |
| 0,16 | -0,09 | Ebf1;Ebf4;Ebf3;Ebf2 | Transcription factor COE4;Transcription factor COE3;Transcription factor COE2;Transcription factor COE1                           |
| 0,16 | -0,17 | Arhgap17            |                                                                                                                                   |
| 0,16 | 0,09  | Pdcd4               | Programmed cell death protein 4                                                                                                   |
| 0,16 | 0,06  | Clta                | Clathrin light chain A                                                                                                            |
| 0,16 | -0,04 | Fxr1;Fxr2           | Fragile X mental retardation syndrome-related protein 1                                                                           |
| 0,16 | 0,02  | Psmc2               | 26S protease regulatory subunit 7                                                                                                 |
| 0,16 | -0,10 | Dusp7               | Dual specificity protein phosphatase 7                                                                                            |

|      |       |                  |                                                                                                                                                                                             |
|------|-------|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0,16 | 0,04  | Pdk1             | [Pyruvate dehydrogenase (acetyl-transferring)] kinase isozyme 1, mitochondrial                                                                                                              |
| 0,16 | -0,07 | Pdap1            | 28 kDa heat- and acid-stable phosphoprotein                                                                                                                                                 |
| 0,16 | 0,04  | Lta4h            | Leukotriene A-4 hydrolase                                                                                                                                                                   |
| 0,16 | -0,06 | Srp9             | Signal recognition particle 9 kDa protein                                                                                                                                                   |
| 0,16 | -0,03 | Sgta             | Small glutamine-rich tetratricopeptide repeat-containing protein alpha                                                                                                                      |
| 0,16 | -0,02 | Wdr43            | WD repeat-containing protein 43                                                                                                                                                             |
| 0,16 | 0,08  | D17Wsu92e        | Uncharacterized protein C6orf106 homolog                                                                                                                                                    |
| 0,16 | -0,14 | Pfkl             | ATP-dependent 6-phosphofructokinase, liver type                                                                                                                                             |
| 0,16 | 0,04  | Pdia4            | Protein disulfide-isomerase A4                                                                                                                                                              |
| 0,15 | 0,07  | Mpi              | Mannose-6-phosphate isomerase                                                                                                                                                               |
| 0,15 | 0,07  | Dnmt3a           | DNA (cytosine-5)-methyltransferase 3A                                                                                                                                                       |
| 0,15 | 0,04  | Trap1            | Heat shock protein 75 kDa, mitochondrial                                                                                                                                                    |
| 0,15 | 0,07  | Rnf114           | E3 ubiquitin-protein ligase RNF114                                                                                                                                                          |
| 0,15 | -0,06 | Ube2c            | Ubiquitin-conjugating enzyme E2 C                                                                                                                                                           |
| 0,15 | 0,13  | Ash2l            | Set1/Ash2 histone methyltransferase complex subunit ASH2                                                                                                                                    |
| 0,15 | 0,05  | Rsb1             | Round spermatid basic protein 1                                                                                                                                                             |
| 0,15 | 0,10  | Enpep            | Glutamyl aminopeptidase                                                                                                                                                                     |
| 0,15 | -0,06 | Celf2            | CUGBP Elav-like family member 2                                                                                                                                                             |
| 0,15 | 0,02  | Tbc1d15          | TBC1 domain family member 15                                                                                                                                                                |
| 0,15 | 0,04  | Sec62            | Translocation protein SEC62                                                                                                                                                                 |
| 0,15 | -0,11 | Ccdc134          | Coiled-coil domain-containing protein 134                                                                                                                                                   |
| 0,15 | -0,06 | Adar             | Double-stranded RNA-specific adenosine deaminase                                                                                                                                            |
| 0,15 | -0,05 | Sirt1            | NAD-dependent protein deacetylase sirtuin-1;SirtT1 75 kDa fragment                                                                                                                          |
| 0,15 | -0,03 | Snrnp70          | U1 small nuclear ribonucleoprotein 70 kDa                                                                                                                                                   |
| 0,15 | 0,06  | Mdc1             | Mediator of DNA damage checkpoint protein 1                                                                                                                                                 |
| 0,15 | -0,09 | Tns3             | Tensin-3                                                                                                                                                                                    |
| 0,15 | -0,12 | Phf5a            | PHD finger-like domain-containing protein 5A                                                                                                                                                |
| 0,15 | 0,04  | Tacc3            | Transforming acidic coiled-coil-containing protein 3                                                                                                                                        |
| 0,15 | -0,03 | Npm3             | Nucleoplasmin-3                                                                                                                                                                             |
| 0,15 | -0,12 | Dnajc8           | DnaJ homolog subfamily C member 8                                                                                                                                                           |
| 0,15 | -0,06 | Nup88            | Nuclear pore complex protein Nup88                                                                                                                                                          |
| 0,15 | -0,05 | Tipr1            | TIP41-like protein                                                                                                                                                                          |
| 0,15 | -0,06 | Rps26            | 40S ribosomal protein S26                                                                                                                                                                   |
| 0,15 | -0,06 | Mfap1            | Microfibrillar-associated protein 1                                                                                                                                                         |
| 0,15 | -0,06 | Lck;Fyn;Src;Yes1 | Non-specific protein-tyrosine kinase;Proto-oncogene tyrosine-protein kinase LCK;Tyrosine-protein kinase Fyn;Tyrosine-protein kinase Yes;Neuronal proto-oncogene tyrosine-protein kinase Src |
| 0,15 | -0,05 | Cbx1             | Chromobox protein homolog 1                                                                                                                                                                 |
| 0,15 | -0,07 | Os9              | Protein OS-9                                                                                                                                                                                |
| 0,15 | -0,06 | Psmb3;Gm4950     | Proteasome subunit beta type;Proteasome subunit beta type-3                                                                                                                                 |
| 0,15 | -0,06 | Pycr2            | Pyrroline-5-carboxylate reductase;Pyrroline-5-carboxylate reductase 2                                                                                                                       |
| 0,15 | -0,09 | Atxn2            | Ataxin-2                                                                                                                                                                                    |
| 0,15 | -0,11 | Vps35            | Vacuolar protein sorting-associated protein 35                                                                                                                                              |
| 0,15 | -0,04 | Mtpn             | Myotrophin                                                                                                                                                                                  |
| 0,15 | 0,04  | Gmppb            | Mannose-1-phosphate guanylttransferase beta                                                                                                                                                 |
| 0,15 | 0,10  | Sh3gl2;Sh3gl1    | Endophilin-A1;Endophilin-A2                                                                                                                                                                 |
| 0,14 | -0,03 | Thoc6            | THO complex subunit 6 homolog                                                                                                                                                               |
| 0,14 | -0,09 | Morf4l2          | Mortality factor 4-like protein 2                                                                                                                                                           |
| 0,14 | 0,07  | Pdcd10           | Programmed cell death protein 10                                                                                                                                                            |
| 0,14 | 0,03  | Mphosph6         | M-phase phosphoprotein 6                                                                                                                                                                    |
| 0,14 | 0,03  | Fam175b          | BRISC complex subunit Abro1                                                                                                                                                                 |
| 0,14 | 0,09  | Arhgap25         | Rho GTPase-activating protein 25                                                                                                                                                            |
| 0,14 | -0,03 | Srrt             | Serrate RNA effector molecule homolog                                                                                                                                                       |

|      |       |                   |                                                                                                                                     |
|------|-------|-------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| 0,14 | -0,34 | Vwa5b1            | von Willebrand factor A domain-containing protein 5B1                                                                               |
| 0,14 | -0,07 | Polr3f            | DNA-directed RNA polymerase III subunit RPC6                                                                                        |
| 0,14 | -0,04 | Irgm1             | Immunity-related GTPase family M protein 1                                                                                          |
| 0,14 | -0,08 | Ankrd13a          | Ankyrin repeat domain-containing protein 13A                                                                                        |
| 0,14 | 0,05  | Pus10             | Putative tRNA pseudouridine synthase Pus10                                                                                          |
| 0,14 | -0,05 | Ogfr              | Opioid growth factor receptor                                                                                                       |
| 0,14 | 0,09  | Cecr2             |                                                                                                                                     |
| 0,14 | -0,05 | Dnttip1           | Deoxynucleotidyltransferase terminal-interacting protein 1                                                                          |
| 0,14 | -0,07 | Itpa              | Inosine triphosphate pyrophosphatase                                                                                                |
| 0,14 | -0,07 | Znf326            | DBIRD complex subunit ZNF326                                                                                                        |
| 0,14 | 0,07  | Kpna3             | Importin subunit alpha;Importin subunit alpha-4                                                                                     |
| 0,14 | -0,04 | Scaf4             |                                                                                                                                     |
| 0,14 | 0,07  | Kdm1a             | Lysine-specific histone demethylase 1A                                                                                              |
| 0,14 | 0,04  | Picalm            | Phosphatidylinositol-binding clathrin assembly protein                                                                              |
| 0,14 | -0,07 | Zc3h4             | Zinc finger CCCH domain-containing protein 4                                                                                        |
| 0,14 | 0,06  | Srpk3;Srpk1;Srpk2 | SRSF protein kinase 3;SRSF protein kinase 1;SRSF protein kinase 2;SRSF protein kinase 2 N-terminal;SRSF protein kinase 2 C-terminal |
| 0,14 | 0,04  | Gm17296           |                                                                                                                                     |
| 0,14 | -0,15 | Cbx5              | Chromobox protein homolog 5                                                                                                         |
| 0,14 | 0,07  | Adcy8             | Adenylate cyclase type 8                                                                                                            |
| 0,14 | -0,14 | Cdk6              | Cyclin-dependent kinase 6                                                                                                           |
| 0,13 | -0,03 | Babam1            | BRISC and BRCA1-A complex member 1                                                                                                  |
| 0,13 | -0,02 | Smek2;Smek1       | Serine/threonine-protein phosphatase 4 regulatory subunit 3B;Serine/threonine-protein phosphatase 4 regulatory subunit 3A           |
| 0,13 | 0,04  | Clcc1             | Chloride channel CLIC-like protein 1                                                                                                |
| 0,13 | 0,02  |                   | Uncharacterized protein C9orf117 homolog                                                                                            |
| 0,13 | -0,03 | Rab14             | Ras-related protein Rab-14                                                                                                          |
| 0,13 | -0,06 | Rpl13             | 60S ribosomal protein L13                                                                                                           |
| 0,13 | -0,03 | Psmc5             | 26S protease regulatory subunit 8                                                                                                   |
| 0,13 | -0,03 | Tulp3             | Tubby-related protein 3                                                                                                             |
| 0,13 | -0,03 | Tyms              | Thymidylate synthase                                                                                                                |
| 0,13 | 0,04  | Ranbp10           | Ran-binding protein 10                                                                                                              |
| 0,13 | -0,05 | Psmc12            | 26S proteasome non-ATPase regulatory subunit 12                                                                                     |
| 0,13 | 0,06  | Pcid2             | PCI domain-containing protein 2                                                                                                     |
| 0,13 | -0,11 | Npm1;Gm5611       | Nucleophosmin                                                                                                                       |
| 0,13 | 0,05  | Opa1              | Dynamin-like 120 kDa protein, mitochondrial;Dynamin-like 120 kDa protein, form S1                                                   |
| 0,13 | 0,07  | Txlng             | Gamma-taxilin                                                                                                                       |
| 0,13 | -0,05 | Gmps              | GMP synthase [glutamine-hydrolyzing]                                                                                                |
| 0,13 | -0,07 |                   | MLV-related proviral Env polyprotein;Surface protein;Transmembrane protein                                                          |
| 0,13 | 0,07  | Orc6              | Origin recognition complex subunit 6                                                                                                |
| 0,13 | 0,03  | Tmem123           | Porimin                                                                                                                             |
| 0,13 | -0,06 | Hadhb             | Trifunctional enzyme subunit beta, mitochondrial;3-ketoacyl-CoA thiolase                                                            |
| 0,13 | -0,05 | Psma3             | Proteasome subunit alpha type;Proteasome subunit alpha type-3                                                                       |
| 0,13 | -0,03 | Smc3              | Structural maintenance of chromosomes protein;Structural maintenance of chromosomes protein 3                                       |
| 0,13 | 0,06  | Traf1             | TRAF-type zinc finger domain-containing protein 1                                                                                   |
| 0,13 | -0,05 | Dnajc2            | DnaJ homolog subfamily C member 2;DnaJ homolog subfamily C member 2, N-terminally processed                                         |
| 0,13 | -0,05 | Msh6              | DNA mismatch repair protein Msh6                                                                                                    |
| 0,13 | 0,07  | Tomm6             | Mitochondrial import receptor subunit TOM6 homolog                                                                                  |
| 0,13 | -0,02 | Steap3            | Metalloreductase STEAP3                                                                                                             |
| 0,13 | 0,07  | Ncdn              | Neurochondrin                                                                                                                       |
| 0,12 | -0,03 | Ubap2             | Ubiquitin-associated protein 2                                                                                                      |
| 0,12 | -0,03 | Bag6              | Large proline-rich protein BAG6                                                                                                     |

|      |       |                                         |                                                                                                                                                                 |
|------|-------|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0,12 | -0,06 | Eef1d                                   | Elongation factor 1-delta                                                                                                                                       |
| 0,12 | 0,02  | Psmd4                                   | 26S proteasome non-ATPase regulatory subunit 4                                                                                                                  |
| 0,12 | -0,06 | Trmt112                                 | Multifunctional methyltransferase subunit TRM112-like protein                                                                                                   |
| 0,12 | 0,06  | Ngm                                     | Neugrin                                                                                                                                                         |
| 0,12 | -0,03 | Gm5218;Gm17669;Rpl29;Gm10709            | 60S ribosomal protein L29                                                                                                                                       |
| 0,12 | 0,04  | Lrrc59                                  | Leucine-rich repeat-containing protein 59                                                                                                                       |
| 0,12 | -0,02 | Atp5d                                   | ATP synthase subunit delta, mitochondrial                                                                                                                       |
| 0,12 | 0,05  | Ppm1b                                   | Protein phosphatase 1B                                                                                                                                          |
| 0,12 | 0,10  | Tpm4                                    | Tropomyosin alpha-4 chain                                                                                                                                       |
| 0,12 | -0,04 | Atp6v1f                                 | V-type proton ATPase subunit F                                                                                                                                  |
| 0,12 | 0,06  | Nhp2                                    | H/ACA ribonucleoprotein complex subunit 2                                                                                                                       |
| 0,12 | -0,13 | Gmfb                                    | Glia maturation factor beta                                                                                                                                     |
| 0,12 | 0,05  | Aco2                                    | Aconitate hydratase, mitochondrial                                                                                                                              |
| 0,12 | -0,02 | Gpatch8                                 | G patch domain-containing protein 8                                                                                                                             |
| 0,12 | -0,05 | Psme3                                   | Proteasome activator complex subunit 3                                                                                                                          |
| 0,12 | 0,04  | Prdx5                                   | Peroxiredoxin-5, mitochondrial                                                                                                                                  |
| 0,12 | -0,02 | Tceb1                                   | Transcription elongation factor B polypeptide 1                                                                                                                 |
| 0,12 | -0,03 | Rap1b;Rap1a                             | Ras-related protein Rap-1b;Ras-related protein Rap-1A                                                                                                           |
| 0,12 | 0,05  | Apobec3                                 | DNA dC->dU-editing enzyme APOBEC-3                                                                                                                              |
| 0,12 | -0,07 | Bid                                     | BH3-interacting domain death agonist;BH3-interacting domain death agonist p15;BH3-interacting domain death agonist p13;BH3-interacting domain death agonist p11 |
| 0,12 | 0,03  | Gpx1                                    | Glutathione peroxidase 1                                                                                                                                        |
| 0,12 | -0,07 | Nudt5                                   | ADP-sugar pyrophosphatase                                                                                                                                       |
| 0,12 | -0,24 | Hmgn3                                   | High mobility group nucleosome-binding domain-containing protein 3                                                                                              |
| 0,12 | 0,06  | Kdelc1                                  | KDEL motif-containing protein 1                                                                                                                                 |
| 0,12 | 0,02  | Racgap1                                 | Rac GTPase-activating protein 1                                                                                                                                 |
| 0,12 | -0,08 | Hist1h2bc;Hist1h2bh;Hist1h2bm;Hist2h2bb | Histone H2B type 1-C/E/G;Histone H2B type 1-H;Histone H2B;Histone H2B type 2-B;Histone H2B type 1-M                                                             |
| 0,12 | 0,04  | Qki                                     | Protein quaking                                                                                                                                                 |
| 0,12 | -0,02 | Rpl4                                    | 60S ribosomal protein L4                                                                                                                                        |
| 0,12 | 0,04  | Srsf4                                   | Serine/arginine-rich splicing factor 4                                                                                                                          |
| 0,12 | 0,03  | Macf1                                   | Microtubule-actin cross-linking factor 1                                                                                                                        |
| 0,12 | 0,03  | Dnm1l                                   | Dynamin-1-like protein                                                                                                                                          |
| 0,11 | -0,06 | Ap1s1                                   | AP-1 complex subunit sigma-1A                                                                                                                                   |
| 0,11 | -0,09 | Pck2                                    | Phosphoenolpyruvate carboxykinase [GTP], mitochondrial                                                                                                          |
| 0,11 | -0,07 | Dok1                                    | Docking protein 1                                                                                                                                               |
| 0,11 | 0,06  | Htatsf1                                 | HIV Tat-specific factor 1 homolog                                                                                                                               |
| 0,11 | -0,06 | Plp2                                    | Proteolipid protein 2                                                                                                                                           |
| 0,11 | -0,02 | Copa                                    | Coatomer subunit alpha;Coatomer subunit alpha;Xenin;Proxenin                                                                                                    |
| 0,11 | -0,03 | Pdha1                                   | Pyruvate dehydrogenase E1 component subunit alpha;Pyruvate dehydrogenase E1 component subunit alpha, somatic form, mitochondrial                                |
| 0,11 | -0,04 | Ddb1                                    | DNA damage-binding protein 1                                                                                                                                    |
| 0,11 | 0,03  | Surf6                                   | Surfeit locus protein 6                                                                                                                                         |
| 0,11 | -0,08 | Lnpep                                   | Leucyl-cystinyl aminopeptidase                                                                                                                                  |
| 0,11 | -0,03 | Wdr1                                    | WD repeat-containing protein 1                                                                                                                                  |
| 0,11 | -0,03 | Bcl7c                                   | B-cell CLL/lymphoma 7 protein family member C                                                                                                                   |
| 0,11 | -0,04 | Rtf1                                    | RNA polymerase-associated protein RTF1 homolog                                                                                                                  |
| 0,11 | 0,03  | Stoml2                                  | Stomatin-like protein 2, mitochondrial                                                                                                                          |
| 0,11 | -0,03 | Suc1a2                                  | Succinyl-CoA ligase [ADP-forming] subunit beta, mitochondrial                                                                                                   |
| 0,11 | -0,05 | Nomo1                                   | Nodal modulator 1                                                                                                                                               |
| 0,11 | 0,03  | Lypla1                                  | Acyl-protein thioesterase 1                                                                                                                                     |
| 0,11 | 0,03  | Exosc8                                  | Exosome complex component RRP43                                                                                                                                 |
| 0,11 | 0,02  | Emd                                     | Emerin                                                                                                                                                          |

