Master Thesis

Phenotypic Consequences of Homozygous/Compound Heterozygous Germline Mutations in Tumor Suppressor Genes/Oncogenes Included in a Commercial Tumor Panel (TruSight® Hereditary Cancer Panel, Illumina)

submitted by

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Woerth am Rhein, October 2020

1. Reviewer:

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Self-declaration

I hereby declare that I have made this present work without any unauthorized help of third parties and the use of other than the specified aids. The ideas taken directly or indirectly from external sources are identified as such.
The Master Thesis has not yet been submitted either in Austria or abroad in the same or similar form.

Woerth am Rhein, October 2020

Rangen Wali eh

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Contents

List of abbreviations

(-/-)	Gene knockout
-ve	Negative
+ve	Positive
AA	Amino Acid
AFP	Alpha Feto Protein
ALL	Acute Lymphocytic Leukemia
ANA	Anti-Nuclear Antibody
ASD	Atrial Septal Defect
BER	Base Excision Repair
BM	Bone Marrow
BMF	Bone Marrow Failure
BP	Birth Prevalence
BWt	Birth Weight
C/S	Caesarian Section
Ca	Cancer
CAL	Cafe`-Au-Lait
Comp.Hete.	Compound Heterozygous
Cons.	Consangious
CT-Scan	Computed Tomography Scan
DD	Developmental Delay
DDH	Developmental Dysplasia of Hip
DEB	Diepoxybutane
DNA	Deoxyribonucleic Acid
DNA DSB	DNA Double-Strand Break
Dx	Diagnosis
FAMMM	Familial Atypical Multi Mole Melanoma
FAP	Familial Adenomatous Polyposis
FTT	Failure To Thrive
G6PD	Glucose-6-Phosphate-Dehydrogenase
GH	Growth Hormone
GOF	Gain Of Function

GR	Growth Retardation
GTP	Guanosine Triphosphate
GTPase	Guanosine Triphosphatase
GWs	Gestational Weeks
HC	Head Circumference
Homo.	Homozygous
HR	Homologous Recombination
Ht	Height
Hx	History
ICL	Interstrand Crosslinks
IHC	Immunohistochemical staining
IUGR	Intrauterine Growth Retardation
Lab.	Laboratory
LOF	Loss Of Function
MRI	Magnetic Resonance Imaging
MSI	Microsatellite Instability
MTC	Medullary Thyroid Carcinoma
NER	Nucleotide Excision Repair
OCGs	Oncogenes
OW/EBD	Orphanet Worldwide/European Bibliographic Data
PC	Parents are Carriers
PCC	Pheochromocytoma
PDA	Patent Ductus Arteriosus
PTH	Parathyroid Hormone
RD	Respiratory Distress
SD	Standard Deviation
SNP	Single Nucleotide Polymorphism
TGF-β	Transforming Growth Factor-β
TSGs	Tumor Suppressor Genes
Tx	Treatment
U/S	Ultrasound
VSD	Ventricular Septal Defect
Wnt	Wingless signal pathway
Wt	Weight

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Zusammenfassung

Monoallelische Keimbahnmutationen von Tumorsuppressorgenen (TSG) und Onkogenen (OCG) sind für die Entstehung erblischer Tumorsyndrome verantwortlich. Biallelische Keimbahnmutationen von TSG und OCG können zusätzlich zu Krebsveranlagung, bei Kindern, angeborene Anomalien und schwerwiegende Erkrankungen verursachen. Einige solcher Krankheiten sind bekannt und besser untersucht und werden in der genetischen Beratung besprochen. Um die Phänotypen zu beschreiben, die bei biallelischen Keimbahnausfällen von bestimmten TSG und OCG hervorgerufen werden, wurde für die Gene, die im routinmäßig sequenzierten Genpanel (TruSight Cancer, Illumina) (TSC) enthalten sind, eine systematische Aufarbeitung der vorhandenen diesbezüglichen Literatur in PubMed vorgenommen.

Es wurde die Literatursuche auf Arbeiten zu homozygot oder compound heterozygot vorliegenden Mutationen der Kandidatengene eingegrenzt. Des Weiteren wurde nach konkreter Information zur geschätzten Prevalenz der bekannten Syndrome gesucht. Das Ziel der Arbeit ist eine systematische Einordnung des vorhandenen Wissens hinsichtlich homozygoter und compound heterozygoter Keimbahnmutationen der TSC-Genen, zur Optimierung der onkogenetischen Beratung. Die Ergebnisse wurden gemäß ihrer phänoptypischen Beschreibung in OMIM kategorisiert. Für bisher nicht beschriebene Phänotypen beim Menschen wurde nach Möglichkeit Studien mit Mausmodellen, die Phänotypen der Genausfälle bescrieben haben, erfasst. So konnten für fast alle TSC-Gene Erkenntnisse über Effekte einer biallelischen Mutation erhoben werden.

Zusammenfassend lässt sich festhalten, dass die intakte Funktion zumindest eines Allels der meisten TSG und OCG essentiell für die embryonale Entwicklung ist, der biallelesche Ausfall ist oft mit Entwicklungsanomalien assoziiert und nicht selten überhaupt letal. Diese Zusammenstellung soll einen hilfeichen Überblick für die genetische Beratung von Mutationsträger*innen in TSC-Genen bieten, und insbesondere die Diskussion hinsichtlich einer etwaigen Partnertestung, sowie in der Folge einer pränatalen Diagnostik, unterstützen.

Abstract

Biallelic germline mutations in tumor suppressor genes (TSG) and oncogenes (OCG) could cause congenital anomalies and serious illnesses in children apart from cancer predisposition. Some of these diseases are well known and studied. Biallelic mutations in TSGs and OCGs may cause syndromes different from that induced by their heterozygous mutations. In an attempt to describe the phenotypes associated with biallelic mutations of a list of TSGs and OCGs included in a routinely sequenced gene panel (TruSight Cancer, Illumina) (TSC) and the predicted prevalence of their associated syndromes, we systematically reviewed the reported articles published in PubMed to expand our knowledge and facilitate the oncogenetic counseling. For this purpose, we included literature on homozygous/compound heterozygous mutations in the TSC-genes. The results were categorized according to their phenotypic description in OMIM. For genes without heretofore-described phenotypes, we explored mouse model studies describing the phenotypes of the gene knockouts. We could find phenotype descriptions linked to biallelic mutations for almost all of the TSC-genes.

In summary, the intact function of at least one allele of most TSGs and OCGs is essential for normal embryonic development, and their biallelic mutations are often associated with developmental anomalies and not uncommonly lethal. This work represents a potentially helpful overview for the genetic counseling of TSC-gene mutation carriers, especially concerning the discussion of partner testing prior to family planning.

Keywords: Tumor suppressor genes, oncogenes, germline mutation, homozygosity, compound heterozygosity, embryonic development, congenital anomalies, consanguinity, uniparental disomy, genetic counseling, gene knockout.

1. Introduction

1.1 Tumor suppressor genes and oncogenes

Tumor suppressor genes (TSGs) and oncogenes (OCGs) play significant roles in embryogenesis, in addition to their known role in carcinogenesis (Quenby et al., 1999).
TSGs prevent carcinogenesis, and the inactivation of one copy is compatible with normal biological processes. A biallelic loss of function (LOF) increases the risk of malignant transformation in the cell (L.-H. Wang et al., 2018). The function of TSGs has been well studied over the years, and their most important functions are DNA damage repair, inhibition of cell division, induction of apoptosis, and inhibition of metastasis (Sun and Yang, 2010; L.-H. Wang et al., 2018). OCGs are a group of genes which are over-activated {gain of function (GOF)} in cancer (Inoue and Fry, 2017). An activating mutation in one copy of OCGs is sufficient to abnormally increase the rate of cell proliferation (Vogelstein and Kinzler, 2004).

Germline mutations (mutation in gametes) in TSGs and OCGs are passed on to offsprings. They promote genomic instability and predispose the affected individual to an increased lifetime risk for developing certain tumors ("cancer syndromes") (Rahbari et al., 2015).

There are cancer-predisposing genes known to impact tissue patterning, positional identity, and proliferation during embryonic development. This group includes genes such as APC, NF1, PTCH1, PTEN, SMAD4, TSC1, TSC2, and WT1. Their proteins initiate the stream of information from ligand-dependent cell surface receptors to families of nuclear transcription factors regulating proliferative and developmental programs. Aberrant regulation of these genes may influence cell's progression to terminally differentiated, non-proliferating states, thus permitting the buildup of additional mutations, leading to the development of a fully tumorigenic phenotype (Sherr, 2004).

1.2 Congenital anomalies and cancer-related genes

Along with cancer predisposition, the phenotype of hereditary cancer syndromes may encompass developmental abnormalities. The latter might involve various tissues and organs, commonly resulting in embryonic malformation that hinders the birth of viable homozygous offsprings. However, the anomalies may be detected in heterozygous carriers as well. This lethality explains the lacking of human homozygote for mutations in some cancer-related genes (Ben-Yosef and Benvenisty, 1999).

In some of the syndromes, there is a correlation between developmentally affected tissues and tumor types (Ben-Yosef and Benvenisty, 1999). The link between childhood tumors and some congenital abnormalities (like Aniridia with Wilms tumor syndrome) points to a potential association between oncogenesis and the disruption of normal developmental processes (Moore, 2013).

As some of the cancer-related genes are involved in DNA repair, their mutations may have direct biological effects on embryonic development. The presumed role of TSGs in cell differentiation elucidates the occurrence of developmental abnormalities following their homozygous inactivation. Developmental abnormalities may be due to the hyperproliferative nature of the mutated cells or are caused directly by the inactivation of the differentiative function of a TSG (Ben-Yosef and Benvenisty, 1999). It is conceivable that mutations of some OCGs might be the basic molecular lesion, at least in a proportion of cases, which present with congenital anomalies and cancer (Anbazhagan and Raman, 1997; Li, Huang and Wei, 2019).

1.3 Consanguinity and endogamy

Consanguinity refers to the mating of closely related individuals, with an increased risk of autosomal recessive diseases in their offspring. Another related term, "endogamy," describes the intra-community marriage, which leads to the clustering of founder mutations. Consanguineous and/or endogamous offspring have an increased level of homozygosity, which in turn tremendously raises the possibility of the autozygous state (inheriting identical

ancestral genomic segments from both parents) in any allele (Erzurumluoğlu, 2015). A more substantial effect is expected when the parents are more closely related (Woods et al., 2006). This effect explains the increased frequency of extremely rare autosomal recessive disorders in populations with a high level of consanguinity (and/or endogamy) (Erzurumluoğlu, 2015).

The frequency of consanguineous union shows quite diversity according to the ethnic background, different geographic regions (Fan et al., 2013), religious and cultural contexts (Ben Haj Ali et al., 2019).

The consanguineous marriages symbolize an increased risk for congenital malformations in the offspring. Most of the affected children show congenital anomalies or multiple malformations, dysmorphic features, failure to thrive (FTT)/growth retardation (GR) or short stature, and developmental delay (DD)/intellectual disability (Fan et al., 2013).

1.4 Uniparental disomy

Uniparental disomy (UPD) is the event of inheriting both homologs of the same chromosome from one parent, with no chromosome from the other parent. Inheriting both homologous chromosomes from one parent is known as heterodisomy, while carrying duplicates of one chromosome is referred as isodisomy. Meroisodisomy is a combination of both aforementioned events (Zeng et al., 2006). UPD may encompass a whole chromosome or only a segment of the chromosome (Eggermann, Mackay and Tümer, 2018). The commonest explicated mechanism in constitutional UPD is considered to be a meiotic non-disjunction error during gametogenesis, followed by trisomy rescue (Zeng et al., 2006).

The type of UPD is linked to the time of its occurrence. In constitutional UPD, as it is a meiotic error in the germline, all cells in the organism have the same UPD (Tuna, Knuutila and Mills, 2009). This UPD could be demonstrated in a proportion of cases with homozygous mutations in non-consanguineous families (Zeng et al., 2006). Nevertheless, this event can arise during mitotic cell division as well, here UPD is observed in a portion of somatic cells and is termed acquired UPD. The latter is commonly found in cancer cells (Tuna, Knuutila and Mills, 2009). UPD is well known for its connection to imprinting disorders, leading to lack of expression of a functional allele (Donovan et al., 2016).

As the routine cytogenetic technologies could not detect UPD, its prevalence is unknown (Makishima and Maciejewski, 2011). The most commonly used molecular techniques for genetic testing of UPD are either microsatellite testing, or methylation studies of imprinted loci, and single nucleotide polymorphism (SNP) microarrays (Hoppman et al., 2018).

2. Aim of the Research

This study aimed to systematically compile the syndromes and phenotypes described so far concerning the biallelic germline mutation in the genes that are included in a commercial tumor panel (TruSight Hereditary Cancer, Illumina) (TSC). It is intended to provide a helpful overview for genetic counseling, based on the recognized and reported phenotypes for each gene. Furthermore, we sought the current estimated prevalence of the known syndromes in OMIM or by exploring the number of reported cases published to date.

3. Material and Methods

Literature research in PubMed was achieved for a systematic review of the papers and reported cases that have been published about detection and description of germline biallelic mutations in TSGs and OCGs that are included in the TSC tumor panel.
This work only considers the clinical presentations caused by biallelic (homozygous and compound heterozygous) germline mutations, regardless of gender, ethnicity, and the age of the patient by the time of the publication. Somatic mutations were excluded. Only papers published in English were used.

For more comprehensive research, the synonyms of the genes that are documented in the Orphanet database (the list is attached) were considered. For genes without reported cases of biallelic germline mutations in humans to date, we explored literature on mouse models, in which experimental whole knockout of these genes were tested, and phenotypes were described. Homozygous and compound heterozygous mutations were studied without preference. No conditional gene knockout in mice was included.

The following terms were used for searching: “Homozygous/compound heterozygous germline mutations in tumor suppressor genes/oncogenes,” “Germline biallelic LOF in cancer-related genes,” “Constitutional mutations in tumor suppressor genes/oncogenes,” “Congenital anomalies due to mutations in cancer-related genes,” “Infantile tumor,” “Recessive mutation (each gene separately),” “Cancer and developmental anomalies,” “Tumor suppressor gene/oncogene knockout in mice,” “Consanguinity and rare autosomal recessive diseases,” “Role of tumor suppressor genes/oncogenes in embryogenesis,” “Neonatal/pediatric cancer,” “Biallelic mutation in dominant inherited cancer-related genes,” “ Gene name (-/-) or null mice.” and others.

Prevalence or the numbers of published cases of rare diseases already listed in OMIM were extracted from the latest version of Orphanet Worldwide/European Bibliographic Data (OW/EBD) published in January 2020-Number 1 or through exploring the reported cases presented in PubMed to date (when possible). Information about gene location was obtained from Orphanet.

Considering the length of our gene list and our intention to obtain clarification and order while listing the results, we categorized the genes into different groups and subgroups as following:

Group 1: Genes with known diseases, which includes:

Group 1.1: Fanconi Anemia (FA) genes group

Group 1.2: Constitutional Mismatch Repair Deficiency (CMMRD) syndrome-related genes

Group 1.3: Xeroderma Pigmentosum (XP)-related genes

Group 1.4: Others: demonstrates single gene syndromes and diseases that are described in OMIM with known prevalence (for most of them).

Group 2: Genes with solitary reported cases: presents the rare cases that are not recorded in OMIM or the biallelic form of the phenotype is not mentioned.

Group 3: Genes without human case reports but knockout sequela in mouse models: is organized for those genes that their germline biallelic mutations are not reported yet in humans but in mice.

Group 4: Genes without available reports, neither in humans nor in mice: represents the list of genes for which no biallelic germline phenotype is reported, neither in humans nor in mice.

For a realistic presentation of the phenotypes, randomly chosen case reports are presented for all genes in group 1.

