Masterthesis

Genetic Predispositions for Major Depressive Disorder

A Review of Literature

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Statutory Declaration

I declare on my honour that I have written this dissertation independently and without assistance, that no sources other than those cited were used and that the sources used verbatim or in substance have been marked as such.

Brunn/Gebirge, June 2021 Anna Hofbauer eh

Abstract

Background: Mental disorders gained more and more significance over the last few decades. Major Depressive Disorder (MDD) belong to the affective disorders, which includes low mood, anhedonia, and fatigue as main symptoms. Other possible symptoms can also include insomnia, loss of appetite, reduced concentration, low self-esteem and, in severe cases MDD, it can lead to suicide. The aetiology of MDD is mostly unknown, but it is a combination of genetic predisposition and environmental factors.

Methods: In this literature review, I summarized articles out of the databases PubMed and ELSEVIER published between the 1st of January 2019 and the 28th of February 2021 concerning genetic predispositions associating with MDD. I have also set criteria for exclusion, such as containing a small sample size, animal studies, the main focus on other mental disorders, possible drug targets or treatment response.

Results: Out of 245 papers, 22 were summarized as they pervade all the required criteria. The recapped genetic predispositions included DNA modifications, single nucleotide polymorphisms, and a gene, that could be associated with MDD. The functions range from vesicle transport, receptors of signal transduction in various tissues, to possible influences on emotional and behavioural features.

Conclusion: The results suggest that many different genes influence the development of MDD. Studies on genetic predispositions for mental disorders improve the probability of getting MDD, possible remission and recurrence, treatment response, and drug targets.

Keywords: Major Depressive Disorder, review of literature, SNP, DNA modifications, drug targets, biomarker

Zusammenfassung

Hintergrund: Psychische Erkrankungen haben in den letzten Jahrzehnten immer mehr an Bedeutung in unserer Gesellschaft erlangt. Depressionen gehören zu den affektiven Störungen und gehen mit den Symptomen der depressiven Stimmung, Antriebslosigkeit und Interessensverlust einher. Weiters leiden Erkrankte meist auch an Schlafstörungen, Verlust des Appetits, Konzentrationsschwierigkeiten, rascher Ermüdung und möglicher Selbstmordgedanken. Die genaue Ursache der Erkrankung ist größtenteils unbekannt, setzt sich aber bekannterweise aus Umweltfaktoren und genetischer Prädispositionen zusammen.

Methoden: In dieser Literaturrecherche, wurden Artikel aus den Datenbanken PubMed und ELSEVIER zusammengefasst, welche zwischen 1. Januar 2019 und 28. Februar 2021 veröffentlicht wurden. Ausschlusskriterien waren unter anderem eine zu geringe Teilnehmeranzahl, Studien an Tieren, Fokus auf einer anderen mentalen Erkrankung oder Medikamenten- bzw. Behandlungsreaktion.

Ergebnis: Aus 245 Artikel wurden 22 ausgewählt, welche den gewünschten Kriterien entsprochen haben und zusammengefasst. Bei den genetischen Prädispositionen handelt es sich sowohl um DNS-Modifikationen und Single Nukleotid Polymorphismen (SNP) als auch um ein Gen, welche neu mit Depressionen assoziiert werden konnten. Die Funktionen der betroffenen Gene reichen von Vesikeltransport, Rezeptoren für Signaltransduktionen in vielen verschiedenen Geweben, als auch um möglichen Einfluss auf Verhalten und Gedächtnis.

Fazit: Die Ergebnisse zeigen auf, viele verschiedene Gene können auf die Entstehung von Depressionen einwirken. Das neu erreichte Wissen der Forschung über die genetischen Grundlagen bietet mögliche Ausgangspunkte zur Kalkulation von Erkrankungswahrscheinlichkeiten, Remission und Wiederkehr der Depression, Behandlungsreaktionen und Angriffsmöglichkeiten für neuentwickelte Pharmazeutika.

Schlagwörter: Depressionen, Literaturrecherche, SNP, DNS Modifikationen, Behandlungsreaktionen, Medikamententargets

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Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ALFF	Amplitude of Low-Frequency Fluctuation
BDNF	Brain-Derived Neurotrophic Factor
Chr	Chromosome
CpG	CpG-Dinucleotides
DEG	Differentially Expressed Genes
DMR	Differentially Methylated Region
DNA	Deoxyribonucleic Acid
DRD2	D2 Dopamine Receptor
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
eQTL	Expression Quantitative Trait Loci
GPI	Glycosylphosphatidylinositol
GRCh38	Genome Reference Consortium Human Build 38
GWAS	Genome-Wide Association Study
GxE	Gene by Environment Interaction
GxG	Gene by Gene Interaction
GxGxE	Gene by Gene by Environmental Interaction
HPA	Hypothalamic-Pituitary-Adrenal
ICD 10	International Statistical Classification of Diseases and Related Health Problems number 10
IRS1	Insulin Receptor Substrate 1
MAP	Rush Memory and Aging Project
MDD	Major Depressive Disorder

MEF2C	Myocyte-specific Enhancer Binding Factor 2C
miRNA	MicroRNA
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MTHFR	5,10-Methylenetetrahydrofolate reductase
NCBI	National Centre for Biotechnology Information
NEGR1	neuronal growth regulator 1
NR3C1	glucocorticoid receptor gene
PGC	Psychiatric Genomics Consortium
PMDD	Premenstrual Dysphoric Disorder
PTSD	Post-Traumatic Stress Disorder
qRT-PCR	quantitative Real Time-Polymerase Chainreaction
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RMFG	Right Medial Frontal Gyrus
ROS	Religious Orders Study
SLC6A4	Serotonin Transporter Gene
SLE	Stressful Life Events
SNP	Single Nucleotide Polymorphisms
SNRI	Serotonin and Noradrenaline Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
TCA	Tricyclic Antidepressant
TGFB1	Transforming Growth Factor beta 1
TMT	Trail making Test
TNFα	Tumour Necrosis Factor α

TSST	Trier Social Stress Test

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1 Introduction

Mental disorders have been gaining a considerable amount of prevalence and significance in the last few decades. Especially the number of people diagnosed with Major Depressive Disorder (MDD) continues to grow yearly. While approximately 5 % of the Austrian population got the diagnosis in the year 2014, the count has reached about 20 % in 2019 (Kessler, Tat Chiu, *et al.*, 2005; Smith, 2014; Nicole Kolisch, 2016). About twice as many women are affected as men and the disease is the main reason people have lived for years with disabilities (Vos *et al.*, 2012) and increases the global morality and suicidal rates (Gotlib and Joormann, 2010; Bode *et al.*, 2017). The aetiology of MDD is complex and different for every patient, but it is known that the pathophysiological changes is caused by a combination of inheritance, genetics and environmental factors (Meyer-Lindenberg and Weinberger, 2006). Yet, in many medical disciplines the genetics are used for calculating risks in recurrence, treatment, or drug response, it is not used in psychiatry routines. However, research is focusing on the genetic background of the mental disorder and a possible way to utilize it for everyday tasks.

1.1 Clinical picture and Symptoms

Major Depressive Disorder (MDD), Clinical Depression or commonly known by its simplified form as Depression, is a mental disease where patients are suffering a combination of a low mood state, lack of interests and sorrow, which affects many parts of the patients' life. The illness impairs their social life through mood and behaviour impacts as well as their bodily functions, such as sleep and appetite (Rakel, 1999).

The patients will be diagnosed via two possible criterion outlines, the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) or the ICD-10 (International Statistical Classification of Diseases and Related Health Problems number 10). In the ICD-10 there are three main symptoms, two need to be perceivable at least two weeks, and seven criteria for somatic symptoms, which can differ in every patient (WHO, 1992).

1. **Depressed, low mood:**

This criterion will differ between patients. While some experience hopelessness, despair, and dejection, others describe the feeling of numbness. The patients can neither sense happiness nor sadness. Many report a strong fear of the future and a high expression of insecurity. Patients express it by being irritated very quickly and any obligation are a challenge, such as keeping up social contacts. The state of low mood can vary from day to day, or even throughout the entirety of a day.