|      |       |               |                                                                                                                                           |
|------|-------|---------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| 0,11 | -0,07 | Acsf2         | Acyl-CoA synthetase family member 2, mitochondrial                                                                                        |
| 0,11 | 0,06  | Alkbh5        | RNA demethylase ALKBH5                                                                                                                    |
| 0,11 | 0,03  | Bud13         | BUD13 homolog                                                                                                                             |
| 0,11 | 0,03  | Sec31a        | Protein transport protein Sec31A                                                                                                          |
| 0,11 | -0,03 | Coil          | Coilin                                                                                                                                    |
| 0,11 | -0,04 | Hnrmpa2b1     | Heterogeneous nuclear ribonucleoproteins A2/B1                                                                                            |
| 0,11 | 0,02  | Bms1          |                                                                                                                                           |
| 0,10 | -0,03 | Pias2;Pias1   | E3 SUMO-protein ligase PIAS2;E3 SUMO-protein ligase PIAS1                                                                                 |
| 0,10 | -0,04 | Stt13         | Hsc70-interacting protein                                                                                                                 |
| 0,10 | 0,05  | Ndufs7        | NADH dehydrogenase [ubiquinone] iron-sulfur protein 7, mitochondrial                                                                      |
| 0,10 | 0,04  | Plxna1        | Plexin-A1                                                                                                                                 |
| 0,10 | 0,03  | Hmox2         | Heme oxygenase 2                                                                                                                          |
| 0,10 | 0,04  | Sars2         | Serine--tRNA ligase, mitochondrial                                                                                                        |
| 0,10 | 0,03  | Cops4         | COP9 signalosome complex subunit 4                                                                                                        |
| 0,10 | 0,02  | Pla2          | Phospholipase A-2-activating protein                                                                                                      |
| 0,10 | -0,03 | Sash3         | SAM and SH3 domain-containing protein 3                                                                                                   |
| 0,10 | 0,01  | Sf3b1         | Splicing factor 3B subunit 1                                                                                                              |
| 0,10 | 0,04  | Rad23b        | UV excision repair protein RAD23 homolog B                                                                                                |
| 0,10 | 0,04  | Psmc9         | 26S proteasome non-ATPase regulatory subunit 9                                                                                            |
| 0,10 | 0,03  | Rrm2;Rrm2b    | Ribonucleoside-diphosphate reductase subunit M2;Ribonucleoside-diphosphate reductase subunit M2 B                                         |
| 0,10 | 0,05  | Dlgap5        | Disks large-associated protein 5                                                                                                          |
| 0,10 | 0,06  | Eya3          | Eyes absent homolog;Eyes absent homolog 3                                                                                                 |
| 0,10 | -0,02 | Ehmt1         | Histone-lysine N-methyltransferase EHMT1                                                                                                  |
| 0,10 | 0,02  | Exosc5        | Exosome complex component RRP46                                                                                                           |
| 0,10 | -0,05 | Mtdh          | Protein LYRIC                                                                                                                             |
| 0,10 | 0,03  | Tmpo          | Lamina-associated polypeptide 2, isoforms alpha/zeta                                                                                      |
| 0,10 | -0,01 | Smchd1        | Structural maintenance of chromosomes flexible hinge domain-containing protein 1                                                          |
| 0,10 | 0,03  | Pkn1          | Serine/threonine-protein kinase N1                                                                                                        |
| 0,10 | -0,05 | Fam114a2      | Protein FAM114A2                                                                                                                          |
| 0,10 | 0,05  | Timeless      | Protein timeless homolog                                                                                                                  |
| 0,10 | -0,07 | Slc39a10      | Zinc transporter ZIP10                                                                                                                    |
| 0,10 | -0,02 | Arfgap2       | ADP-ribosylation factor GTPase-activating protein 2                                                                                       |
| 0,09 | 0,03  | Ints8         | Integrator complex subunit 8                                                                                                              |
| 0,09 | -0,01 | Kif11         | Kinesin-like protein KIF11                                                                                                                |
| 0,09 | 0,09  | Ppp6c         | Serine/threonine-protein phosphatase 6 catalytic subunit;Serine/threonine-protein phosphatase 6 catalytic subunit, N-terminally processed |
| 0,09 | 0,03  | Camk2d        | Calcium/calmodulin-dependent protein kinase type II subunit delta                                                                         |
| 0,09 | -0,10 | Flnb          | Filamin-B                                                                                                                                 |
| 0,09 | 0,03  | Eif4g1        | Eukaryotic translation initiation factor 4 gamma 1                                                                                        |
| 0,09 | 0,14  | Clgn          | Calmegin                                                                                                                                  |
| 0,09 | -0,03 | Wdr73         | WD repeat-containing protein 73                                                                                                           |
| 0,09 | -0,04 | Bod1l         |                                                                                                                                           |
| 0,09 | -0,03 | Myo1g         | Unconventional myosin-Ig                                                                                                                  |
| 0,09 | 0,18  | Il2ra         | Interleukin-2 receptor subunit alpha                                                                                                      |
| 0,09 | 0,02  | Dph2          | Diphthamide biosynthesis protein 2                                                                                                        |
| 0,09 | 0,14  | Sptan1        | Spectrin alpha chain, non-erythrocytic 1                                                                                                  |
| 0,09 | 0,02  | Stag2         | Cohesin subunit SA-2                                                                                                                      |
| 0,09 | -0,03 | Eif4a3;Gm8994 | Eukaryotic initiation factor 4A-III;Eukaryotic initiation factor 4A-III, N-terminally processed                                           |
| 0,09 | 0,07  | Tor1aip2      | Torsin-1A-interacting protein 2                                                                                                           |
| 0,09 | 0,04  | Oxct1         | Succinyl-CoA:3-ketoacid coenzyme A transferase 1, mitochondrial                                                                           |
| 0,09 | 0,09  | Slamf6        | SLAM family member 6                                                                                                                      |
| 0,09 | 0,04  | Cggbp1        | CGG triplet repeat-binding protein 1                                                                                                      |

|      |       |                        |                                                                                                        |
|------|-------|------------------------|--------------------------------------------------------------------------------------------------------|
| 0,09 | -0,01 | Sephs1                 | Selenide, water dikinase 1                                                                             |
| 0,09 | -0,05 | Gbe1                   | 1,4-alpha-glucan-branching enzyme                                                                      |
| 0,09 | -0,02 | Wdr36                  |                                                                                                        |
| 0,09 | -0,03 | Elf3k                  | Eukaryotic translation initiation factor 3 subunit K                                                   |
| 0,09 | 0,03  | Scrib                  | Protein scribble homolog                                                                               |
| 0,09 | -0,06 | Ccm2                   | Cerebral cavernous malformations protein 2 homolog                                                     |
| 0,09 | 0,02  | Mcm3                   | DNA helicase;DNA replication licensing factor MCM3                                                     |
| 0,09 | 0,06  | Prkip1                 | PRKR-interacting protein 1                                                                             |
| 0,09 | -0,05 | Ppp2r5d                |                                                                                                        |
| 0,09 | 0,02  | Pggt1b                 | Geranylgeranyl transferase type-1 subunit beta                                                         |
| 0,09 | -0,02 | Got2                   | Aspartate aminotransferase, mitochondrial                                                              |
| 0,09 | 0,03  | Dera                   | Deoxyribose-phosphate aldolase                                                                         |
| 0,09 | -0,03 | Me2;Me3                | NAD-dependent malic enzyme, mitochondrial;NADP-dependent malic enzyme, mitochondrial                   |
| 0,09 | 0,04  | Esyt1                  | Extended synaptotagmin-1                                                                               |
| 0,09 | -0,03 | Sae1                   | SUMO-activating enzyme subunit 1;SUMO-activating enzyme subunit 1, N-terminally processed              |
| 0,09 | -0,02 | Pa2g4                  | Proliferation-associated protein 2G4                                                                   |
| 0,09 | 0,03  | Tgoln1;Tgoln2          | Trans-Golgi network integral membrane protein 1;Trans-Golgi network integral membrane protein 2        |
| 0,09 | 0,04  | Srsf3;Gm12355          | Serine/arginine-rich splicing factor 3                                                                 |
| 0,09 | 0,03  | Ptpn11                 | Tyrosine-protein phosphatase non-receptor type 11                                                      |
| 0,09 | -0,03 | Chchd4                 | Mitochondrial intermembrane space import and assembly protein 40                                       |
| 0,09 | -0,03 | Kifc5b;Kifc1           | Kinesin-like protein;Kinesin-like protein KIFC1                                                        |
| 0,08 | 0,03  | Hspa8                  | Heat shock cognate 71 kDa protein                                                                      |
| 0,08 | 0,01  | Ddx47                  | Probable ATP-dependent RNA helicase DDX47                                                              |
| 0,08 | -0,06 | Znf22                  | Zinc finger protein 22                                                                                 |
| 0,08 | 0,02  | Cbfb                   | Core-binding factor subunit beta                                                                       |
| 0,08 | -0,04 | Timm44                 | Mitochondrial import inner membrane translocase subunit TIM44                                          |
| 0,08 | -0,03 | Ap2b1                  | AP complex subunit beta;AP-2 complex subunit beta                                                      |
| 0,08 | -0,04 | Atg3                   | Ubiquitin-like-conjugating enzyme ATG3                                                                 |
| 0,08 | 0,04  | Pmpcb                  | Mitochondrial-processing peptidase subunit beta                                                        |
| 0,08 | -0,04 | 1110005A23Rik;Sarnp    | SAP domain-containing ribonucleoprotein                                                                |
| 0,08 | 0,04  | Fip11                  | Pre-mRNA 3-end-processing factor FIP1                                                                  |
| 0,08 | -0,02 | Pafah1b1               | Platelet-activating factor acetylhydrolase 1B subunit alpha                                            |
| 0,08 | 0,05  | Galk2                  | N-acetylgalactosamine kinase                                                                           |
| 0,08 | 0,03  | Pop1                   |                                                                                                        |
| 0,08 | -0,03 | C330027C09Rik;Kiaa1524 | Protein CIP2A                                                                                          |
| 0,08 | 0,04  | Ube2d3                 | Ubiquitin-conjugating enzyme E2 D3                                                                     |
| 0,08 | 0,07  | Capza2                 | F-actin-capping protein subunit alpha-2                                                                |
| 0,08 | -0,03 | Psbm1                  | Proteasome subunit beta type;Proteasome subunit beta type-1                                            |
| 0,08 | -0,02 | Uba2                   | SUMO-activating enzyme subunit 2                                                                       |
| 0,08 | 0,01  | Exosc7                 | Exosome complex exonuclease RRP42                                                                      |
| 0,08 | -0,05 | Chmp4b                 | Charged multivesicular body protein 4b                                                                 |
| 0,08 | -0,02 | Elf3c                  | Eukaryotic translation initiation factor 3 subunit C                                                   |
| 0,08 | 0,03  | Iqgap1                 | Ras GTPase-activating-like protein IQGAP1                                                              |
| 0,08 | -0,02 | Zc3h13                 |                                                                                                        |
| 0,08 | -0,05 | Lap3                   | Cytosol aminopeptidase                                                                                 |
| 0,08 | -0,01 | Ppp2r5a                | Serine/threonine-protein phosphatase 2A 56 kDa regulatory subunit alpha isoform                        |
| 0,08 | 0,04  | Clip1                  | CAP-Gly domain-containing linker protein 1                                                             |
| 0,08 | -0,03 | Rrbp1                  | Ribosome-binding protein 1                                                                             |
| 0,08 | 0,03  | Ppan                   | Suppressor of SWI4 1 homolog                                                                           |
| 0,08 | -0,02 | Fmr1;Fxr2              | Fragile X mental retardation protein 1 homolog;Fragile X mental retardation syndrome-related protein 2 |

|      |       |                          |                                                                                                                                                             |
|------|-------|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0,08 | 0,01  | Unc45a                   | Protein unc-45 homolog A                                                                                                                                    |
| 0,08 | -0,03 | Eif4b                    | Eukaryotic translation initiation factor 4B                                                                                                                 |
| 0,08 | 0,01  | Rars                     | Arginine--tRNA ligase, cytoplasmic                                                                                                                          |
| 0,08 | 0,02  | Larp1                    | La-related protein 1                                                                                                                                        |
| 0,08 | 0,05  | Cfdp1                    | Craniofacial development protein 1                                                                                                                          |
| 0,08 | -0,03 | Ankfy1                   | Rabankyrin-5                                                                                                                                                |
| 0,08 | 0,02  | Coa6                     | Cytochrome c oxidase assembly factor 6 homolog                                                                                                              |
| 0,08 | -0,02 | Eif4ebp1                 | Eukaryotic translation initiation factor 4E-binding protein 1                                                                                               |
| 0,08 | -0,03 | Otulin                   | Ubiquitin thioesterase otulin                                                                                                                               |
| 0,08 | -0,01 | Rwdd1                    | RWD domain-containing protein 1                                                                                                                             |
| 0,07 | 0,06  | Tmem119                  | Transmembrane protein 119                                                                                                                                   |
| 0,07 | -0,03 | Atp5g3;Atp5g1;Atp5g2     | ATP synthase F(0) complex subunit C1, mitochondrial;ATP synthase F(0) complex subunit C3, mitochondrial;ATP synthase F(0) complex subunit C2, mitochondrial |
| 0,07 | 0,02  | Cmas                     | N-acetylneuraminate cytidyltransferase                                                                                                                      |
| 0,07 | -0,06 | Pik3ap1                  | Phosphoinositide 3-kinase adapter protein 1                                                                                                                 |
| 0,07 | -0,03 | Psma7                    | Proteasome subunit alpha type;Proteasome subunit alpha type-7                                                                                               |
| 0,07 | 0,05  | Ttc7;Ttc7a               | Tetratricopeptide repeat protein 7A                                                                                                                         |
| 0,07 | -0,03 | Gstp1                    | Glutathione S-transferase P 1                                                                                                                               |
| 0,07 | 0,04  | Coro1a                   | Coronin;Coronin-1A                                                                                                                                          |
| 0,07 | 0,02  | Cdc23                    | Cell division cycle protein 23 homolog                                                                                                                      |
| 0,07 | -0,05 | Rpl22l1                  | 60S ribosomal protein L22-like 1                                                                                                                            |
| 0,07 | 0,03  | Thoc2                    | THO complex subunit 2                                                                                                                                       |
| 0,07 | -0,04 | Gnai2                    | Guanine nucleotide-binding protein G(i) subunit alpha-2                                                                                                     |
| 0,07 | -0,04 | Qrich1                   | Glutamine-rich protein 1                                                                                                                                    |
| 0,07 | -0,02 | Rab10                    | Ras-related protein Rab-10                                                                                                                                  |
| 0,07 | -0,02 | Pdhx                     | Pyruvate dehydrogenase protein X component, mitochondrial                                                                                                   |
| 0,07 | 0,03  | Sf3a1                    | Splicing factor 3A subunit 1                                                                                                                                |
| 0,07 | -0,03 | Nup153                   |                                                                                                                                                             |
| 0,07 | -0,05 | Hadha                    | Trifunctional enzyme subunit alpha, mitochondrial;Long-chain enoyl-CoA hydratase;Long chain 3-hydroxyacyl-CoA dehydrogenase                                 |
| 0,07 | -0,04 | Dnajc9                   | DnaJ homolog subfamily C member 9                                                                                                                           |
| 0,07 | -0,02 | Psmd1                    | 26S proteasome non-ATPase regulatory subunit 1                                                                                                              |
| 0,07 | -0,01 | Wdr46                    | WD repeat-containing protein 46                                                                                                                             |
| 0,07 | 0,02  | Vac14                    | Protein VAC14 homolog                                                                                                                                       |
| 0,07 | 0,06  | Clec14a                  | C-type lectin domain family 14 member A                                                                                                                     |
| 0,07 | -0,08 | Psme2;PSME2b             | Proteasome activator complex subunit 2                                                                                                                      |
| 0,07 | 0,01  | Pcna                     | Proliferating cell nuclear antigen                                                                                                                          |
| 0,07 | 0,01  | Ddx39;Ddx39a;Ddx39b      | ATP-dependent RNA helicase DDX39A                                                                                                                           |
| 0,07 | 0,03  | Usp24                    | Ubiquitin carboxyl-terminal hydrolase;Ubiquitin carboxyl-terminal hydrolase 24                                                                              |
| 0,07 | -0,04 | Mlec                     | Malectin                                                                                                                                                    |
| 0,07 | 0,08  | Aimp2                    | Aminoacyl tRNA synthase complex-interacting multifunctional protein 2                                                                                       |
| 0,07 | -0,01 | Arhgef1                  | Rho guanine nucleotide exchange factor 1                                                                                                                    |
| 0,07 | -0,03 | Pygo2                    |                                                                                                                                                             |
| 0,07 | 0,02  | Rpl11;Gm5093;Gm1003<br>6 | 60S ribosomal protein L11                                                                                                                                   |
| 0,07 | 0,03  | Pisd;Gm20671             | Phosphatidylserine decarboxylase proenzyme;Phosphatidylserine decarboxylase alpha chain;Phosphatidylserine decarboxylase beta chain                         |
| 0,07 | -0,02 | Ddx27                    | Probable ATP-dependent RNA helicase DDX27                                                                                                                   |
| 0,06 | -0,02 | Stip1                    | Stress-induced-phosphoprotein 1                                                                                                                             |
| 0,06 | 0,05  | Capg                     |                                                                                                                                                             |
| 0,06 | -0,04 | Cndp2                    | Cytosolic non-specific dipeptidase                                                                                                                          |
| 0,06 | -0,03 | Psma6                    | Proteasome subunit alpha type-6                                                                                                                             |
| 0,06 | -0,03 | Gps1                     | COP9 signalosome complex subunit 1                                                                                                                          |
| 0,06 | 0,01  | Smc4                     | Structural maintenance of chromosomes protein;Structural maintenance of chromosomes                                                                         |

|      |       |                                        |                                                                                                                                                                                   |
|------|-------|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|      |       |                                        | protein 4                                                                                                                                                                         |
| 0,06 | 0,02  | Rps17                                  | 40S ribosomal protein S17                                                                                                                                                         |
| 0,06 | 0,05  | Xpo1                                   | Exportin-1                                                                                                                                                                        |
| 0,06 | -0,03 | Ifi35                                  | Interferon-induced 35 kDa protein homolog                                                                                                                                         |
| 0,06 | -0,03 | Snx1                                   | Sorting nexin-1                                                                                                                                                                   |
| 0,06 | -0,01 | Wash1                                  | WAS protein family homolog 1                                                                                                                                                      |
| 0,06 | -0,01 | Kif15                                  | Kinesin-like protein KIF15                                                                                                                                                        |
| 0,06 | -0,03 | Camk2b;Camk2g                          | Calcium/calmodulin-dependent protein kinase type II subunit gamma;Calcium/calmodulin-dependent protein kinase type II subunit beta                                                |
| 0,06 | -0,04 | Ociad1                                 | OCIA domain-containing protein 1                                                                                                                                                  |
| 0,06 | 0,03  | Mad11                                  | Mitotic spindle assembly checkpoint protein MAD1                                                                                                                                  |
| 0,06 | 0,02  | Ssr3                                   | Translocon-associated protein subunit gamma                                                                                                                                       |
| 0,06 | 0,02  | Rabepk                                 | Rab9 effector protein with kelch motifs                                                                                                                                           |
| 0,06 | -0,03 | Get4                                   | Golgi to ER traffic protein 4 homolog                                                                                                                                             |
| 0,06 | 0,00  | Cse1l                                  | Exportin-2                                                                                                                                                                        |
| 0,06 | -0,02 | Prdx1                                  | Peroxiredoxin-1                                                                                                                                                                   |
| 0,06 | -0,03 | Lsm2                                   | U6 snRNA-associated Sm-like protein LSM2                                                                                                                                          |
| 0,06 | -0,04 | Phf14                                  | PHD finger protein 14                                                                                                                                                             |
| 0,06 | 0,04  | Wrip1                                  | ATPase WRNIP1                                                                                                                                                                     |
| 0,06 | -0,03 | Ppp1r14b                               | Protein phosphatase 1 regulatory subunit 14B                                                                                                                                      |
| 0,06 | -0,02 | Srp72                                  | Signal recognition particle subunit SRP72                                                                                                                                         |
| 0,06 | 0,01  | Hnmpk;Gm7964                           | Heterogeneous nuclear ribonucleoprotein K                                                                                                                                         |
| 0,06 | 0,02  | Hist2h3b;Hist1h3b;Hist1h3a;H3f3a;H3f3c | Histone H3;Histone H3.2;Histone H3.1;Histone H3.3;Histone H3.3C                                                                                                                   |
| 0,06 | 0,01  |                                        | Uncharacterized protein C17orf62 homolog                                                                                                                                          |
| 0,06 | -0,02 | Cd93                                   | Complement component C1q receptor                                                                                                                                                 |
| 0,06 | 0,05  | M6pr                                   | Cation-dependent mannose-6-phosphate receptor                                                                                                                                     |
| 0,06 | 0,03  |                                        | Uncharacterized protein C17orf85 homolog                                                                                                                                          |
| 0,05 | 0,02  | Pbk                                    | Lymphokine-activated killer T-cell-originated protein kinase                                                                                                                      |
| 0,05 | 0,02  | Chchd3                                 | MICOS complex subunit Mic19                                                                                                                                                       |
| 0,05 | 0,03  | Uqcrls1                                | Cytochrome b-c1 complex subunit Rieske, mitochondrial;Cytochrome b-c1 complex subunit 11                                                                                          |
| 0,05 | -0,05 | Ppp2r1b                                | Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A beta isoform                                                                                                  |
| 0,05 | -0,04 | Keap1                                  | Kelch-like ECH-associated protein 1                                                                                                                                               |
| 0,05 | -0,02 | Ranbp3                                 | Ran-binding protein 3                                                                                                                                                             |
| 0,05 | -0,07 | Fabp5                                  | Fatty acid-binding protein, epidermal                                                                                                                                             |
| 0,05 | -0,02 | Mut                                    | Methylmalonyl-CoA mutase, mitochondrial                                                                                                                                           |
| 0,05 | -0,01 | Exosc1                                 | Exosome complex component CSL4                                                                                                                                                    |
| 0,05 | -0,02 | Atp6v1g1                               | V-type proton ATPase subunit G 1                                                                                                                                                  |
| 0,05 | -0,03 | Rpn2                                   | Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 2                                                                                                          |
| 0,05 | 0,01  | Psm6                                   | 26S proteasome non-ATPase regulatory subunit 6                                                                                                                                    |
| 0,05 | -0,02 | Rhog                                   | Rho-related GTP-binding protein RhoG                                                                                                                                              |
| 0,05 | -0,02 | Gcn11                                  |                                                                                                                                                                                   |
| 0,05 | 0,02  | Hspa14                                 | Heat shock 70 kDa protein 14                                                                                                                                                      |
| 0,05 | -0,02 | Wbp11                                  | WW domain-binding protein 11                                                                                                                                                      |
| 0,05 | 0,03  | Sept6;Sept8                            | Septin-6;Septin-8                                                                                                                                                                 |
| 0,05 | -0,04 | Mdh2                                   | Malate dehydrogenase, mitochondrial                                                                                                                                               |
| 0,05 | 0,02  | Hnmpul2                                | Heterogeneous nuclear ribonucleoprotein U-like protein 2                                                                                                                          |
| 0,05 | 0,00  | Nup155                                 | Nuclear pore complex protein Nup155                                                                                                                                               |
| 0,05 | 0,02  | Dna2                                   | DNA replication ATP-dependent helicase/nuclease DNA2;DNA replication nuclease DNA2;DNA replication ATP-dependent helicase DNA2                                                    |
| 0,05 | 0,03  | Mthfd2                                 | Bifunctional methylenetetrahydrofolate dehydrogenase/cyclohydrolase, mitochondrial;NAD-dependent methylenetetrahydrofolate dehydrogenase;Methylenetetrahydrofolate cyclohydrolase |
| 0,05 | 0,04  | Acadvl                                 | Very long-chain specific acyl-CoA dehydrogenase, mitochondrial                                                                                                                    |
| 0,05 | -0,01 | Nup188                                 | Nucleoporin NUP188 homolog                                                                                                                                                        |