4. Results and Discussion

Biallelic germline mutation in TSGs and OCGs can cause developmental anomalies and serious illnesses (Jiang et al., 2006; Pasic et al., 2013). Expanded targeting trials on mice revealed the engagement of TSG and OCG protein functions in the normal developmental processes of embryogenesis (Bertolino et al., 2003; Clarke et al., 1992; Hasumi et al., 2009; Mettus and Rane 2003; Patel et al., 2015; Shen-Li et al., 2000; Smirlado et al., 2005). Collecting and structuring available information on this issue is of increasing importance and necessity, since oncogenetic analysis has increasingly gained popularity. Thus an increasing number of heterozygous TSG and OCG mutation carriers are identified, who may experience various concerns and anguishes in family planning.

Regulation of cell proliferation and differentiation are the two fundamental functions of TSGs and OCGs. Cancer predisposition and developmental abnormalities are possible consequences of mutations that induce hyperproliferation or underdifferentiation.

Considering their putative roles in cellular processes, germline biallelic mutation in TSGs or OCGs in recessive syndromes would be expected to be lethal or would result in viability but with severe developmental problems. Some of these cancer-related genes cause various developmental manifestations involving different tissues and organs, even in the heterozygous state.

Some of the tumors and developmental anomalies related to a constitutional biallelic mutation in TSGs are already known, like Fanconi anemia and ataxia telangiectasia, and have been extensively studied. On the contrary, other TSGs and OCGs have not yet been well discussed in this context. This work concentrated on exploring the whole extent of all reported cases regarding germline biallelic mutations in the TSGs and OCGs, listed in the TSC panel, to provide the genetic counselors with the latest knowledge concerning the consequence of the occurrence of such a genetical incident. For a better overview, the outcomes are categorized into different groups (Fig. 1 and 2).

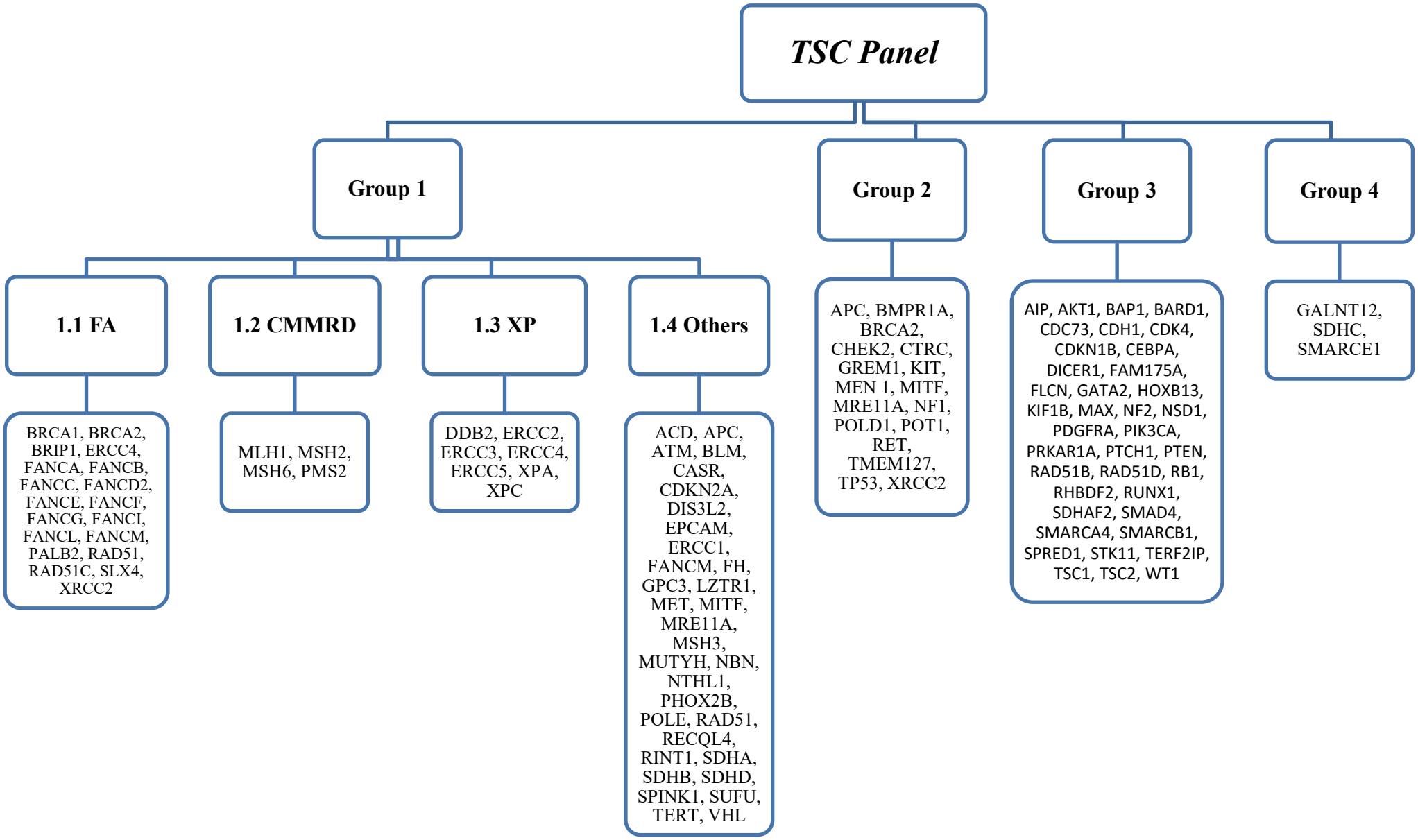

Figure 1: an overview graphic shows the distribution of the TSC genes to the groups and subgroups.

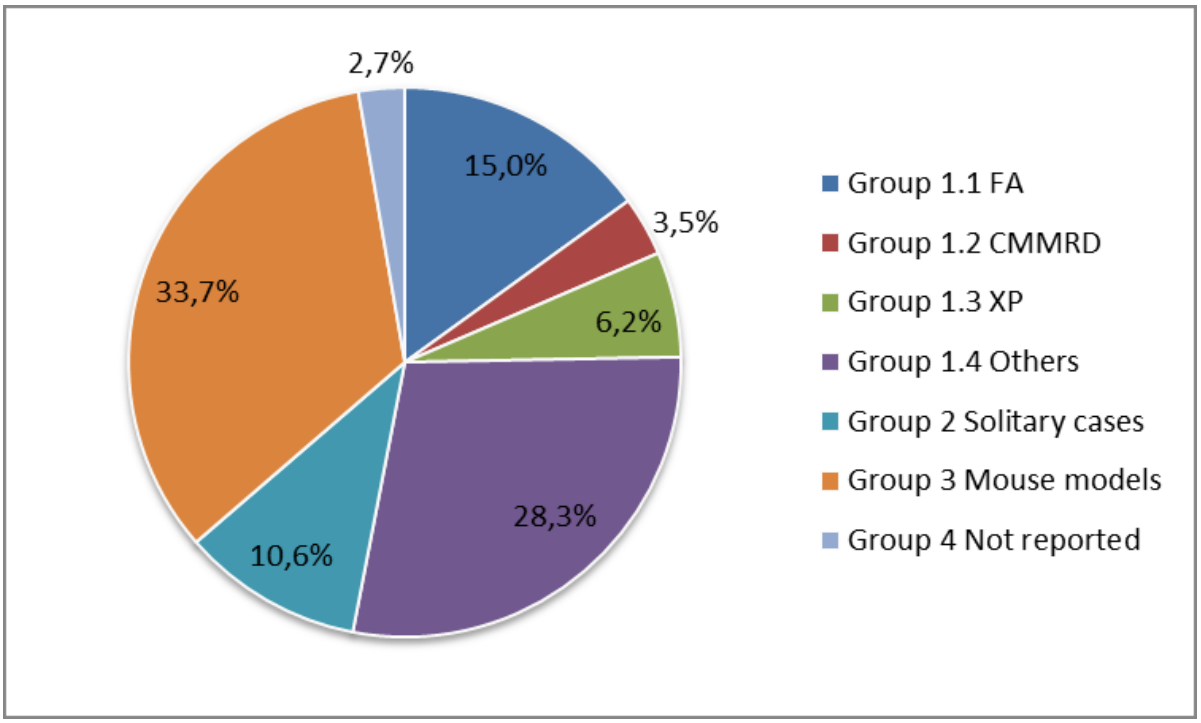

Figure 2: shows the percentage of each categorized group of the genes included in the TSC panel.

4.1 Group 1: Genes with known diseases

4.1.1 Group 1.1: Fanconi Anemia (FA) genes group

During embryogenesis, cellular replication and apoptosis rates are well balanced. This mechanism is fundamental for the proper development of different organs. Any impairment of the DNA damage repair system due to mutations in the FA complementary groups could force the disturbance of multi-organ development in the embryo (Vetro et al., 2015).

FA is a rare heterogeneous disorder characterized by a combination of congenital physical abnormalities, chromosome instability, bone marrow failure, and a considerably increased disposition for both solid organ and hematological malignancies (Yates et al., 2006). Some affected patients often suffer from infertility that includes premature menopause in females and altered sperm production in males (like FA type D1 caused by biallelic BRCA2 mutation) (França and Mendonca, 2019).
The newest reported worldwide prevalence is 0.3 in 100,000 in Orphanet bibliographic data.
FA exhibits different modes of inheritance, mostly an autosomal recessive pattern, yet autosomal dominant (RAD51) (Takenaka et al., 2019) and X-linked recessive (FANCB) (Holden, 2006) have been recognized.

Congenital anomalies like skeletal deformities, microphthalmia, and urogenital anomalies can be seen by the majority of FA patients. These Anomalies are likewise included in a non-random disorder known as VACTERL association, which is the acronym for Vertebral anomalies, Anal atresia, Cardiovascular malformations, Tracheo-Esophageal fistula, Renal, and Limb abnormalities, and its diagnosis needs at least 3 of the listed anomalies. There is a high correlation between the presence of the VACTERL association and FA. However, FA-related findings like brain abnormalities, growth retardation, and skin manifestations are absent in the VACTERL association. A combination of the anomalies mentioned above represents an additional monogenic syndrome acknowledged as VACTERL with hydrocephalus phenotype (VACTERL-H), which occasionally also shows a positive chromosome breakage test (Holden, 2006).

This enhances the necessity to perform a chromosome breakage test in all cases with VACTERL/VACTERL-H phenotype (Vetro et al., 2015).
VACTERL-H has a genetically heterogeneous background, and its inheritance within the affected families harmonizes with both autosomal recessive and sex-linked mode, similar to FA. VACTERL-H can also be just a serious manifestation of FA (Holden, 2006).
A helpful tool for differentiation between autosomal recessive FA manifesting the VACTERL-H phenotype from X-linked recessive FA type B is the X-inactivation study of FANCB gene between questionable carriers, by which a skewed X-inactivation is expected in up to 100% in peripheral blood leukocytes, fibroblasts, and urothelial cells privileging the mutated FANCB. This non-random skewing of X-inactivation is uncommon in the general population (Holden, 2006).

All different clinical manifestations of FA do not appear simultaneously. The congenital anomalies are mostly detected prenatally or shortly after delivery, followed by bone marrow failure between 5-15 years of age, and expanded risk of leukemia and myelodysplastic syndrome during adulthood, with a subsequent lifetime risk for solid tumor formation (Soulier, 2011).
The FA chromosome's liability for breakage and instability by exposing T-cells to mitomycin (MMC) or diepoxybutane (DEB) is the main diagnostic criterion in FA patients (Walsh et al., 2017). These agents induce DNA interstrand crosslinks (ICL) (Umaña et al., 2011), and the abnormal activation of the checkpoint pathways and DNA damage repair proteins have been suggested as an underlying etiology for the ICL sensitivity of the chromosomes (Cantor and Brosh, 2014).

Twenty-one different FANC genes have been reported in the literature: ***FANCA, FANCB, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ, FANCL, FANCM, FANCN, FANCO, FANCP, FANCQ, FANCR, FANCS, FANCU*** (Tab. 1) (these are included in our panel), FANCT (also known as UBE2T), and the newly classified FA gene, REV7 (also known as MAD2L2 or FANCV). These FA proteins are all part of a common multi-subunit protein complex (Zareifar et al., 2019).
Three functionally- and physically-correlated groups of FANC genes are categorized in DNA repair signaling pathway:
Group 1: A nuclear multi-protein core complex with E3 ubiquitin ligase activity, consists of 8 subunits (FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM),

which are also called upstream FA pathway proteins. This complex mediates the main event in the FA/BRCA pathway, which is FANCD2-FANCI dimer monoubiquitination upon DNA damage.

Group 2: Consists of FANCD2 and FANCI heterodimers. They form the ID complex required in the DNA ICL repair process. After monoubiquitination by E3 ubiquitin ligase, FANCD2 would be directed toward chromatins at the subnuclear region, which is the site for DNA damage repair.

Group 3: Products of downstream FA pathway proteins, including BRCA2, PALB2, BRIP1, SLX4, BRCA1, and RAD51C (Kitao and Takata, 2011; Soulier, 2011). This group is also partly involved in genome stability through contribution to homologous recombination (HR). Monoubiquinated FANCD2 would induce BRCA2 and RAD51 loading onto chromatin complex at the damage site of DNA through binding to BRCA2 (Kitao and Takata, 2011).

XRCC2 gene functions in conjunction with a vital component in the HR, RAD51 family, in HR-mediated double-strand break (DSB) repair. Its activity depends on a fundamental C-terminus, which was truncated in the displayed case, leading to impairment in HR and a magnified liability to DNA DSBs in the cells. Noticing similar phenotypes in XRCC2 mutated mice confirmed the involvement of the XRCC2 gene in FA pathogenesis (Shamseldin, Elfaki, and Alkuraya, 2012).

ERCC4 maintains genome stability and prevents congenital anomalies, cancer formation, bone marrow failure, and premature aging (Bogliolo et al., 2013). It plays a role in both the FA/BRCA pathway upon ICL DNA damage as well as in the nucleotide excision repair (NER) pathway. That is why its mutation can result either in FA or in xeroderma pigmentosum (XP). In the FA/BRCA pathway, it is required for unhooking of a crosslink. It interacts crucially with SLX4 and ERCC1, and the nucleolytic strand incision 5′ to the ICL belongs to its main action, while in NER, it operates unrestrained from SLX4 (Popp et al., 2018).

As a FANCD2 downstream protein, screening of the ERCC4 gene should be established in suspicion of familial breast and ovarian cancers (Bogliolo et al., 2013).

Noteworthy, the term FA-like phenotype is analogous to FA. However, there is no bone marrow failure, and this phenomenon typically follows the biallelic mutations in BRCA1, RAD51, and RAD51C genes (Catucci et al., 2017).

There is a considerable variation about the frequency of BRCA1/2 mutations in different ethnic groups; however, the overall population prevalence of BRCA1 and BRCA2 mutation carriers is assessed to be about 1 in 400 to 1 in 800, respectively (Macedo, Alemar and Ashton-Prolla, 2019). The carrier frequency of truncating PALB2 mutations is ~1−2% in many populations (Catucci et al., 2014).

The majority of FA-associated genes are TSGs, and their heterozygous germline mutations predispose the carriers to various cancers.
BRCA1, BRCA2, BRIP1, PALB2, ERCC4, FANCA, FANCB, FANCC, FANCD2, FANCF, FANCG, RAD51, FANCI, SLX4, RAD51C, and XRCC2 are TSGs. FANCE is an OCG. FANCL acts as a TSG and as an OCG, depending on its alternative splice variant, in which the shorter variant, FAVL, promotes oncogenesis in sporadic bladder cancers and provides the tumor cells the resistance to cisplatin, while the longer variant, the wild type, acts as a TSG. The heterozygous mutations in the FA genes cause a variety of cancers, including breast cancer in males and females. The cancer risk for the following organs are increased: ovaries, prostate, pancreas, colorectum, stomach, liver, gall bladder, bile duct, cervix, uterus, bone, esophagus, pharynx, larynx, buccal cavity, eyes, thyroid, bladder, head and neck, spleen, skin, brain, and hematolymphoid system (Abbasi and Rasouli, 2017; Ali, Delozier and Chaudhary, 2019; Bogliolo et al., 2013; Bredel et al., 2005; Chandrasekharappa et al., 2017; Chen et al., 2018; García et al., 2008; Guervilly and Gaillard, 2015; Kennedy and Shimamura, 2019; Komatsu et al., 2017; Lage et al., 2008; Liu, Wang and Zheng, 2010; Mersch et al., 2014; Osorio et al., 2012; Park et al., 2012; Shah et al., 2013; Sinha et al., 2008; Slavin et al., 2017; Somyajit, Subramanya and Nagaraju, 2010; Wu et al., 2020; Xia et al., 2020; Yuan, Xu and Liao, 2012; D. Zhang, 2016; X. Zhang et al., 2016).