2. **Loss of interests and joylessness:**

This condition is also known as anhedonia. It describes the decreasing level of activities and the high energy that is required for everyday areas like household chores, personal hygiene, or professions. When a patient goes through this issue, it also interferes with hobbies or leisure time activities.

3. **Lethargy and fatigue**:

The lack of energy and fatigue can be linked to listlessness. It expresses the self-awareness of a patient, who feels barely resilient and exhausted while going through their daily activities like cooking, getting dressed or being social. It is often related to the patient's withdrawal e.g., heading the bed.

Next to the three main symptoms, there are six further criteria, which combination can differ in every MDD patient.

4. **Reduced concentration and attention** but also difficulties in decision-making are common symptoms in MDD. Often patient's thinking is characterized by self-doubt, fears, and recurring pondering.
5. **Reduced self-confidence and self-esteem** can be observed even in patients who have a stable self-confidence aside the depressed episodes. They feel a loss of competence in any aspect of life such as profession, social contacts, hobbies, and household.
6. Most patients also experience feeling **guilty and worthless.**
7. **Negative and pessimistic future predictions:** MDD patients have unrealistically negative and highly pessimistic prospect for the future. They

believe their aetiopathology will get worse and they experience every day as a burden.

8. **Insomnia or hypersomnia:** Most patients suffer from insomnia, the trouble of falling asleep and sleeping through the night. The urge for more sleep (hypersomnia) is uncommon but can also be a symptom for MDD.
9. **Decreased appetite:** in depressed episodes the appetite is diminished, and the patients have to force themselves to eat. This symptom will be concomitant with weight loss.
10. **Suicide, suicidal ideation, or self-harm** are very frequent in MDD patients. They believe that only a quick death, another untreatable disease, or an accident, can redeem themselves.

On the basis of those criteria a diagnosis will be generated and also the severity will be determined (WHO, 1992).

1.2 Classification and differential diagnosis

The ICD-10 subclassifies unipolar depression disorders into major depression disorder, which are categorized as mild, moderate, severe, and psychotic forms, and dysthymia also known as persistent depressive disorder. As mentioned before, the severity is determined based on the number of characterized symptoms (WHO, 1992; Benazzi, 2006). The diagnosis dysthymia comes along with a depressed mood for a minimum of two years. It can alternate with major depression episodes, but mostly less intense symptoms (Akiskal, 1983; Moore and Bona, 2001). Furthermore, the symptoms can alter depending on the patient's age. While more adults suffer from anhedonia and concentration loss, weight chances, energy loss and insomnia are more common in adolescents (Rice *et al.*, 2019).

Since other diseases contain depressive episodes as their symptoms, they can be falsely diagnosed with MDD or need to be ruled out before the respective diagnosis. One of those illnesses is the bipolar disorder. Patients with this condition are suffering from depressive episodes alternating with periods of ecstatic and elevated mood, which is called mania (Mitchell and Malhi, 2004). In

the year 2006, Albanese et al. researched the misdiagnosis of bipolar disorder and perceived that almost half of their patients received false diagnosis (Albanese *et al.*, 2006).

Other medical conditions which are linked to depressive episodes are the postpartum depression, seasonal affective disorder, disruptive mood dysregulation disorder and premenstrual dysphoric disorder (PMDD). Depression can also be a side effect of medication (Kulkarni, 2007).

1.3 Development and aetiology of MDD

Equally to other mental disorders the aetiology of MDD cannot be bound to one specific cause, but more likely a combination of genetics and environmental factors. In the 1980s, a thesis was generated. It included a modified version originally evolved for the characterisation of Schizophrenia (Bleuler, 1963), which states that stressful life events (SLEs) may lead to a vulnerability or diathesis. These can trigger genetic predispositions to provoke the development to MDD (Bebbington, 1987). It is hypothesized that the interaction between the vulnerability and the influence of stress have a stronger impact together than individually. The model also suggests that the effect of stress and diathesis are not only additive but multiplicative (Monroe and Simons, 1991). The sensitivity genes are affected by factors emanated from the diathesis-stress model can be analysed as a gene by environment interaction (GxE). The results of GxE studies are often negative or discordant, as they target only single loci in already well-known candidate genes. For instance, in the serotonin transporter gene (*SLC6A4*) researcher found a length polymorphism (*5HTTLPR*) which could be associated with MDD and is now the focus in many GxE studies (Risch *et al.*, 2009; Haberstick *et al.*, 2016). However, the diminution on one locus disregards the fact that MDD, like other mental disorders, is a polygenic trait. Consequently, many genetic alleles with a low impact have a higher influence together than one single variant with a larger effect. Nonetheless, such GxE studies are obstructed by the necessity of immensely broad samples to examine small effects with the necessary

requirements to determine environmental stress factors to conclude in convincing results (Colodro-Conde *et al.*, 2018). Hence, MDD is induced by a combination of inheritance, polygenic risk, the vulnerability to stress and other environmental factors, the research for aetiology and development of this disorder needs more focus on the single components, but more important focus on the combination and interaction of them all.

1.4 Treatment of MDD

MDD is commonly treated with a combination of psychotherapy and medication. It also can help to adjust the lifestyle to diminish one's symptoms. Patients with suicidal thoughts should be placed in a hospital through the treatment duration (Wang, Ma and Xiao, 2019).

In the last decades, a variety of antidepressant medications have been developed. Important parameters for prescribing the correct antidepressant are the patient's age, the severity of the symptoms, other existent diseases, the pharmacological mechanisms, and efficiency of the possible medication. Selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), serotonin and noradrenaline reuptake inhibitors (SNRI) are the most used antidepressants in MDD therapy. The antidepressants prevent the reuptake of the neurotransmitters, which causes the concentration level of those molecules to increase in the synaptic cleft (Szałach *et al.*, 2019). Another effect antidepressant medication can have, is to influence immunomodulatory characteristic. The activity and the quantity of immune cells can be regulated by antidepressants and also the expression of serotonin transporters on T-lymphocytes (Peña *et al.*, 2005; Ahern, 2011).

Another part of an effective treatment for patients with MDD is meeting with a therapist regularly for psychotherapy, which is also designated as psychological therapy. This part of treatment in handling the disease can help a patient accommodate to stressful situations or pressure and finding a more positive attitude. While boosting self-esteem and developing better communication skills, psychotherapy helps regain enjoyment and allows them to handle upsetting conditions. There are different kinds of psychotherapy, such as cognitive

behavioural therapy, interpersonal therapy, or group therapy (Kerr Michael, 2020). Moreover, medication and therapy are proven changes in the patient's lifestyle can help enhance MDD symptoms and could avoid the outbreak of the disease in people with predispositions or higher risks. As one of the symptoms in MDD is a drastic change of appetite, looking out for foods that are associated with benefitting the mental health are essential (Akbaraly *et al.*, 2009; Ouwens, van Strien and van Leeuwe, 2009; Roca *et al.*, 2016). Studies have shown that exercise, especially outdoors, can improve symptoms and the patient's mood (Trivedi *et al.*, 2011; Toups *et al.*, 2017).

1.5 Purpose of my thesis

The significance of mental disorders has increased in the last few years, especially the genetic compound behind the diseases. Additionally, the beneficial applications that come along with the knowledge, such as predispositions, vulnerability to stress, drug response, treatment, and probability of recurrence.

In 2018 Howard et al. published their results out of a genome-wide association study (GWAS), where they could identify 102 single nucleotide polymorphisms (SNPs) associated with MDD (Howard *et al.*, 2018). Since then, more than two years have passed, and new studies have been published. The purpose of my thesis is to give an overview what happened since the original study was published in the field of MDD and its genetic compound.

2 Material and Methods

Since my thesis is a literature review, I searched through databases PubMed and ELSEVIER. My first step was to filter for all possible phrases of MDD (major depression, major depressive disorder and MDD). My next step was to limit the article's language to English or German. Afterwards, I restricted the results to those that include genetic predispositions or association with the disorder. My fourth parameter was the publication date. I only looked for articles published between the 1st of January 2019 and the 28th of February in 2021. This limitation was due to the publication of Howard et al. in 2018 and the start of my research in February. Last but not least, I excluded reviews, books and encyclopaedic entries.