|      |       |                |                                                                                      |
|------|-------|----------------|--------------------------------------------------------------------------------------|
| 0,05 | -0,02 | Ahcy1          | Putative adenosylhomocysteinase 2                                                    |
| 0,05 | 0,03  | Ctbp1;Ctbp2    | C-terminal-binding protein 1;C-terminal-binding protein 2                            |
| 0,05 | -0,04 | Aldh2          | Aldehyde dehydrogenase, mitochondrial                                                |
| 0,05 | -0,01 | Dars           | Aspartate--tRNA ligase, cytoplasmic                                                  |
| 0,05 | 0,01  | Cops7a         | COP9 signalosome complex subunit 7a                                                  |
| 0,05 | 0,02  | Slk            | STE20-like serine/threonine-protein kinase                                           |
| 0,05 | -0,01 | Sod2           | Superoxide dismutase;Superoxide dismutase [Mn], mitochondrial                        |
| 0,05 | 0,02  | Gpd2           | Glycerol-3-phosphate dehydrogenase;Glycerol-3-phosphate dehydrogenase, mitochondrial |
| 0,05 | -0,02 | Rplp0;Gm8730   | 60S acidic ribosomal protein P0                                                      |
| 0,05 | -0,02 | Tpt1           | Translationally-controlled tumor protein                                             |
| 0,05 | -0,02 | Ctps1          | CTP synthase 1                                                                       |
| 0,05 | -0,01 | Top2b          | DNA topoisomerase 2-beta                                                             |
| 0,05 | 0,05  | Npepl1         | Probable aminopeptidase NPEPL1                                                       |
| 0,05 | -0,02 | Ppa2           | Inorganic pyrophosphatase 2, mitochondrial                                           |
| 0,04 | 0,04  | Eif3d          | Eukaryotic translation initiation factor 3 subunit D                                 |
| 0,04 | 0,04  | Mrpl40         | 39S ribosomal protein L40, mitochondrial                                             |
| 0,04 | -0,03 |                | Uncharacterized protein C7orf50 homolog                                              |
| 0,04 | 0,01  | Trim24         | Transcription intermediary factor 1-alpha                                            |
| 0,04 | 0,02  | Thrap3         | Thyroid hormone receptor-associated protein 3                                        |
| 0,04 | 0,01  | Atp5c1         | ATP synthase subunit gamma;ATP synthase subunit gamma, mitochondrial                 |
| 0,04 | 0,01  | Psmc3          | 26S proteasome non-ATPase regulatory subunit 3                                       |
| 0,04 | -0,01 | Prmt3          | Protein arginine N-methyltransferase 3                                               |
| 0,04 | -0,01 | Pitrm1         | Presequence protease, mitochondrial                                                  |
| 0,04 | -0,02 | Pabpc4;Gm10110 | Polyadenylate-binding protein                                                        |
| 0,04 | -0,02 | Arhgap4        |                                                                                      |
| 0,04 | 0,01  | Arglu1         | Arginine and glutamate-rich protein 1                                                |
| 0,04 | -0,01 | Eif3f          | Eukaryotic translation initiation factor 3 subunit F                                 |
| 0,04 | -0,01 | Chaf1b         | Chromatin assembly factor 1 subunit B                                                |
| 0,04 | 0,01  | Etfb           | Electron transfer flavoprotein subunit beta                                          |
| 0,04 | -0,01 | Mrps2          | 28S ribosomal protein S2, mitochondrial                                              |
| 0,04 | -0,01 | Ahsa1          | Activator of 90 kDa heat shock protein ATPase homolog 1                              |
| 0,04 | -0,03 | Coro1c         | Coronin;Coronin-1C                                                                   |
| 0,04 | 0,03  | Ube2o          | E2/E3 hybrid ubiquitin-protein ligase UBE2O                                          |
| 0,04 | -0,01 | Eps15l1        | Epidermal growth factor receptor substrate 15-like 1                                 |
| 0,04 | -0,01 | Tex10          | Testis-expressed sequence 10 protein                                                 |
| 0,04 | 0,01  | Csnk1d         | Casein kinase I isoform delta                                                        |
| 0,04 | 0,02  | Cirbp          | Cold-inducible RNA-binding protein                                                   |
| 0,04 | 0,01  | Ati3           | Atlastin-3                                                                           |
| 0,04 | -0,01 | Myg1           | UPF0160 protein MYG1, mitochondrial                                                  |
| 0,04 | 0,02  | Sh3kbp1        | SH3 domain-containing kinase-binding protein 1                                       |
| 0,04 | -0,02 | Adsl           | Adenylosuccinate lyase                                                               |
| 0,04 | 0,02  | Myh14          | Myosin-14                                                                            |
| 0,04 | -0,01 | Dnmt1          | DNA (cytosine-5)-methyltransferase 1                                                 |
| 0,04 | -0,01 | Mapk1          | Mitogen-activated protein kinase 1                                                   |
| 0,04 | -0,03 | Dnajb6         | DnaJ homolog subfamily B member 6                                                    |
| 0,04 | 0,01  | Arih1          | E3 ubiquitin-protein ligase ARIH1                                                    |
| 0,04 | 0,01  | Cs;Csl         | Citrate synthase, mitochondrial;Citrate synthase                                     |
| 0,04 | 0,01  | Tin2           | Talin-2                                                                              |
| 0,04 | -0,02 | Dnajc11        | DnaJ homolog subfamily C member 11                                                   |
| 0,03 | 0,03  | Rsb1l          |                                                                                      |
| 0,03 | -0,02 | Ubtf           | Nucleolar transcription factor 1                                                     |
| 0,03 | 0,00  | Uba1           | Ubiquitin-like modifier-activating enzyme 1                                          |

|      |       |                      |                                                                                                                                                                                                                                        |
|------|-------|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0,03 | -0,01 | Ppp1ca;Ppp1cc;Ppp1cb | Serine/threonine-protein phosphatase;Serine/threonine-protein phosphatase PP1-alpha catalytic subunit;Serine/threonine-protein phosphatase PP1-gamma catalytic subunit;Serine/threonine-protein phosphatase PP1-beta catalytic subunit |
| 0,03 | 0,02  | Pgam5                | Serine/threonine-protein phosphatase PGAM5, mitochondrial                                                                                                                                                                              |
| 0,03 | 0,01  | Dnajc3               | DnaJ homolog subfamily C member 3                                                                                                                                                                                                      |
| 0,03 | -0,01 | Tcerg1               | Transcription elongation regulator 1                                                                                                                                                                                                   |
| 0,03 | 0,00  | Dld                  | Dihydrolipoyl dehydrogenase;Dihydrolipoyl dehydrogenase, mitochondrial                                                                                                                                                                 |
| 0,03 | -0,02 | Pdia3                | Protein disulfide-isomerase A3                                                                                                                                                                                                         |
| 0,03 | 0,01  | Npepps               | Puromycin-sensitive aminopeptidase                                                                                                                                                                                                     |
| 0,03 | 0,02  | Ttc5                 | Tetratricopeptide repeat protein 5                                                                                                                                                                                                     |
| 0,03 | -0,02 | Brd4                 | Bromodomain-containing protein 4                                                                                                                                                                                                       |
| 0,03 | 0,01  | Rbm25                | RNA-binding protein 25                                                                                                                                                                                                                 |
| 0,03 | -0,01 | Mcm4                 | DNA replication licensing factor MCM4                                                                                                                                                                                                  |
| 0,03 | -0,04 | Psma2                | Proteasome subunit alpha type-2                                                                                                                                                                                                        |
| 0,03 | 0,00  | Samsn1;Sash1         | SAM domain-containing protein SAMS1-1;SAM and SH3 domain-containing protein 1                                                                                                                                                          |
| 0,03 | 0,02  | Ctcf                 | Transcriptional repressor CTCF                                                                                                                                                                                                         |
| 0,03 | -0,01 | Slain1               | SLAIN motif-containing protein 1                                                                                                                                                                                                       |
| 0,03 | -0,01 | Anp32e               | Acidic leucine-rich nuclear phosphoprotein 32 family member E                                                                                                                                                                          |
| 0,03 | -0,01 | Bcas2                | Pre-mRNA-splicing factor SPF27                                                                                                                                                                                                         |
| 0,03 | -0,01 | Ogdh                 | 2-oxoglutarate dehydrogenase, mitochondrial                                                                                                                                                                                            |
| 0,03 | 0,01  | Prksh                | Glucosidase 2 subunit beta                                                                                                                                                                                                             |
| 0,03 | -0,01 | Tpm3;Tpm3-rs7        |                                                                                                                                                                                                                                        |
| 0,03 | -0,01 | Rpl36a               | 60S ribosomal protein L36a                                                                                                                                                                                                             |
| 0,03 | -0,02 | Iqgap3               |                                                                                                                                                                                                                                        |
| 0,03 | -0,01 | Usp5                 | Ubiquitin carboxyl-terminal hydrolase;Ubiquitin carboxyl-terminal hydrolase 5                                                                                                                                                          |
| 0,03 | -0,01 | Rangap1              | Ran GTPase-activating protein 1                                                                                                                                                                                                        |
| 0,03 | -0,01 | Rnf2                 | E3 ubiquitin-protein ligase RING2                                                                                                                                                                                                      |
| 0,03 | 0,01  | 2700060E02Rik        | UPF0568 protein C14orf166 homolog                                                                                                                                                                                                      |
| 0,03 | -0,01 | Thoc1                | THO complex subunit 1                                                                                                                                                                                                                  |
| 0,03 | 0,02  | Eth1                 | Persulfide dioxygenase ETHE1, mitochondrial                                                                                                                                                                                            |
| 0,03 | -0,01 | Rbm2                 | RNA-binding motif protein, X-linked 2                                                                                                                                                                                                  |
| 0,03 | -0,01 | Mapre1               | Microtubule-associated protein RP/EB family member 1                                                                                                                                                                                   |
| 0,03 | 0,00  | Lmn1                 | Lamin-B1                                                                                                                                                                                                                               |
| 0,03 | 0,01  | Sugt1                | Suppressor of G2 allele of SKP1 homolog                                                                                                                                                                                                |
| 0,03 | 0,01  | Aacs                 | Acetoacetyl-CoA synthetase                                                                                                                                                                                                             |
| 0,03 | -0,01 | Pgm2                 | Phosphoglucomutase-2                                                                                                                                                                                                                   |
| 0,03 | -0,01 | Pus1                 | tRNA pseudouridine synthase;tRNA pseudouridine synthase A, mitochondrial                                                                                                                                                               |
| 0,03 | 0,01  | Ubx4                 | UBX domain-containing protein 4                                                                                                                                                                                                        |
| 0,03 | -0,01 | Rnmt                 | mRNA cap guanine-N7 methyltransferase                                                                                                                                                                                                  |
| 0,03 | -0,02 | Nbas                 |                                                                                                                                                                                                                                        |
| 0,03 | 0,00  | Ppp1r12a             | Protein phosphatase 1 regulatory subunit 12A                                                                                                                                                                                           |
| 0,03 | 0,02  | Acadm                | Medium-chain specific acyl-CoA dehydrogenase, mitochondrial                                                                                                                                                                            |
| 0,03 | -0,02 | Slc25a12             | Calcium-binding mitochondrial carrier protein Aralar1                                                                                                                                                                                  |
| 0,02 | -0,02 | Dnajc17              | DnaJ homolog subfamily C member 17                                                                                                                                                                                                     |
| 0,02 | -0,01 | Map1s                | Microtubule-associated protein 1S;MAP1S heavy chain;MAP1S light chain                                                                                                                                                                  |
| 0,02 | 0,01  | Rbm34                | RNA-binding protein 34                                                                                                                                                                                                                 |
| 0,02 | 0,02  | Slc7a1               | High affinity cationic amino acid transporter 1                                                                                                                                                                                        |
| 0,02 | 0,02  | Fkbp1a               | Peptidyl-prolyl cis-trans isomerase FKBP1A;Peptidyl-prolyl cis-trans isomerase                                                                                                                                                         |
| 0,02 | -0,02 | Chmp2b               | Charged multivesicular body protein 2b                                                                                                                                                                                                 |
| 0,02 | 0,01  | Uba6                 | Ubiquitin-like modifier-activating enzyme 6                                                                                                                                                                                            |
| 0,02 | 0,01  | Tpr                  | Nucleoprotein TPR                                                                                                                                                                                                                      |
| 0,02 | 0,01  | Whsc1l1              | Histone-lysine N-methyltransferase;Histone-lysine N-methyltransferase NSD3                                                                                                                                                             |
| 0,02 | 0,01  | Copg1                | Coatomer subunit gamma-1                                                                                                                                                                                                               |

|      |       |                                   |                                                                                                                  |
|------|-------|-----------------------------------|------------------------------------------------------------------------------------------------------------------|
| 0,02 | 0,01  | Nptn                              | Neuroplastin                                                                                                     |
| 0,02 | 0,00  | Cnot8                             | CCR4-NOT transcription complex subunit 8                                                                         |
| 0,02 | 0,01  | Atp5j                             | ATP synthase-coupling factor 6, mitochondrial                                                                    |
| 0,02 | -0,02 | Mrpl39                            | 39S ribosomal protein L39, mitochondrial                                                                         |
| 0,02 | -0,01 | Pds5a                             | Sister chromatid cohesion protein PDS5 homolog A                                                                 |
| 0,02 | -0,01 | Nup54                             | Nuclear pore complex protein Nup54                                                                               |
| 0,02 | -0,02 | Necap2                            | Adaptin ear-binding coat-associated protein 2                                                                    |
| 0,02 | 0,00  | Ddx3x;D1Pas1;Ddx3y                | ATP-dependent RNA helicase DDX3X;ATP-dependent RNA helicase DDX3Y;Putative ATP-dependent RNA helicase P110       |
| 0,02 | -0,01 | Nipbl                             | Nipped-B-like protein                                                                                            |
| 0,02 | -0,02 | Fdx1                              | Adrenodoxin, mitochondrial                                                                                       |
| 0,02 | 0,00  | Xpr1                              | Xenotropic and polytropic retrovirus receptor 1                                                                  |
| 0,02 | 0,01  | Acat1                             | Acetyl-CoA acetyltransferase, mitochondrial                                                                      |
| 0,02 | -0,01 | Mos                               | Proto-oncogene serine/threonine-protein kinase mos                                                               |
| 0,02 | 0,01  | Slc16a1                           | Monocarboxylate transporter 1                                                                                    |
| 0,02 | 0,01  | Syk                               | Tyrosine-protein kinase;Tyrosine-protein kinase SYK                                                              |
| 0,02 | 0,01  | Lrch3                             | Leucine-rich repeat and calponin homology domain-containing protein 3                                            |
| 0,02 | 0,00  |                                   |                                                                                                                  |
| 0,02 | -0,01 | Klc1                              | Kinesin light chain 1                                                                                            |
| 0,02 | -0,01 | Rpl21                             | 60S ribosomal protein L21                                                                                        |
| 0,02 | 0,01  | Letm1                             | LETM1 and EF-hand domain-containing protein 1, mitochondrial                                                     |
| 0,02 | 0,00  | Syncrip                           | Heterogeneous nuclear ribonucleoprotein Q                                                                        |
| 0,02 | 0,00  | Ap1b1                             | AP complex subunit beta;AP-1 complex subunit beta-1                                                              |
| 0,02 | 0,00  | Aifm1                             | Apoptosis-inducing factor 1, mitochondrial                                                                       |
| 0,02 | 0,00  | Rabgap1                           | Rab GTPase-activating protein 1                                                                                  |
| 0,02 | -0,01 | Grwd1                             | Glutamate-rich WD repeat-containing protein 1                                                                    |
| 0,01 | 0,00  | Bysl                              | Bystin                                                                                                           |
| 0,01 | -0,01 | Armt1                             | Protein-glutamate O-methyltransferase                                                                            |
| 0,01 | 0,00  | Wdr74                             | WD repeat-containing protein 74                                                                                  |
| 0,01 | -0,01 | Cdc42                             | Cell division control protein 42 homolog                                                                         |
| 0,01 | 0,01  | Clpb                              | Caseinolytic peptidase B protein homolog                                                                         |
| 0,01 | 0,00  | 2510003E04Rik;Kbp                 | KIF1-binding protein                                                                                             |
| 0,01 | 0,00  | Shmt2                             | Serine hydroxymethyltransferase                                                                                  |
| 0,01 | 0,00  | Acly                              | ATP-citrate synthase                                                                                             |
| 0,01 | 0,00  | Glud1                             | Glutamate dehydrogenase 1, mitochondrial                                                                         |
| 0,01 | 0,00  | Otud4                             | OTU domain-containing protein 4                                                                                  |
| 0,01 | 0,01  | Ppp1r8                            | Nuclear inhibitor of protein phosphatase 1                                                                       |
| 0,01 | -0,01 | Tuba1c;Tuba1a;Tuba1b;Tuba3a;Tuba8 | Tubulin alpha-1C chain;Tubulin alpha-1A chain;Tubulin alpha-1B chain;Tubulin alpha-3 chain;Tubulin alpha-8 chain |
| 0,01 | 0,01  | Acss1                             | Acetyl-coenzyme A synthetase;Acetyl-coenzyme A synthetase 2-like, mitochondrial                                  |
| 0,01 | 0,00  | Grhpr                             | Glyoxylate reductase/hydroxypyruvate reductase                                                                   |
| 0,01 | 0,01  | Myl12a;Myl12b                     | Myosin regulatory light chain 12B                                                                                |
| 0,01 | -0,01 | Sh3bgrl3                          | SH3 domain-binding glutamic acid-rich-like protein 3                                                             |
| 0,01 | 0,00  | Snx9                              | Sorting nexin-9                                                                                                  |
| 0,01 | 0,00  | Elf6                              | Eukaryotic translation initiation factor 6                                                                       |
| 0,01 | 0,00  | Cdv3                              | Protein CDV3                                                                                                     |
| 0,01 | 0,01  | Dnm2                              | Dynamin-2                                                                                                        |
| 0,01 | 0,00  | Gtf2e1                            | General transcription factor IIE subunit 1                                                                       |
| 0,01 | 0,00  | Vta1                              | Vacuolar protein sorting-associated protein VTA1 homolog                                                         |
| 0,01 | 0,01  | Capzb                             | F-actin-capping protein subunit beta                                                                             |
| 0,01 | 0,00  | Tspan31                           | Tetraspanin-31                                                                                                   |
| 0,01 | 0,00  | Pcbp2;Pcbp3                       | Poly(rC)-binding protein 2;Poly(rC)-binding protein 3                                                            |
| 0,01 | 0,00  | Atf7                              | Cyclic AMP-dependent transcription factor ATF-7                                                                  |

|      |      |                |                                                                                                                                  |
|------|------|----------------|----------------------------------------------------------------------------------------------------------------------------------|
| 0,01 | 0,00 | Gpatch4        | G patch domain-containing protein 4                                                                                              |
| 0,01 | 0,00 | Dck            | Deoxycytidine kinase                                                                                                             |
| 0,01 | 0,00 | Atp5b          | ATP synthase subunit beta, mitochondrial                                                                                         |
| 0,01 | 0,01 | Tifa           | TRAF-interacting protein with FHA domain-containing protein A                                                                    |
| 0,01 | 0,00 | Msh2           | DNA mismatch repair protein Msh2                                                                                                 |
| 0,00 | 0,00 | Tyw3           | tRNA wybutosine-synthesizing protein 3 homolog                                                                                   |
| 0,00 | 0,00 | Mtap           | S-methyl-5-thioadenosine phosphorylase                                                                                           |
| 0,00 | 0,00 | Ccdc9          | Coiled-coil domain-containing protein 9                                                                                          |
| 0,00 | 0,00 | Map4k1         | Mitogen-activated protein kinase kinase kinase kinase 1;Mitogen-activated protein kinase kinase kinase kinase                    |
| 0,00 | 0,00 | Cdk5rap3       | CDK5 regulatory subunit-associated protein 3                                                                                     |
| 0,00 | 0,00 | Hnrnpm         | Heterogeneous nuclear ribonucleoprotein M                                                                                        |
| 0,00 | 0,00 | Osgep          | Probable tRNA N6-adenosine threonylcarbamoyltransferase                                                                          |
| 0,00 | 0,00 | Canx           | Calnexin                                                                                                                         |
| 0,00 | 0,00 | Uqcrc2         | Cytochrome b-c1 complex subunit 2, mitochondrial                                                                                 |
| 0,00 | 0,00 | Homer3         | Homer protein homolog 3                                                                                                          |
| 0,00 | 0,00 | Mpc2           | Mitochondrial pyruvate carrier 2                                                                                                 |
| 0,00 | 0,00 | Rab8a          | Ras-related protein Rab-8A                                                                                                       |
| 0,00 | 0,00 | Cd72           | B-cell differentiation antigen CD72                                                                                              |
| 0,00 | 0,00 | Atxn3          | Ataxin-3                                                                                                                         |
| 0,00 | 0,00 | Timm8b         | Mitochondrial import inner membrane translocase subunit Tim8 B                                                                   |
| 0,00 | 0,00 | Erlin1;Erlin2  | Erlin-2;Erlin-1                                                                                                                  |
| 0,00 | 0,00 | Rac1;Rac2;Rac3 | Ras-related C3 botulinum toxin substrate 2;Ras-related C3 botulinum toxin substrate 1;Ras-related C3 botulinum toxin substrate 3 |