FA-related genes	TSG/ OCG / Dual	Gene location	Associated presentation	Mutation/aberrated transcription	Phenotypes in humans (randomly chosen reported cases)	References
BRCA1	**TSG**	**17q21.31**	Mild FA-like phenotype + early onset breast Ca	c.181T>G , (p.Cys61Gly) + c.5096G>A , (p.Arg1699Gln)	A 30-year-old ♀ with early invasive ductal carcinoma, right-side hearing loss, celiac disease, left-side congenital hip dislocation. Short stature, microcephaly, triangular face with low-placed ears, and skin hyperpigmentation {Cafe`-Au-Lait (CAL)} macules. Normal chromosomal fragility test. Parents were carriers (PC).	(Keupp et al., 2019)
BRCA2 ~3%*	**TSG**	**13q13.1**	FA	c.8057T>C , (p.Leu2686Pro) + c.9672dupA , (p.Tyr3225fs)	A 3-year-old ♂ with history (Hx) of intrauterine growth retardation (IUGR), low birth weight (BWt), duodenal atresia, neonatal jaundice, hypothermia, presumed sepsis, patent ductus arteriosus, left-side developmental dysplasia of hip (DDH), bilateral microphthalmia, unusual facies, a mild bilateral sensorineural hearing loss. Mild GR, development of multiple CAL macules, glioblastoma multiforme with multiple metastases, death at the age of 4 years. PC. Non-Cons.	(Dodgshun et al., 2016)
BRIP1 ~2%*	**TSG**	**17q23.2**	FA	Truncating homozygous c.2392C>T , (p.Arg798*)	4 Saudi patients between 2-10 years of age, all sharing severe aplastic anemia, height (Ht)/weight (Wt) <3rd standard deviation (SD), microcephaly, CAL spots, hypopigmentation, and renal anomalies (single kidney, horseshoe kidney, left ectopic atrophic kidney). The individual features were absent/hypoplastic thumbs, small ears, duodenal atresia, right shoulder deformity, bilateral DDH, congenital heart defect, undescended testes, ectopic posterior pituitary. Parents were Cons.	(Ghazwani et al., 2016)
ERCC4	**TSG**	**16p13.12**	FA	c.1484_1488delCTCAA , (p.Thr495Asnfs*6) in exon 8 + c.2065C>A , (p.Arg689Ser) in exon 11	A ♀ with bilateral absent thumbs, microsomy, esophageal atresia, a ventrally translocated anus, and dysplastic low-set ears. Bone marrow failure (BMF) at the age of 2 years, died at the age of 4 years from a hemorrhagic shock after bone marrow (BM) transplantation. Non-Cons. +ve chromosome-fragility test. No clinical sign of photosensitivity.	(Bogliolo et al., 2013)
				c.2371_2398dup28 in exon 11 , (p.Ile800Thrfs*24) + c.689T>C , (p. Leu230Pro)	A redheaded teenager with a Hx of unclassified FA, perinatal GR, short stature, pronounced microcephaly, CAL spots, an ostium-primum defect, biliary atresia with fibrosis of the liver, BMF, +ve chromosome-fragility test. No spontaneous or UV-light-induced skin lesions were reported at the age of 10 years. PC.	
FANCA 60%-70%*	**TSG**	**16q24.3**	FA	c.2546delC , (p.Ser849Phefs*40) + novel splice-site mutation, c.3627-1G>A , in intron 36 (p.Asp1209Glufs*33)	A 4-year-old ♂ with recurrent abdominal pain and hematochezia, recurrent pneumonia, epistaxis, easy bruising, urinary urgency, perineal area pain. Short stature, clinodactyly with brachymesophalangia on bilateral 5th fingers. Multiple CAL spots on the right knee, left thigh, pelvis, and right buttock. Development of persistent thrombocytopenia. PC.	(Lee et al., 2012)

FANCB ~2%*	**TSG**	**Xp22.2**	FA presented as X-linked VACTERL-H syndrome	Hemizygous G to A substitution in intron 7, +5 within the splice-donor site (GTAAGT-GTAAAT). Skipping of exon 7 causes a frameshift and results in a stop codon at position 446 of the open reading frame.	A terminated ♂ fetus at 20 gestational weeks (GWs) with multiple congenital abnormalities, cervical vertebral defects, absent thumbs and radii, unilateral renal agenesis, and bilateral cerebral ventriculomegaly. Wt 240 g, had a crown-rump length of 23.8 cm and a head circumference (HC) of 15.8 cm. Patent cerebral aqueduct and incomplete lung lobation at necropsy. +ve chromosome breakage test. Another stillborn in the family with similar congenital abnormalities. Mother was a carrier and showed 100% skewed X-inactivation.	(Holden, 2006)
			FA with VACTERL Association	0.532 Mb deletion in Xp22.2 inclusive total FANCB gene	A ♂ newborn with spontaneous term vaginal delivery, BWt < 10^{th} SD, length ($25–50^{th}$ SD), HC at 25^{th} SD. Absent radii with absent thumbs, bilateral 2nd rib hypoplasia, anal atresia with a fistula in the perineal raphe, esophageal atresia with distal tracheoesophageal fistula, thrombocytopenia, absence of the left kidney, C2-C7 block fusion of the vertebral bodies with the absence of intervertebral disks, moderate hypoplasia of the C1 ring, moderate canal stenosis. TAPVR, large PDA with left to right shunting, PFO, atrial septal defect (ASD), two ventricular septal defects (VSD), hemodynamic and respiratory instability. Died from cardiorespiratory arrest at the age of 132 days. +ve chromosome breakage test. No brain abnormality, mother was a carrier.	(Umaña et al., 2011)
FANCC ~14%*	**TSG**	**9q22.32**	FA	Extreme truncating c.455_456dupA + c.1390C>T , (p.Q464X) in exon 13 lacking 93 C-terminal AA.	A 7-year-old ♀, +ve family Hx of FA, short stature, and a thumb anomaly.	(Yates et al., 2006)
				c.1390C>T , (p.Q464X) + c.996G>A substitution at the last base pair of exon 9, splice site mutation	A 5-year-old child with pancytopenia, short stature, absent radii and thumbs, and CAL spots. +ve chromosomal breakage analysis in both patients. Neither patient showed clonal cytogenetic abnormalities, nor had histopathological or clinical evidence of either acute leukemia or myelodysplasia.	
FANCD2 %3*	**TSG**	**3p25.3**	FA with lymphopenia and combined immune deficiency	c.2444G->A in exon 26 , (p.R815Q) + deletion of exons 2-18 of FANCD2 on the second allele	An 11-year-old ♀ with numerous congenital anomalies including mesomelia and radial ray defects. Postnatal diagnosis (Dx) of TAPVR cardiac defect. +ve DNA breakage analysis. Hx of multiple febrile illnesses without any proven bacteremia or atypical infections, developed S.pneumoniae sepsis, required hospitalization, low vaccine titers after receiving a vaccination, one episode of human metapneumovirus (hMPV) infection, severe B- and T-cell population abnormalities by immunophenotyping, HIV was excluded, mild-to-moderate BMF. PC.	(Deniskin et al., 2019)
FANCE ~3%*	**OCG**	**6p21.31**	FA	Homozygous c.355<T , gln119-to-ter (Q119X)	The first patient with FANCE FA. A 1.5-year-old Turkish ♂ with psychomotor retardation, GR, retarded bone age, brachycephaly, hypotelorism, epicanthus, syndactyly, brachydactyly, renal dystopia, cryptorchism, an asymmetrical skeletal	(Wegner et al., 1996; Joenje et al.,

					anomaly with a double distal phalanx of the left thumb and hypoplasia of the right thumb. Typical hematological features of the disorder developed at the age of 2.5 years, about 1 year after Dx, died at 6.3 years of age from pulmonary hemorrhage. +ve chromosomal instability and hypersensitivity to DEB and Trenimon. PC. Cons.	1995; De Winter et al., 2000)
FANCF 2%*	**TSG**	**11p14.3**	FA	Homozygous c.534delG in exon1, (p.G178 fs.)	A 3.5-year-old ♀, with petechia and nasal bleeding. Her Ht and HC < 3rd SD, Wt around the 5th SD. Short stature, poor Wt gain, microcephaly, skin hyperpigmentation. 2 episodes of pneumonia. Anemia, leukopenia and thrombocytopenia. Presented megakaryocyte and moderate to severe hypocellular BM on BM aspiration and trephine biopsy. +ve chromosomal breakage test. PC. Cons.	(Zareifar et al., 2019)
FANCG ~10%*	**TSG**	**9p13.3**	FA	Homozygous c.883dupG in exon 7 , (p. Asp295Glyfs*14)	An 11-year-old ♂ child with short stature, hyperpigmentation, rudimentary accessory thumb in the right hand, syndactyly 4th and 5th toes in the right leg. BM aspiration and biopsy suggestive of myeloid leukemia. +ve breakage chromosome test. +ve family Hx of leukemia. PC. Cons.	(Solanki et al., 2017)
FANCI ~1%*	**TSG**	**15q26.1**	FA with VACTERL association	Novel mutation c.3041G>A , (p.Cys1014Tyr) + c.1461T>A , (p.Tyr487X)	A 3-year-old ♀, prematurely born via Caesarian Section (C/S), with congenital anomalies (cervical vertebral anomaly, VSD, patent foramen ovale, horseshoe kidney, and absent thumb). Diagnosed with FA at age 5 months based on elevated chromosome breakage. Hypothyroidism, marked short stature, microcephaly, a small triangular face ("Fanconi facies"). BM hypocellularity (40%). PC. Non-Cons.	(Savage et al., 2015)
FANCL	**Dual**	**2p16.1**	FA with VACTERL-H association	Homozygous c.430del , (p.Ser144Leufs*6)	A ♀ neonate born by C/S at 42 + 2 GWs with Hx of severe IUGR and hydrocephalus on prenatal U/S. Hugely enlarged lateral cerebral ventricles with severely diminished brain mantle parenchyma. BWt (–3 SD), length (–3.5 SD), and HC (+0.37 SD). Macrocephaly with prominent occiput, high frontal hairline, short palpebral fissures, slight upslant microphthalmia, indiscernible pupils, severe bilateral microtia with absent meatus, depressed nasal tip, short philtrum, cleft palate, small mandible, short neck, short forearms, bilaterally absent thumbs and radius, hypoplastic ulnae, 11 ribs on the right side, asymmetrically hypoplastic sacrum, VSD, PDA, slight hypoplasia of the right kidney, severe hypoplasia of the left kidney, and anal atresia with rectovaginal fistula. +ve chromosome breakage test. Died 2 days after birth. Parents were not tested. Non-Cons.	(Vetro et al., 2015)
FANCM	**TSG**	**14q21.2**	No FA case due to pure FANCM mutation has been reported.			(Catucci et al., 2017)
PALB2	**TSG**	**16p12.2**	Atypical FA	Truncating c.1676_1677delAAinsG , (p.Gln559ArgfsTer2) in exon 4 + c.2586+1G>A in the first base of intron 6 , (p.Thr839_Lys862del) results in frameskip of exon 6	A 12-year-old ♀ with enlarged cervical lymph nodes and enlarged tonsils, B-cell non-Hodgkin lymphoma stage II on histopathology. Mild learning difficulty, problematic speech and pronunciation, Ht/Wt <3rd SD, dysmorphic features and dermatological findings like right gluteus nevus and Mongol spot at the sacral area, slightly elevated serum alpha-fetoprotein (AFP) and elevated IgM. A younger sister recovered from non-Hodgkin lymphoma at the age of 3.5 years, with elevated AFP, Ht/Wt <3rd SD, epicanthus, CAL spot on the left shoulder, and a larger	(Byrd et al., 2016)

					one on the left hip, more profound learning difficulty, and speech impairment. +ve chromosome breakage. PC.	
RAD51	**TSG**	**15q15.1**	Atypical FA in autosomal dominant form	A de novo dominant-negative RAD51 mutation c.725A>G , (p.Gln242Arg)	A 9-year-old Japanese ♀, delivered at 34 GWs, with BWt (−2.1 SD), Ht (−2.7 SD), HC (−1.6 SD), delayed motor development, strabismus, myopia, submucous cleft palate, bilateral hearing impairment, scoliosis, laryngomalacia, and gastroesophageal reflux. By the age of 9 years and 2 months, GR, Wt (−2.3 SD), Ht (−5.1 SD), HC (−3.4 SD), severe intellectual disability, dysmorphic features included a narrow forehead, down slanting eyebrows, palpebral fissures, epicanthus, telecanthus, a wide and prominent nose, a full lip, micrognathia, a round face, short neck, a hypoplastic thumb, and CAL macules. +ve chromosome breakage test. No BMF. No sign of mirror movement. Non-Cons.	(Takenaka et al., 2019)
RAD51C	**TSG**	**17q22**	FA-like disorder	Homozygous mutation c.773G>A in exon 5 , (p.R258H)	A 10-year-old aged ♂ with extensive congenital abnormalities including short stature, bilateral radial hypoplasia, anal atresia, bilateral cryptorchidism, small genitalia, bilateral cystic dysplasia of the kidneys and chronic renal failure. +ve chromosome breakage test. No hematological abnormalities or Ca by the age of 10 years. Hx of death of 2 siblings with similar anomalies. PC. Cons.	(Vaz et al., 2010)
SLX4	**TSG**	**16p13.3**	FA	Homozygous c.286delA , (p.Thr96LeufsX30)	An 18-year-old ♂ patient with FA diagnosed at the age of 9 years, short stature (–2.5 SD at the age of 9 and –4.5 SD at the age of 18), hypoplastic right thumb, dysmorphic features like Almond-shaped face, short palpebral fissures, bulbous nasal tip, micrognathia, small eyes, microcephaly (–2.5 SD), hypopigmented skin spot on back, bilateral hearing loss, hypoplastic malleus, narrow external ear canals. +ve chromosomal breakage test. BMF, by the time of Dx, received hematopoietic stem cell transplantation at 10 years of age. PC. Cons.	(Stoepker et al., 2011)
XRCC2	**TSG**	**7q36.1**	FA	Homozygous mutation in c.643C>T , (p.Arg215*)	A 2.5-year-old Saudi child with Hx of IUGR (length 41 cm, Wt 2.6 kg, HC 30.5 cm), left facial nerve palsy, microcephaly, bilaterally absent thumbs, left ectopic kidney, hemodynamically stable PDA, complete absence of the first metacarpal and scaphoid bones bilaterally, absent left radius, and hypoplastic right radius. Severe GR with microcephaly on follow-up visits. +ve chromosome breakage test. Parents were Cons.	(Shamseldin et al., 2012)

Table 1: demonstrates the presentation of FA-related genes and their clinical manifestations in randomly chosen case reports.

Age of the patient corresponds to the time of the original publication. Only relevant normal examinations and investigations are mentioned. Only relevant therapeutic measures are noted.

* % of FA attributed to pathogenic variants in each gene is taken from NCBI GeneReviews. PFO: patent foramen ovale; TAPVR: total anomalous pulmonary venous return. Dual: the gene acts as TSG and as OCG.