I started with 245 articles, 162 in PubMed and 83 in ELSEVIER. Afterwards, I excluded articles that where in both databases to avoid an overlap. I selected the most recent or the most broadly reported version of the published study. Subsequently, I filtered for articles I had full access to. Then I read the abstract and divided the articles according to specific criteria.

My first criteria were if their direct focus was on MDD within the studies. If MDD was a differential diagnosis or just for comparison, I excluded the paper.

Next point was the size of a study and how many participants were examined. Studies with participants under 50 individuals each group were excluded, as the conclusion of the results is mainly restricted.

I wanted to focus on the genetic predispositions of MDD, as such I eliminated all papers in which the drug response or the prediction of recurrence was the studies target. Last but not least, I only included studies that were conducted on humans. Any animal studies were removed.

In the end I received a list of 22 papers that met my principles and started investigating the newfound data. Additional information used in Tables 1-9, was replenished with the National Centre for Biotechnology Information (NCBI), specific the databases for SNPs and Genes.

3 Results

Table 1: Summary of new DNA modification which are associated with MDD

GENE	GENE-ID	GENE NAME	LOCATION	EXON COUNT	MODIFICATION	ASSOCIATION	POPULATION	REFERENCES
BDNF	627	brain derived neurotrophic factor	11p14.1	12	Methylation of CpG 7.8.9 of promotor I	Visual memory (rs908867)	Caucasians of Iberian Peninsula ancestry	(Ferrer *et al.*, 2019)
					Methylation	Deterioration of long-term memory (rs925946)	Caucasians of Iberian Peninsula ancestry	(Ferrer *et al.*, 2019)
NR3C1	2908	nuclear receptor subfamily 3 group C member 1	5q31.3	16	Hypermethylation of 1 F CpG island	Dysregulation of HPA axis, blunted cortisol reaction	Belgian	(Bakusic *et al.*, 2020)
SLC6A4	6532	solute carrier family 6 member 4	17q11.2	15	Hypermethylation	Higher cortisol response to stress	Belgian	(Bakusic *et al.*, 2020)

YOD1	55432	YOD1 deubiquitinase	1q32.1	4	Methylation on positions: chr1:207224388; chr1:207224102; chr1:207224331; chr1:207224227	Late-life MDD	Caucasian	(Hüls *et al.*, 2020)
UGT8	7368	UDP glycosyltransferase 8	4q26	10	Methylation on position: chr4:115320920	Late-life MDD	Caucasian	(Hüls *et al.*, 2020)
FNDC3B	64778	fibronectin type III domain containing 3B	3q26.31	30	Methylation on position: chr3:171873675	Late-life MDD	Caucasian	(Hüls *et al.*, 2020)
SLIT2	9353	slit guidance ligand 2	4p15.31	40	Methylation on position: chr4:20253130	Late-life MDD	Caucasian	(Hüls *et al.*, 2020)

Newly described DNA modifications associated with MDD; genename, gene-ID and official full gene name, genomic location and exon count, form and genomic position of modification, association according to the denoted reference, population in which the study was conducted and the used reference

Table 2: Summary of newfound differentially methylated regions (DMR) in MDD via monozygotic twin study published from Zhu et al. (Zhu *et al.*, 2019)

GENE	GENE-ID	GENE NAME	LOCATION	EXONE COUNT	MODIFICATION	START	END	SIZE
AAK1	22848	AP2 associated kinase 1	2p13.3	22	Hypermethylation	69,870,526	69,871,424	899
ACTL6A	86	actin like 6A	3q26.33	14	Hypermethylation	179,280,056	179,280,746	691
ANKRD22	118932	ankyrin repeat domain 22	10q23.31	6	Hypermethylation	90,611,604	90,612,228	625
ANXA2R	389289	annexin A2 receptor	5p12	2	Hypermethylation	43,037,123	43,037,666	544
C16ORF95	100506581	chromosome 16 open reading frame 95	16q24.2	7	Hypermethylation	87,351,006	87,351,824	819
C17ORF64	124773	chromosome 17 open reading frame 64	17q23.2	9	Hypomethylation	58,499,300	58,500,186	887
CDK14	5218	cyclin dependent kinase 14	7q21.13	17	Hypomethylation	90,224,158	90,225,380	1223

CHAMP1	283489	chromosome alignment maintaining phosphoprotein 1	13q34	3	Hypermethylation	114,814,024	114,814,401	378
CHST10	9486	carbohydrate sulfotransferase 10	2q11.2	11	Hypermethylation	101,034,246	101,034,295	50
CREB3L4	148327	cAMP responsive element binding protein 3 like 4	1q21.3	13	Hypermethylation	153,940,616	153,941,285	670
CTH	1491	cystathionine gamma-lyase	1p31.1	13	Hypermethylation	70,876,598	70,877,381	784
FAM20B	9917	FAM20B glycosaminoglycan xylosylkinase	1q25.2	11	Hypermethylation	178,994,834	178,995,133	300
FANCC	2176	FA complementation group C	9q22.32	22	Hypermethylation	98,079,646	98,080,622	977
GAREM2	150946	GRB2 associated regulator of MAPK1 subtype 2	2p23.3	11	Hypermethylation	26,395,359	26,395,859	501
HSPB11	51668	heat shock protein family B (small) member 11	1p32.3	9	Hypermethylation	54,411,017	54,412,009	993

KDM2B	84678	lysine demethylase 2B	12q24.31	29	Hypomethylation	122,019,031	122,019,117	87
KIAA0513	9764	KIAA0513	16q24.1	15	Hypomethylation	85,096,632	85,097,151	520
LPAR2	9170	lysophosphatidic acid receptor 2	19p13.11	5	Hypermethylation	19,739,060	19,739,414	355
MAFF	23764	MAF bZIP transcription factor F	22q13.1	4	Hypermethylation	38,598,577	38,599,166	590
MAGI2	9863	membrane associated guanylate kinase, WW and PDZ domain containing 2	7q21.11	29	Hypermethylation	78,400,383	78,400,769	387
NFATC3	4775	nuclear factor of activated T cells 3	16q22.1	12	Hypermethylation	68,118,822	68,119,261	440
NNT	23530	nicotinamide nucleotide transhydrogenase	5p12	26	Hypermethylation	43,602,380	43,603,353	974
NOX5	79400	NADPH oxidase 5	15q23	18	Hypomethylation	69,222,400	69,223,018	619
PCDHA1	56147	protocadherin alpha 1	5q31.3	4	Hypermethylation	140,777,344	140,777,655	312

PCDHGA11	56105	protocadherin gamma subfamily A, 11	5q31.3	4	Hypermethylation	140,800,398	140,800,983	586
PICALM	8301	phosphatidylinositol binding clathrin assembly protein	11q14.2	23	Hypermethylation	85,779,252	85,780,378	1127
PRPF31 (RP11)	26121	pre-mRNA processing factor 31	19q13.42	13	Hypomethylation	8,457,538	8,458,392	855
PRSS21	10942	serine protease 21	16p13.3	6	Hypermethylation	2,866,834	2,868,001	1168
RAB38	23682	member RAS oncogene family	11q14.2	6	Hypermethylation	87,908,134	87,908,805	672
SF3B3	23450	splicing factor 3b subunit 3	16q22.1	26	Hypermethylation	70,557,411	70,557,707	297
SLC30A3	7781	solute carrier family 30 member 3	2p23.3	12	Hypermethylation	27,485,922	27,486,460	539
SORBS2	8470	sorbin and SH3 domain containing 2	4q35.1	39	Hypermethylation	186,732,926	186,733,331	406
SPRED2	200734	sprouty related EVH1 domain containing 2	2p14	10	Hypermethylation	65,594,021	65,595,186	1166

SWSAP1	126074	SWIM-type zinc finger 7 associated protein 1	19p13.2	2	Hypomethylation	11,484,448	11,485,452	1005
TMEM5 (RXYLT1)	1032	ribitol xylosyltransferase 1	12q14.2	8	Hypermethylation	64,173,610	64,174,367	758
TRIM39	56658	tripartite motif containing 39	6p22.1	10	Hypermethylation	30,297,174	30,297,941	768
WT1	7490	WT1 transcription factor	11p13	12	Hypermethylation	32,454,216	32,455,025	810
ZBTB45	84878	zinc finger and BTB domain containing 45	19q13.43	6	Hypermethylation	59,030,662	59,031,081	420
ZNF212	7988	zinc finger protein 212	7q36.1	5	Hypermethylation	148,936,572	148,937,410	839

Newly described DNA methylated regions (DMRs) published from Zhu et al. (Zhu *et al.*, 2019); genename, gene-ID and official full gene name, genomic location and exon count, form of methylation (hyper- or hypomethylation), the regions start and end stated in base pairs and the size of the region also in base pairs.