DGAT assay

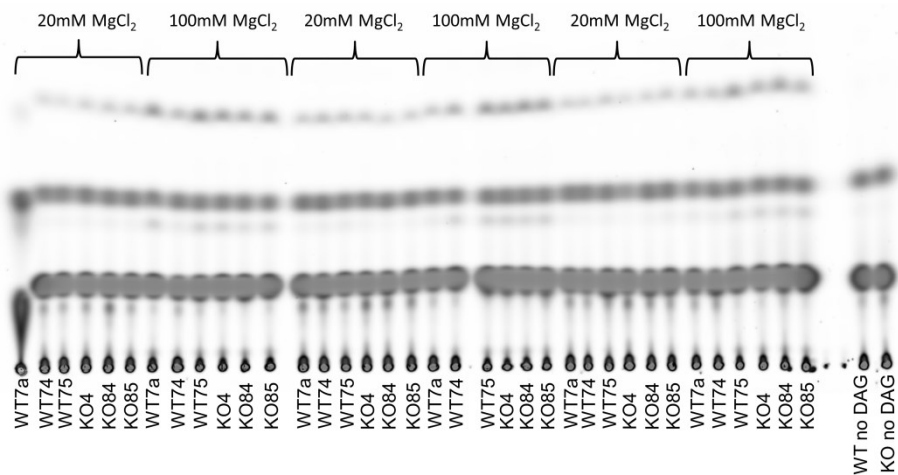


Figure S 7: DGAT assay

## Proteins identified from DABGE in-gel digest

**Table S 3: Proteins identified from in-gel digest of spot 1 from DABGE gel (Figure 21)**

| Accession | Name                                                                                                                      | Score   |
|-----------|---------------------------------------------------------------------------------------------------------------------------|---------|
| P11499    | Heat shock protein HSP 90-beta OS=Mus musculus GN=Hsp90ab1 PE=1 SV=2 - [HS90B_MOUSE]                                      | 1089,51 |
| Q99K10    | Aconitate hydratase, mitochondrial OS=Mus musculus GN=Aco2 PE=1 SV=1 - [ACON_MOUSE]                                       | 864,3   |
| P49718    | DNA replication licensing factor MCM5 OS=Mus musculus GN=Mcm5 PE=2 SV=1 - [MCM5_MOUSE]                                    | 826,74  |
| Q9D0R2    | Threonyl-tRNA synthetase, cytoplasmic OS=Mus musculus GN=Tars PE=1 SV=2 - [SYTC_MOUSE]                                    | 812,89  |
| Q8BQ30    | Phostensin OS=Mus musculus PE=1 SV=1 - [PHTNS_MOUSE]                                                                      | 789,31  |
| Q8R146    | Acylamino-acid-releasing enzyme OS=Mus musculus GN=Apeh PE=2 SV=2 - [APEH_MOUSE]                                          | 773,17  |
| P07901    | Heat shock protein HSP 90-alpha OS=Mus musculus GN=Hsp90aa1 PE=1 SV=4 - [HS90A_MOUSE]                                     | 728,3   |
| Q9WTX8    | Mitotic spindle assembly checkpoint protein MAD1 OS=Mus musculus GN=Mad1i1 PE=2 SV=1 - [MD1L1_MOUSE]                      | 592,34  |
| Q8R2Q4    | Ribosome-releasing factor 2, mitochondrial OS=Mus musculus GN=Gfm2 PE=2 SV=2 - [RRF2M_MOUSE]                              | 562,9   |
| P07742    | Ribonucleoside-diphosphate reductase large subunit OS=Mus musculus GN=Rrm1 PE=1 SV=1 - [RIR1_MOUSE]                       | 507,36  |
| Q9WUA3    | 6-phosphofructokinase type C OS=Mus musculus GN=Pfkp PE=1 SV=1 - [K6PP_MOUSE]                                             | 450,11  |
| P02535    | Keratin, type I cytoskeletal 10 OS=Mus musculus GN=Krt10 PE=1 SV=3 - [K1C10_MOUSE]                                        | 448,47  |
| Q60865    | Caprin-1 OS=Mus musculus GN=Caprin1 PE=1 SV=2 - [CAPR1_MOUSE]                                                             | 439,7   |
| P09405    | Nucleolin OS=Mus musculus GN=Ncl PE=1 SV=2 - [NUCL_MOUSE]                                                                 | 405,69  |
| Q9Z110    | Delta-1-pyrroline-5-carboxylate synthase OS=Mus musculus GN=Aldh18a1 PE=2 SV=1 - [P5CS_MOUSE]                             | 365,48  |
| P60710    | Actin, cytoplasmic 1 OS=Mus musculus GN=Actb PE=1 SV=1 - [ACTB_MOUSE]                                                     | 356,64  |
| Q01853    | Transitional endoplasmic reticulum ATPase OS=Mus musculus GN=Vcp PE=1 SV=4 - [TERA_MOUSE]                                 | 329,12  |
| P12382    | 6-phosphofructokinase, liver type OS=Mus musculus GN=Pfk1 PE=1 SV=3 - [K6PL_MOUSE]                                        | 310,7   |
| Q6NXH9    | Keratin, type II cytoskeletal 73 OS=Mus musculus GN=Krt73 PE=1 SV=1 - [K2C73_MOUSE]                                       | 286,76  |
| Q9ER72    | Cysteinyl-tRNA synthetase, cytoplasmic OS=Mus musculus GN=Cars PE=1 SV=2 - [SYCC_MOUSE]                                   | 265,33  |
| Q9Z1F9    | SUMO-activating enzyme subunit 2 OS=Mus musculus GN=Uba2 PE=2 SV=1 - [SAE2_MOUSE]                                         | 257,69  |
| Q91VR5    | ATP-dependent RNA helicase DDX1 OS=Mus musculus GN=Ddx1 PE=1 SV=1 - [DDX1_MOUSE]                                          | 256,98  |
| O70551    | Serine/threonine-protein kinase SRPK1 OS=Mus musculus GN=Srp1 PE=1 SV=2 - [SRPK1_MOUSE]                                   | 244,75  |
| Q9EQH3    | Vacuolar protein sorting-associated protein 35 OS=Mus musculus GN=Vps35 PE=1 SV=1 - [VPS35_MOUSE]                         | 236,95  |
| P04104    | Keratin, type II cytoskeletal 1 OS=Mus musculus GN=Krt1 PE=1 SV=4 - [K2C1_MOUSE]                                          | 227,12  |
| Q61881    | DNA replication licensing factor MCM7 OS=Mus musculus GN=Mcm7 PE=2 SV=1 - [MCM7_MOUSE]                                    | 203,59  |
| P68373    | Tubulin alpha-1C chain OS=Mus musculus GN=Tuba1c PE=1 SV=1 - [TBA1C_MOUSE]                                                | 157,4   |
| P0CG49    | Polyubiquitin-B OS=Mus musculus GN=Ubb PE=1 SV=1 - [UBB_MOUSE]                                                            | 153,28  |
| P07724    | Serum albumin OS=Mus musculus GN=Alb PE=1 SV=3 - [ALBU_MOUSE]                                                             | 138,82  |
| Q9JK91    | DNA mismatch repair protein Mlh1 OS=Mus musculus GN=Mlh1 PE=2 SV=1 - [MLH1_MOUSE]                                         | 136,47  |
| Q9QYB5    | Gamma-adducin OS=Mus musculus GN=Add3 PE=1 SV=1 - [ADDG_MOUSE]                                                            | 132,9   |
| P63017    | Heat shock cognate 71 kDa protein OS=Mus musculus GN=Hspa8 PE=1 SV=1 - [HSP7C_MOUSE]                                      | 125,58  |
| Q8BGZ7    | Keratin, type II cytoskeletal 75 OS=Mus musculus GN=Krt75 PE=1 SV=1 - [K2C75_MOUSE]                                       | 122,18  |
| P13020    | Gelsolin OS=Mus musculus GN=Gsn PE=1 SV=3 - [GELS_MOUSE]                                                                  | 120,52  |
| Q8BMI3    | ADP-ribosylation factor-binding protein GGA3 OS=Mus musculus GN=Gga3 PE=2 SV=1 - [GGA3_MOUSE]                             | 118,36  |
| Q8BIJ7    | RUN and FYVE domain-containing protein 1 OS=Mus musculus GN=Rufy1 PE=1 SV=1 - [RUFY1_MOUSE]                               | 89,34   |
| P19001    | Keratin, type I cytoskeletal 19 OS=Mus musculus GN=Krt19 PE=2 SV=1 - [K1C19_MOUSE]                                        | 71,33   |
| Q3UV17    | Keratin, type II cytoskeletal 2 oral OS=Mus musculus GN=Krt76 PE=2 SV=1 - [K22O_MOUSE]                                    | 58,16   |
| Q9JIX8    | Apoptotic chromatin condensation inducer in the nucleus OS=Mus musculus GN=Acin1 PE=1 SV=2 - [ACINU_MOUSE]                | 57,85   |
| P46061    | Ran GTPase-activating protein 1 OS=Mus musculus GN=Rangap1 PE=1 SV=1 - [RAGP1_MOUSE]                                      | 48,09   |
| Q8K3H0    | DCC-interacting protein 13-alpha OS=Mus musculus GN=Appl1 PE=1 SV=1 - [DP13A_MOUSE]                                       | 34,11   |
| Q7SIG6    | Arf-GAP with SH3 domain, ANK repeat and PH domain-containing protein 2 OS=Mus musculus GN=Asap2 PE=1 SV=3 - [ASAP2_MOUSE] | 30,94   |
| Q9Z1E4    | Glycogen [starch] synthase, muscle OS=Mus musculus GN=Gys1 PE=1 SV=2 - [GYS1_MOUSE]                                       | 26,43   |
| Q8VEK3    | Heterogeneous nuclear ribonucleoprotein U OS=Mus musculus GN=Hnrnpu PE=1 SV=1 - [HNRPU_MOUSE]                             | 24,93   |

**Table S 4: Proteins identified from in-gel digest of spot 2 from DABGE gel (Figure 21)**

| Accession | Name                                                                                                                      | Score   |
|-----------|---------------------------------------------------------------------------------------------------------------------------|---------|
| Q99K10    | Aconitate hydratase, mitochondrial OS=Mus musculus GN=Aco2 PE=1 SV=1 - [ACON_MOUSE]                                       | 1747,52 |
| P11499    | Heat shock protein HSP 90-beta OS=Mus musculus GN=Hsp90ab1 PE=1 SV=2 - [HS90B_MOUSE]                                      | 1443,65 |
| P07901    | Heat shock protein HSP 90-alpha OS=Mus musculus GN=Hsp90aa1 PE=1 SV=4 - [HS90A_MOUSE]                                     | 1061,32 |
| Q9WUA3    | 6-phosphofructokinase type C OS=Mus musculus GN=Pfkp PE=1 SV=1 - [K6PP_MOUSE]                                             | 1001,48 |
| P49718    | DNA replication licensing factor MCM5 OS=Mus musculus GN=Mcm5 PE=2 SV=1 - [MCM5_MOUSE]                                    | 932,26  |
| P07742    | Ribonucleoside-diphosphate reductase large subunit OS=Mus musculus GN=Rrm1 PE=1 SV=1 - [RIR1_MOUSE]                       | 867,06  |
| Q9D0R2    | Threonyl-tRNA synthetase, cytoplasmic OS=Mus musculus GN=Tars PE=1 SV=2 - [SYTC_MOUSE]                                    | 854,79  |
| Q8R146    | Acylamino-acid-releasing enzyme OS=Mus musculus GN=Apeh PE=2 SV=2 - [APEH_MOUSE]                                          | 750,41  |
| Q9Z110    | Delta-1-pyrroline-5-carboxylate synthase OS=Mus musculus GN=Aldh18a1 PE=2 SV=1 - [P5CS_MOUSE]                             | 659,61  |
| Q9Z1F9    | SUMO-activating enzyme subunit 2 OS=Mus musculus GN=Uba2 PE=2 SV=1 - [SAE2_MOUSE]                                         | 599,72  |
| Q9ER72    | Cysteinyl-tRNA synthetase, cytoplasmic OS=Mus musculus GN=Cars PE=1 SV=2 - [SYCC_MOUSE]                                   | 503,31  |
| Q91VR5    | ATP-dependent RNA helicase DDX1 OS=Mus musculus GN=Ddx1 PE=1 SV=1 - [DDX1_MOUSE]                                          | 479,71  |
| Q01853    | Transitional endoplasmic reticulum ATPase OS=Mus musculus GN=Vcp PE=1 SV=4 - [TERA_MOUSE]                                 | 473,36  |
| Q8K3H0    | DCC-interacting protein 13-alpha OS=Mus musculus GN=Appl1 PE=1 SV=1 - [DP13A_MOUSE]                                       | 458,7   |
| P09405    | Nucleolin OS=Mus musculus GN=Ncl PE=1 SV=2 - [NUCL_MOUSE]                                                                 | 404,47  |
| Q61881    | DNA replication licensing factor MCM7 OS=Mus musculus GN=Mcm7 PE=2 SV=1 - [MCM7_MOUSE]                                    | 399,2   |
| Q9EQH3    | Vacuolar protein sorting-associated protein 35 OS=Mus musculus GN=Vps35 PE=1 SV=1 - [VPS35_MOUSE]                         | 393,86  |
| P12382    | 6-phosphofructokinase, liver type OS=Mus musculus GN=Pfk1 PE=1 SV=3 - [K6PL_MOUSE]                                        | 377,28  |
| P02535    | Keratin, type I cytoskeletal 10 OS=Mus musculus GN=Krt10 PE=1 SV=3 - [K1C10_MOUSE]                                        | 377,16  |
| Q60865    | Caprin-1 OS=Mus musculus GN=Caprin1 PE=1 SV=2 - [CAPR1_MOUSE]                                                             | 335,29  |
| P63017    | Heat shock cognate 71 kDa protein OS=Mus musculus GN=Hspa8 PE=1 SV=1 - [HSP7C_MOUSE]                                      | 334,46  |
| P60710    | Actin, cytoplasmic 1 OS=Mus musculus GN=Actb PE=1 SV=1 - [ACTB_MOUSE]                                                     | 319,44  |
| P04104    | Keratin, type II cytoskeletal 1 OS=Mus musculus GN=Krt1 PE=1 SV=4 - [K2C1_MOUSE]                                          | 317,61  |
| Q8BQ30    | Phostensin OS=Mus musculus PE=1 SV=1 - [PHTNS_MOUSE]                                                                      | 295,35  |
| Q6NXH9    | Keratin, type II cytoskeletal 73 OS=Mus musculus GN=Krt73 PE=1 SV=1 - [K2C73_MOUSE]                                       | 244,65  |
| Q9QUR6    | Prolyl endopeptidase OS=Mus musculus GN=Prep PE=2 SV=1 - [PPCE_MOUSE]                                                     | 229,71  |
| O70551    | Serine/threonine-protein kinase SRPK1 OS=Mus musculus GN=Srp1 PE=1 SV=2 - [SRPK1_MOUSE]                                   | 194,63  |
| Q8BGZ7    | Keratin, type II cytoskeletal 75 OS=Mus musculus GN=Krt75 PE=1 SV=1 - [K2C75_MOUSE]                                       | 190,82  |
| P0CG49    | Polyubiquitin-B OS=Mus musculus GN=Ubb PE=1 SV=1 - [UBB_MOUSE]                                                            | 175,62  |
| Q9QYB5    | Gamma-adducin OS=Mus musculus GN=Add3 PE=1 SV=1 - [ADDG_MOUSE]                                                            | 163,01  |
| Q61316    | Heat shock 70 kDa protein 4 OS=Mus musculus GN=Hspa4 PE=1 SV=1 - [HSP74_MOUSE]                                            | 109,57  |
| Q3UV17    | Keratin, type II cytoskeletal 2 oral OS=Mus musculus GN=Krt76 PE=2 SV=1 - [K22O_MOUSE]                                    | 80,82   |
| Q9JK91    | DNA mismatch repair protein Mlh1 OS=Mus musculus GN=Mlh1 PE=2 SV=1 - [MLH1_MOUSE]                                         | 80,47   |
| P10126    | Elongation factor 1-alpha 1 OS=Mus musculus GN=Eef1a1 PE=1 SV=3 - [EF1A1_MOUSE]                                           | 74,33   |
| P07724    | Serum albumin OS=Mus musculus GN=Alb PE=1 SV=3 - [ALBU_MOUSE]                                                             | 67,71   |
| Q61699    | Heat shock protein 105 kDa OS=Mus musculus GN=Hsph1 PE=1 SV=2 - [HS105_MOUSE]                                             | 52,51   |
| P68368    | Tubulin alpha-4A chain OS=Mus musculus GN=Tuba4a PE=1 SV=1 - [TBA4A_MOUSE]                                                | 44,16   |
| Q7SIG6    | Arf-GAP with SH3 domain, ANK repeat and PH domain-containing protein 2 OS=Mus musculus GN=Asap2 PE=1 SV=3 - [ASAP2_MOUSE] | 28,64   |
| Q9JLV5    | Cullin-3 OS=Mus musculus GN=Cul3 PE=1 SV=1 - [CUL3_MOUSE]                                                                 | 27,71   |
| Q9WTX8    | Mitotic spindle assembly checkpoint protein MAD1 OS=Mus musculus GN=Mad1l1 PE=2 SV=1 - [MD1L1_MOUSE]                      | 26,59   |
| Q9D662    | Protein transport protein Sec23B OS=Mus musculus GN=Sec23b PE=2 SV=1 - [SC23B_MOUSE]                                      | 26,2    |
| Q8VEK3    | Heterogeneous nuclear ribonucleoprotein U OS=Mus musculus GN=Hnrmpu PE=1 SV=1 - [HNRPU_MOUSE]                             | 24,5    |