4.1.2 Group 1.2: Constitutional Mismatch Repair Deficiency (CMMRD) syndrome-related genes

Mismatch repair (MMR) genes (Tab. 2), {***mutL homolog 1 (MLH1), mutS homolog 2 (MSH2), mutS homolog 6 (MSH6), PMS1 homolog 2, mismatch repair system component (PMS2)*** and PMS1 homolog 1, mismatch repair system component (PSM1)} are responsible for the elimination of replication single base mismatches, and DNA deletions and insertions that tend to cause genome instability. The latter is demonstrated as microsatellite instability (MSI), which is a frequent MMR deficient phenotype observed by the hereditary non-polyposis colorectal carcinoma {Lynch syndrome (LS)} (Whiteside et al., 2002).

LS is induced through heterozygous mutation in one of the mismatch repair genes with an autosomal dominant mode of inheritance. Biallelic germline mutation in these genes prompts an autosomal recessively inherited constitutional mismatch repair deficiency (CMMRD) syndrome with a hypermutated phenotype, which is usually accompanied by a known childhood tumor spectrum including hematological and brain tumors, and dermatological manifestations like CAL macules (Gallinger et al., 2004). To date, only about 150 patients with CMMRD have been declared worldwide. More than 50% of CMMRD cases are caused by biallelic PMS2 gene mutations (M. Xu et al., 2019).

The development of hematological malignancies like leukemia and lymphoma is not rare in MMR deficiency. MMR deficiency-stimulated lymphoma though has not been observed within LS families but has been witnessed in Turcot's syndrome and Muir-Torre syndrome, which are defined as LS variants. The association between lymphoma and MMR deficiency is explained partly by MMR deficiency-induced secondary repair deficiency in genes, which are important for T-cell and B-cell differentiation, or through possible loss of apoptosis induction by MMR deficiency (Whiteside et al., 2002).

Loss of heterozygosity (LOH) by heterozygous MMR gene mutation carriers results in MSI and lack of MMR gene staining on immunohistochemistry (IHC) during examination of the tumor tissue only, while in MMR deficient cases similar results should be shown not only in tumor tissues but in normal tissues as well (Leenen et al., 2011).

Gallinger et al. (2004) revealed two siblings with homozygous MLH1 mutation. The displayed patient presented with the manifestation of NF1 phenotype and gastrointestinal adenocarcinoma at an unusually early age, unlike so far reported hematological and central nervous system tumors. This has been related to a significantly elevated proliferation rate in bone marrow, and brain neural and glial cells. The NF1 phenotype is a common finding in patients with MMR deficiency, probably because of MMR deficiency-induced NF1 somatic mutation rate elevation.
M. Xu et al. (2019) concluded that the reported homozygous pathogenic variant in MSH6 was the result of an uncredited consanguineous relationship between the parents, based on the uncommonness of the reported variant, the identity of all MSH6 SNPs between the parents, and relying on the fact that the family lived in a closed population.

MMR genes all act as TSGs (Ganster et al., 2010; Lage et al., 2008; Zink et al., 2002). Patients with LS are prone to develop any type of caners. The tumor spectrum encompasses a wide range of malignancies, including cancer in the colon, endometrium, stomach, small intestine, biliary tract, skin, central nervous system, ovary, kidney, urinary tract, breast, thyroid, lung, and prostate gland (Watson and Riley, 2005).

The aggregate carrier frequency of any MMR gene mutation is calculated to be 0.359% (1:279), relying on the carrier frequency of pathogenic germline variants in the MMR genes within the general population, which is estimated to be 0.051% (1:1946) for MLH1 mutations, 0.035% (1:2841) for MSH2 mutations, 0.132% (1:758) for MSH6 mutations, and 0.140% (1:714) for PMS2 mutations (Boland, Yurgelun and Boland, 2018).

CMMRD-related genes	TSG/ OCG / Dual	Gene location	Associated presentation	Mutation/aberrant transcription	Phenotypes in humans (randomly chosen reported cases)	References
MLH1	**TSG**	**3p22.2**	Duodenal adenocarcinoma and NF1 features	homozygous, codon 687CGG→TGG in exon 18 , (p.Arg687Trp)	An 11-year-old ♂ with Hx of fatigue, abdominal pain, Wt loss, and iron-deficiency anemia. On physical examination: cachectic-appearance, several CAL macules on his lower back. +ve occult blood stools. Multiple hepatic lesions on abdominal U/S. Abdominal CT and MRI suggested thickening and infiltration of the duodenojejunal junction, a mass in the pelvis outside the bowel, and bilateral lung lesions. On needle biopsy of the liver: metastatic tumor composed of glandular structures with focal cribriform changes. Neoplastic cells showed mucin secretion by staining and were +ve for pan-cytokeratin (CK), CK20, CK8, CK18, epithelial membrane antigen, and carcinoembryonic antigen, but were -ve for CK7, CD30, S100. -ve AFP, and alpha-1 antitrypsin. On side-viewing endoscopy: normal stomach and proximal duodenum, no visible polyps. Colonoscopy showed an annular constricting tumor almost completely occluded the lumen. Duodenal biopsy showed a tubulovillous adenoma with foci of high-grade dysplasia in continuity with intramucosal and invasive adenocarcinoma. High-frequency MSI, IHC staining detected MSH2, MSH6, and weak MLH1. Died 10 months after the Dx with widespread lung and abdominal metastases, ascites, and malignant pleural effusion. PC and Ca-free. Cons. +ve family Hx of colorectal and gastric Ca.	(Gallinger et al., 2004)
MSH2	**TSG**	**2p21-p16.3**	T-cell ALL with NF1 features	Novel homozygous mutation in intron 10 splice acceptor at position 1662–1 G< A transition (relative to the ATG translational start site) results in skipping of exon 11 to exon 12	A 2-year-old ♂ with normal Ht, Wt <3rd SD, HC of 2nd SD, presented with FTT and a gastrointestinal infection that led to the Dx of T-cell acute lymphocytic leukemia (ALL) and IgA deficiency. He had multiple CAL spots, which fulfilled one diagnostic criterion of NF1, but no neurofibromas, axillary or inguinal freckling, Lisch nodules, optic glioma, sphenoid wing dysplasia, pseudoarthrosis, or previous Hx of malignancy. In the absence of a second diagnostic criterion, the Dx of NF-1 was not wholly met at the proband's young age. –ve family Hx of NF-1 or Ca indicative of LS. PC. Non-Cons, but have the same ethnic, religious, and geographic background (ancestral mutation).	(Whiteside et al., 2002)

MSH6	**TSG**	**2p16.3**	Non-cancerous colorectal adenomatous polyps	Homozygous c.3261del , (p.Phe1088Serfs*2) , resulted in deletion of a cytosine residue in exon 5	A 12-year-old ♂ with anal neoplasm and rectal bleeding. On colonoscopy: 5 polyps located at sigmoid colon and rectum were tubular adenomas, with hyperplasia/low-degree dysplasia observed in the largest polyp. On subsequent medical examinations: skin pigmentations on his back and arms, with at least one typical CAL spot in the left arm. Small bowel examination was not performed. No immunological testing was performed. NGS hereditary colorectal Ca syndromes gene panel approach revealed no pathogenic variant in APC or MUTYH genes. Therefore, the Dx of CMMRD was clearly established at a molecular level. PC and asymptomatic. Non-Cons. +ve family Hx of Ca (his paternal grandfather with lung Ca at 60, his maternal grandmother with a brain tumor in her 50s).	(M. Xu et al., 2019)
PMS2	**TSG**	**7p22.1**	Colonic adenocarcinoma and medulloblastoma	large biallelic deletions (exons 7–11 and exons 7– 14)	An 11-year-old ♀ patient with abdominal pain, bloody diarrhea, Hx of multiple pneumonia and otitis media. Diagnosed with systemic lupus based on pancytopenia, proteinuria, along with high titer anti-nuclear antibody (ANA), anti-double-stranded DNA, and anti-smooth muscle antibodies. On CT-Scan: bronchiectasis of uncertain etiology. On physical examination: several hypopigmented areas and overall mottled pigmentation. 10 months later, at the age of 12 presented with intussusception. Colonoscopy revealed two sizable colonic polyps. Pathology showed both to be tubulovillous adenomas, one with a central area of adenocarcinoma penetrating the bowel wall into surrounding lymphatic tissue. Four hypodense areas in the liver consistent with metastatic adenocarcinoma. On brain MRI: a cerebellar tumor was of classical medulloblastoma type. No significant family Hx of malignancy. After chemotherapy and radiation, developed sudden onset dizziness, bitemporal headache, slurred speech, and ataxia. MRI was consistent with leukoencephalopathy and necrosis in the pons, middle cerebellar peduncles, and midbrain. 2 years from Dx, new hepatic adenocarcinoma lesions were noted. Pulmonary compromise and progressive leukoencephalopathy 3.5 years from Dx. +ve tumor MSI testing. -ve genetic studies for FAP.	(Lindsay et al., 2013)

Table 2: demonstrates the presentation of CMMRD-related genes with exemplary cases. Age of the patient corresponds to the time of the original publication. Dual: the gene acts as TSG and OCG.

4.1.3 Group 1.3: Xeroderma Pigmentosum (XP)-related genes

XP disease (Tab. 3) has a birth prevalence of 0.23/100,000 in Europe (OW/EBD) and it is an autosomal recessive genodermatosis with 100% penetrance. It is characterized by extreme sunlight sensitivity with eventual conduction of sunburn, skin pigment changes, and a highly elevated propensity of skin cancers. Only 60% of XP affected individuals demonstrate the photosensitivity symptoms, which are evident in the first weeks of life and need days to weeks to subside. The initial symptom by the other 40% of XP patients is a remarkably growing number of lentigines (freckle-like pigmentation) in sun-exposed areas with hypopigmented macules between the lentigines and telangiectasia. Dryness, roughness, and atrophy of skin would result in premature skin aging. Without stringent sun protection, in-situ melanocyte and keratinocyte malignancy would occur, and eventually, multiple basal cell carcinomas, invasive squamous cell carcinomas and melanomas, as XP patients are at an increased risk up to 10,000-folds for development of non-melanoma skin cancers and 2000-folds of melanoma under the age of 20. Apart from skin neoplasms, XP patients have a 50-folds tendency for internal neoplasm development. Ocular abnormalities in XP include photophobia, prominent conjunctival injection, severe keratitis, and neoplasms. 20-30% of patients have neurological findings of poorly understood mechanisms and of varying severities, which are the result of progressive neuronal degeneration resulting in sensorineural deafness, ataxia, areflexia, microcephaly, intellectual deficiency, and visual impairment. The severity of clinical manifestations relies on exposure to sunlight, the affected complementation group, the specific character of the mutation, and other unknown factors. XP is caused by mutations in one of the eight known genes, the proteins of seven of these genes (XP-A through G) (their functions are displayed in Tab. 3) are responsible for the NER process, which repairs DNA damages caused by the ultraviolet-induced photoproducts (the eighth gene is not involved in NER and not in our panel). NER includes rapid transcription-coupled repair (TCR) and the slow global genome repair (GGR). Contrary to all other XP complementation groups, XPC and XPE are dispensable in TCR, cells from XP-C and XP-E patients have only defective GGR, but are proficient in TCR (Lehmann, McGibbon and Stefanini, 2011).

Defective NER leads to multiple rare autosomal recessive photosensitivity syndromes like XP, UV-sensitive syndrome, cerebro-oculo-facio-skeletal syndrome, trichothiodystrophy

(TTD), Cockayne syndrome (CS), XP combined with CS (XP/CS), and XPF/ERCC1 syndrome (XFE) (Soltys et al., 2013).
Patients with XP-A are typically the most severely affected with early onset of cutaneous, ocular, and neurological manifestations, and in the majority of cases, death within the second or third decade of life. XP-A cells are most susceptible to UV-light damage and show extremely low NER level (Sidwell et al., 2006).

Biallelic mutations in ERCC2 (XPD) and ERCC3 (XPB) genes, which encipher transcription factor IIH (TFIIH) subunits, lead besides XP to TTD, which has a birth prevalence of 0.12/100,000 in Europe (OW/EBD) and is a rare, mostly autosomal recessive inherited (X-linked recessive pattern have been reported as well) disease. TTD has a broad spectrum of cutaneous manifestations, immune-, neurologic- and developmental abnormalities. On a systematic review of 112 TTD cases, skin findings were demonstrated in 79% of cases, mostly in the form of photosensitivity and/or ichthyosis, 42% of the cases stated photosensitivity. About one-third of the patients with ichthyosis birthed with a collodion membrane. Neurological abnormalities were found in 86% of cases, and encompassed microcephaly, motoric dysfunction, developmental delay, and intellectual impairment. Besides, growth retardation in 81%, ocular abnormalities in 51%, recurrent infections in 45%, and other less common findings like gonadal dysgenesis, pregnancy complications, and defects in the hepatic, skeletal, cardiac, and hematologic systems were recorded. Neutropenia, immune deficiency, and subsequent recurrent infection, mostly viral, could prompt early mortality in TTD patients. The popular acronyms like PIBIDS, IBIDS, and BIDS used to delineate the phenotypes demonstrated in TTD, including Photosensitivity, Ichthyosis, Brittle hair, Intellectual impairment, Decreased fertility, and Short stature, are erroneous. Since the additional features showed by TTD patients are not considered in these three acronyms, furthermore, explicitly 36% of patients did not fit into one of these three classes (Lund and Stein, 2019).
While TTD and CS do not predispose to skin cancers, XP patients have an extreme raised lifetime risk of developing skin cancer induced by sunlight exposure (Emmert et al., 2009).

XPD gene exhibits two vital functions, one in NER, the other one as a subunit of the basal transcription factor TFIIH required for the proper function of RNA polymerase II. Regarding which mutation results in which phenotype, it has been hypothesized that the mutation which impacts its DNA repairing role would result in XP, and the one which impacts its

transcriptional role of TFIIH without DNA repair disturbance would induce TTD. Clinical differentiation between TTD and CS is based on typical brittle sulfur-deficient hair with a tiger-tail pattern on polarized microscopy in TTD, and cachectic dwarfism, cataracts, pigmentary retinopathy, and spasticity in CS (Emmert et al., 2009).

Patients with CS suffer mostly from postnatal failure to thrive, profound cachexia later in life, sun sensitivity, short stature, a characteristic facial appearance, sexual underdevelopment, increased deep tendon reflex (in contrast to XP), progressive ataxia, sensorineural deafness, visual loss, premature aging and early death. Radiological findings are the absence of myelin and cerebral atrophy on brain MRI and prominent basal ganglia calcification on brain CT-Scan. In contrary to neurodegeneration noticed in XP, a demyelinating neuropathy is the main histological finding in CS (Kraemer et al., 2007).

Patients with the XP/CS complex have a mixture of symptoms of both diseases, so they have sun sensitivity, develop the freckling and other pigmentary changes of XP, and have short stature, retinal degeneration, and sexual underdevelopment as in CS (Kraemer et al., 2007). These XP/CS cases are caused mainly by mutations in the XPB, XPD, or XPG gene. The latter encodes an essential endonuclease required for the incision step of NER (Soltys et al., 2013).

XP-C with the main function in the GGR pathway (Lehmann, McGibbon and Stefanini, 2011), represents the most prevalent type of XP (Tang et al., 2018).

The XPE patients with their insufficient sunburn reaction would have a postponed diagnosis of XP to adulthood. They are predisposed mostly to squamous cell carcinoma, basal cell carcinoma, and malignant melanoma. UV-induced DNA damage is recognized by the UV-DDB complex, which is formed by binding of DDB2/XPE and DDB1 proteins. The complex conscripts other proteins of the global repair pathway to commence DNA repair (Yang et al., 2020).

Mutation in the ERCC4 gene results in the XP-F category, which represents 10% of all XP cases. The tight heterodimer complex of ERCC1 and ERCC4 imparts a pivotal excision step of NER with its 5’ nuclease activity. For the XP-F category is a less tendency for skin neoplasms and a late presentation mostly after the 4th decade of life predicted. XP-F associated neurodegeneration is a slow process, and the linked neurological presentations include chorea, sensorineural hearing loss, gait disturbance, ataxia, cognitive decline, neuropathy, cerebral and cerebellar atrophy (Shanbhag et al., 2018).