Table 3: Summary of SNPs associated with suicides and suicide attempts

GENE	SNPS	ALLELE	GENOMIC POSITION	FREQUENCY	POPULATION	REFERENCES
LDHB	rs1677091	A>C / A>T	chr12:21627917	A=0.278447	European American	(Levey *et al.*, 2019)
ARNTL2	rs683813	C>T	chr12:27447398	C=0.144965	African American	(Levey *et al.*, 2019)
FAH / CTXND1	rs72740082	A>T	chr15:80215797	T=0.062508	African American	(Levey *et al.*, 2019)
INTRONIC REGION ON CHR 18	rs11876255	A>G / A>T	chr18:38331390	G=0.012885	African American	(Levey *et al.*, 2019)
GABRG2 (PROTECTING)	rs211034	A>C / A>G	chr5:16210271	A=0.307005	Chinese	(Yin *et al.*, 2020)
ARC	rs7465272	T>A / T>C	chr8:142610477	A=0.200815	Korean	(Crisafulli *et al.*, 2021)

Newly discovered SNPs that are associated with suicides or suicide attempts, genename, possible SNP with allele and frequency (TOPMED), genomic position with GRCh38.p12 as reference genome, population in which the study was conducted and the used reference

Table 4: Summary of newly described SNPs in intronic regions

GENE	SNPS	ALLELE	GENOMIC POSITION	FREQUENCY	ASSOCIATION	POPULATION	REFERENCES
WFDC11	rs6073833	T>C / T>G	chr20:45651255	G=0.211272	Psychological distress	Japanese	(Koshimizu *et al.*, 2019)
MEF2C-AS2	rs454214	C>A / C>G / C>T	chr5:88707586	T=0.453866	Promotes cognition	Han Chinese	(Hou *et al.*, 2020)
SIRT1	rs12415800	G>A / G>C	chr10:67864422	A=0.049838	Lower mRNA levels - smaller cerebellar gray matter volume	Han Chinese	(Liu *et al.*, 2019)
CACNA1C	rs11832738	G>A	chr12:2581536	G=0.402013	influencing spontaneous brain activity	Han Chinese	(Liu *et al.*, 2020)
LHPP	rs35936514	C>T	chr10:124556401	T=0.110944	structural and functional changes in gray matter	Chinese	(Cui, Gong, *et al.*, 2020)

SNPs that are associated with MDD and are located in intronic regions, genename, possible SNP with allele and frequency (TOPMED), genomic position with GRCh38.p12 as reference genome population in which the study was conducted and the used reference

Table 5: Summary of SNPs interacting and react to environmental factors

GENE	SNPS	ALLELE	GENOMIC POSITION	FREQUENCY	POPULATION	REFERENCES
FOXO1	rs17592371	C>T	chr13:40600012	T=0.119704	Han Chinese	(M. Zhao *et al.*, 2020)
	rs2297626	T>C	chr13:40659865	C=0.133641	Han Chinese	(M. Zhao *et al.*, 2020)
A2M	rs669	T>C	chr12:9079672	C=0.309537	Han Chinese	(M. Zhao *et al.*, 2020)
	rs226415	C>T	chr12:9086638	C=0.473775	Han Chinese	(M. Zhao *et al.*, 2020)
TGFB1	rs12462166	T>C	chr19:41351499	T=0.306686	Han Chinese	(M. Zhao *et al.*, 2020)

SNPs that are associated with MDD and are interacting with environmental factors and each other in GxG and GxGxE experiments, genename, possible SNP with allele and frequency (TOPMED), genomic position with GRCh38.p12 as reference genome, population in which the study was conducted and the used reference

Table 6: New identified gene associated with MDD

GENE	GENE-ID	GENE NAME	LOCATION	EXON COUNT	GENE TYPE		POPULATION	REFERENCES
FLOT1	10211	Flotillin 1	6p21.33	14	protein coding	May be influenced by rs2523593	Chinese	(Zhong *et al.*, 2019)

Newfound with MDD associated gene; genename, gene-ID, official full gene name, genomic location and exon count, the gene type, additional information, population in which the study was conducted and the used reference

Table 7: Summary of newly discovered SNPs associated with changes in mRNA levels and are located in regulatory regions

GENE	SNPS	ALLELE	GENOMIC POSITION	FREQUENCY	ASSOCIATION	POPULATION	REFERENCES
MIR34C	rs2187473	C>G / C>T	chr11:111513121	T=0.122149	Immediate and delayed memory	Chinese	(Sun *et al.*, 2020)
IRS-1	rs13411764	A>G	chr2:227071194	G=0.266159	As haplotype with rs3820926 risk factor	Han Chinese	(Wang *et al.*, 2020)

	rs3820926	G>T	chr2:227061905	G=0.356404	As haplotype with rs13411764 risk factor	Han Chinese	(Wang *et al.*, 2020)
TNF	rs1799724	C>T	chr6:31574705	T=0.088574	Somatic symptoms	Han Chinese	(J. Zhao *et al.*, 2020)

SNPs that are associated with changes in mRNA levels and MDD or in are located in regulatory regions, genename, possible SNP with allele and frequency (TOPMED), genomic position with GRCh38.p12 as reference genome, association or additional information, population in which the study was conducted and the used reference

Table 8: Summary of newfound differentially expressed genes (DEG) in MDD via monozygotic twin study from Zhu et al. (37)

GENE	GENE-ID	GENE NAME	LOCATION	EXON COUNT	START	END	SIZE
AC025259.1			Chr12		52,076,841	52,082,084	5243
AL356273.3			Chr1		185,292,384	185,294,372	1988

ALG12	79087	ALG12 alpha-1,6-mannosyltransferase	22q13.33	12	49,900,229	49,918,458	18,229
C11ORF54	28970	chromosome 11 open reading frame 54	11q21	13	93,741,591	93,764,749	23,158
C16ORF74	404550	chromosome 16 open reading frame 74	16q24.1	5	85,690,084	85,751,129	61,045
CBR1	873	carbonyl reductase 1	21q22.12	3	36,069,941	36,073,166	3225
GGH	8836	gamma-glutamyl hydrolase	8q12.3	10	63,015,079	63,039,171	24,092
GUSBP9	118126072	GUSB pseudogene 9	5q13.2		71,197,646	71,208,130	10,484
KNOP1	400506	lysine rich nucleolar protein 1	16p12.3	6	19,701,934	19,718,235	16,301
MGAT4A	11320	alpha-1,3-mannosyl-glycoprotein 4-beta-N-acetylglucosaminyltransferase A	2q11.2	17	98,619,106	98,731,126	112,020

MRPS18B	28973	mitochondrial ribosomal protein S18B	6p21.33	7	30,617,709	30,626,395	8686
NDUFA8	4702	NADH:ubiquinone oxidoreductase subunit A8	9q33.2	5	122,144,058	122,159,819	15,761
PECR	55825	peroxisomal trans-2-enoyl-CoA reductase	2q35	10	215,996,329	216,082,955	86,626
PEX11B	8799	peroxisomal biogenesis factor 11 beta	1q21.1	5	145,911,350	145,918,837	7487
PLK3	1263	polo like kinase 3	1p34.1	15	44,800,225	44,805,990	5765
RABGEF1	27342	RAB guanine nucleotide exchange factor	7q11.21	24	66,682,164	66,811,464	129,300
RGCC	28984	regulator of cell cycle	13q14.11	7	41,457,559	41,470,882	13,323
RRP7A	27341	ribosomal RNA processing 7 homolog A	22q13.2	7	42,509,968	42,519,802	9834