**Table S 5: Proteins identified from in-gel digest of spot 3 from DABGE gel (Figure 21)**

| Accession | Name                                                                                                                      | Score   |
|-----------|---------------------------------------------------------------------------------------------------------------------------|---------|
| P63017    | Heat shock cognate 71 kDa protein OS=Mus musculus GN=Hspa8 PE=1 SV=1 - [HSP7C_MOUSE]                                      | 6509,31 |
| P38647    | Stress-70 protein, mitochondrial OS=Mus musculus GN=Hspa9 PE=1 SV=2 - [GRP75_MOUSE]                                       | 4517,14 |
| P17879    | Heat shock 70 kDa protein 1B OS=Mus musculus GN=Hspa1b PE=1 SV=3 - [HS71B_MOUSE]                                          | 2013,3  |
| P16627    | Heat shock 70 kDa protein 1-like OS=Mus musculus GN=Hspa1l PE=2 SV=4 - [HS71L_MOUSE]                                      | 1253,56 |
| Q9JIG7    | Coiled-coil domain-containing protein 22 OS=Mus musculus GN=Ccdc22 PE=2 SV=1 - [CCD22_MOUSE]                              | 806,36  |
| Q99MN1    | Lysyl-tRNA synthetase OS=Mus musculus GN=Kars PE=1 SV=1 - [SYK_MOUSE]                                                     | 789,2   |
| P14824    | Annexin A6 OS=Mus musculus GN=Anxa6 PE=1 SV=2 - [ANXA6_MOUSE]                                                             | 572,18  |
| P50516    | V-type proton ATPase catalytic subunit A OS=Mus musculus GN=Atp6v1a PE=1 SV=2 - [VATA_MOUSE]                              | 372,6   |
| Q9QUR6    | Prolyl endopeptidase OS=Mus musculus GN=Prep PE=2 SV=1 - [PPCE_MOUSE]                                                     | 331,8   |
| Q6NXH9    | Keratin, type II cytoskeletal 73 OS=Mus musculus GN=Krt73 PE=1 SV=1 - [K2C73_MOUSE]                                       | 295,79  |
| Q8R3C0    | UPF0557 protein C10orf119 homolog OS=Mus musculus PE=2 SV=1 - [CJ119_MOUSE]                                               | 295,7   |
| Q7TSV4    | Phosphoglucomutase-2 OS=Mus musculus GN=Pgm2 PE=1 SV=1 - [PGM2_MOUSE]                                                     | 262,15  |
| P02535    | Keratin, type I cytoskeletal 10 OS=Mus musculus GN=Krt10 PE=1 SV=3 - [K1C10_MOUSE]                                        | 261,82  |
| P04104    | Keratin, type II cytoskeletal 1 OS=Mus musculus GN=Krt1 PE=1 SV=4 - [K2C1_MOUSE]                                          | 245,47  |
| P29341    | Polyadenylate-binding protein 1 OS=Mus musculus GN=Pabpc1 PE=1 SV=1 - [PABP1_MOUSE]                                       | 236,16  |
| Q8R349    | Cell division cycle protein 16 homolog OS=Mus musculus GN=Cdc16 PE=2 SV=1 - [CDC16_MOUSE]                                 | 202     |
| Q8BGZ7    | Keratin, type II cytoskeletal 75 OS=Mus musculus GN=Krt75 PE=1 SV=1 - [K2C75_MOUSE]                                       | 200,24  |
| P21619    | Lamin-B2 OS=Mus musculus GN=Lmnb2 PE=1 SV=2 - [LMNB2_MOUSE]                                                               | 185,84  |
| Q8BH43    | Wiskott-Aldrich syndrome protein family member 2 OS=Mus musculus GN=Wasf2 PE=1 SV=1 - [WASF2_MOUSE]                       | 159,22  |
| Q91VH2    | Sorting nexin-9 OS=Mus musculus GN=Snx9 PE=1 SV=1 - [SNX9_MOUSE]                                                          | 151,4   |
| P07724    | Serum albumin OS=Mus musculus GN=Alb PE=1 SV=3 - [ALBU_MOUSE]                                                             | 146,47  |
| Q6P1B1    | Xaa-Pro aminopeptidase 1 OS=Mus musculus GN=Xpnpep1 PE=2 SV=1 - [XPP1_MOUSE]                                              | 103,33  |
| Q91YD3    | mRNA-decapping enzyme 1A OS=Mus musculus GN=Dcp1a PE=1 SV=1 - [DCP1A_MOUSE]                                               | 99,03   |
| P49710    | Hematopoietic lineage cell-specific protein OS=Mus musculus GN=Hcls1 PE=1 SV=1 - [HCLS1_MOUSE]                            | 98,51   |
| P0CG49    | Polyubiquitin-B OS=Mus musculus GN=Ubb PE=1 SV=1 - [UBB_MOUSE]                                                            | 90,22   |
| Q8VED5    | Keratin, type II cytoskeletal 79 OS=Mus musculus GN=Krt79 PE=1 SV=2 - [K2C79_MOUSE]                                       | 84,47   |
| P10404    | MLV-related proviral Env polyprotein OS=Mus musculus PE=2 SV=3 - [ENV1_MOUSE]                                             | 73,65   |
| Q6A028    | Switch-associated protein 70 OS=Mus musculus GN=Swap70 PE=1 SV=2 - [SWP70_MOUSE]                                          | 58,4    |
| P97494    | Glutamate--cysteine ligase catalytic subunit OS=Mus musculus GN=Gclc PE=2 SV=4 - [GSH1_MOUSE]                             | 47,35   |
| Q61233    | Plastin-2 OS=Mus musculus GN=Lcp1 PE=1 SV=4 - [PLSL_MOUSE]                                                                | 39,16   |
| Q99KN9    | Clathrin interactor 1 OS=Mus musculus GN=Clint1 PE=1 SV=2 - [EPN4_MOUSE]                                                  | 36,77   |
| Q7SIG6    | Arf-GAP with SH3 domain, ANK repeat and PH domain-containing protein 2 OS=Mus musculus GN=Asap2 PE=1 SV=3 - [ASAP2_MOUSE] | 31,03   |
| Q8BFZ3    | Beta-actin-like protein 2 OS=Mus musculus GN=Actb2 PE=1 SV=1 - [ACTBL_MOUSE]                                              | 27,36   |

**Table S 6: Proteins identified from in-gel digest of spot 4 from DABGE gel (Figure 21)**

| Accession | Name                                                                                                                      | Score   |
|-----------|---------------------------------------------------------------------------------------------------------------------------|---------|
| P63017    | Heat shock cognate 71 kDa protein OS=Mus musculus GN=Hspa8 PE=1 SV=1 - [HSP7C_MOUSE]                                      | 6630,61 |
| P17879    | Heat shock 70 kDa protein 1B OS=Mus musculus GN=Hspa1b PE=1 SV=3 - [HS71B_MOUSE]                                          | 2853,31 |
| Q61696    | Heat shock 70 kDa protein 1A OS=Mus musculus GN=Hspa1a PE=1 SV=2 - [HS71A_MOUSE]                                          | 2705,88 |
| Q61233    | Plastin-2 OS=Mus musculus GN=Lcp1 PE=1 SV=4 - [PLSL_MOUSE]                                                                | 2290,82 |
| P16627    | Heat shock 70 kDa protein 1-like OS=Mus musculus GN=Hspa1l PE=2 SV=4 - [HS71L_MOUSE]                                      | 1896,65 |
| P17156    | Heat shock-related 70 kDa protein 2 OS=Mus musculus GN=Hspa2 PE=1 SV=1 - [HSP72_MOUSE]                                    | 1863,51 |
| P14824    | Annexin A6 OS=Mus musculus GN=Anxa6 PE=1 SV=2 - [ANXA6_MOUSE]                                                             | 1017,29 |
| P38647    | Stress-70 protein, mitochondrial OS=Mus musculus GN=Hspa9 PE=1 SV=2 - [GRP75_MOUSE]                                       | 932,32  |
| P21619    | Lamin-B2 OS=Mus musculus GN=Lmn2 PE=1 SV=2 - [LMNB2_MOUSE]                                                                | 891,15  |
| P50516    | V-type proton ATPase catalytic subunit A OS=Mus musculus GN=Atp6v1a PE=1 SV=2 - [VATA_MOUSE]                              | 701,99  |
| P02535    | Keratin, type I cytoskeletal 10 OS=Mus musculus GN=Krt10 PE=1 SV=3 - [K1C10_MOUSE]                                        | 400,31  |
| P04104    | Keratin, type II cytoskeletal 1 OS=Mus musculus GN=Krt1 PE=1 SV=4 - [K2C1_MOUSE]                                          | 297,32  |
| Q6NXH9    | Keratin, type II cytoskeletal 73 OS=Mus musculus GN=Krt73 PE=1 SV=1 - [K2C73_MOUSE]                                       | 222,39  |
| P40142    | Transketolase OS=Mus musculus GN=Tkt PE=1 SV=1 - [TKT_MOUSE]                                                              | 221,2   |
| Q99MN1    | Lysyl-tRNA synthetase OS=Mus musculus GN=Kars PE=1 SV=1 - [SYK_MOUSE]                                                     | 192,65  |
| Q9CWX8    | Sorting nexin-2 OS=Mus musculus GN=Snx2 PE=1 SV=2 - [SNX2_MOUSE]                                                          | 191,71  |
| Q8R349    | Cell division cycle protein 16 homolog OS=Mus musculus GN=Cdc16 PE=2 SV=1 - [CDC16_MOUSE]                                 | 181,6   |
| Q8BGZ7    | Keratin, type II cytoskeletal 75 OS=Mus musculus GN=Krt75 PE=1 SV=1 - [K2C75_MOUSE]                                       | 178,67  |
| P07724    | Serum albumin OS=Mus musculus GN=Alb PE=1 SV=3 - [ALBU_MOUSE]                                                             | 164,39  |
| Q6P1B1    | Xaa-Pro aminopeptidase 1 OS=Mus musculus GN=Xpnpep1 PE=2 SV=1 - [XPP1_MOUSE]                                              | 159,77  |
| Q61414    | Keratin, type I cytoskeletal 15 OS=Mus musculus GN=Krt15 PE=1 SV=2 - [K1C15_MOUSE]                                        | 157,8   |
| P0CG49    | Polyubiquitin-B OS=Mus musculus GN=Ubb PE=1 SV=1 - [UBB_MOUSE]                                                            | 144,98  |
| Q8R060    | Protein zwilch homolog OS=Mus musculus GN=Zwilch PE=2 SV=1 - [ZWILC_MOUSE]                                                | 114,71  |
| Q8VED5    | Keratin, type II cytoskeletal 79 OS=Mus musculus GN=Krt79 PE=1 SV=2 - [K2C79_MOUSE]                                       | 78,84   |
| Q8BMA6    | Signal recognition particle 68 kDa protein OS=Mus musculus GN=Srp68 PE=2 SV=1 - [SRP68_MOUSE]                             | 71,25   |
| P60710    | Actin, cytoplasmic 1 OS=Mus musculus GN=Actb PE=1 SV=1 - [ACTB_MOUSE]                                                     | 68,42   |
| Q3UV17    | Keratin, type II cytoskeletal 2 oral OS=Mus musculus GN=Krt76 PE=2 SV=1 - [K22O_MOUSE]                                    | 60,59   |
| Q7TSV4    | Phosphoglucomutase-2 OS=Mus musculus GN=Pgm2 PE=1 SV=1 - [PGM2_MOUSE]                                                     | 54,38   |
| Q8R3C0    | UPF0557 protein C10orf119 homolog OS=Mus musculus PE=2 SV=1 - [CJ119_MOUSE]                                               | 46,99   |
| Q3TTY5    | Keratin, type II cytoskeletal 2 epidermal OS=Mus musculus GN=Krt2 PE=1 SV=1 - [K22E_MOUSE]                                | 40,28   |
| Q7SIG6    | Arf-GAP with SH3 domain, ANK repeat and PH domain-containing protein 2 OS=Mus musculus GN=Asap2 PE=1 SV=3 - [ASAP2_MOUSE] | 32,52   |
| P68368    | Tubulin alpha-4A chain OS=Mus musculus GN=Tuba4a PE=1 SV=1 - [TBA4A_MOUSE]                                                | 28,19   |
| Q99KN9    | Clathrin interactor 1 OS=Mus musculus GN=Clint1 PE=1 SV=2 - [EPN4_MOUSE]                                                  | 27,33   |
| A6PWY4    | WD repeat-containing protein 76 OS=Mus musculus GN=Wdr76 PE=2 SV=1 - [WDR76_MOUSE]                                        | 20,89   |

**Table S 7: Proteins identified from in-gel digest of spot 5 from DABGE gel (Figure 21)**

| Accession | Name                                                                                                                                                      | Score   |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| P63017    | Heat shock cognate 71 kDa protein OS=Mus musculus GN=Hspa8 PE=1 SV=1 - [HSP7C_MOUSE]                                                                      | 5170,7  |
| Q6IFX2    | Keratin, type I cytoskeletal 42 OS=Mus musculus GN=Krt42 PE=1 SV=1 - [K1C42_MOUSE]                                                                        | 3463,53 |
| Q9QWL7    | Keratin, type I cytoskeletal 17 OS=Mus musculus GN=Krt17 PE=1 SV=3 - [K1C17_MOUSE]                                                                        | 2639,61 |
| Q61781    | Keratin, type I cytoskeletal 14 OS=Mus musculus GN=Krt14 PE=1 SV=2 - [K1C14_MOUSE]                                                                        | 2612,6  |
| P50446    | Keratin, type II cytoskeletal 6A OS=Mus musculus GN=Krt6a PE=2 SV=3 - [K2C6A_MOUSE]                                                                       | 2171,9  |
| Q9Z2K1    | Keratin, type I cytoskeletal 16 OS=Mus musculus GN=Krt16 PE=1 SV=3 - [K1C16_MOUSE]                                                                        | 2043,96 |
| Q922U2    | Keratin, type II cytoskeletal 5 OS=Mus musculus GN=Krt5 PE=1 SV=1 - [K2C5_MOUSE]                                                                          | 1717,15 |
| P17156    | Heat shock-related 70 kDa protein 2 OS=Mus musculus GN=Hspa2 PE=1 SV=1 - [HSP72_MOUSE]                                                                    | 1408,75 |
| P38647    | Stress-70 protein, mitochondrial OS=Mus musculus GN=Hspa9 PE=1 SV=2 - [GRP75_MOUSE]                                                                       | 1294,47 |
| P17879    | Heat shock 70 kDa protein 1B OS=Mus musculus GN=Hspa1b PE=1 SV=3 - [HS71B_MOUSE]                                                                          | 1285,3  |
| Q61414    | Keratin, type I cytoskeletal 15 OS=Mus musculus GN=Krt15 PE=1 SV=2 - [K1C15_MOUSE]                                                                        | 1200,55 |
| P19001    | Keratin, type I cytoskeletal 19 OS=Mus musculus GN=Krt19 PE=2 SV=1 - [K1C19_MOUSE]                                                                        | 1009,16 |
| P16627    | Heat shock 70 kDa protein 1-like OS=Mus musculus GN=Hspa1l PE=2 SV=4 - [HS71L_MOUSE]                                                                      | 976,2   |
| P04104    | Keratin, type II cytoskeletal 1 OS=Mus musculus GN=Krt1 PE=1 SV=4 - [K2C1_MOUSE]                                                                          | 886,35  |
| Q02257    | Junction plakoglobin OS=Mus musculus GN=Jup PE=1 SV=3 - [PLAK_MOUSE]                                                                                      | 688,04  |
| Q3UV17    | Keratin, type II cytoskeletal 2 oral OS=Mus musculus GN=Krt76 PE=2 SV=1 - [K22O_MOUSE]                                                                    | 679,48  |
| Q6NXH9    | Keratin, type II cytoskeletal 73 OS=Mus musculus GN=Krt73 PE=1 SV=1 - [K2C73_MOUSE]                                                                       | 673,12  |
| Q61233    | Plastin-2 OS=Mus musculus GN=Lcp1 PE=1 SV=4 - [PLSL_MOUSE]                                                                                                | 566,11  |
| Q8VED5    | Keratin, type II cytoskeletal 79 OS=Mus musculus GN=Krt79 PE=1 SV=2 - [K2C79_MOUSE]                                                                       | 528,24  |
| Q8BMF4    | Dihydrolipoyllysine-residue acetyltransferase component of pyruvate dehydrogenase complex, mitochondrial OS=Mus musculus GN=Dlat PE=1 SV=2 - [ODP2_MOUSE] | 499,96  |
| Q3TTY5    | Keratin, type II cytoskeletal 2 epidermal OS=Mus musculus GN=Krt2 PE=1 SV=1 - [K22E_MOUSE]                                                                | 465,65  |
| P02535    | Keratin, type I cytoskeletal 10 OS=Mus musculus GN=Krt10 PE=1 SV=3 - [K1C10_MOUSE]                                                                        | 409,15  |
| P50516    | V-type proton ATPase catalytic subunit A OS=Mus musculus GN=Atp6v1a PE=1 SV=2 - [VATA_MOUSE]                                                              | 396,89  |
| Q7TSV4    | Phosphoglucomutase-2 OS=Mus musculus GN=Pgm2 PE=1 SV=1 - [PGM2_MOUSE]                                                                                     | 328,17  |
| P14824    | Annexin A6 OS=Mus musculus GN=Anxa6 PE=1 SV=2 - [ANXA6_MOUSE]                                                                                             | 198,74  |
| Q99MN1    | Lysyl-tRNA synthetase OS=Mus musculus GN=Kars PE=1 SV=1 - [SYK_MOUSE]                                                                                     | 178,84  |
| P17897    | Lysozyme C-1 OS=Mus musculus GN=Lyz1 PE=1 SV=1 - [LYZ1_MOUSE]                                                                                             | 143,02  |
| Q61495    | Desmoglein-1-alpha OS=Mus musculus GN=Dsg1a PE=2 SV=2 - [DSG1A_MOUSE]                                                                                     | 100,48  |
| P0CG49    | Polyubiquitin-B OS=Mus musculus GN=Ubb PE=1 SV=1 - [UBB_MOUSE]                                                                                            | 91,93   |
| Q61171    | Peroxiredoxin-2 OS=Mus musculus GN=Prdx2 PE=1 SV=3 - [PRDX2_MOUSE]                                                                                        | 88,53   |
| Q8R349    | Cell division cycle protein 16 homolog OS=Mus musculus GN=Cdc16 PE=2 SV=1 - [CDC16_MOUSE]                                                                 | 75,97   |
| Q8R0W0    | Epiplakin OS=Mus musculus GN=Eppk1 PE=1 SV=2 - [EPIPL_MOUSE]                                                                                              | 63,53   |
| Q6A028    | Switch-associated protein 70 OS=Mus musculus GN=Swap70 PE=1 SV=2 - [SWP70_MOUSE]                                                                          | 44,73   |
| Q7SIG6    | Arf-GAP with SH3 domain, ANK repeat and PH domain-containing protein 2 OS=Mus musculus GN=Asap2 PE=1 SV=3 - [ASAP2_MOUSE]                                 | 36,06   |
| P60710    | Actin, cytoplasmic 1 OS=Mus musculus GN=Actb PE=1 SV=1 - [ACTB_MOUSE]                                                                                     | 29,83   |
| Q8C6G8    | WD repeat-containing protein 26 OS=Mus musculus GN=Wdr26 PE=1 SV=2 - [WDR26_MOUSE]                                                                        | 23,25   |