XP is diagnosed clinically. Genetic testing and robust cellular testes (reduced level of unscheduled DNA synthesis and subsequent complementation analysis) would verify the diagnosis (Yang et al., 2020).

Regarding the role of XP-related genes in cancer, DDB2 acts as a TSG and as an OCG (Gilson et al., 2019). ERCC2 acts as a TSG in glioma (Huang et al., 2014). ERCC3 is an OCG in hepatocellular carcinoma (Li et al., 2018; Zhang et al., 2020). ERCC5 acts as an OCG in gastric cancer (Kanda, 2015). ERCC4 and XPA are TSGs (Ariyoshi et al., 2001; Neven et al., 2018). XPC is a TSG in lung carcinoma (Cui et al., 2015).

The heterozygous germline mutations in the XP-related genes are involved in cancers of colorectum, pancreas, breast, ovaries, uterine, cervix, prostate, larynx, thyroid, head and neck, central nervous system, lung, sarcoma, malignant melanoma, and non-melanoma skin cancers (Bernstein et al., 2013; S. H. Chan et al., 2017; Gilson et al., 2019; Potjer et al., 2019; Rump et al., 2016; Santos et al., 2013; Yang, Zhang and Sun, 2016).

XP-related genes	TSG/ OCG/ Dual	Gene location	Protein function/ pathway	Different XP presentations	Mutation/aberrant transcription	Phenotypes in humans (randomly chosen reported cases)	References
DDB2/ XPE	**Dual**	**11p11.2**	Damage recognition/ NER (GGR)	XP	Novel homozygous c.111_112del in exon 1 , (p.A39Efs*6)	A 28-year-old Chinese ♀ with recurrent ulceration, bleeding, and crusted nodules on her nose. On examination: normal mental development, numerous freckle-like hyperpigmented macules on her face and neck with an ulcerated bleeding nodule on her nose. Reticulate hyper- and hypopigmented macules on her arm, dry skin throughout her body, could not be relieved by using cream. Hx of acute sunburn was denied. Her brother with similar clinical characteristics, suffered burns 5 years ago, had an extensive scar and a 0.5 cm × 1 cm hyperpigmented nodule on his face. A biopsy confirmed the Dx of basal cell carcinoma of the hyperpigmented nodules on the nose of the proband and her brother. PC and healthy. Cons.	(Yang et al., 2020)
ERCC 2/XPD	**TSG**	**19q13.32**	5' to 3' Helicase / NER (GGR + TCR)*	XP with neurological symptoms	Deletion of a guanine in a GGGG run c.2009delG , (p.Gly670Alafs*39) + c.2047C>T , (p.Arg683Trp)	A 16-year-old Caucasian ♂. His severe sun-sensitivity was noted at 3 months of age, after short sun exposure developed solar dermatitis with persistent erythema and delayed clearing, dry skin, but no blistering or edematous swellings. The early childhood exposures affected mainly the face. Clinical Dx of XP was made at 2 years of age. Developed mild freckling on his lower lips, conjunctival pterygium, and conjunctivitis but no skin Ca. Progressive sensorineural hearing loss since 11 years of age, absent deep tendon reflexes, progressive mental impairment. Short stature (Ht ~10th SD, Wt ~25th SD). On MRI with contrast: diffuse frontal cerebral atrophy and dilated ventricles. No brittle hair or tiger-tail pattern on polarized microscopy, no cachectic dwarfism, cataracts, pigmentary retinopathy, or spasticity. Markedly reduced post-UV cell survival, reduced NER capability, and XPD complementation group assignment. PC healthy. Non-Cons. Older sister was healthy and a heterozygous carrier.	(Emmert et al., 2009) *(Oh et al., 2006)
ERCC 3/XPB	**OCG**	**2q14.3**	3' to 5' Helicase / NER (GGR + TCR)	XP/CS	c.807–808delTT , (p.F270X) + c.2218-6C>A , p.Q739insX42	A 32-year-old ♀ was the first identified XPB patient with a severe form of the XP/CS complex. Displayed severe features of XP (extreme sensitivity to sunlight with blistering in infancy, pigmentation abnormalities, and multiple skin cancers) as well as of CS (wizened facial appearance, dwarfism, sensorineural deafness, microcephaly, severe mental retardation, microphthalmia, corneal scarring, cataracts, optic atrophy, pigmentary retinal degeneration, abnormal (flat) electroretinogram, hyperreflexia, ataxia, decreased nerve conduction velocity, enlarged cerebral ventricles, basal ganglia calcifications, and immature sexual development). Reduced post UV-RNA synthesis recovery and cell XPB protein expression. Intellectual impairment but still socially acceptable interactive (IQ of 40). Numerous skin cancers began at 15 years of age. SCC of her eyelid treated with radiotherapy with a good response. Died of cardiovascular disease at 33 years of age.	(Oh et al., 2006)

ERCC 4/XPF	**TSG**	**16p13.12**	5' Nuclease /NER (GGR + TCR)*	XP with progressive neurodegeneration	c.2395C>T , (p.Arg799Trp) + c.1376C>A , (p.Ser459*)	A 52-year-old ♀ in a wheelchair with a 20-year Hx of progressive dystonia, gait ataxia, hearing loss, and worsening cognition. Hx of photosensitivity with blistering skin lesions after limited sun exposure resulted in multiple facial lentigines and basal cell carcinomas as a teenager. Through aggressive photoprotection: minimal freckling but multiple scars from basal cell carcinoma resections. Maternal Hx of mild postural tremor, no similarly affected relatives. On neurologic examination: disoriented, partly amnestic, struggled to follow simple commands, had dystonic and choreiform movements of the head and neck, mild ataxic dysarthria, a coarse, irregular appendicular tremor, ataxia, spasticity, brisk reflexes and upgoing toes. On brain MRI: global cerebral atrophy and inner table hyperostosis. Significant NER impairment in fibroblast cells. No electrophysiologic evidence of polyneuropathy. Normal optic disc. Died at age 54 years from secondary medical complications.	(Shanbhag et al., 2018) *(Mori et al., 2017)
ERCC 5/XPG	**OCG**	**13q33.1**	3' Nuclease /NER (GGR + TCR)	XP with defective NER but no oxidative-stress-induced damage repair deficiency	c.83C>A , (p.Ala28Asp) + c.2904G>C , (p.Trp968Cys)	Two patients in a sibling pair with average development and good general health by avoiding sunlight exposure. The older patient, a 22-year-old ♀, first observed to be sun-sensitive when she was a newborn, had diffuse erythema and desquamation after short sun exposure; it recurred after varying degrees of sun exposure. On examination: mild erythema and desquamation on the face, mainly on the forehead, malar region, nasal dorsum, tiny vesicles on her lower lip, multiple solar lentigines on sun-exposed areas of the body, including the face, neck, shoulders, and upper back, had photophobia with redness and watering of the eyes during sun exposure. The younger 17-year-old ♂ patient with slight erythema and desquamation on the face, especially on the nasal dorsum, had also multiple solar lentigines on his central face and a few lentigines on the upper trunk, first exhibited sun sensitivity as a newborn with the same clinical manifestations as his sister and also reported episodes of photophobia. +ve NER impairment test in fibroblasts. No Hx of skin Ca or skin precursors. No surgically removed lesion. Parents were non-Cons.	(Soltys et al., 2013)
XPA	**TSG**	**9q22.33**	Damage verification/ NER (GGR + TCR)	XP with spindle cell melanoma	Novel homozygous mutation of A<G at the eighth nucleotide of intron 4 causing aberrant splicing and a non-functional truncated XP-A protein, with <5% normally spliced mRNA.	A 61-year-old ♀ with a lesion on her right shoulder for a few months. A lesion of unknown pathology been excised from her nose 1 year before. Hx of skin freckling development since the age of 3 years. A few sun exposure resulted in mild symptoms of sunburn, erythema, and skin burning. No Hx of blistering, no sunscreen protect usage. Hx of intermittent red, sore, watery eyes. On examination: a golf-ball-sized pink polypoid tumor over the posterior aspect of the right shoulder, xerosis, widespread freckling, and hypopigmented macules very prominent in the sun-exposed areas, with pale freckling of the unexposed sites, two dark macules, one over the left side of the neck, the other in the left supraclavicular fossa. On neurological examination: absent deep tendon reflexes, a glove and stocking sensory neuropathy, no hearing difficulty.	(Sidwell et al., 2006)

						Ophthalmological examination: hypermetropia, bilateral trichiasis, and bilateral early cataract formation. Histological examination of the excised lesion: a malignant spindle cell tumor, situated in the mid dermis, fairly well-circumscribed but with an infiltrative margin. The tumor cells were spindle-shaped with pleomorphic vesicular nuclei, no identified pigment, small prominent thin-walled blood vessels, and numerous aggregates of plasma cells. Mitoses present at 6–7 per 10 high-power fields. On IHC: +ve tumor cells for CD34, strong diffuse positivity for S-100 protein and -ve for cytokeratins, desmin, HMB-45, Factor VIII, smooth muscle actin, and CD68. –ve immunofluorescence studies. Dx of malignant spindle cell melanoma was considered. Severe NER impairment. No family Hx of skin disorders. Parents were Cons.	
XPC	**TSG**	**3p25.1**	Damage recognition / NER (GGR)*	XP with ovarian teratoma	c.2218_2220delCTC , (p.Glu740_740del) in exon 12 + c.2257dupC , (p.Arg753fs) in exon 13	A 29-year-old ♀ with freckle-like pigmentation, initially on the bridge of the nose, a year and a half after sun exposure, then spread to the neck, the upper limbs, and the hands. No symptom of sunburn, no sun protection usage until 20 years of age. No skin Ca or neurological alterations. Suffered from poor vision and photophobia from an early age. On ophthalmologic examination: conjunctivitis along with congenital fundal lesions and macular shift. Her father and grandfather had Hx of cataract. A year prior, the proband was diagnosed with ovarian teratoma. On biopsy: mature cystic teratoma on the left ovary with mature brain tissue. A definite Dx of XP-C was made based on clinical features and gene detection. -ve family Hx. Half brother and sister were also carriers. PC. Non-Cons.	(Tang et al., 2018) *(Rivera-Begeman et al., 2007)

Table 3: demonstrates the presentation of XP-related genes with examplary cases.

Age of the patient corresponds to the time of the original publication. Only relevant normal examinations and laboratory investigations are mentioned.

GGR: global genome repair pathway; TCR: transcription-coupled repair pathway; TLS: translesion synthesis; SCC: squamous cell carcinoma; CS: Cockayne syndrome; Dual: the gene acts as TSG and OCG.

* Points to the reference in the same row of the table.

4.1.4 Group 1.4: Others

Shelterin complex subunit and telomerase recruitment factor (ACD) gene (Tab. 4) encodes the telomere-binding protein TPP1. The name of ACD gene refers to adrenocortical dysplasia homolog {mouse}. TPP1 plays a significant role in telomere maintenance (Guo et al., 2014).

The far end of a chromosome, the telomere, is one of the imperative genome stability maintaining factors. A telomere is built from non-conserved repetitive hexameric sequences, prone to progressive shortening over multiple cell cycles due to the end replication problem. To some measure, a ribonucleoprotein known as telomerase counteracts this loss and attaches the repeats to the 3′ end of the leading strand (Else et al., 2009). The active telomerase complex is composed of RNA template (TERC), the catalytic reverse transcriptase (TERT), and the RNA-binding protein dyskerin (Guo et al., 2014).

The peculiar T-loop structure of the DNA at the telomeres is defensive, and the specified shelterin complex safeguards the chromosomal ends from DNA damage signaling and DNA repair, and enhances telomerase recruitment (Else et al., 2009).

Shelterin complex is a group of six protective protein factors (TRF1, TRF2, POT1, TPP1, TIN2, and RAP1). It enables a cell to discern the DNA damages from normal chromosomal ends. TRF1 and TRF2 interact with double-stranded DNA, POT1 interacts with single-stranded telomeric one. The rest are interconnectors within the shelterin complex (Else et al., 2009). RAP1 binds to TRF2 to hinder the occurrence of any deviant non-homologous end jointing at the telomere (Jones et al., 2013).

The binding of TPP1 to the telomere occurs by interaction with TIN2. This recruits the single-stranded DNA binding protein POT1 to telomeres to form POT1/TPP1 heterodimer (Guo et al., 2014). Hence, ACD is needed for POT1 recruitment to the telomere (Else et al., 2009).

Heterozygous and homozygous germline pathogen variants of the ACD gene result in a mucocutaneous disorder known as dyskeratosis congenita (DC) (Tummala et al., 2018).

DC is one of the short telomere syndromes (Guo et al., 2014) and portrays through abnormal skin pigmentation, oral leukoplakia, nail dystrophy, peripheral pancytopenia, and bone marrow failure. DC is a rare (Tummala et al., 2018) and a potent cancer-predisposing syndrome, including leukemia and squamous cell carcinoma. The disease is complicated by pulmonary fibrosis, dental abnormalities, stenosis of the lacrimal ducts, urethra, or esophagus (Savage et al., 2011), liver fibrosis/cirrhosis, and emphysema (Walsh et al., 2017). Hoyeraal Hreidarsson syndrome (HHS) and Revesz syndrome are the severe presentations of the DC,

and characterized by cerebellar hypoplasia, and intracranial calcification with exudative retinopathy, respectively (Savage et al., 2011).

The hallmark of DC is the hematopoietic failure, which is ascribable to telomere shortening that in turn induces hematopoietic stem cell premature aging (Tummala et al., 2018).

DC is a heterogeneous disease. Germline mutation in one of nine known DC-causing genes is found in approximately 70% of DC cases. The product of these genes are all involved in telomere biology (Kocak et al., 2014). The defective genes in DC and HHS are a group of telomerase complex-related genes (TERT and TERC), telomerase transporting gene, telomerase stability-related genes, and genes involved in telomere replication (Tummala et al., 2018). The inheritance mode of DC is gene-dependent, X-linked, autosomal dominant, and autosomal recessive modes have been reported. Telomere length is measured in white blood cells by flow cytometry with fluorescent in situ hybridization. DC is diagnosed when the value of telomere length lies under the first percentile for the corresponding age (Walsh et al., 2017).

Both variants of the displayed cases showed impaired TERT binding capacity and affected the highly conserved oligonucleotide-binding (OB)-fold domain in TPP1 and constellated in the telomerase recruitment site "TEL patch of TPP1" (patches of amino acids on the surface of TPP1, serves telomerase binding). The alliance between TPP1 OB-fold and telomerase is of great relevance for telomerase maturation, transport, and recruitment to telomeres by Cajal bodies (Tummala et al., 2018).

Mutation in the ACD acts as an oncogenic driver mutation in leukemia cells (Spinella et al., 2015). It predisposes to familial melanoma (Aoude et al., 2015) and myelodysplastic syndrome (Kennedy and Shimamura, 2019).

The Adenomatous Polyposis Coli (APC) gene (Tab. 4 and 5) is mainly expressed in the brain, colon, small intestine, and to a lesser degree in the bone marrow (Refseq).

The lethality of APC gene knockout in mice during early embryogenesis had not permitted a competently researched role of APC in bone development. In contrast, the background of limb development by the Wnt/β-catenin (wingless-type integration site family) signal pathway, to which APC belongs, has been broadly studied. The known duty of the APC gene is assistance in β-catenin degradation. The latter controls transcriptional regulation of numerous Wnt-signaling target genes, including LRP4, which has been identified to cause Cenani-Lenz syndrome (CLS) (Patel et al., 2015).

CLS is characterized by renal abnormalities, facial dysmorphism, and distinctive skeletal defects, mainly syndactyly, radio-ulnar synostosis, and mesomelia. The unique pattern of the syndactyly affects the hands more severely (Patel et al., 2015).