SEMA3C	10512	semaphorin 3C	7q21.11	20	80,742,538	80,922,359	179,821
TMEM170B	100113407	transmembrane protein 170B	6p24.2	3	11,538,278	11,583,524	45,246
TNFAIP8L2	79626	TNF alpha induced protein 8 like 2	1q21.3	2	151,156,629	151,159,749	3120
TRIM21	6737	tripartite motif containing 21	11p15.4	7	4,384,897	4,393,696	8799
TRPT1	83707	tRNA phosphotransferase 1	11q13.1	9	64,223,799	64,226,254	2455
TTI2	80185	TELO2 interacting protein 2	8p12	8	33,473,386	33,513,601	40,215
ZNF101	94039	zinc finger protein 101	19p13.11	7	19,668,796	19,683,509	14,713
ZNF200	7752	zinc finger protein 200	16p13.3	7	3,222,325	3,236,221	13,896
ZNF487	642819	zinc finger protein 487	10q11.21	8	43,436,841	43,483,179	46,338
ZNF493	284443	zinc finger protein 493	19p12	5	21,397,119	21,427,573	30,454

ZNF772	400720	zinc finger protein 772	19q13.43	5	57,466,663	57,477,570	10,907
ZNF816	125893	zinc finger protein 816	19q13.41	5	52,949,379	52,962,911	13,532

Newly described differentially expressed genes (DEGs) published from Zhu et al. (Zhu *et al.*, 2019); genename, gene-ID and official full gene name, genomic location and exon count, the regions start and end stated in base pairs and the size of the region also in base pairs

Table 9: Summary of newly discovered SNPs associated with MDD

GENE	SNPS	ALLELE	GENOMIC POSITION	FREQUENCY	POPULATION	REFERENCES
MTHFR	rs1801133	C>T	chr1:11796321	A=0.289739	Han Chinese	(Z. Li *et al.*, 2020)
MUC21	rs9368649	A>G	chr6:30971106	G=0.108810	European and Chinese	(Amare *et al.*, 2020)
DRD2	rs4648317	G>A	chr11:113460810	A=0.173595	Han Chinese	(He *et al.*, 2019)
	rs7131056	A>C / A>G	chr11:113459052	A=0.483825	Han Chinese	(He *et al.*, 2019)

BDNF	rs6265	C>T	chr11:27658369	T=0.164325	Malaysian Population	(Faris Aldoghachi *et al.*, 2019)

Newfound SNPs that are associated with MDD, genename, possible SNP with allele and frequency (TOPMED), genomic position with GRCh38.p12 as reference genome, population in which the study was conducted and the used reference

4 Discussion

The importance of genetics in modern medicine has been growing over the last decades and is a significant part of treatment in some fields, for example in oncology. A patient's genome can support clinical predictions in treatment response and recurrence. Although, the number of MDD patients is increasing annually, in the psychiatric field genetics are not used in daily tasks. Therefore, I dedicated my thesis to summarize the most important results of studies that concentrated on genetic predispositions for MDD published during the last two years.

4.1 DNA modification and gene expression

It has been shown that epigenetics, therefore deoxyribonucleic acid (DNA) modifications, their effect on gene expression and consequently messenger ribonucleic acid (mRNA) levels, influence the development of psychiatric disorders significantly (Mill and Petronis, 2007; Story Jovanova *et al.*, 2018). Hence, DNA methylation affect transcription when they are located in promotor regions and were examined as a source for mood disorders, their severity and as prediction for remission as well as treatment response (Newell-Price, Clark and King, 2000; Li *et al.*, 2019). All genes are listed in Table 1, which show altered DNA modifications in MDD patients compared to the healthy controls.

4.1.1 DNA methylation in late-life depression

Hüls et al. published results for different DNA methylation levels in brain tissue and how that can be associated with MDD in adults. The study worked with over 600 deceased participants out of two different cohorts (Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP)). The researcher were able to identify 4 loci (*YOD1, UGT8, FNDC3B* and *SLIT2*) which hold modified methylation and can be related to MDD as epigenetic factors (Hüls *et al.*, 2020).

The deubiquitinase *YOD1* is highly conserved and works in the regulation of interleukin-1, which signals pathway through triggering TRAF6/p62 and is, therefore, important in the regulation of inflammation (Schimmack *et al.*, 2017).

Additionally, the function of its convergence protein in yeast *OUT1* contains the degradation of falsely folded proteins in the endoplasmic reticulum (Rumpf and Jentsch, 2006). Hence, those results suggest a role for *YOD1* in depression. *UGT8* was discovered to be a biomarker in breast cancer and lung metastases but also has higher expression levels in brain tissue from patients with MDD (Le-Niculescu *et al.*, 2009; Dzie¸giel *et al.*, 2010).

4.1.2 BDNF

The gene regulation of the brain-derived neurotrophic factor (*BDNF*) is known for its influence on neurocognitive functions. As such, the symptom of cognitive deficiency in MDD patients is common and DNA modulations adjust the gene's activity, Ferrer and colleagues analysed eleven SNPs and two promotor regions and their methylation status within the *BDNF* gene (Ferrer *et al.*, 2019). The study was conducted with Caucasians of the Iberian Peninsula and included 64 MDD patients, as well as 71 healthy individuals, all in their mid to late 50s, with more female percentage (72% MDD patients, 63% in the control group).

The results of this study link two noncoding SNPs (rs908867 and rs925946) and different DNA modification levels in promotor regions with cognitive function alongside an interaction between sex, childhood trauma questionnaire scores, which was analysed in the early stage of the study, and a MDD diagnosis (Ferrer *et al.*, 2019). Participants with those two SNPs showed lower accomplishments in the cognitive tasks, like processing speed, visual learning, and memory. Furthermore, the SNP rs908867 could be linked to visual memory and various methylation in the promotor I of *BDNF* (Ferrer *et al.*, 2019).

Another study assumed a correlation between the *BDNF* plasma level and the SNP rs6265 (Table 7). The participants, 300 Malaysian individuals each were divided into MDD patients and a control group, whose ages range from 18 to 65 years, were genotyped. They filled out questionnaires for geographic data, threatening events, supplement intake, physical activity, and clinical characteristics. The findings did not show significant differences in the *BDNF* plasma levels between the variant genotypes, but suggest a substantial role of rs6265 in the risk of MDD in Malaysian population (Faris Aldoghachi *et al.*, 2019).

4.1.3 NR3C1 and SLC6A4

Bakusic et al. focused on the epigenetic dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis stress response in MDD patients. They concentrated on the DNA methylation of the serotonin transporter gene (SLC6A4) and the glucocorticoid receptor gene (NR3C1). Alterations in *NR3C1* DNA modification correlating with MDD is interrogated in only few studies (Na *et al.*, 2014; Bustamante *et al.*, 2016; Roy, Shelton and Dwivedi, 2017) lacking any functional analysis of the HPA axis activity. Moreover, results to longitudinal research about *NR3C1* modifications in calculating a patient's aetiopathology and possible recurrence with MDD are still missing.

For this study, Bakusic et al. recruited 80 MDD patients and 58 healthy controls. Additionally to the Trier Social Stress Test (TSST), the patient's salivary cortisol levels were repeatedly measured (Bakusic *et al.*, 2020). MDD patients show an increased methylation in the examined genes and had dampened cortisol reactivity in the TSST. The methylation in the CpG20 island in the *NR3C1* gene showed diminished improvement on patient's symptoms (Bakusic *et al.*, 2020).

4.2 DMR and DEG findings

Zhu et al. investigated the correlation between altered DNA methylation and genes that are differentially expressed, and MDD. Therefore, they designed a genome-wide methylation study and gene expression in peripheral blood monocytes. The samples were collected from 79 monozygotic twin pairs. As a result from integrative DNA methylome and transcriptome analysis, 39 DMRs (33 hypermethylated, 6 hypomethylated) (shown in Table 2) and 30 DEG (14 upregulated, 16 downregulated) (results in Table 8) could be identified and linked with MDD (Zhu *et al.*, 2019). The associated genes are involved in various cell processes, such as signalling pathways for stress response, mTOR signalling, nerve growth factor receptor signalling, neuron apoptosis, and insulin receptor signalling.

The most significant DMR associated with MDD was the *PRSS21* gene. The *PRSS21* encodes for a glycosylphosphatidylinositol (GPI)-linked serine protease,

which belongs to the trypsin family of serine proteases. It has been shown that the brain can co-opt the activities of these proteases. It can interfere with the regulation of various processes including learning, social behaviour or synaptic activity (Almonte and Sweatt, 2011). When these proteins alter in their normal activity, it can lead to neurological disorders such as Parkinson's disease, stroke, Alzheimer's disease, and traumatic brain injury (Almonte and Sweatt, 2011).