**Table S 8: Proteins identified from in-gel digest of spot 6 from DABGE gel (Figure 21)**

| Accession | Name                                                                                                                             | Score   |
|-----------|----------------------------------------------------------------------------------------------------------------------------------|---------|
| P60710    | Actin, cytoplasmic 1 OS=Mus musculus GN=Actb PE=1 SV=1 - [ACTB_MOUSE]                                                            | 9051,18 |
| P68033    | Actin, alpha cardiac muscle 1 OS=Mus musculus GN=Actc1 PE=1 SV=1 - [ACTC_MOUSE]                                                  | 4592,92 |
| Q8BFZ3    | Beta-actin-like protein 2 OS=Mus musculus GN=Actb2 PE=1 SV=1 - [ACTBL_MOUSE]                                                     | 3871,85 |
| Q9JIF0    | Protein arginine N-methyltransferase 1 OS=Mus musculus GN=Prmt1 PE=1 SV=1 - [ANM1_MOUSE]                                         | 881     |
| O35685    | Nuclear migration protein nudC OS=Mus musculus GN=Nudc PE=1 SV=1 - [NUDC_MOUSE]                                                  | 836,29  |
| Q9R1T2    | SUMO-activating enzyme subunit 1 OS=Mus musculus GN=Sae1 PE=2 SV=1 - [SAE1_MOUSE]                                                | 760,47  |
| P63017    | Heat shock cognate 71 kDa protein OS=Mus musculus GN=Hspa8 PE=1 SV=1 - [HSP7C_MOUSE]                                             | 429,86  |
| Q8BK64    | Activator of 90 kDa heat shock protein ATPase homolog 1 OS=Mus musculus GN=Ahsa1 PE=2 SV=2 - [Ahsa1_MOUSE]                       | 392,84  |
| P68373    | Tubulin alpha-1C chain OS=Mus musculus GN=Tuba1c PE=1 SV=1 - [TBA1C_MOUSE]                                                       | 303,98  |
| P04104    | Keratin, type II cytoskeletal 1 OS=Mus musculus GN=Krt1 PE=1 SV=4 - [K2C1_MOUSE]                                                 | 274,38  |
| P02535    | Keratin, type I cytoskeletal 10 OS=Mus musculus GN=Krt10 PE=1 SV=3 - [K1C10_MOUSE]                                               | 274,24  |
| Q9CQM9    | Glutaredoxin-3 OS=Mus musculus GN=Glx3 PE=1 SV=1 - [GLRX3_MOUSE]                                                                 | 271,42  |
| Q6NXH9    | Keratin, type II cytoskeletal 73 OS=Mus musculus GN=Krt73 PE=1 SV=1 - [K2C73_MOUSE]                                              | 259,86  |
| P03958    | Adenosine deaminase OS=Mus musculus GN=Ada PE=1 SV=3 - [ADA_MOUSE]                                                               | 145,73  |
| Q3TXU5    | Deoxyhypusine synthase OS=Mus musculus GN=Dhps PE=2 SV=1 - [DHYS_MOUSE]                                                          | 131,33  |
| O35479    | Heterogeneous nuclear ribonucleoprotein G OS=Mus musculus GN=Rbmh PE=1 SV=1 - [HNRPG_MOUSE]                                      | 129,39  |
| Q01147    | Cyclic AMP-responsive element-binding protein 1 OS=Mus musculus GN=Creb1 PE=1 SV=1 - [CREB1_MOUSE]                               | 114,93  |
| Q9QZQ8    | Core histone macro-H2A.1 OS=Mus musculus GN=H2afy PE=1 SV=3 - [H2AY_MOUSE]                                                       | 98      |
| P63038    | 60 kDa heat shock protein, mitochondrial OS=Mus musculus GN=Hspd1 PE=1 SV=1 - [CH60_MOUSE]                                       | 92,8    |
| Q8BGZ7    | Keratin, type II cytoskeletal 75 OS=Mus musculus GN=Krt75 PE=1 SV=1 - [K2C75_MOUSE]                                              | 88,62   |
| Q7TPD2    | Protein FAM185A OS=Mus musculus GN=Fam185a PE=2 SV=1 - [F185A_MOUSE]                                                             | 87,35   |
| P82343    | N-acylglucosamine 2-epimerase OS=Mus musculus GN=Renbp PE=2 SV=3 - [REBPP_MOUSE]                                                 | 87,17   |
| Q8CCS6    | Polyadenylate-binding protein 2 OS=Mus musculus GN=Pabpn1 PE=2 SV=3 - [PABP2_MOUSE]                                              | 83,05   |
| P24288    | Branched-chain-amino-acid aminotransferase, cytosolic OS=Mus musculus GN=Bcat1 PE=2 SV=2 - [BCAT1_MOUSE]                         | 82,87   |
| Q9Z2K1    | Keratin, type I cytoskeletal 16 OS=Mus musculus GN=Krt16 PE=1 SV=3 - [K1C16_MOUSE]                                               | 81,54   |
| Q9Z2X1    | Heterogeneous nuclear ribonucleoprotein F OS=Mus musculus GN=Hnmpf PE=1 SV=3 - [HNRPF_MOUSE]                                     | 81,03   |
| Q9CQN1    | Heat shock protein 75 kDa, mitochondrial OS=Mus musculus GN=Trap1 PE=1 SV=1 - [TRAP1_MOUSE]                                      | 79,35   |
| P46718    | Programmed cell death protein 2 OS=Mus musculus GN=Pdcd2 PE=2 SV=2 - [PDCD2_MOUSE]                                               | 77,61   |
| P52432    | DNA-directed RNA polymerases I and III subunit RPAC1 OS=Mus musculus GN=Polr1e PE=1 SV=2 - [RPAC1_MOUSE]                         | 68,9    |
| P0CG49    | Polyubiquitin-B OS=Mus musculus GN=Ubb PE=1 SV=1 - [UBB_MOUSE]                                                                   | 59,2    |
| Q9Z2Y3    | Homer protein homolog 1 OS=Mus musculus GN=Homer1 PE=1 SV=2 - [HOME1_MOUSE]                                                      | 54,3    |
| O54734    | Dolichyl-diphosphooligosaccharide--protein glycosyltransferase 48 kDa subunit OS=Mus musculus GN=Ddost PE=1 SV=1 - [OST48_MOUSE] | 52,9    |
| Q60668    | Heterogeneous nuclear ribonucleoprotein D0 OS=Mus musculus GN=Hnmpd PE=1 SV=2 - [HNRPD_MOUSE]                                    | 52,89   |
| Q9R0N0    | Galactokinase OS=Mus musculus GN=Galk1 PE=2 SV=1 - [GALK1_MOUSE]                                                                 | 44,41   |
| Q3UV17    | Keratin, type II cytoskeletal 2 oral OS=Mus musculus GN=Krt76 PE=2 SV=1 - [K22O_MOUSE]                                           | 37,42   |
| Q7SIG6    | Arf-GAP with SH3 domain, ANK repeat and PH domain-containing protein 2 OS=Mus musculus GN=Asap2 PE=1 SV=3 - [ASAP2_MOUSE]        | 36,86   |

**Table S 9: Proteins identified from in-gel digest of spot 7 from DABGE gel (Figure 21)**

| Accession | Name                                                                                                                      | Score   |
|-----------|---------------------------------------------------------------------------------------------------------------------------|---------|
| P60710    | Actin, cytoplasmic 1 OS=Mus musculus GN=Actb PE=1 SV=1 - [ACTB_MOUSE]                                                     | 7943,55 |
| P68033    | Actin, alpha cardiac muscle 1 OS=Mus musculus GN=Actc1 PE=1 SV=1 - [ACTC_MOUSE]                                           | 4405,45 |
| Q8BFZ3    | Beta-actin-like protein 2 OS=Mus musculus GN=Actb2 PE=1 SV=1 - [ACTBL_MOUSE]                                              | 3646    |
| Q9JIF0    | Protein arginine N-methyltransferase 1 OS=Mus musculus GN=Prmt1 PE=1 SV=1 - [ANM1_MOUSE]                                  | 621,86  |
| Q8BK64    | Activator of 90 kDa heat shock protein ATPase homolog 1 OS=Mus musculus GN=Ahsa1 PE=2 SV=2 - [AHS1_MOUSE]                 | 552,92  |
| P42209    | Septin-1 OS=Mus musculus GN=Sept1 PE=2 SV=2 - [SEPT1_MOUSE]                                                               | 350,76  |
| P02535    | Keratin, type I cytoskeletal 10 OS=Mus musculus GN=Krt10 PE=1 SV=3 - [K1C10_MOUSE]                                        | 309,06  |
| P04104    | Keratin, type II cytoskeletal 1 OS=Mus musculus GN=Krt1 PE=1 SV=4 - [K2C1_MOUSE]                                          | 261,63  |
| Q6NXH9    | Keratin, type II cytoskeletal 73 OS=Mus musculus GN=Krt73 PE=1 SV=1 - [K2C73_MOUSE]                                       | 196,65  |
| Q8BGZ7    | Keratin, type II cytoskeletal 75 OS=Mus musculus GN=Krt75 PE=1 SV=1 - [K2C75_MOUSE]                                       | 112,41  |
| Q3UV17    | Keratin, type II cytoskeletal 2 oral OS=Mus musculus GN=Krt76 PE=2 SV=1 - [K22O_MOUSE]                                    | 73      |
| P82343    | N-acetylglucosamine 2-epimerase OS=Mus musculus GN=Renbp PE=2 SV=3 - [RENBP_MOUSE]                                        | 53,5    |
| Q3TTY5    | Keratin, type II cytoskeletal 2 epidermal OS=Mus musculus GN=Krt2 PE=1 SV=1 - [K22E_MOUSE]                                | 36,23   |
| P18242    | Cathepsin D OS=Mus musculus GN=Ctsd PE=1 SV=1 - [CATD_MOUSE]                                                              | 35,02   |
| Q3TXU5    | Deoxyhypusine synthase OS=Mus musculus GN=Dhps PE=2 SV=1 - [DHYS_MOUSE]                                                   | 34,89   |
| P58742    | Aladin OS=Mus musculus GN=Aaas PE=1 SV=1 - [AAAS_MOUSE]                                                                   | 32,49   |
| Q7SIG6    | Arf-GAP with SH3 domain, ANK repeat and PH domain-containing protein 2 OS=Mus musculus GN=Asap2 PE=1 SV=3 - [ASAP2_MOUSE] | 30,61   |

**Table S 10: Proteins identified from in-gel digest of spot 8 from DABGE gel (Figure 21)**

| Accession | Name                                                                                                                       | Score   |
|-----------|----------------------------------------------------------------------------------------------------------------------------|---------|
| P63101    | 14-3-3 protein zeta/delta OS=Mus musculus GN=Ywhaz PE=1 SV=1 - [1433Z_MOUSE]                                               | 3619,21 |
| P68254    | 14-3-3 protein theta OS=Mus musculus GN=Ywhaq PE=1 SV=1 - [1433T_MOUSE]                                                    | 2210,99 |
| P62259    | 14-3-3 protein epsilon OS=Mus musculus GN=Ywhae PE=1 SV=1 - [1433E_MOUSE]                                                  | 1691,07 |
| O70251    | Elongation factor 1-beta OS=Mus musculus GN=Eef1b PE=1 SV=5 - [EF1B_MOUSE]                                                 | 1039,2  |
| P60710    | Actin, cytoplasmic 1 OS=Mus musculus GN=Actb PE=1 SV=1 - [ACTB_MOUSE]                                                      | 1010,31 |
| P61982    | 14-3-3 protein gamma OS=Mus musculus GN=Ywhag PE=1 SV=2 - [1433G_MOUSE]                                                    | 946,44  |
| Q9CQV8    | 14-3-3 protein beta/alpha OS=Mus musculus GN=Ywhab PE=1 SV=3 - [1433B_MOUSE]                                               | 895,64  |
| P21107    | Tropomyosin alpha-3 chain OS=Mus musculus GN=Tpm3 PE=1 SV=2 - [TPM3_MOUSE]                                                 | 784,98  |
| P17918    | Proliferating cell nuclear antigen OS=Mus musculus GN=Pcna PE=1 SV=2 - [PCNA_MOUSE]                                        | 757,17  |
| P68510    | 14-3-3 protein eta OS=Mus musculus GN=Ywhah PE=1 SV=2 - [1433F_MOUSE]                                                      | 612,9   |
| P58771    | Tropomyosin alpha-1 chain OS=Mus musculus GN=Tpm1 PE=1 SV=1 - [TPM1_MOUSE]                                                 | 551,25  |
| Q8BFZ3    | Beta-actin-like protein 2 OS=Mus musculus GN=Actb2 PE=1 SV=1 - [ACTBL_MOUSE]                                               | 467,56  |
| P02535    | Keratin, type I cytoskeletal 10 OS=Mus musculus GN=Krt10 PE=1 SV=3 - [K1C10_MOUSE]                                         | 422,59  |
| P11499    | Heat shock protein HSP 90-beta OS=Mus musculus GN=Hsp90ab1 PE=1 SV=2 - [HS90B_MOUSE]                                       | 408,48  |
| P47963    | 60S ribosomal protein L13 OS=Mus musculus GN=Rpl13 PE=2 SV=3 - [RL13_MOUSE]                                                | 346,91  |
| P08113    | Endoplasmic reticulum protein OS=Mus musculus GN=Hsp90b1 PE=1 SV=2 - [ENPL_MOUSE]                                          | 321,88  |
| Q60817    | Nascent polypeptide-associated complex subunit alpha OS=Mus musculus GN=Naca PE=1 SV=1 - [NACA_MOUSE]                      | 311,29  |
| Q9R0P4    | Small acidic protein OS=Mus musculus GN=Smad PE=1 SV=1 - [SMAD_MOUSE]                                                      | 266,1   |
| P04104    | Keratin, type II cytoskeletal 1 OS=Mus musculus GN=Krt1 PE=1 SV=4 - [K2C1_MOUSE]                                           | 235,64  |
| Q6IRU2    | Tropomyosin alpha-4 chain OS=Mus musculus GN=Tpm4 PE=2 SV=3 - [TPM4_MOUSE]                                                 | 234,15  |
| P20152    | Vimentin OS=Mus musculus GN=Vim PE=1 SV=3 - [VIME_MOUSE]                                                                   | 227,69  |
| Q8BGZ7    | Keratin, type II cytoskeletal 75 OS=Mus musculus GN=Krt75 PE=1 SV=1 - [K2C75_MOUSE]                                        | 224,61  |
| P57776    | Elongation factor 1-delta OS=Mus musculus GN=Eef1d PE=1 SV=3 - [EF1D_MOUSE]                                                | 188,75  |
| Q6NXH9    | Keratin, type II cytoskeletal 73 OS=Mus musculus GN=Krt73 PE=1 SV=1 - [K2C73_MOUSE]                                        | 163,42  |
| Q61599    | Rho GDP-dissociation inhibitor 2 OS=Mus musculus GN=Arhgdib PE=1 SV=3 - [GDIR2_MOUSE]                                      | 120,52  |
| Q3TTY5    | Keratin, type II cytoskeletal 2 epidermal OS=Mus musculus GN=Krt2 PE=1 SV=1 - [K22E_MOUSE]                                 | 102,68  |
| Q8VED5    | Keratin, type II cytoskeletal 79 OS=Mus musculus GN=Krt79 PE=1 SV=2 - [K2C79_MOUSE]                                        | 96,23   |
| P34022    | Ran-specific GTPase-activating protein OS=Mus musculus GN=Ranbp1 PE=1 SV=2 - [RANG_MOUSE]                                  | 87,15   |
| Q3TCN2    | Putative phospholipase B-like 2 OS=Mus musculus GN=Pibd2 PE=1 SV=2 - [PLBL2_MOUSE]                                         | 86,81   |
| Q9EQU5    | Protein SET OS=Mus musculus GN=Set PE=1 SV=1 - [SET_MOUSE]                                                                 | 76,52   |
| P14206    | 40S ribosomal protein SA OS=Mus musculus GN=Rpsa PE=1 SV=4 - [RSSA_MOUSE]                                                  | 72,74   |
| Q9CR27    | WASH complex subunit CDC53 OS=Mus musculus GN=Ccdc53 PE=2 SV=1 - [CCD53_MOUSE]                                             | 71,97   |
| Q64G17    | Putative acidic leucine-rich nuclear phosphoprotein 32 family member C OS=Mus musculus GN=Anp32c PE=5 SV=3 - [AN32C_MOUSE] | 69,65   |
| Q9Z2U1    | Proteasome subunit alpha type-5 OS=Mus musculus GN=Psma5 PE=1 SV=1 - [PSA5_MOUSE]                                          | 58,23   |
| P0CG49    | Polyubiquitin-B OS=Mus musculus GN=Ubb PE=1 SV=1 - [UBB_MOUSE]                                                             | 50,92   |
| Q80TR8    | Protein VPRBP OS=Mus musculus GN=Vprbp PE=2 SV=4 - [VPRBP_MOUSE]                                                           | 39,29   |
| P28656    | Nucleosome assembly protein 1-like 1 OS=Mus musculus GN=Nap111 PE=1 SV=2 - [NP111_MOUSE]                                   | 36,43   |
| Q8BGB7    | Enolase-phosphatase E1 OS=Mus musculus GN=Enoph1 PE=2 SV=1 - [ENOPH_MOUSE]                                                 | 35,52   |
| Q08024    | Core-binding factor subunit beta OS=Mus musculus GN=Cbfb PE=1 SV=1 - [PEBB_MOUSE]                                          | 32,94   |
| Q7SIG6    | Arf-GAP with SH3 domain, ANK repeat and PH domain-containing protein 2 OS=Mus musculus GN=Asap2 PE=1 SV=3 - [ASAP2_MOUSE]  | 0       |

**Table S 11: Proteins identified from in-gel digest of spot 9 from DABGE gel (Figure 21)**

| Accession | Name                                                                                                                      | Score   |
|-----------|---------------------------------------------------------------------------------------------------------------------------|---------|
| P63101    | 14-3-3 protein zeta/delta OS=Mus musculus GN=Ywhaz PE=1 SV=1 - [1433Z_MOUSE]                                              | 5222,89 |
| P68254    | 14-3-3 protein theta OS=Mus musculus GN=Ywhaq PE=1 SV=1 - [1433T_MOUSE]                                                   | 2072,27 |
| P61982    | 14-3-3 protein gamma OS=Mus musculus GN=Ywhag PE=1 SV=2 - [1433G_MOUSE]                                                   | 1258,01 |
| Q9CQV8    | 14-3-3 protein beta/alpha OS=Mus musculus GN=Ywhab PE=1 SV=3 - [1433B_MOUSE]                                              | 1115,02 |
| P62259    | 14-3-3 protein epsilon OS=Mus musculus GN=Ywhae PE=1 SV=1 - [1433E_MOUSE]                                                 | 1032,9  |
| P68510    | 14-3-3 protein eta OS=Mus musculus GN=Ywhah PE=1 SV=2 - [1433F_MOUSE]                                                     | 799,53  |
| P17918    | Proliferating cell nuclear antigen OS=Mus musculus GN=Pcna PE=1 SV=2 - [PCNA_MOUSE]                                       | 613,73  |
| P21107    | Tropomyosin alpha-3 chain OS=Mus musculus GN=Tpm3 PE=1 SV=2 - [TPM3_MOUSE]                                                | 503,29  |
| O70251    | Elongation factor 1-beta OS=Mus musculus GN=Eef1b PE=1 SV=5 - [EF1B_MOUSE]                                                | 474,17  |
| P60710    | Actin, cytoplasmic 1 OS=Mus musculus GN=Actb PE=1 SV=1 - [ACTB_MOUSE]                                                     | 451,74  |
| P58771    | Tropomyosin alpha-1 chain OS=Mus musculus GN=Tpm1 PE=1 SV=1 - [TPM1_MOUSE]                                                | 371,84  |
| P02535    | Keratin, type I cytoskeletal 10 OS=Mus musculus GN=Krt10 PE=1 SV=3 - [K1C10_MOUSE]                                        | 368,79  |
| Q6NXH9    | Keratin, type II cytoskeletal 73 OS=Mus musculus GN=Krt73 PE=1 SV=1 - [K2C73_MOUSE]                                       | 361,32  |
| P11499    | Heat shock protein HSP 90-beta OS=Mus musculus GN=Hsp90ab1 PE=1 SV=2 - [HS90B_MOUSE]                                      | 354,48  |
| P04104    | Keratin, type II cytoskeletal 1 OS=Mus musculus GN=Krt1 PE=1 SV=4 - [K2C1_MOUSE]                                          | 310,32  |
| Q9R0P4    | Small acidic protein OS=Mus musculus GN=Smad PE=1 SV=1 - [SMAD_MOUSE]                                                     | 271,9   |
| Q60817    | Nascent polypeptide-associated complex subunit alpha OS=Mus musculus GN=Naca PE=1 SV=1 - [NACA_MOUSE]                     | 258,18  |
| P14206    | 40S ribosomal protein SA OS=Mus musculus GN=Rpsa PE=1 SV=4 - [RSSA_MOUSE]                                                 | 257,93  |
| P20152    | Vimentin OS=Mus musculus GN=Vim PE=1 SV=3 - [VIME_MOUSE]                                                                  | 242,55  |
| P57776    | Elongation factor 1-delta OS=Mus musculus GN=Eef1d PE=1 SV=3 - [EF1D_MOUSE]                                               | 232,93  |
| Q9JKB1    | Ubiquitin carboxyl-terminal hydrolase isozyme L3 OS=Mus musculus GN=Uchl3 PE=1 SV=2 - [UCHL3_MOUSE]                       | 224,42  |
| Q6IFX2    | Keratin, type I cytoskeletal 42 OS=Mus musculus GN=Krt42 PE=1 SV=1 - [K1C42_MOUSE]                                        | 173,65  |
| P99024    | Tubulin beta-5 chain OS=Mus musculus GN=Tubb5 PE=1 SV=1 - [TBB5_MOUSE]                                                    | 172,09  |
| Q9Z2U1    | Proteasome subunit alpha type-5 OS=Mus musculus GN=Pma5 PE=1 SV=1 - [PSA5_MOUSE]                                          | 166,06  |
| Q61599    | Rho GDP-dissociation inhibitor 2 OS=Mus musculus GN=Arhgdib PE=1 SV=3 - [GDIR2_MOUSE]                                     | 165,29  |
| Q9CR29    | Coiled-coil domain-containing protein 43 OS=Mus musculus GN=Ccdc43 PE=1 SV=1 - [CCD43_MOUSE]                              | 155,38  |
| Q8BGZ7    | Keratin, type II cytoskeletal 75 OS=Mus musculus GN=Krt75 PE=1 SV=1 - [K2C75_MOUSE]                                       | 131,71  |
| Q3TTY5    | Keratin, type II cytoskeletal 2 epidermal OS=Mus musculus GN=Krt2 PE=1 SV=1 - [K22E_MOUSE]                                | 129,58  |
| Q99PT1    | Rho GDP-dissociation inhibitor 1 OS=Mus musculus GN=Arhgdia PE=1 SV=3 - [GDIR1_MOUSE]                                     | 117,08  |
| Q8VED5    | Keratin, type II cytoskeletal 79 OS=Mus musculus GN=Krt79 PE=1 SV=2 - [K2C79_MOUSE]                                       | 110,81  |
| P47963    | 60S ribosomal protein L13 OS=Mus musculus GN=Rpl13 PE=2 SV=3 - [RL13_MOUSE]                                               | 74,76   |
| P0CG49    | Polyubiquitin-B OS=Mus musculus GN=Ubb PE=1 SV=1 - [UBB_MOUSE]                                                            | 63,64   |
| P20029    | 78 kDa glucose-regulated protein OS=Mus musculus GN=Hspa5 PE=1 SV=3 - [GRP78_MOUSE]                                       | 57,75   |
| Q8BGB7    | Enolase-phosphatase E1 OS=Mus musculus GN=Enoph1 PE=2 SV=1 - [ENOPH_MOUSE]                                                | 54,09   |
| P34022    | Ran-specific GTPase-activating protein OS=Mus musculus GN=Ranbp1 PE=1 SV=2 - [RANG_MOUSE]                                 | 38,9    |
| Q9CPX6    | Ubiquitin-like-conjugating enzyme ATG3 OS=Mus musculus GN=Atg3 PE=1 SV=1 - [ATG3_MOUSE]                                   | 38,14   |
| Q9EQU5    | Protein SET OS=Mus musculus GN=Set PE=1 SV=1 - [SET_MOUSE]                                                                | 36,82   |
| Q7SIG6    | Arf-GAP with SH3 domain, ANK repeat and PH domain-containing protein 2 OS=Mus musculus GN=Asap2 PE=1 SV=3 - [ASAP2_MOUSE] | 30,41   |
| Q08024    | Core-binding factor subunit beta OS=Mus musculus GN=Cbfb PE=1 SV=1 - [PEBB_MOUSE]                                         | 30,14   |