Patel et al. (2015) disclosed the first and the only reported CLS cases resulted from biallelic germline APC mutation to date. Four patients presented with characteristic CLS features and scoliosis due to upregulation of the Wnt/β-catenin signaling pathway. The splicing mutation resulted in 2 transcripts, one with ∼80% reduced efficiency of the wild-type splicing and an aberrant transcript, which completely skips exon 5 and severely truncating the APC protein.
Sharing the same ultimate pathway between APC and LRP4 explains the association of their deficiencies with the same syndrome. Similar dysmorphic features were epitomized in mice with bone-specific APC knockout due to β-catenin overexpression (Patel et al., 2015).

APC exists in free form in both cytoplasm and nucleus. In the cytoplasm, it is involved in cytoplasmic β-catenin degradation, and in the nucleus, it diverts excess β-catenin to the cytoplasm. The ß-catenin level determines the Wnt-signal pathway activity degree. Normally, APC binds to “Ct BP” (C-terminal binding protein) at the Wnt-activated MYC promoter to prevent binding of nuclear β-catenin to the T-cell factor 4, which activates the target genes for abnormal proliferation and lead to production of a considerable quantity of c-MYC (c-myelocytomatosis viral oncogene homolog). The inactivation of APC would impact its cytoplasmic action and lead to β-catenin up-regulation. The truncating protein in the nucleus is powerless against the excess level of β-catenin and cannot detract it from binding to MYC promotor, and this consequently leads to polyposis (Al-Qattan and Alkuraya, 2018).
FAP is usually caused by truncation of the APC protein in the "mutation cluster region", which is between amino acid 1,000-1,600. On the contrary, CLS was caused by early APC truncation similar to the attenuated form of FAP at the 5' end of the gene. It has been anticipated that the activated Wnt-signal pathway may collaterally activate BMP (bone morphogenetic protein) pathway, and this is occasionally adequate to suspend the C-MYC overexpression. Thus, the excessive nuclear β-catenin acts only on chondrogenesis/osteogenesis, but no phenotype of polyposis will be detected (Al-Qattan and Alkuraya, 2018).

Further, monoallelic germline mutation in the APC gene results in “desmoid tumor,” a non-cancerous myofibrous neoplasm originating from musculoaponeurotic structures. A rare

germline mutation results in a substitution of lysine for isoleucine at codon 1307 (I1307K). This point mutation at the sequence AAATAAAA at the nucleotide 3920 transverses T to A and produces a homopolymer tract (A)8, which is genetically very sensitive and disposed to somatic mutations. The latter may result in frameshift and total loss of the APC gene (Zauber et al., 2008). The author reported an Ashkenazi female with desmoid tumor. The patient had indeed a combination of a homozygous germline mutation in the APC gene and a somatic transition in the ß-catenin gene in codon 41 of adenine to guanine in the first position. The position of codon 1307 in the APC gene is crucial for its proper function in β-catenin controlling. Its loss leads to ß-catenin accumulation and induces cell proliferation and carcinogenesis {like colorectal carcinoma (CRC)} due to increasing target gene expression as a result of ß-catenin up-regulation (Zauber et al., 2008).

The APC*I1307K variant is ancestrally-associated, and all reported cases in these studies for colorectal cancer were Ashkenazi Jews, where I1307K allele frequency of APC gene is estimated to be detected in 6.1% of unselected cohorts, and a higher percentage up to 10-15% is expected in a cohort with positive personal and family history of CRC (Woodage et al., 1998; Zauber et al., 2005).
APC is a TSG (Lage et al., 2008). Heterozygous germline mutation in the APC gene compels the autosomal dominant adenomatous polyposis coli, in which hundreds to thousands of colorectal adenomas develop during adolescence and young adulthood. The patients have a higher risk to develop Wnt-activated medulloblastoma, gastric and duodenal cancer (Kurahashi et al., 1995; Łastowska et al., 2018).

Ataxia-Telangiectasia Mutated (ATM) gene (Tab. 4) is responsible for codifying ATM kinase, a DNA DSB repair kinase (Amirifar et al., 2019; Gilad et al., 1998), which serves cell cycle regulation after a DNA DSB by applying cell cycle delay through phosphorylation of checkpoint kinase CHEK2 and p53. Lack of this phosphorylation is the underlying reason in G1-cell cycle arrest defect and G2-cell gathering after exposing cells to ionizing radiation in ataxia-telangiectasia (A-T) patients (Angèle et al., 2003).
ATM is a member of the phosphatidylinositol kinase-like kinase (PIKK) family of serine/threonine kinases (Horowitz et al., 2008).

DNA damaging processes like DNA DSB at heterochromatin and ionized radiation would activate ATM DNA damage sensor kinase. During DNA DSB, activated ATM phosphorylates

transcriptional corepressor Kruppel-associated box (KRAB) associated protein 1 (KAP1) and enhances access of DNA repair machinery to the heterochromatin, and also phosphorylates telomeric repeat binding factor 1 (TRF1), which negatively regulates telomere elongation, in order to abolish apoptosis and diminish cell radio-sensitivity by maintaining the telomere length. ATM is part of the specialized DSB repair mechanisms in physiological processes like an aggregation of the T-cell receptor and immunoglobulin (Ig) genes by V(D)J recombination, meiotic recombination and efficient class switch recombination in mature B-cells, which are essential standpoints in explanation of lymphoma predisposition, immune dysfunction, and sterility in A-T affected patients. Nevertheless, for other A-T demonstrations like pulmonary diseases, telangiectasia, and insulin resistance, additional yet non-explicable functions of the ATM gene are assumed, that need to be studied further (Amirifar et al., 2019).

A-T is a complex, autosomal recessively inherited DNA repair disorder, caused by biallelic mutation in the ATM gene. The disease is characterized by neurodegeneration with progressive ataxia, telangiectasias, predisposition to various malignancies, severe immunodeficiency, an elevated level of alpha-fetoprotein, sensitivity to ionizing radiation, chromosomal instability, type II diabetes, growth retardation, and gonadal atrophy (Amirifar et al., 2019; Gilad et al., 1998).

Close to one-third of A-T patients would suffer from malignancies, mainly T-cell leukemia and B-cell lymphoma (Babaei et al., 2005).

Wheelchair confinement by the second decade of life is expected. Except in some locked population, ATM compound heterozygous mutations prevail homozygous mutations (Carranza et al., 2016).

The large size of the ATM gene allows poor mutation detection. Deletions, insertions, splice site mutations, and nonsense mutations are commonly identified, all induce truncation of the protein. Missense mutations were seldom found in patients with classical A-T. Various clinical features, severity, and prognosis of the disease could be explained through these disparate mutations. The mutations are located throughout the gene with no hotspots been reported, and it is difficult to distinguish them from polymorphisms (Jiang et al., 2006).

Compared to hypomorphic mutation, which has some residual ATM kinase activity, the null mutation in the ATM gene produces a non-functional gene protein that is related to lower life expectancy due to prior onset of malignancies (Micol et al., 2011). Cancer development, respiratory disease, and immunodeficiency in A-T patients are genotype-dependent (van Os et al., 2019).

ATM is a TSG (Bueno et al., 2014). The heterozygous ATM carrier frequency in the population is estimated to be 0.5–1% (Rainville and Rana, 2014). Its mutation has been associated with leukemia, lymphoma, and breast cancer (Bernstein et al., 2013).

BLM RecQ like helicase (BLM) gene (Tab. 4) codifies a DNA helicase, Bloom syndrome protein, which is a member of the well-conserved RecQ subfamily of ATP-dependent, 3′–5′ DNA helicases. RecQ family encloses a cluster of essential nuclear proteins that function in the preservation of genomic integrity (Horowitz et al., 2008; Jian-Bing et al., 2016).

Biallelic BLM gene mutation causes Bloom syndrome (BS), which refers to a rare autosomal-recessive multiple malignancy-prone disorder that presents with specific clinical manifestations including photosensitivity, telangiectasia similar facial erythema, immunodeficiency, hypogonadism (Jian-Bing et al., 2016), pre- and postnatal growth deficiency, short stature, gastrointestinal reflux, insulin resistance, and recurrent infection. Around one-third of diagnosed cases are of Ashkenazi Jewish descents by reason of a founder mutation (Walsh et al., 2017).

Different cancers have been diagnosed in patients with BS during childhood such as, lymphoma, acute lymphoblastic leukemia, acute myeloid leukemia, gastrointestinal, genital and urinary tract carcinoma, sarcoma, Wilms tumor, medulloblastoma, and retinoblastoma (Walsh et al., 2017).

BS is characterized at the cellular level by an increased rate of error-prone HR, driving correspondingly elevated rates of sister chromatid exchanges (hypercombination), and losses of heterozygosity (Horowitz et al., 2008).

In BS cells, there is a deficiency in replication control and a decreased DNA replication fork velocity by the inability to resolve stalled DNA structures. Also, BLM deficiency could lead to the accumulation of replication intermediates, which in turn leads to ATM repair activation. A normal functioning BLM focalizes to the area of single-strand DNA and composes a complex with topoisomerase IIIα at stalled DNA replication forks, aids resolving Holliday junction-containing recombination intermediates and suppresses HR (Horowitz et al., 2008).

BLM is a TSG (Chandra et al., 2013). Its heterozygous mutation has been detected in a wide range of tumors, including leukemia, lymphoma, carcinoma of breast, kidney, larynx, prostate, endometrium, lung, pancreas, ovary, cervix, and stomach (Kluźniak et al., 2019).

Breast cancer associated protein (BRCA2) gene (Tab. 1, 4 and 5) germline mutation-induced Fanconi anemia showed seldom incomprehensible manifestations and, unlike other subtypes,

a diverse spectrum of childhood cancers. Apart from predisposition to breast, ovarian and other cancers, BRCA2 is the third recognized predisposing gene that causes Wilms tumor, which is referred to an embryonal tumor of the kidney. Additionally, a combination of renal and brain tumors is known as the Wilms2 tumor. Irradiation by biallelic BRCA2 mutation might be considered as a relevant risk for developing other primary tumors due to radiation hypersensitivity and raised somatic mutation rate (Reid, 2005).

Biallelic BRCA2 truncating mutations have been reported in patients with ovarian dysgenesis as well. BRCA2 is one of the DNA-repair genes involved in meiotic recombination, and an intact BRCA2 protein is essential for proper ovarian function (Turchetti et al., 2019).

Turchetti et al. (2019) reported three young Chinese patients with premature ovarian insufficiency, who were biallelic BRCA2 mutation carriers and had no sign of malignancies (neither solid nor hematological). Presentation of the patients with primary amenorrhea in early adulthood rather than congenital anomalies and multiple tumors in early childhood has been related to the residual BRCA2 function. These affected young women should have increased cancer surveillance and genetic analysis due to increased cancer incidence in adults who are BRCA2 mutation carriers.

Calcium sensing receptor (CASR) gene (Tab. 4) encodes a plasma membrane calcium-sensing protein, which is a cell surface protein of the superfamily of the 7-membrane-spanning, G protein-coupled receptor, expressed in the parathyroids, kidneys, and thyroid C-cells (Kobayashi et al., 1997). CASR is concerned with maintaining extracellular ionized calcium concentration of a narrow range (1.1–1.3 mmol/L) by controlling parathyroid hormone (PTH) secretion and urinary calcium excretion (Sun et al., 2018).

Neonatal severe hyperparathyroidism (NSHPT) is a rare and potentially lethal disorder caused by both monoallelic and biallelic variants of the CASR gene. Early medical intervention and/or parathyroidectomy are life-saving measures and crucial for long-term survival. Neuromotor retardation is a lifelong consequence of microcephaly and/or hypercalcemia. The maximal serum calcium level has been linked to homozygous CASR mutations (Marx and Sinaii, 2019).

NSHPT is manifested by respiratory distress, dehydration, hypotonia, failure to thrive, and metabolic bone diseases. NSHPT usually presents in the first weeks of life (Sun et al., 2018).

Familial hypocalciuric hypercalcemia (FHH) type 1 is caused by a heterozygous mutation in the CASR gene, and is usually identified by the family members of NSHPT patients. FHH is inherited autosomal dominantly (Marx and Sinaii, 2019) and is usually asymptomatic with

mild to moderate lifelong hypercalcemia, relative hypocalciuria, and normal parathyroid level (Miyashiro et al., 2004).

Both FHH and NSHPT result from LOF mutations in the CASR gene, mostly of missense variants that affect the calcium-binding site in the extracellular domain of its protein. The result is a generalized resistance to extracellular calcium (Miyashiro et al., 2004).

Germline GOF mutations in CASR mostly of missense variants induce the autosomal dominant hypocalcemia (ADH) type 1, which describes mild-to-moderate hypocalcemia with inappropriately low or normal PTH, increased serum phosphate, and increased urinary calcium excretion in relation to the serum calcium level. The mutation drives the receptor to be more sensitive to calcium (Bastepe, 2018). The hypocalcemia may sometimes have a presentation of pseudo-Bartter syndrome (Vahe et al., 2017).

Certain CASR polymorphisms have been involved in cancer. In the latter, CASR displays a dual role, as a TSG and as an OCG, depending on the tissue involved, prevents or promotes tumorigenesis. In parathyroid or colon cancer, CASR deficiency provides the tissues with a malignant property of proliferation enhancement and terminal cell differentiation inhibition, pointing to CASR as a TSG. However, in prostate and breast tumors, CASR is overexpressed and increases the risk of bone metastasis (Vahe et al., 2017).

Cyclin dependent kinase inhibitor 2A (CDKN2A) (Tab. 4) with its CDK4 blockage property, is one of the CDKs activity inhibitors and interdicts S-phase cell entry. In addition to many solid tumors, CDKN2A mutations are behind some sporadic, and most of the familial melanoma cases (Pavel et al., 2003).

The displayed homozygous germline CDKN2A mutation was identified during the analysis of CDKN2A in 13 of 15 dutch families driven from endogamous inhabitants with suspicion of familial atypical multiple mole melanoma (FAMMM). The latter informs the simultaneous incidents of atypical nevi and cutaneous malignant melanoma in the family (Gruis et al., 1995).

Apart from Glucose-6-Phosphate-Dehydrogenase (G6PD) deficiency and homozygous CDKN2A mutation, the reported male patient was a carrier for a heterozygous variant in the melanocortin receptor 1 gene as well, with an unexplored association to the risk of melanoma. It remains to assume the plausibility of involvement of these compound deficiencies in cell-cycle control and cellular protection against oxidative cell damages, which result in excessive intracellular oxidative stress and DNA hypermutability, in development, and expansion of malignant melanoma in this patient. Besides, the coaction between G6PD deficiency and

CDKN2A total inactivation could not be excluded. G6PD enzyme is avowed as a housekeeping enzyme that takes over the initial step in the pentose phosphate pathway, a fundamental sugar source for DNA, RNA, and coenzyme synthesis. Its deficiency is an X-linked recessive disorder and demonstrably involved in DNA DSB repair defect (Pavel et al., 2003).

The viability of a potential CDKN2A knockout human is remarkable, given its delicate role in cell cycle commandment. It also leads to the conclusion of the existence of a potential redundant gene, which may refund CDKN2A deficiency.
CDKN2A is a TSG (Pavel et al., 2003). Its heterozygous mutation is involved in FAMMM and pancreatic cancer, less frequently, in the colon, breast, and ovarian carcinoma (Foulkes et al., 1997).