The *PECR* gene appeared to be expressed differentially in MDD patients and SNPs in this gene were associated with alcohol dependence (Treutlein *et al.*, 2009; Zhu *et al.*, 2019). It encodes for the peroxisomal trans-2-enoyl-CoA reductase which plays an important role in energy production in mitochondria.

The function of zinc in synaptic activity and neuronal plasticity was also uncovered through studies. Their results suggested an association between zinc deficiency and neurodegenerative as well as mood disorders (Hagmeyer, Haderspeck and Grabrucker, 2014; Doboszewska *et al.*, 2017). The study of Zhu et al. demonstrated that numerous of the zinc family were differentially methylated or expressed and support the position zinc dysregulation may play in MDD (Zhu *et al.*, 2019).

4.3 SNPs associated with suicide and suicide attempts

The researcher Crisafulli et al. investigated the severity in mood disorders in two different ethnologies, European and Korean. These were set according to four examined SNPs in the genes which are encoding for the activity regulated cytoskeleton associated protein (*ARC)* (Crisafulli *et al.*, 2021). The protein plays an important role in the cytoskeleton regulation (Lyford *et al.*, 1995; Messaoudi *et al.*, 2007). First, the research team explore the possible treatment efficiency in different mood disorder but could not find any significant differences. However, the SNP rs7465272 could be associated with a suicide risk in the Korean samples (Crisafulli *et al.*, 2021).

Meanwhile, Yin and colleagues explore the possible association of polymorphisms in the GABA A receptor γ2 subunit (GABRG2) near the alternatively spliced exon with childhood trauma and the consequences of the risk with suicide attempts.

Thus, the research group examined five SNPs of the probed gene in three different groups, 94 suicide attempters, 168 non-suicide attempters who are suffering from MDD or bipolar disorder, and 100 people as healthy control. Additionally, to collect data on demographics, suicide attempts and depression severity, the subjects were genotyped as well as analysed for childhood trauma and lifetime aggression and impulsivity. The SNP rs211034A was identified as a protective factor for suicide attempts and as haplotype with the SNP rs211035 the genotype GA showed a lower rate of suicide attempts (Yin *et al.*, 2020).

There was another study that investigated the correlation of suicide, suicide attempts and specific genotypes. It got published by Levey et al. in 2019. They conducted a GWAS with 2.439 European Americans and 3.881 African Americans. In European Americans one SNP (rs1677091) near the *LDHB* gene was found, which is involved in anaerobic energy production. Three significant SNPs were identified in African American: rs683813 in the *ARNTL2* gene participating in circadian clock regulation, rs72740082 in *FAH*, a component in the tyrosine catabolism, and rs11876255, located in an intronic region on chromosome 18 (Levey *et al.*, 2019).

4.4 Intron variant

It has been shown that SNPs in intronic regions can have a crucial influence on genes. Newly found intronic SNPs are listed in Table 4.

4.4.1 MEF2C-AS2

The gene myocyte-specific enhancer binding factor 2C (*MEF2C)* encodes a transcription factor, which plays a crucial role in the regulation in the maturation process of neurons (Kavalali *et al.*, 1999). The gene is expressed during the early stages of brain development and sustains expression in different adult brain regions, such as the cortex, hippocampus, amygdala and dentate gyrus (Leifer, Golden and Kowall, 1994; Black and Cripps, 2010; Adachi *et al.*, 2016).

For this study, Hou and colleagues recruited 878 Han Chinese, with an average maturity of 18 years, as part of their control group alongside 384 patients with

MDD with an age range from 18 to 60 years. The group's focus was on personality, depressive symptoms, and subjective well-being. The SNP rs454214 upstream of the *MEF2C* gene could be linked to MDD (Hou *et al.*, 2020).

4.4.2 CACNA1C

The calcium channel, which is encoded in the *CACNA1C* gene, regulates the calcium influx in many different types of cells and plays a crucial role in brain and heart cell functions (Backes *et al.*, 2014). It was already described in the context of depression (Rao *et al.*, 2016; Musazzi *et al.*, 2019). Liu et al. recruited 116 MDD patients and 66 individuals as healthy control, who were additionally divided into genotype groups as well. The study investigated the connection among the SNP rs11832738 in the *CACNA1C* gene and the amplitude of low-frequency fluctuation (ALFF) in MDD patients. The right medial frontal gyrus (RMFG) was the main affected brain region. Furthermore, patients with the G allele in the examined SNP, showed a significant correlation of the ALFF of the RMFG and the disorders severity. This relation between the SNP and the severity was caused by modified spontaneous activity of RMFG (Liu *et al.*, 2020). The brain region has already be reported to be associated with MDD, as it plays a crucial role in the regulation of processing emotions and various cognitive functions, for example working memory, attentional processing or decision-making (Geng *et al.*, 2019; Wang *et al.*, 2019).

4.4.3 LHPP

Although the gene *LHPP* is highly expressed in the brain and includes a SNP (rs35936514) that was already associated with MDD (Neff *et al.*, 2009; CONVERGE consortium, 2015), the mechanism how the gene is involved in MDD is relatively unknown. *LHPP* encodes the enzyme phospholysine phosphohistidine inorganic pyrophosphate phosphatase. Cui et al. investigated how the diverse gene variation influences the function and the structure of the grey matter in the brain (Cui, Wang, *et al.*, 2020). For this purpose, 50 patients diagnosed with MDD and 113 individuals for healthy control were examined and genotyped for the specific SNP. As a result, MDD patients with the risk T allele in the rs35936514

SNP show a functional connectivity modification in the hippocampus and lower volume of grey matter in the prefrontal cortex. They also contain grey matter alterations in the medial prefrontal cortex, the posterior cingulate cortex, and the temporal cortex. Those brain regions are part of the default mode network. Those results indicate a relation between the default mode network and the *LHPP* polymorphism (Cui, Wang, *et al.*, 2020).

4.5 FoxO1, A2M, TFGβ1 and environmental factors

As mentioned before, it is more likely that not one of a candidate's gene of large effect is responsible for the development of MDD, but many possible variants with small impact combined. Additionally, it is well known that environmental factors play a crucial role and requires further investigation.

In 2020, Zhao et al. published their results when they investigated GxE interactions as well as gene by gene (GxG) and gene by gene by environment (GxGxE) interactions, respectively. The study worked with two groups that each consisted of 800 Han Chinese, was hypothesis-free, cross-tissue, -species and omics-based. The research group examined three possible candidate genes: Forkhead box transcription factor O1 (*FoxO1*), alpha-2-Macroglobulin (*A2M*) and Transforming Growth Factor beta 1 (*TGFB1*) (Cattaneo *et al.*, 2018). FoxO1 activates in its role as a transcription factor by affecting various genes for many different cellular processes, such as genes responsible for autophagy and apoptosis, cell cycle checkpoints, regulation of metabolism and immune system (Kandula *et al.*, 2016; Liu *et al.*, 2016). The main functions of the cytokine TGFB1 include controlling embryogenesis, cell differentiation and immune response (Massagué, 1998).

Zhao et al. found an association with MDD and the following SNPs: rs17592371 and rs2297626 (*FoxO1*), rs669 and rs226415 (*A2M*) and rs12462166 (*TGF-β1*), whose results are shown in Table 5. Additionally, results about the interaction with environmental factors in MDD patients and the SNPs rs17592371 and rs28553411 (*FoxO1*), rs10842847, rs10842849, and rs226415 (*A2M*), and rs12462166 and rs12983775 (*TGF-β1*) advocate a probable connection between the origin of MDD and these genes (M. Zhao *et al.*, 2020).