**Table S 12: Proteins identified from in-gel digest of spot 10 from DABGE gel (Figure 21)**

| Accession | Name                                                                                                                      | Score   |
|-----------|---------------------------------------------------------------------------------------------------------------------------|---------|
| Q9QYB1    | Chloride intracellular channel protein 4 OS=Mus musculus GN=Clc4 PE=1 SV=3 - [CLIC4_MOUSE]                                | 1657,67 |
| P60710    | Actin, cytoplasmic 1 OS=Mus musculus GN=Actb PE=1 SV=1 - [ACTB_MOUSE]                                                     | 1272,3  |
| Q9CQ60    | 6-phosphogluconolactonase OS=Mus musculus GN=Pgls PE=2 SV=1 - [6PGL_MOUSE]                                                | 732,91  |
| P02535    | Keratin, type I cytoskeletal 10 OS=Mus musculus GN=Krt10 PE=1 SV=3 - [K1C10_MOUSE]                                        | 546,93  |
| P63073    | Eukaryotic translation initiation factor 4E OS=Mus musculus GN=Eif4e PE=1 SV=1 - [IF4E_MOUSE]                             | 423,8   |
| P23492    | Purine nucleoside phosphorylase OS=Mus musculus GN=Pnp PE=1 SV=2 - [PNPH_MOUSE]                                           | 395,87  |
| P62702    | 40S ribosomal protein S4, X isoform OS=Mus musculus GN=Rps4x PE=2 SV=2 - [RS4X_MOUSE]                                     | 301,22  |
| Q6NXH9    | Keratin, type II cytoskeletal 73 OS=Mus musculus GN=Krt73 PE=1 SV=1 - [K2C73_MOUSE]                                       | 266,05  |
| P04104    | Keratin, type II cytoskeletal 1 OS=Mus musculus GN=Krt1 PE=1 SV=4 - [K2C1_MOUSE]                                          | 226,16  |
| Q6PEB6    | Mps one binder kinase activator-like 3 OS=Mus musculus GN=Mobk13 PE=1 SV=1 - [MOBL3_MOUSE]                                | 196,35  |
| P68254    | 14-3-3 protein theta OS=Mus musculus GN=Ywhaq PE=1 SV=1 - [1433T_MOUSE]                                                   | 156,45  |
| Q8BGZ7    | Keratin, type II cytoskeletal 75 OS=Mus musculus GN=Krt75 PE=1 SV=1 - [K2C75_MOUSE]                                       | 155,26  |
| P97372    | Proteasome activator complex subunit 2 OS=Mus musculus GN=Psme2 PE=2 SV=4 - [PSME2_MOUSE]                                 | 144,62  |
| P47757    | F-actin-capping protein subunit beta OS=Mus musculus GN=Capzb PE=1 SV=3 - [CAPZB_MOUSE]                                   | 119,33  |
| Q9D6N5    | Dr1-associated corepressor OS=Mus musculus GN=Drp1 PE=2 SV=3 - [NC2A_MOUSE]                                               | 107,73  |
| Q3UV17    | Keratin, type II cytoskeletal 2 oral OS=Mus musculus GN=Krt76 PE=2 SV=1 - [K22O_MOUSE]                                    | 101,71  |
| P0CG49    | Polyubiquitin-B OS=Mus musculus GN=Ubb PE=1 SV=1 - [UBB_MOUSE]                                                            | 100,54  |
| P63101    | 14-3-3 protein zeta/delta OS=Mus musculus GN=Ywhaz PE=1 SV=1 - [1433Z_MOUSE]                                              | 98,43   |
| Q9JKX6    | ADP-sugar pyrophosphatase OS=Mus musculus GN=Nudt5 PE=1 SV=1 - [NUDT5_MOUSE]                                              | 95,69   |
| P70202    | Latexin OS=Mus musculus GN=Lxn PE=1 SV=2 - [LXN_MOUSE]                                                                    | 87,34   |
| Q61206    | Platelet-activating factor acetylhydrolase IB subunit beta OS=Mus musculus GN=Pafah1b2 PE=1 SV=2 - [PA1B2_MOUSE]          | 85,81   |
| Q3TTY5    | Keratin, type II cytoskeletal 2 epidermal OS=Mus musculus GN=Krt2 PE=1 SV=1 - [K22E_MOUSE]                                | 67      |
| P63017    | Heat shock cognate 71 kDa protein OS=Mus musculus GN=Hspa8 PE=1 SV=1 - [HSP7C_MOUSE]                                      | 62,08   |
| P47963    | 60S ribosomal protein L13 OS=Mus musculus GN=Rpl13 PE=2 SV=3 - [RL13_MOUSE]                                               | 38,27   |
| P34022    | Ran-specific GTPase-activating protein OS=Mus musculus GN=Ranbp1 PE=1 SV=2 - [RANG_MOUSE]                                 | 33,8    |
| Q7SIG6    | Arf-GAP with SH3 domain, ANK repeat and PH domain-containing protein 2 OS=Mus musculus GN=Asap2 PE=1 SV=3 - [ASAP2_MOUSE] | 29      |

**Table S 13: Proteins identified from in-gel digest of spot 11 from DABGE gel (Figure 21)**

| Accession | Name                                                                                                             | Score   |
|-----------|------------------------------------------------------------------------------------------------------------------|---------|
| Q9QYB1    | Chloride intracellular channel protein 4 OS=Mus musculus GN=Clc4 PE=1 SV=3 - [CLIC4_MOUSE]                       | 1061,67 |
| P60710    | Actin, cytoplasmic 1 OS=Mus musculus GN=Actb PE=1 SV=1 - [ACTB_MOUSE]                                            | 819,22  |
| Q9CQ60    | 6-phosphogluconolactonase OS=Mus musculus GN=Pgl5 PE=2 SV=1 - [6PGL_MOUSE]                                       | 735,54  |
| P23492    | Purine nucleoside phosphorylase OS=Mus musculus GN=Pnp PE=1 SV=2 - [PNPH_MOUSE]                                  | 396,14  |
| P63017    | Heat shock cognate 71 kDa protein OS=Mus musculus GN=Hspa8 PE=1 SV=1 - [HSP7C_MOUSE]                             | 298,85  |
| P04104    | Keratin, type II cytoskeletal 1 OS=Mus musculus GN=Krt1 PE=1 SV=4 - [K2C1_MOUSE]                                 | 285,15  |
| P97372    | Proteasome activator complex subunit 2 OS=Mus musculus GN=Psme2 PE=2 SV=4 - [PSME2_MOUSE]                        | 284,55  |
| Q61206    | Platelet-activating factor acetylhydrolase IB subunit beta OS=Mus musculus GN=Pafah1b2 PE=1 SV=2 - [PA1B2_MOUSE] | 277,04  |
| P63073    | Eukaryotic translation initiation factor 4E OS=Mus musculus GN=Eif4e PE=1 SV=1 - [IF4E_MOUSE]                    | 275,27  |
| Q6NXH9    | Keratin, type II cytoskeletal 73 OS=Mus musculus GN=Krt73 PE=1 SV=1 - [K2C73_MOUSE]                              | 265,67  |
| P63101    | 14-3-3 protein zeta/delta OS=Mus musculus GN=Ywhaz PE=1 SV=1 - [1433Z_MOUSE]                                     | 233,47  |
| P67778    | Prohibitin OS=Mus musculus GN=Phb PE=1 SV=1 - [PHB_MOUSE]                                                        | 232,62  |
| P62702    | 40S ribosomal protein S4, X isoform OS=Mus musculus GN=Rps4x PE=2 SV=2 - [RS4X_MOUSE]                            | 230,85  |
| Q99PT1    | Rho GDP-dissociation inhibitor 1 OS=Mus musculus GN=Arhgdia PE=1 SV=3 - [GDIR1_MOUSE]                            | 171,7   |
| Q8BGZ7    | Keratin, type II cytoskeletal 75 OS=Mus musculus GN=Krt75 PE=1 SV=1 - [K2C75_MOUSE]                              | 146     |
| Q9D6N5    | Dr1-associated corepressor OS=Mus musculus GN=Drp1 PE=2 SV=3 - [NC2A_MOUSE]                                      | 95,86   |
| Q61599    | Rho GDP-dissociation inhibitor 2 OS=Mus musculus GN=Arhgdib PE=1 SV=3 - [GDIR2_MOUSE]                            | 95,33   |
| P47963    | 60S ribosomal protein L13 OS=Mus musculus GN=Rpl13 PE=2 SV=3 - [RL13_MOUSE]                                      | 88,38   |
| P0CG49    | Polyubiquitin-B OS=Mus musculus GN=Ubb PE=1 SV=1 - [UBB_MOUSE]                                                   | 86,35   |
| Q9Z2X1    | Heterogeneous nuclear ribonucleoprotein F OS=Mus musculus GN=Hnmpf PE=1 SV=3 - [HNRPF_MOUSE]                     | 84,66   |
| P02535    | Keratin, type I cytoskeletal 10 OS=Mus musculus GN=Krt10 PE=1 SV=3 - [K1C10_MOUSE]                               | 81,72   |
| P34022    | Ran-specific GTPase-activating protein OS=Mus musculus GN=Ranbp1 PE=1 SV=2 - [RANG_MOUSE]                        | 79,64   |
| O70435    | Proteasome subunit alpha type-3 OS=Mus musculus GN=Pma3 PE=1 SV=3 - [PSA3_MOUSE]                                 | 77,94   |
| P70202    | Latexin OS=Mus musculus GN=Lxn PE=1 SV=2 - [LXN_MOUSE]                                                           | 54,79   |
| Q9Z1Q5    | Chloride intracellular channel protein 1 OS=Mus musculus GN=Clc1 PE=1 SV=3 - [CLIC1_MOUSE]                       | 52,89   |
| P61979    | Heterogeneous nuclear ribonucleoprotein K OS=Mus musculus GN=Hnmpk PE=1 SV=1 - [HNRPK_MOUSE]                     | 37,09   |
| P63038    | 60 kDa heat shock protein, mitochondrial OS=Mus musculus GN=Hspd1 PE=1 SV=1 - [CH60_MOUSE]                       | 30,07   |
| P97371    | Proteasome activator complex subunit 1 OS=Mus musculus GN=Psme1 PE=2 SV=2 - [PSME1_MOUSE]                        | 28,21   |
| P68368    | Tubulin alpha-4A chain OS=Mus musculus GN=Tuba4a PE=1 SV=1 - [TBA4A_MOUSE]                                       | 25,59   |

# Vector maps

Created with SnapGene®

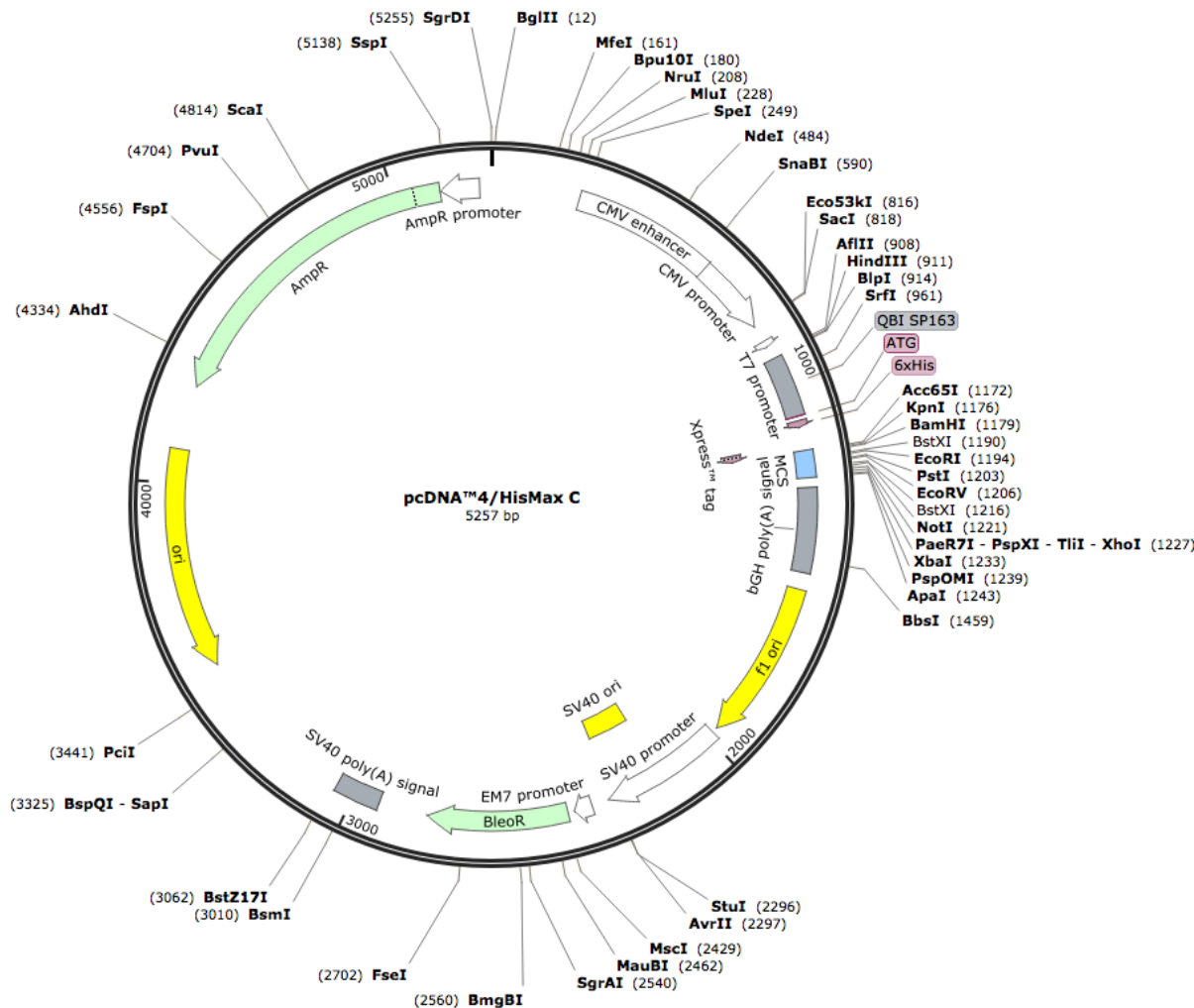


Figure S 8: Vector map of pcDNA4/Hismax C. Restriction sites used for cloning PLBD2 were KpnI and EcoRI. Source: [www.snapgene.com/resources](http://www.snapgene.com/resources)

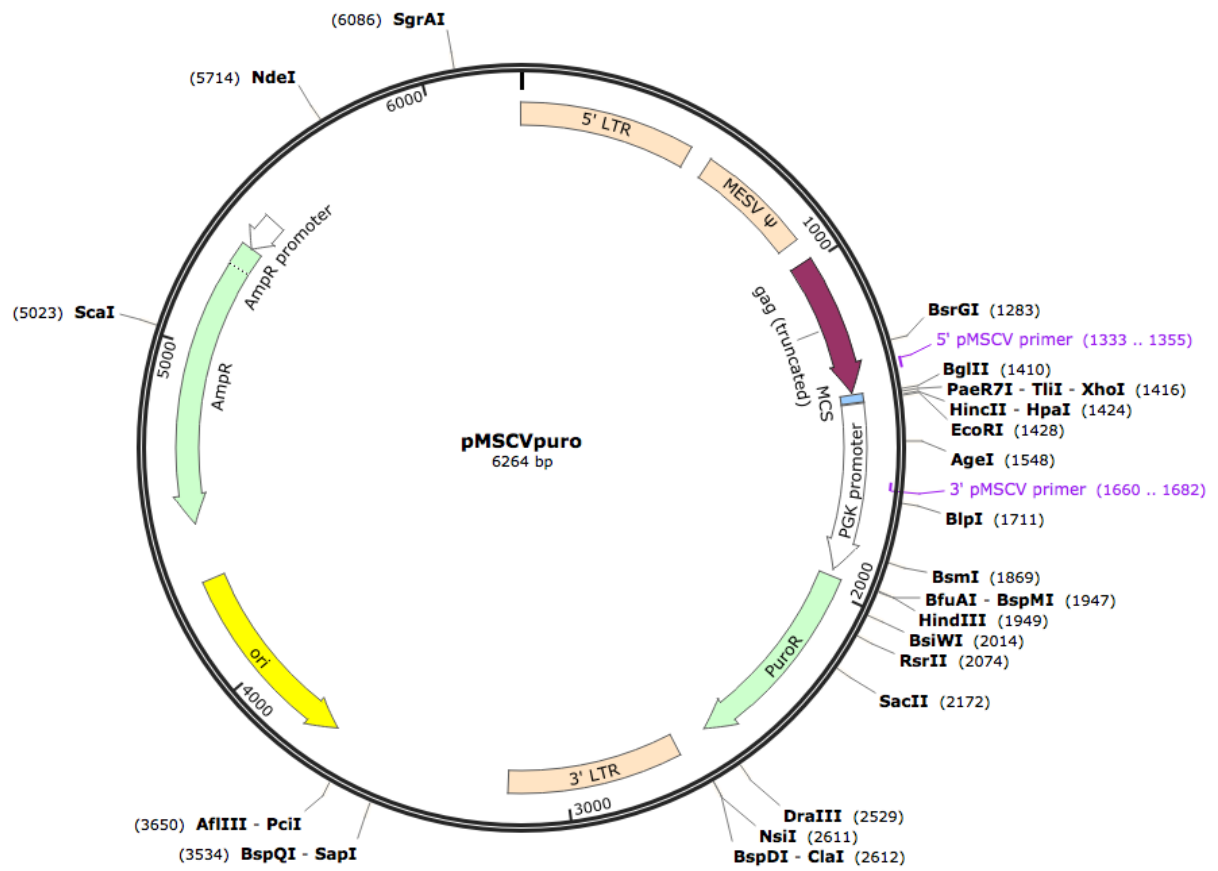


Figure S 9: Vector map of pMSCV puro. Restriction sites used for cloning PLBD2 were HpaI EcoRI.  
Source: [www.snapgene.com/resources](http://www.snapgene.com/resources)