DIS3 like 3′-5′ exoribonuclease 2 (DIS3L2) gene (Tab. 4) is a highly conserved RNase II/RNB family element engaged in many vital cellular processes, including RNA metabolism, cell division, proliferation, differentiation, and programmed cell death (Luan et al., 2019). DIS3L2 function is exosome-related and is concerned with the direction of various facets of cellular RNA metabolism, including stable nuclear RNA molecule maturations, aberrant transcript eradications, and nonsense-mediated decay of transcripts with a premature stop codon (Astuti et al., 2012).
The 3′-5′ exoribonuclease activity of DIS3L2 serves degradation of single- and double-stranded RNA substrates as well, whereby the polyuridylation in the 3′ end of RNA transcripts appears as a decay signal for DIS3L2. Substrates such as Let-7 precursor, mature microRNA, aberrant mRNAs, and a variety of short and long non-coding RNAs are identified and degraded by DIS3L2 (Luan et al., 2019).
Biallelic germline mutation in DIS3L2 is related to an autosomal recessive congenital overgrowth syndrome known as Perlman syndrome that overlaps with Beckwith-Wiedemann syndrome. The disorder is characterized by macrosomia, hypotonia, developmental delay, hydronephrosis, organomegaly and peculiar dysmorphic features including, prominent forehead, flat nasal bridge, deep-set eyes, low-set ears, and inverted V-shaped upper lip (Astuti et al., 2012). Macrosomia, polyhydramnios, and visceromegaly are the most identified antenatal sonographic findings (DeRoche et al., 2004).

Perlman syndrome is associated with poor prognosis and a high neonatal mortality rate (Astuti et al., 2012). The leading causes of early neonatal death are mostly respiratory distress and/or renal failure (Soma et al., 2017).

Perlman syndrome is concordant with a remarkably high incidence rate of Wilms tumor in up to 64% of infants outliving the neonatal period, which alludes to a conserved role of DIS3L2 in nephrogenesis (Astuti et al., 2012), and a leading role of miRNA in Wilms tumor development. The Lin28 let-7 system has been contributed to Wilms tumor development in patients with DIS3L2 mutations (Tian et al., 2014).

DIS3L2 acts as a TSG and an OCG in different cancer types. Howbeit, the collaboration of DIS3L2 with the OCG lin28 (Luan et al., 2019), which is a potent regulator of stem cell self-renewal and differentiation (Tian et al., 2014), in maturation inhibition of the tumor-suppressive Let-7 family of microRNAs, points to DIS3L2 oncogenic capacity (Luan et al., 2019). DIS3L2 tumor-suppressive role has been supported by the fact that DIS3L2 has an inhibitory effect on cell cycle progression, through inhibiting the expression of cell cycle regulator cyclin D1, and suppression of lncRNAAC105461.1 impact on colorectal cancer's stem-cell-like characteristics. Heterozygous DIS3L2 mutation has been identified in sporadic Wilms tumor cases (Astuti et al., 2012).

Epithelial Cellular Adhesion Molecule (EPCAM) gene (Tab. 4) enciphers an interepithelial adhesion molecule required for normal barrier function in enterocytes, and plays an important role in cellular proliferation, migration, maturation, and differentiation pathways (Das et al., 2019). EPCAM is involved in the Wingless (Wnt)/ß-catenin signaling pathway, which is involved as well in the maintenance and differentiation of the intestinal stem cells. Loss of EPCAM leads to defects in epithelial integrity. Biallelic mutation in the EPCAM gene results in congenital tufting enteropathy (CTE), which is a rare autosomal recessively inherited severe enteropathy in infancy with clinical and histological manifestations. The clinical marks of CTE include intractable diarrhea leading to failure to thrive in early infancy. Duodenal histology is distinguished by wavering villous atrophy, focal epithelial tufts, and crypt hyperplasia (Das et al., 2019; Thoeni et al., 2014).

In CTE, EPCAM expression is lost while in other CTE resembling congenital enteropathies, EPCAM would be expressed normally. Subsequent to immunohistochemical, histopathological, and ultrastructural analysis of duodenal biopsies, a conclusive diagnosis of CTE would be obtained by molecular analysis. An EPCAM knockout mouse demonstrates corresponding features like CTE in humans. Mostly, mutations sited in exon 3, 4 and 5 of the

EPCAM gene are related to abnormal cell-cell contact function due to lack of the crucial domains (Thoeni et al., 2014). CTE-inducing truncated proteins have been declared to be accumulated in the endoplasmic reticulum (ER) instead of been routed to their normal plasma membrane location. This highlights the probability of participation of the unfolded protein response mechanism in CTE as a result of ER stress (Das et al., 2020).

Noteworthy, truncating EPCAM deletion carriers exhibit DNA mismatch repair MSH2 gene promoter hypermethylation. This accounts for at least 2.8% and 1.1% of the established Lynch syndrome families within the Netherlands and Germany, respectively (Kuiper et al., 2011).

EPCAM acts as an OCG, and its overexpression has been identified in ovarian, gastrointestinal, and colorectal carcinoma (Das et al., 2019).

Excision repair 1 endonuclease non-catalytic subunit (ERCC1) gene (Tab. 4):

The ERCC1 and ERCC4 genes codify two subunits of the essential ERCC1–XPF nuclease, which performs a critical incision step during repairing DNA damages and maintains genome integrity and is part of many repair mechanisms. ERCC1-XPF is the central constituent of NER and acts as an element of ICL repair, double-strand break repair (by HR and end-joining), and assists in base excision repair (BER) and telomere length regulation. The ERCC1-XPF complex serves many of these activities by splitting the 3′ tails of DNA intermediates, and so preparing the damaged DNA for additional processing. For its optimal function is interaction with many other proteins required (Manandhar, Boulware and Wood, 2015).

The complex of XPC-HR23B and DDB takes over the recognition of the genome-wide helical aberrations. A further NER is known as transcription-coupled repair, which repairs DNA damage quickly that blocks RNA polymerase II progression. After damage-recognition follows local unwinding of DNA by the TFIIH complex, and the correct emplacement of the two ERCC1-XPF and XPG endonucleases by XPA and RPA protein. Each of the endonuclease enzymes incises the damaged DNA strand on a side (see Tab. 3), removes aberrant oligonucleotide, and permits resynthesis by DNA polymerase and reconstruction of phosphate bonds by ligase (Jaspers et al., 2007).

A series of genetic diseases like Fanconi anemia, specific category of xeroderma pigmentosum, Cockayne syndrome, XFE progeria, and cerebro-oculofacio-skeletal syndrome could all be induced by biallelic mutations in ERCC1 and ERCC4 gene (Manandhar, Boulware and Wood, 2015).

Despite the central role of ERCC1-XPF in multiple genome integration pathways, mutations in XPF result in a mild XP phenotype and are mostly hypomorphic with substantial residual activity. Jaspers et al. (2007) presented the first ERCC1 deficient patient, with mild NER impairment similar to XPF patients, but surprisingly with a very serious clinical presentation and fatal outcome in early infancy, despite of residual protein activity and considerable DNA repair function. The mutation resulted in a truncated protein lacked a highly conserved C-terminal XPF binding domain, which in turn disturbed the ERCC1-XPF interaction.

ERCC1 is a TSG; its deficiency predicts the resistance to cisplatin. Its heterozygous germline mutation is involved in glioma, ovarian cancer (Liang, Ross and Reed, 1995), bladder carcinoma, testicular carcinoma, lung cancer, head and neck cancer (Kawashima, Takayama and Tsujimura, 2012), gastric carcinoma, colorectal carcinoma (Abyarghamsari et al., 2019), and others.

FA complementation group M (FANCM) gene (Tab. 1 and 4) is a DNA-damage response gene. In spite of being a critical element in the FA molecular pathway, no patient with FA due to pure FANCM mutation has been reported to date. Apart from that, FANCM homozygosity has been identified in individuals without diseases or increased predisposition to cancer. This arouses the suspicion about FANCM been a valid FA gene (Catucci et al., 2017).

Catucci et al. (2017) presented five female cases with biallelic FANCM mutations having clinical phenotypes of breast cancer (2 cases with early-onset, 1 case with bilateral), chemotherapy-related hematological side effects (4 of 5 cases), possibly early menopause, and chromosome fragility {1 of 3 tested cases, because the truncated protein might lack the interaction domain with the DNA-binding mediators MHF1 and MHF2 (FANCM-interacting histone fold protein 1 and 2), and with the Bloom syndrome complex}. No classical FA or FA-like manifestations were noticed, however, the cases showed FA-like cancer susceptibility. This observation insinuates that FANCM biallelic mutation may have a stronger effect on breast cancer risk compared to the risk related to its monoallelic mutation, much like breast cancer risk factor CHEK2 c.1100delC.

Depending on the nature and the location of the biallelic truncating FANCM pathogenic variants, it could lead to a variety of phenotypes, with or without cancer predisposition (Yin et al., 2018).

FANCM is in conjugation with FANCA, -B, -C, -E, -F, -G, and –L part of the core complex, which takes over the early stages of the physiological repair of DNA ICLs. Abolishment of

the monoubiquitination of the ID2 complex has been induced by loss of all core complex members apart from FANCM, which only diminishes the performance of this mechanism, even, FANCM function is not indispensable for FA core complex formation and stabilization (Catucci et al., 2017). Recently, the role of FANCM genes was discarded from the group of FA genes in the installation of bona fide FA clinical and cellular phenotypes (Fouquet et al., 2017).

Several DNA repair and genomic instability disorders, such as FA, have unceasingly being accompanied by hypogonadism, ovarian failure, and/or infertility (Fouquet et al., 2017).

It could be shown through FANCM deficient male mouse models that a defective DNA ICL repair of germ cells results in testes displaying Sertoli cell-only tubules and a progressive loss of germ cells of multiple stages of spermatogenesis, pointing to a diverse role of FANCM, independent to FA pathway. Chromatin remodeling during spermatogenesis demands proper function of the DNA repair system in spermatids, which in turn requires an efficient FANCM gene. This means that defective ICL repair is correlated to male infertility (Yin et al., 2018). A genetic link between primary ovarian insufficiency and defective function of genes in the DNA repair system has been confirmed as well (Fouquet et al., 2017).

FANCM mRNA is expressed and immuno-histochemically shown in germ cells of human fetal and adult ovaries, also throughout ovarian development with the highest level at 14-17 weeks of gestation, the period in which the majority of germ cells are progressing into meiotic prophase I. Hence, FANCM is vital for sustaining primordial germ cell proliferation and proper meiotic recombination (Fouquet et al., 2017).

FANCM deficient female mouse presents with a profound decrease in the number of primary follicles and developing follicles due to Oocyte apoptosis as a result of DNA repair deficiency-induced DNA DSB accumulation over time, leading to reduced oocyte viability. The presence of corpora lutea in FANCM deficient female mouse and the spontaneous pregnancy in the displayed case could be explained by the theory that some follicles evaded the DNA repair defect and attained maturation (Fouquet et al., 2017).

In cancers, FANCM acts as a TSG (Lopes et al., 2019), and it is regarded as a susceptible gene for ovarian cancer (Lopes et al., 2019), triple-negative breast cancer (Kiiski et al., 2014), and colorectal carcinoma (Smith et al., 2013).

Fumarate hydratase (FH) gene (Tab. 4) encodes a critical enzymatic component in the Krebs cycle, fumarate hydratase, which is functionally active in both mitochondria and cytoplasm. Its biallelic mutation is the underlying cause for a rare infantile metabolic disorder with

progressive encephalopathy known as fumarate hydratase deficiency. The latter is defined as recessively inherited hypotonia, seizure, fumaric aciduria, and progressive encephalopathy.
The most common dysmorphic manifestations in FH deficiency, which are considered telltale marks that can be seen antenatally or after birth, are frontal bossing, widely spaced eyes, and depressed nasal bridge. Less common phenotypes are narrow forehead, ear anomalies, and anteverted nares (Coman, Kranc and Christodoulou, 1993).
Zeng et al. (2006) declared the first case of FH deficiency due to Uniparental disomy (UPD). A non-consanguineous relationship between a heterozygous carrier father and a healthy mother resulted in a child with FH deficiency, who inherited a homozygous c. 392C>G mutation (p. P131R) in exon 3 of the FH gene from the father due to parental heterodisomy with partial isodisomy at the distal 1q region.
FH is a TSG (Lage et al., 2008). The carrier of a heterozygous germline mutation in the FH gene is inclined to a rancorous autosomal dominantly inherited syndrome with early outbreak potential, consists of uterine and cutaneous leiomyomas with renal cancer (M.M.Y. Chan et al., 2017; Picaud et al., 2011). The second mentioned demands an intensive screening for its distinctive early invasion and metastasis property. Current guidance promotes screening yearly from the age of 8 years with abdominal MRI (M.M.Y. Chan et al., 2017).

Glypican 3 (GPC3) gene (Tab. 4) is an element in the glypican family and enciphers the extracellular matrix GPC3 protein, which is located on the cell surface to strive signal transduction of various pathways via communication with further cell-surface proteins, aiding in controlling cell proliferation and apoptosis during development, and growth factor function regulation. The glycosyl-phosphatidylinositol (GPI) anchor of the cell membrane provides the binding site to the C-terminus of the GPC3 protein during post-translational modification. Loss of this C-terminus by any truncating mutation (like exon 2-4 duplication) leads to loss of the binding site of the protein to the cell membrane (Mateos et al., 2013).
Simpson-Golabi-Bahmel syndrome type 1 (SGBS1) is an overgrowth and multiple embryonic tumor-predisposing syndrome with an X-linked recessive mode of inheritance, caused by mutations in both GPC3 and the adjacent lying GPC4 genes (Mateos et al., 2013). Both are mapped to the same chromosomal location (Xq26.2) (ORPHANET). However, GPC3 mutations are more frequently found, mostly small and large deletions affecting exon 8 in 50% of cases, missense, point mutations in exon 3, nonsense, and frameshift mutations that spread over the whole gene exons. SGBS1 is verified by prenatal and postnatal overgrowth, congenital anomalies including skeletal, brain, and heart anomalies, organomegaly,

supernumerary nipples, macroglossia, facial dysmorphic features, and various degree of mental retardation. While females need two copies of the mutation to develop the disease, and one mutated allele makes them only asymptomatic carriers or with mild manifestations due to the nature of X-linked recessive inheritance and the effect of X-inactivation, for males, the disease manifestation demands the presence of one mutated allele only (Mateos et al., 2013).
GPC3 is a negative insulin-like growth factor II (IGF-II) regulator. Hence, SGBS1 displays similarity to the Beckwith-Wiedemann syndrome regarding the phenotype, as both syndromes are related to an abnormal IGF-II expression (Cano-Gauci et al., 1999).
GPC3 is a TSG (Thiffault et al., 2004). The tumor spectrum of the GPC3 gene mutation embraces hepatoblastoma, Wilms tumor, gonadoblastoma, neuroblastoma, rhabdomyosarcoma, and hepatocellular carcinoma. Mesotheliomas, breast, and ovarian cancer have been noticed in patients with GPC3 mutations without SGBS1 (Mateos et al., 2013).

Leucine zipper-like transcriptional regulator 1 (LZTR1) gene (Tab. 4) enciphers a protein member of the BTB-Kelch superfamily with cullin 3-containing E3 ubiquitin ligase complex adaptor property, which resides in Golgi complex. LZTR1 is confined to a highly conserved sequence interval, 2.8 Mb centromeric to SMARCB1 and 8.7 Mb centromeric to NF2, and is incorporated in the most commonly ~3 Mb deleted sequence, which causes DiGeorge syndrome (Kehrer-Sawatzki et al., 2016).
LZTR1 germline mutations in almost all exons have been recognized in 38% of familial and 30% of sporadic schwannomatosis cases with wild allele SMARCB1. No meningiomas have been observed heretofore to be exhibited with LZTR1 mutant schwannomatosis, but rather unilateral vestibular schwannomas (Kehrer-Sawatzki et al., 2016).
LZTR1 monoallelic and biallelic mutations in the KELCH domains of LZTR1 have been demonstrated in a small number of patients with autosomal dominant and autosomal recessive Noonan syndrome (NS), respectively. The latter is a malignancy predisposing and a heterogeneous disease. LZTR-associated NS is characterized by congenital heart anomaly and/or cardiomyopathy, distinctive craniofacial features, ectodermal involvement, short stature, coagulation abnormalities, cognitive disabilities (Jacquinet et al., 2020), and cryptorchidism. The craniofacial features include downward slanting palpebral fissures, hypertelorism, low-set and posteriorly rotated ears, and a short and webbed neck (Güemes et al., 2019).
The observed malignancies are mostly childhood leukemia and childhood solid tumors. The NS-related cancer risk is estimated to be 4% at the age of 20 years. NS is related to the

Ras/MAPK (mitogen-activated protein kinase) pathway dysregulation, resulting in ERK prolonged or increased stimulation. The link that connects the cell cycle regulatory function of LZTR1 with the Ras/MAPK pathway is not fully interpreted. However, its contribution to schwannomatosis sheds light on converging action. In the heterozygous status, LZTR1 mutations show incomplete penetrance of NS (Jacquinet et al., 2020). The recessive form is observed to be accompanied by more severe manifestations. NS with an estimated birth prevalence of 1:1,000 -1:2,500 live births is the commonest RASopathy (Güemes et al., 2019). In tumors, LZTR1 acts as a TSG (Kehrer-Sawatzki et al., 2016).