4.6 MicroRNA and depression

MicroRNAs (miRNAs) have developed a rise in significance for different expression levels and the association with neuropsychological diseases (Oved *et al.*, 2012; Liu *et al.*, 2014). Sun et al. focused on the miR-34 family and designed a study to determine the correlation between the miRNA's expression levels as well as cognition tasks, especially memory, in MDD patients. The study recruited 578 MDD patients in total, and 301 individuals as healthy controls. The patients were divided into two groups, one in their first episode of depression (78,2%) and in the other one the patients who were in regression (21,8%) (Sun *et al.*, 2020). For testing purposes, the neuropsychological activity uses two different analyses, which were: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Trail Making Test (TMT). RBANS can show the deficits patients with MDD have in memory, attention and constructional abilities, while TMT helps to evaluate cognitive performances (Sánchez-Cubillo *et al.*, 2009; Faust *et al.*, 2017). Additionally, the results showed a significant relationship between the outcomes in RBANS and TMT with the expression levels in miR-34b/c in MDD patients. There also was a correlation between miR-43c-5p level in peripheral blood leukocytes, delayed-, working memory and language in MDD patients (Sun *et al.*, 2020). Various expression levels of miRNAs in neurons could have a significant impact for the pathophysiology and development of depression (Dwivedi, 2011; Aschrafi *et al.*, 2016). Sun et al. found a correlation between higher cognitive function in delayed- and immediate memory in MDD patients who were genotyped with a CC allele in the SNP rs2187473. The results show that miR-34c plays a role in cognitive functions is supported by the findings that miR-34c induce decreased spine density and shortened dendrites when overexpressed in the hippocampus. It functions as a regulator in the Notch signalling pathway, which regulates differentiation and proliferation in the central nervous system (Guo *et al.*, 2009; Kao, Wang and Tsai, 2018).

4.7 SNPs in regulatory regions

SNPs, which have an impact on the development of MDD, cannot only be available in coding sequences but also in the regulatory region of a gene (Table

7). They affect the binding sites of transcription factors (TF) and alter the gene expression of the corresponding gene.

4.7.1 NEGR1

The SNP rs3101339 is located in the regulatory region of the neuronal growth regulator 1 (*NEGR1*) gene and analysis have shown that the expression of *NEGR1* is downregulated in patients with MDD (S. Li *et al.*, 2020). *NEGR1* is significant for the cortical development, neural morphological maturation and dendritic spine density (Wierenga *et al.*, 2016; Szczurkowska *et al.*, 2018). As the gene is downregulated due to the SNP in the regulatory region, the decreased expression precedes a modified morphology and density of dendritic spines. They have been shown lead to behavioural modification (Singh *et al.*, 2019). However, those results suggest a significant role of *NEGR1* in MDD. There have to be more research how the expression of this gene affects the risk for MDD (S. Li *et al.*, 2020).

4.7.2 TNFα

The cytokine tumour necrosis factor α (TNFα) plays an important role in systematic inflammation and regulation of the immune system during the acute-phase reaction to tissue injury or immunological responses (Rajput and Ware, 2015).

Zhao et al. investigated -857C/T polymorphism (rs1799724) in the regulatory region of TNFα and its influence on the somatic symptom severity in MDD patients. This study was conducted with 807 MDD patients and 822 individuals as healthy control. All participants had a Han Chinese background and were from the same geographic area. They were genotyped and the mRNA levels of TNFα were analysed using qRT-PCR. The SNP has a transcriptional affect and patients with a T/T or T/C genotype show significantly higher levels of the gene's mRNA compared to individuals in control groups or with genotype C/C (J. Zhao *et al.*, 2020).

4.7.3 IRS1

It has been shown that different genotypes in the insulin receptor substrate 1 (*IRS1)* gene have an effect on the risk of postpartum depression or Alzheimer. Research shows that it is most likely inherited (Mielke *et al.*, 2005; Blázquez *et al.*, 2014), but a possible influence for MDD has not been researched yet.

In 2019, Wang et al. published their results of the influence in various genotypes in the *IRS1* gene for MDD in Han Chinese. 583 individuals were examined, and the findings suggest that the SNP rs13411764 has low impact on the expression level of *IRS1*. Furthermore, a second SNP (rs13411714) act simultaneously and as a haplotype both SNPs could increase the risk for MDD (Wang *et al.*, 2020). Additionally, the haplotype with the genotype G-T show a relation between family history and mental illness. However, the outcomings were not able to find any correlation amid the haplotype and the severity of MDD (Wang *et al.*, 2020).

4.7.4 mRNA expression of SIRT1

While various studies in European population validated the hypothesis that noncoding DNA sequences in genes, which are considered increasing the risk of a complex illness, influence gene expression in affected tissue. The amount of published genome-wide transcriptome studies is low. Liu et al. found an association between the SNP rs2415800, which is located near the *SIRT1* gene, and atypical volume of grey matter in the left posterior cerebellar lobe (Liu *et al.*, 2019).

The study was conducted with 1824 MDD cases and 3031 healthy controls in Han Chinese population. Two possible risk loci, which resulted out of a Chinese GWAS, analysed in post mortem brain tissue and peripheral blood samples were examined and the findings show that the mRNA levels of *SIRT1* are lower in MDD cases with the risk SNP rs2415800 than in healthy control (Liu *et al.*, 2019).

The appointed SNP could interfere with other genes as well, CTNNA3, DNAJC12, HERC4, and MYPN. Although *CTNNA3* is expressed in the cerebellum studies, it showed that *CTNNA3* knock out mice do not present any morphological differences in their brain tissue (Folmsbee *et al.*, 2016). Those genes and their

possible risk in MDD have not been the focus on research as much as the impact of *SIRT1*. This area requires more investigation.

4.8 Newfound risk gene

To identify new risk genes for MDD, Zhong et al. merged the results of large-scale MDD GWAS and brain expression quantitative trait loci (eQTL). They analysed the data with a Bayesian statistical framework (*Sherlock*). *Sherlock* identified the gene *FLOT1* which encodes for flotillin 1, a caveolae-associated integral membrane protein (Table 6). Although, there are many studies about this gene's function, it is not fully established. However, the gene is highly conserved, which implicate a crucial function. A study in *Drosophila melanogaster* has shown, that the gene is exceedingly expressed in the fly's brain (Galbiati *et al.*, 1998). Another study stated as results, that *FLOT1* possesses an important part in the central nervous system. Moreover, it is necessary in the differentiation of neurons, outgrowth of axons and their regeneration (Stuermer, 2011). The gene expression of *FLOT1* was consistently upregulated in peripheral blood and in brain samples in European MDD patients (Zhong *et al.*, 2019).

Beside the newfound risk gene, Zhong et al. identified by means of *Sherlock* 18 genes that could increase the risk of MDD when differentially expressed, such as the gene *NOTCH4*. The Notch signalling pathway hold importance for development and differentiation of neurons, and has been associated with Schizophrenia (Redmond *et al.*, 2000; Scheer *et al.*, 2001; Hultman *et al.*, 2013). In addition, the genes *C4A* and *C4B*, encoding for the complement C4A and C4B proteins, are involved in synapse development. Moreover, they were associated with Schizophrenia as well, suggesting an influence in the central nervous system, respectively (Sekar *et al.*, 2016).

4.9 New described SNPs

In Table 9 new described SNPs are listed, which were associated with MDD in the last two years.

4.9.1 DRD2

Another gene that has been associated with MDD is the D2 dopamine receptor (*DRD2*) since it is part of the dopaminergic system. It has been linked to attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD) and Schizophrenia (Badgaiyan, 2010; Gurvich and Rossell, 2014; Duan *et al.*, 2015).

For this study He et al. enlisted 831 Han Chinese, 332 MDD patients and 497 individuals as healthy control. 16 different SNPs were investigated while only two SNPs, rs4648317G and rs7131056A, could be linked to MDD and could be used as markers to predict vulnerability to MDD. In vitro, it was found that rs7131056 C>A might act as an intronic silencer and influences the gene expression of *DRD2* and affect through the dopaminergic system the vulnerability for MDD (He *et al.*, 2019).

4.9.2 MTHFR

In the 5,10-Methylenetetrahydrofolate reductase gene (*MTHFR*) the SNP rs1801133 (C677T) was associated with MDD and especially the T allele or TT genotype was considered to be a risk for mental illness in Asian population (Wu *et al.*, 2013). Studies suggest a relation between the gene and subcortical structure volumes as well as cortical thickness, which can lead to different regulation and processing of emotions (Rive *et al.*, 2013; Persson *et al.*, 2014; Roussotte *et al.*, 2017).