ATGL Western Blots of CRISPR clones

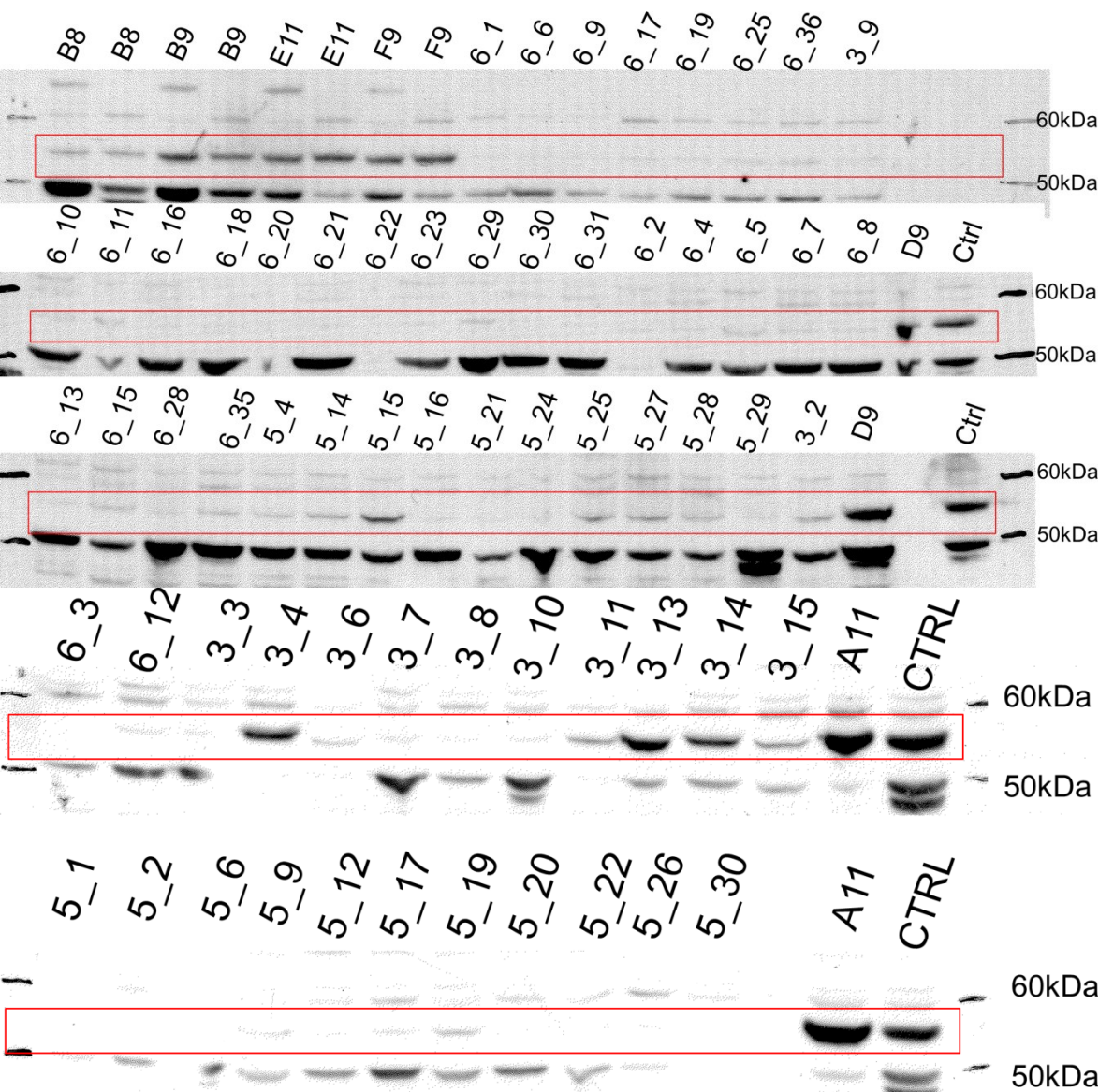


Figure S 10: ATGL Western Blots of CRISPR clones. CTRL: non-transfected parental cell line. A11, B8, B9, E11, F9, D9: transfected with control plasmid

PCRs of CRISPR clones

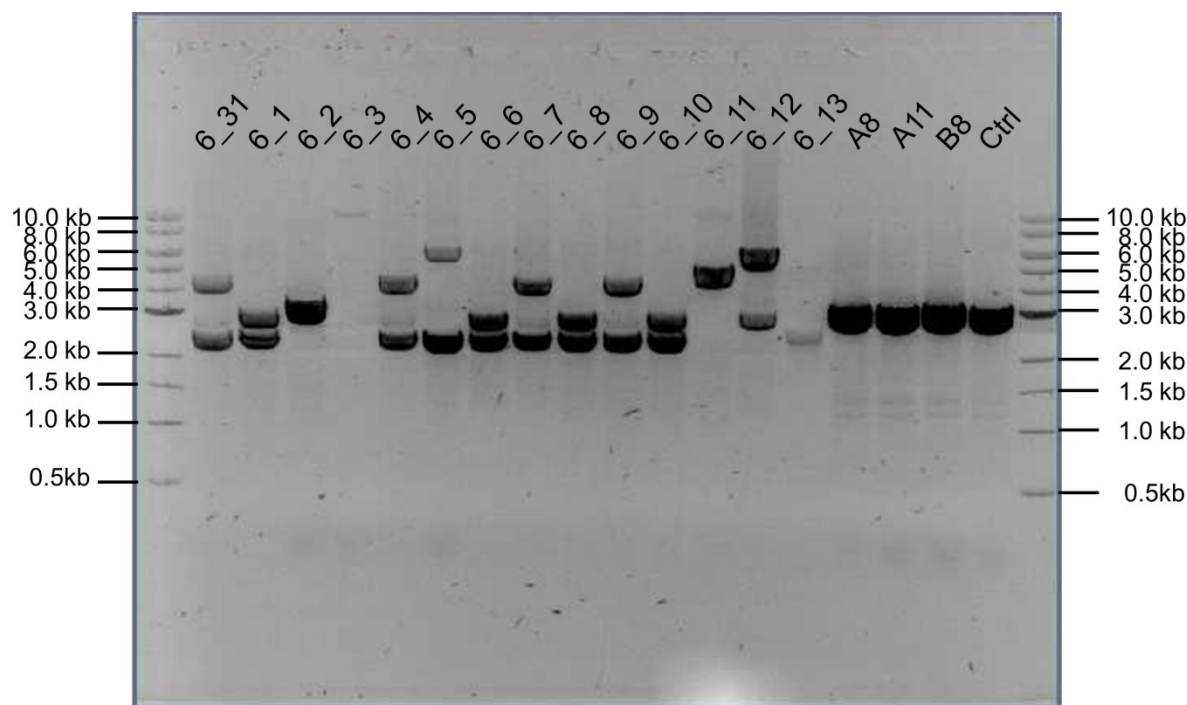


Figure S 11: PCR 1 of CRISPR clones and control clones (A8, A11, B8)

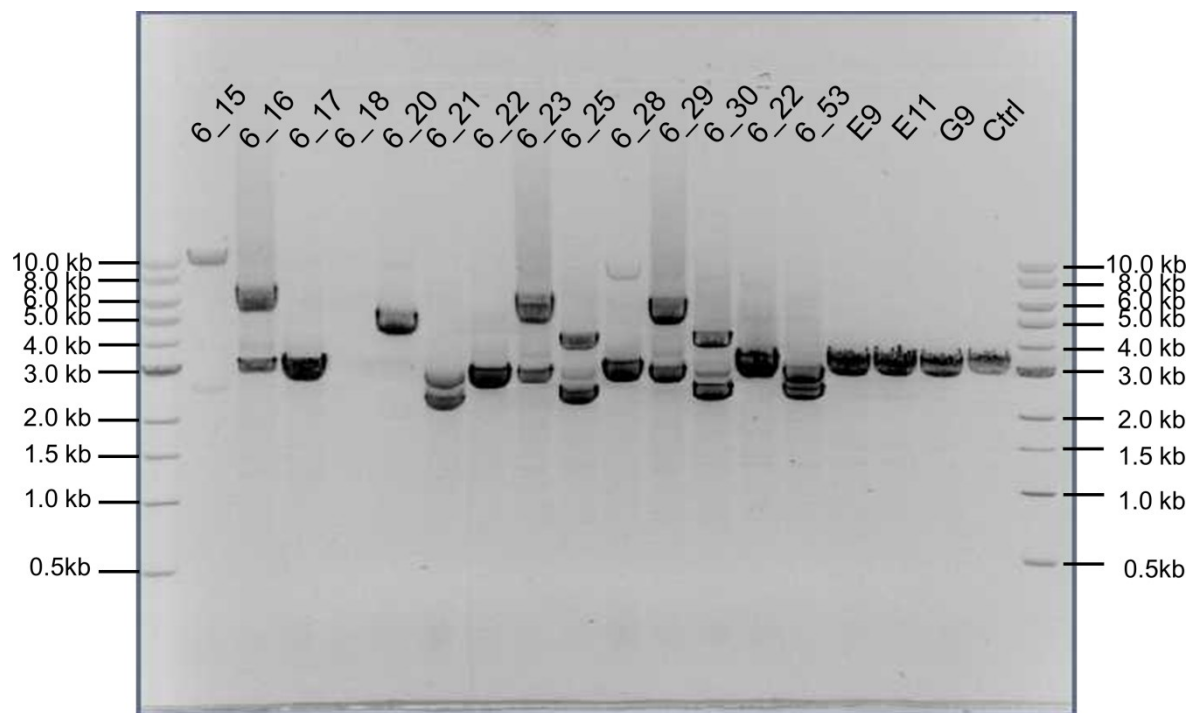


Figure S 12: PCR 2 of CRISPR clones and control clones (E9, E11, G9)

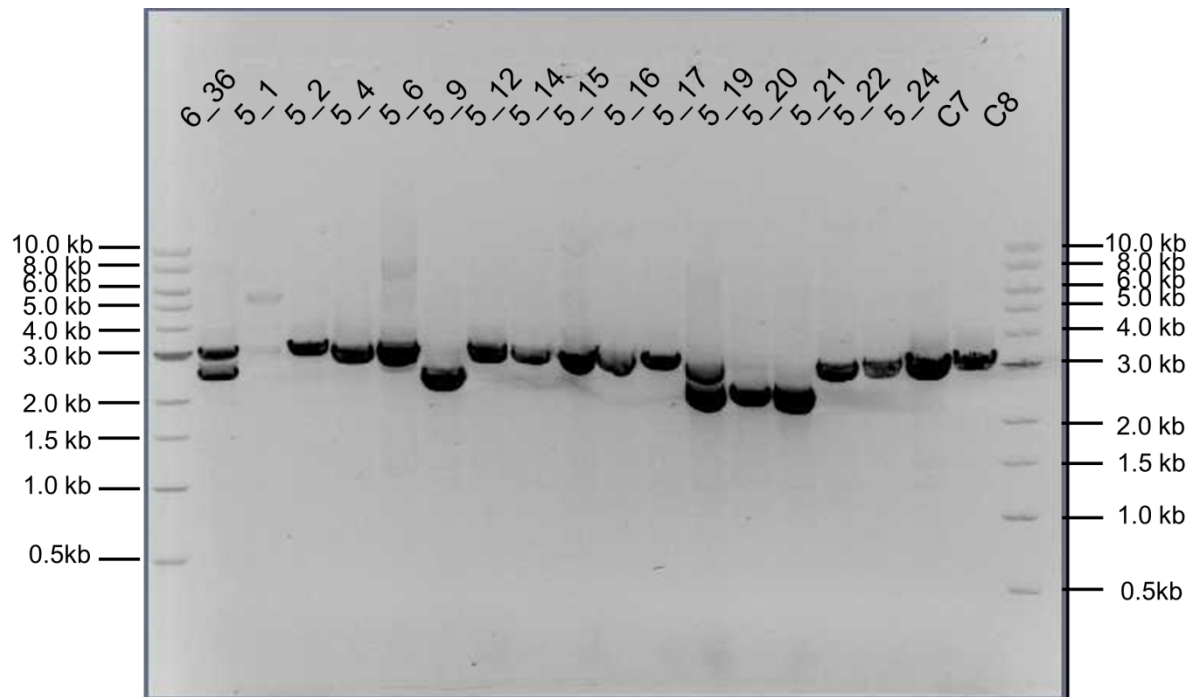


**Figure S 13: PCR 3 of CRISPR clones and control clones (C7, C8)**

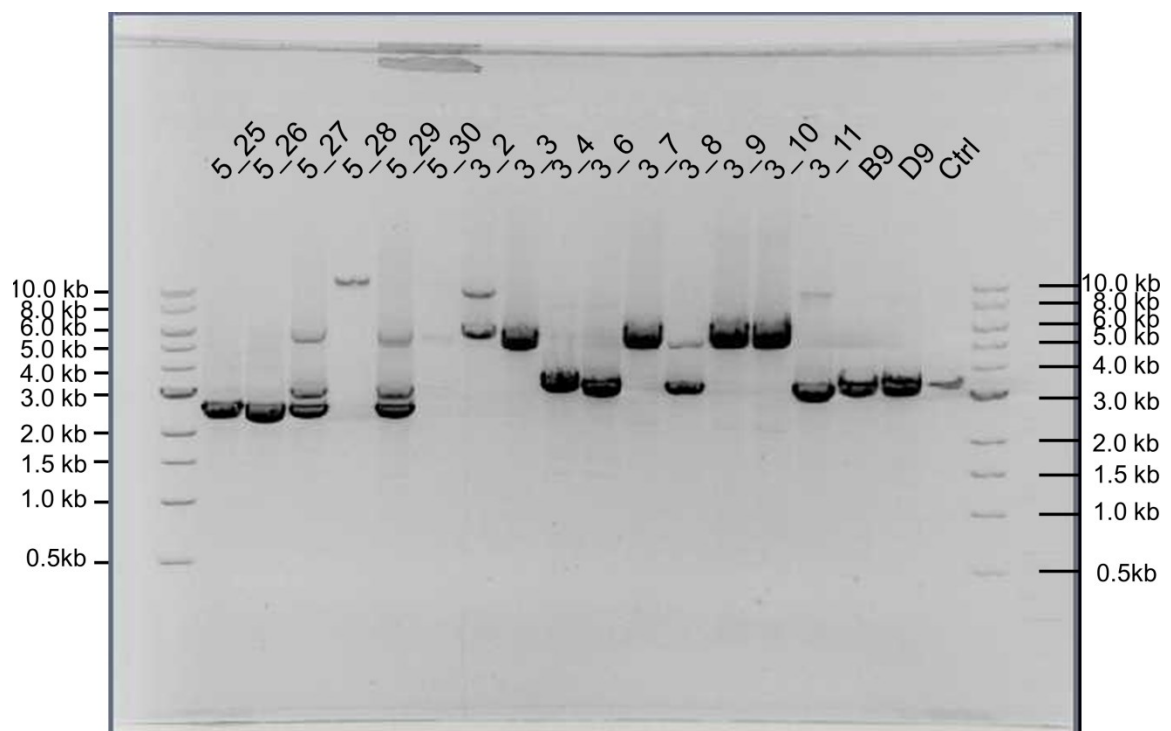


**Figure S 14 PCR 4 of CRISPR clones and control clones (B9, D9). CTRL is the non-transfected parental cell line**

## Staining of lipid droplets

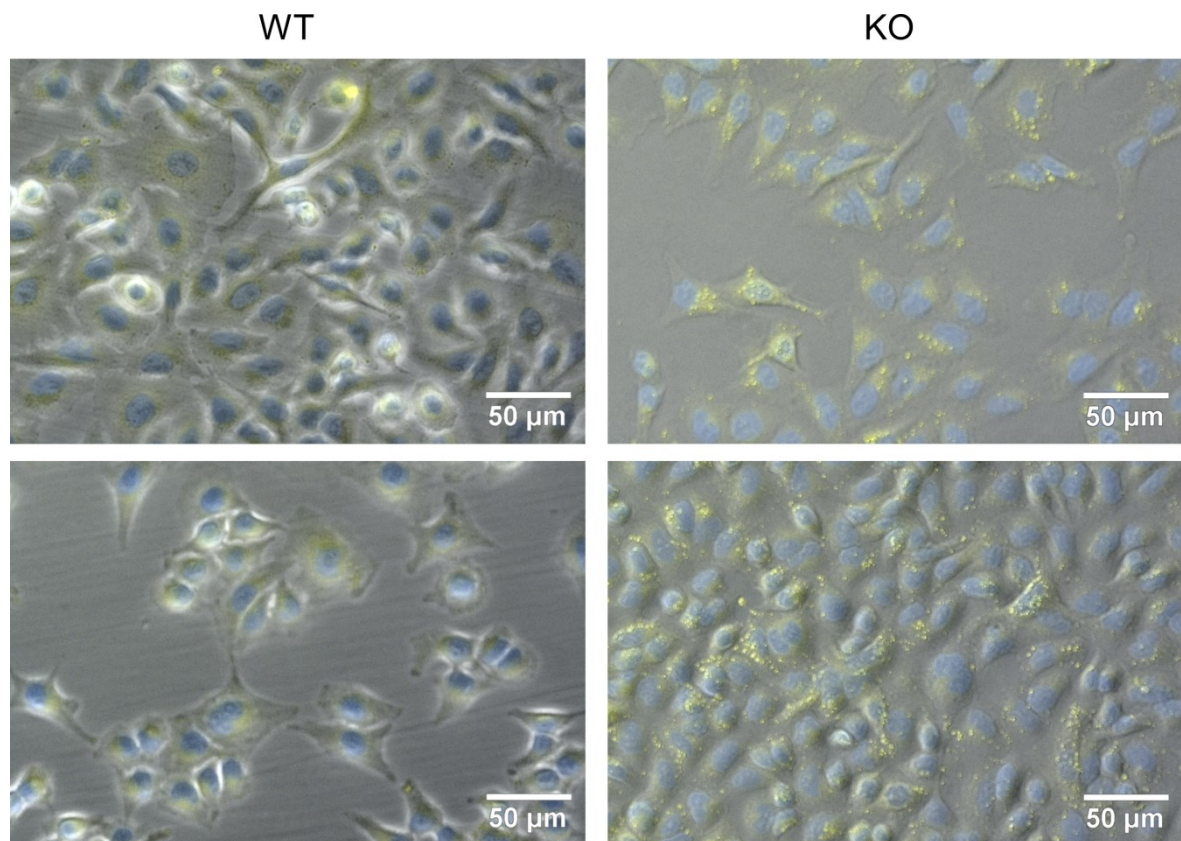


**Figure S 15: Lipid droplets accumulate in ATGL-KO A549 cells. Bodipy staining is shown in yellow, DAPI staining in blue. Top left: WT clone B8. Bottom left: WT clone B9. Top right: KO clone 3\_3. Bottom right: KO clone 3\_7.**

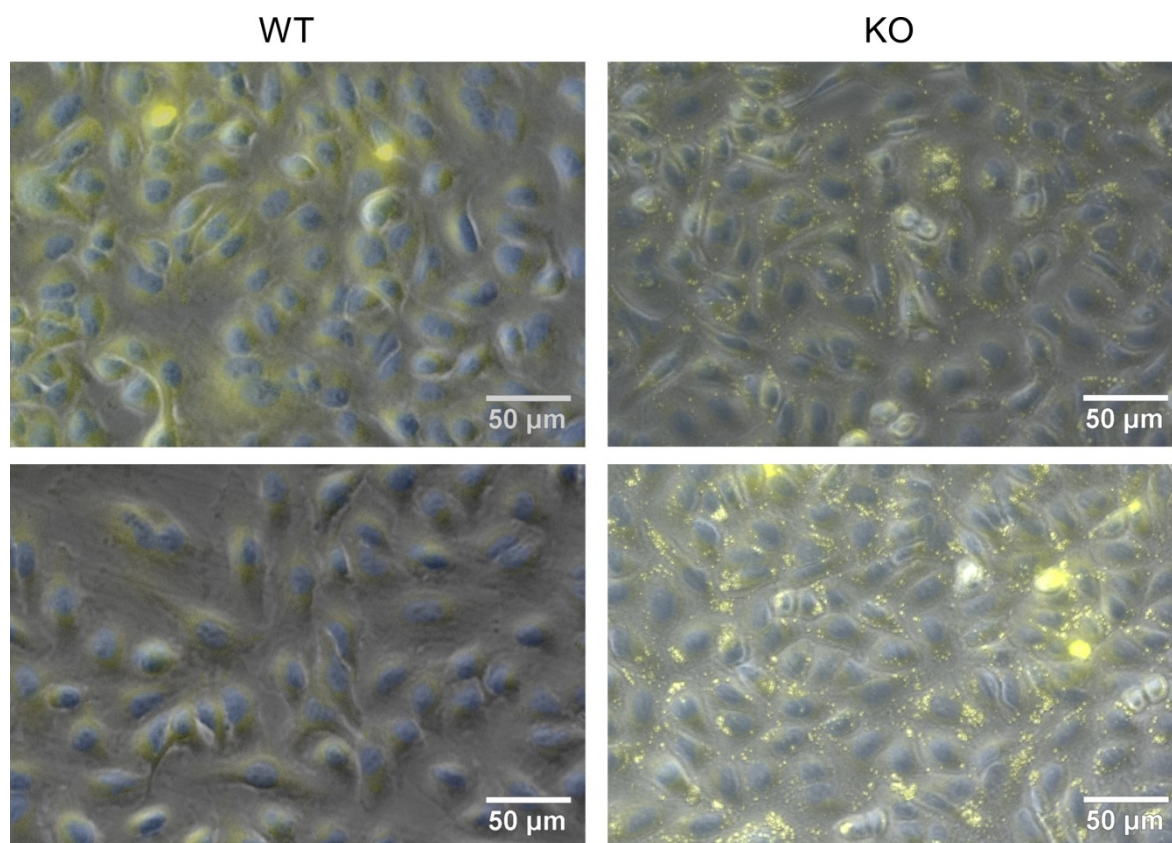


**Figure S 16: Lipid droplets accumulate in ATGL-KO A549 cells. Bodipy staining is shown in yellow, DAPI staining in blue. Top left: WT clone C7. Bottom left: WT clone C8. Top right: KO clone 3\_10. Bottom right: KO clone 6\_3.**