Li et al. designed a study with 127 MDD patients and 101 individuals for a healthy control. They were genotyped for the C677T SNP, underwent T1-weighted MRI, and morphological analysis. In MDD patients the left nucleus accumbens showed a decreased volume and patients with the T allele hold thinner cortical thickness in the left caudal anterior cingulate cortex (Z. Li *et al.*, 2020).

4.10 Limitations

Aside from the studies' results, their limitations merit discussion. First of all, many studies worked with a small sample size. I excluded articles with less than 50 participants for patients and control group each. But even the study with over 8

million SNPs had noticeable limitations by testing a small sample size. Hence, the results need further confirmation with more individuals for each group. Second, while many teams worked with drug naïve MDD patients, some included contestants that already received medicine. It cannot be barred, that antidepressants could influence DNA modification, gene expression or cortisol levels (Ferrer *et al.*, 2019; Bakusic *et al.*, 2020). Therefore, received results with patients that were already in pharmacological treatment, should be repeated with drug naïve patients. Third, depression severity, diagnosis, and childhood trauma, when needed, were mostly identified and classified through self-reported questionnaires in retrospect and can be altered by recall bias or mental stability (Ferrer *et al.*, 2019; Yin *et al.*, 2020). Fourth, studies that were focusing on DNA modification, examined mostly with peripheral blood samples. The results can differ from modifications found in the brain. Although, for example for the *BDNF* gene research has shown that the methylation state in peripheral blood cells are nearly similar to those in brain tissue (Stenz *et al.*, 2015). Finally, many studies are limited to one ethnos, for instance all study's participants are Han Chinese origin. The results are not directly conferrable to for example Caucasian or African. More research is needed to find assimilable genetic predispositions in other populations.

Another point that needs be discussed, is the diagnosis and classification finding. The DSM-5 or ICD-10 are checklists and establish the presence or the absence of a depressive episode (Ramirez *et al.*, 2018; Koukopoulos, Sani and Ghaemi, 2021). This construct of diagnosis suggests a unidimensional and universal depression for each patient, while studies show that there are more than one subtypes of depression (Van Loo *et al.*, 2012; Rantala *et al.*, 2018). Therefore, the genetic component of the aetiology of MDD and possible concomitant pathophysiological changes could help improve the classification for each patient.

4.11 Future research

In 2007 Sullivan and colleagues founded the Psychiatric Genomics Consortium (PGC). The consortium focuses on the genetical predispositions in psychiatric disorders and offer free access to the results for researcher all around the world. The aim is to collect genomic data about fundamental biological mechanisms,

possible usage in clinical practice, and find new potential drug targets (Sullivan *et al.*, 2018). This kind of collaboration is important to push the state of knowledge, and the possibilities genetics present in psychiatrics nowadays.

4.11.1 Finding Biomarkers

MDD belongs to the most prevalent psychic disorders worldwide with a high recurrency and an enormous disparity among patients (Kessler, Chiu, *et al.*, 2005; Moffitt *et al.*, 2010). As mentioned before, a high percentage of patients achieve no response to medicine or have extreme side effects. In addition, research has proven that MDD can cause many changes in biological mechanisms and systems such as brain structure, immunological system, neurotransmitters, and oxidative stress (Krystal *et al.*, 2002; Schlaepfer *et al.*, 2008; Miller and Raison, 2016; Black *et al.*, 2017). This knowledge can help to find biomarkers in concerned persons to predict MDD onset, adequate treatment, or recurrency.

However, no test for one single biomarker has been developed to this day, as no overall biomarker has been discovered yet. The genetical and pathophysiological changes as well as differences amid patients are too wide range (Jentsch *et al.*, 2015). In addition, individual characteristic, such as age or gender, also have an impact on possible biomarkers. Jentsch et al. shows that there are appropriate biomarkers to differentiate men and women that need to be taken into account. Therefore, the research for biomarkers help to classify MDD have many difficulties to overcome and there remain many aspects to take into consideration (Jentsch *et al.*, 2020).

It has been proven, that patients with MDD manifest altered levels of proteins in their blood samples compared to healthy control. For instance, studies have shown that patients with MDD hold decreased levels of vitamin C and superoxide dismutase (Gałecki *et al.*, 2009; Gautam *et al.*, 2012). But their levels for reactive prooxidants are elevated. Even post-translational modifications of proteins can alter in MDD patients compared to healthy individuals, for example the S-glutathionylation. Elevated levels of glutathionylated proteins are associated with oxidative stress (Niwa, 2007). Mathew et al. studied the concentrations of haemoglobin with those modifications in MDD patients, as possible biomarkers.

The levels of glutathionyl haemoglobin were significantly elevated in MDD patients but no differences between pre- and post-treatment individuals could be determined (Mathew *et al.*, 2019).

Problems that need to be considered, are the low sensitivity and specificity among different biomarkers so far. A possible solution, as recommended by some authors, was the analysis of a panel to consider numerous biomarkers instead of a single one (Schmidt, Shelton and Duman, 2011). In addition, structural changes in MDD patient's brains were investigated. It has been proven that concerned individuals show reduced volume in several brain regions such as anterior cingulate cortex, hippocampus, orbitofrontal cortex, and basal ganglia. Likewise, decrease in grey matter volume and cortical thickness, and degradation in white matter integrity are observable in neuroimaging (Dunlop and Mayberg, 2014; Lener and Iosifescu, 2015). Those structural abnormalities underline a possible combination of blood sample analysis and neuroimaging in classifying and predict MDD.

A point that has to be considered in developing biomarkers for MDD is the fact that other mental health disorders that include depressive episodes are often misdiagnosed as MDD, as mentioned before. It is necessary to find biomarkers that are unique for MDD, or can possibly correct the false diagnosis and preclude MDD (Hacimusalar and Eşel, 2018).

4.11.2 Drug response and possible drug targets

Most MDD patients are treated with antidepressants. However, the effectiveness differs tremendously since 60-70 % of treated patients do not encounter remission, and 30-40 % have no response or extreme side effects. The genetic fundamentals in each individual who suffers from MDD leads to different enzyme activities and cell responses to various drug exposure (Wilkinson, 2005). Therefore, research has focused on genetic polymorphisms that could be used as biomarkers that predict a patient's drug response. For instance, the cytochrome P450 (*CYP450*) family, *TNFα* or the *MTHFR* gene played a key role in some investigations as predictor for treatment response (Hodgson *et al.*, 2014). As mentioned before, finding biomarkers for predicting MDD onset and recurrency is extremely difficult.

Besides, literature results are full with inconsistent perceptions (Ma, Zhang and Baloch, 2016).

For example, there are plenty of studies about TNFα, as it is considered to play a role in the pathophysiological changes in MDD, associated with prediction according to treatment and drug response. The results of changes in TNFα levels after medical treatment were inconsistent, as they show increasing, decreasing as well as no changes at all (Narita *et al.*, 2006; Eller *et al.*, 2009; Ragab *et al.*, 2015).

For finding new drug targets a pathway analysis can be applied. It is used to find new possible targets for existing drugs. Therefore, a set of genes with an interested associated phenotype is examined, by deconstructing the proteins that the drug is binding (Gaspar and Breen, 2017). Those analysis help establishing big networks which indicate new targets for already existing drugs or drug developing (Gaspar *et al.*, 2019).

5 Conclusion

In conclusion, the aim of this thesis was to summarize the latest studies for genetical variations and polymorphisms associated with MDD. The results demonstrate the variety of biological systems involved by leading to MDD symptoms. In addition, the genetic compound of mental health disorders shows a significant role in identifying their aetiology. It helps understanding the pathophysiological changes in patients. The various genetical functions altering in MDD patients underlying the heterogeneity and complexity of this disorder. It supports explaining the inconsistency in results throughout different study groups, mentioned before. Knowledge of the genetical features can help manifest personalized medicine in psychiatrics. In the future, understanding a patient's genetical characteristics could predict someone's onset, their treatment response, and their possible state of recurrency. This would lead to find individuals in early states, help finding proper and specific treatment with the highest possible response without or just minimal side effects and reducing hospitalization. Therefore, detailed research is needed to establish more knowledge of the genetic aetiology of MDD.

6 References

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