Mesenchymal epithelial transition factor (MET) proto-oncogene (Tab. 4) is a receptor tyrosine kinase gene that encodes α/β heterodimeric protein, which is expressed in various cell types. The only ligand of MET is hepatocyte growth factor (HGF), which takes over the MET activation and dimerization. The HGF binding initiates auto-phosphorylation of the tyrosine residues of the intracellular tyrosine kinase domain of the MET protein, stimulating various signal pathways over the docking site of the SH2 protein domain. This activation is needed for several biological processes, including cellular- growth, survival, proliferation, migration, invasion, and differentiation (Bousfiha et al., 2019).

MET gene is necessary for embryogenesis, organogenesis (like liver, bones, placenta, kidneys, cerebral cortex, cerebellum, pulmonary, and skeletal muscles), damaged tissue regeneration, and wound healing. Furthermore, the expression of MET protein and hepatocyte growth factor (HGF) in the embryonic cochlea of rat (Bousfiha et al., 2019) and mouse models has been proposed (Mujtaba et al., 2015).

Biallelic germline MET mutation is recently recognized as an underlying cause for autosomal recessive non-syndromic hearing loss in 10 individuals (Bousfiha et al., 2019; Mujtaba et al. 2015).

Deafness is with a 1-2/1000 birth incidence, the commonest sensory deficiency and its sequels mainly impact the speech, communication, education, and psychological development of children. These limitations are in turn reflected in attitude issues, academic obstacles, and social integration. Genetic causes are behind 70% of all hearing loss cases with different patterns of inheritance. In one-third of cases, deafness is a component of certain syndromes, and two-thirds are isolated deafness without any other syndromic manifestations (Bousfiha et al., 2019).

Mujtaba et al. (2015) described for the first time, an oppressive type of non-syndromic hearing loss in a large consanguineous Pakistani family due to a novel homozygous missense mutation, c.2521T>G (p.F841V) in the MET gene within DFNB97 locus.

Noteworthy, non-syndromic recessively inherited DFNB39 deafness in Pakistani and Indian families due to 3 non-coding HGF gene mutations have been reported as well (Bousfiha et al., 2019).

MET is an OCG (Lage et al., 2008). The overexpression of the MET gene is affiliated in advancement and metastasis of many cancers such as hepatocellular, papillary renal carcinoma, gastric, head and neck cancers (Bousfiha et al., 2019), breast, lung, prostate, and bladder carcinoma (Skead and Govender, 2015).

Human Microphthalmia-associated transcription factor (MITF) gene (Tab. 4 and 5) is the master regulator of melanocyte differentiation (Bassoli et al., 2017). The first report of MITF biallelic mutation described a phenotype referred as COMMAD syndrome. The term COMMAD is a complex phenotype referred to Coloboma, Osteopetrosis, Microphthalmia, Macrocephaly, Albinism, and Deafness. The COMMAD clinical presentations convey a regulatory role of the MITF gene in processes that exceed the impaction threshold of monoallelic MITF mutations, namely on bone development and optic-fissure closure. Thus, MITF participates in bone homeostasis and ocular morphogenesis (George et al., 2016).

MITF codifies a basic helix–loop–helix leucine zipper protein and serves as a heterodimer with MIT family transcription factors like TFEB, TFEC, and TFE3. MITF protein in mice is involved in the development of hematopoietic tissue-derived osteoclasts, neural crest-derived melanocytes, mast cells, and neuroectoderm-derived retinal pigment epithelium (RPE). The ocular presentation in COMMAD could be the result of the deregulation of genes driving RPE and neural retina development, whereas osteoporosis in COMMAD is related to the activity disturbance of its binding partner, TFE3, which is fundamental for osteoclast function (George et al., 2016).

Mouse model studies have underscored that merely compound heterozygous MITF mutations of dominant-negative type evoke the severest COMMAD manifestation. In the displayed case, the (c.952_954delAGA {p.Arg318del}) mutation has been tested as a dominant-negative, that only impacts nuclear migration (transcriptional-activation domain) and DNA binding of homo- and heterodimers (DNA binding domain), but does not influence the dimerization of MITF with further MIT family transcription factors (dimerization domains). Mice with a homozygous combination of such mutation display a phenotype that is comparable with the

COMMAD presentation. The molecular mechanism underlying COMMAD syndrome is therefore defined as an allelic consolidation that entails leastwise one dominant-negative mutation in the MITF gene and follows a recessive mode of transmission (George et al., 2016).

Heterozygous MITF mutation is united in two overlapping syndromes, Waardenburg syndrome type 2A (WS2A) and Tietz albinism-deafness syndrome. Both marked with congenital hearing loss and pigmentation defects, this is related to the MITF function in differentiation and endurance of skin melanocytes and cochlea stria vascularis (George et al., 2016). The two syndromes are inherited in an autosomal dominant manner and show variable penetrance, intra- and interfamily expressivity. However, in WS3 and WS4, biallelic mutations are recorded, indicating an autosomal recessive inheritance (Rauschendorf et al., 2018).

The four types of WS are pointing to extra clinical features apart from deafness and pigmentation defect. A representative for WS1 is telecanthus (dystopia canthorum). WS2 with its five subtypes lacks the telecanthus and other midface defects found in WS1, also sensorineural deafness is found more frequently in WS2. Presentation with upper limb anomalies suggests WS3. WS4 with its three variants, is accompanied by Hirschsprung disease (Rauschendorf et al., 2018) or chronic intestinal pseudo-obstruction (Pang et al., 2018).

In the displayed case with WS2A, despite the evidence that the homozygous MITF mutation is not considered as a null mutation, the affected melanocyte-specific transcript appears to be inadequate for melanocyte differentiation, migration, and survival (Rauschendorf et al., 2018). The author suggested a reversing mosaicism with postzygotic loss of homozygosity in his attempt to declare the mechanism underlying pigmentation islands in the index patient. Such a somatic reversion could be the result of one of the so far reported genetic incidents like mitotic gene conversion, second-site mutation, intragenic crossover, and back mutation.

The more profound manifestations and the multi-organ involvement in cases of COMMAD syndrome are attributed to the location of the MITF mutations (exon 2-9), which affect all MITF transcript variants, not only the melanocyte-specific one (Rauschendorf et al., 2018).

Heterozygous MITF mutation increases the risk of melanoma. Bassoli et al. (2017) presented the only reported multiple primary melanoma case due to homozygous germline p.E318K mutation in the MITF gene.

Further, Pang et al. (2018) reported the only identified Waardenburg syndrome (WS) type 4 cases due to homozygous p. R223H mutation in the MITF gene, in two children of a Chinese family, who had classic WS presentations with chronic constipation, and their parents showed mild WS type 2 manifestations. MITF mutation has been detected so far only in WS type 2 patients. WS is manifested by loss of sensorineural hearing and pigmentary abnormalities like iris heterochromia, excessive brown freckles in the skin or patchy depigmentation, and premature hair graying. The persistent constipation was suggestive of Hirschprung disease (which though could not be revealed by barium enema and anorectal manometry studies), and chronic intestinal pseudoobstruction. While the affected children were more severely affected than the parents, who were heterozygous carriers, the underlying pathomechanism was suggested to be a dosage effect, similar to other WS-causing genes.

In cancers, MITF acts as an OCG. Apart from melanoma, its mutations predisposes to renal carcinoma as well (Bertolotto et al., 2011).

MRE11 homolog, double strand break repair nuclease (MRE11A) gene (Tab. 4 and 5) has a DNA nuclease activity and it is part of the MRE11/RAD50/NBN (MRN) protein complex required for DNA DSB repair (Spehalski et al., 2017).

DNA DSB repair is made possible through a proper function of the MRN protein complex and ATM protein (Matsumoto et al., 2011). The three conserved components of MRN complex play vital roles in telomere maintenance, cell cycle response following DNA damage, and in DNA DSB repair by HR and non-homologous end joining (NHEJ). MRN complex is indispensable for both mitotic and meiotic recombination (Borde, 2007). DNA DSB induces ATM activation, which in turn triggers a signaling cascade, which initiates cell cycle checkpoints and/or DNA repair, and apoptosis. The activated ATM leads to the recruitment of the MRN complex, which binds and secures the DNA DSB ends. MRE11A, with its nuclease activity eliminates the covalently attached fractions and induces DNA excision (Spehalski et al., 2017).

Mutations in all three elements of the MRN complex have been recorded in humans. Ataxia-telangiectasia (A-T) is related to ATM mutations and A-T like disorder (A-TLD) to MRE11A mutations. Both syndromes are inherited autosomal recessively and presented with progressive cerebellar ataxia. A-T phenotype has been described as progressive cerebellar ataxia, telangiectasia, growth deficiency, dysarthria, immunodeficiency, and recurrent respiratory tract infections. However, A-TLD exhibits cerebellar ataxia with a later onset and

a slower progression, lacks telangiectasia, and shows no sign of immunodeficiency (Matsumoto et al., 2011).

Mutations in the remaining two genes within the MRE11/RAD50/NBN complex provoke an autosomal recessive hereditary disorder with severe microcephaly. Biallelic germline mutation in the NBN results in Nijmegen breakage syndrome (NBS), whereas of the RAD50 leads to Nijmegen breakage syndrome-like disorder (NBS-LD). NBS is a cancer-predisposing disease, presents with microcephaly, mental and growth retardation, radiation sensitivity, and immunodeficiency. NBS-LD displays similar clinical presentations like NBS, though with no cancer propensity or immunodeficiency (Matsumoto et al., 2011).

Comparable to all hypomorphic mutations observed in humans, the total loss of any of MRN complex members is lethal in mice. Thus the mutated alleles need to retain some degree of function (Spehalski et al., 2017).

The presentation of MRE11A mutations with microcephaly in the displayed cases was clarified by three assumptions: an A-TLD unlike ATM-dependent neural apoptosis, or an NBN mediated microcephaly as a result of MRE11A effect on NBN and RAD50, or through the probability of other gene(s) involvement apart from MRE11A in microcephaly development (Matsumoto et al., 2011).

The NBS or A-TLD diseased mouse models showed that the MRN complex has a tumor suppressor role, as MRN loss predisposed them to malignancies. Nevertheless, mouse models with MRE11A nuclease deficient/MRN deficient B-lymphocytes were not prone to B-cell lymphoma, even with a highly B-cell lymphoma predisposing genetic background. Paradoxically, lack of MRE11A suppressed B-cell lymphomagenesis. This means the MRN complex may not be regarded as a tumor suppressor. On the contrary, cancer progression necessitates the specific DNA nuclease activity of the MRN complex (Spehalski et al., 2017).

In addition to its known tumor suppression effect (Lage et al., 2008), the oncogenic activity of MRE11A has also been studied (Petroni et al., 2018). MRE11A is considered as an ovarian cancer-predisposing gene (W. Li et al., 2019) and an intermediate-risk breast cancer susceptibility gene (Damiola et al., 2014).

MUTS homolog 3 (MSH3) gene (Tab. 4) is one of the DNA mismatch repair (MMR) genes (Edelmann et al., 2000). The MMR pathway is involved in base and indel mispair correction, induced by replication inaccuracies. The mispaired bases are identified by two heterodimers: MutSa consists of MS2-MSH6 for single nucleotide and small insertion/deletion (indel)

mismatches, and MutSb, which consists of MSH2-MSH3 for large base-indel loops. Both exhibit some degree of imbrication regarding their mispair-recognition specificities. The mutator phenotype driven from MMR deficiency is reflected as MSI in tumor DNAs, in which mono-, di-, tri-, and tetranucleotide repeats containing loci might be influenced (Adam et al., 2016).

In colorectal adenomatous polyposis, most of the cases (~30%) are related to germline dominant mutations in the APC gene. Moreover, some cases of colorectal adenomatous polyposis, which are very indicative of having genetic backgrounds, do not demonstrate any germline mutation in APC or other FAP-related novel subtype genes like MUTYH, NTHL1, POLE, and POLD1. Further, there are overlapping features between colorectal polyposis and biallelic MMR constitutional deficiency phenotype (Adam et al., 2016).

Many data resources have proved the significance of MSH3 deficiency in tumorigenesis. However, MSH3 mutations have not been related to Lynch-like phenotypes, like other MMR genes (Adam et al., 2016).

Adam et al. (2016) has uncovered biallelic mutations in the MSH3 gene in two adenomatous polyposis patients lacking germline mutations in known adenomatous polyposis-causing genes. This associates MSH3 deficiency with a high risk of adenomatous polyposis development.

MSH3 mutation results in MSI in dinucleotide repeats containing loci due to loss of MutSb as well as MSI in selected tetranucleotide repeats containing loci; this genetic pattern referred as EMAST (elevated microsatellite alterations at selected tetranucleotide repeats) (Adam et al., 2016).

Terradas et al. (2019) has concluded that despite of their clinical relevance, the biallelic mutations in MSH3 are extremely rare within European populations among unexplained polyposis cases.

It has been shown that MSH3 cooperates with MSH6 in tumor suppression (Edelmann et al., 2000). Certain MSH3 polymorphisms have been involved in colorectal carcinoma and prostatic cancer. MSH3 mutation has been declared to be highly penetrant in breast cancer development (Adam et al., 2016).

Human MutY homolog (MUTYH) gene (Tab. 4) is part of the BER pathway, which performs a significant contribution to the repair of mutations caused by reactive oxygen species. 8-oxo-7,8-dihydro-20 deoxyguanosine (8-oxoG), which is defined as the product of oxidative DNA

damages to guanine, freely mispairs with A residues, leading to G:C→T:A transversion mutation notably at GAA sequences. MUTYH enciphers a Glycosylase, which participates in removing the oxidized base from 8-oxoG:C base pairs in damaged DNA, and its lacking correlates to an increased rate of G>T transversions following DNA oxidative damage. Colorectal tumorigenesis could point to the elevated concentration of oxidative damages in MUTYH deficient colonic epithelium (Baglioni et al., 2005)

MUTYH-associated polyposis (MAP) was first described in 2002. It is predisposed by biallelic germline mutations in the MUTYH gene, inherited autosomal recessively, and characterized by formation of wildly variable precancerous colorectal polyps, usually of attenuated type, which may also be accompanied by serrated lesions. This has been correlated to the intersection of MAP with classical FAP. About half of MAP cases have colorectal cancer by the time of presentation at an average age of 48 years. Furthermore, gastric involvement and extra-intestinal demonstration, especially cutaneous presentation and further blended manifestations are not rare. MSI has also been found in MAP, and its presence should not exclude MAP diagnosis (Buecher et al., 2012).

The deleterious alterations in MUTYH are predominant between approximately 164 known various variants in this gene. The genotype-phenotype association has also been noticed (Buecher et al., 2012).

Regarding the pilomatricomas in the displayed case, G>T transversion mutation in the main pilomatricoma-causing gene CTNNB1 has been identified in some cases. This points to the BER pathway collapse. Besides, both colon cancer and pilomatricomas share the same Wnt-signaling pathway in tumorigenesis, and this could explain the presence of both tumors in the mentioned case (Baglioni et al., 2005).

MUTYH acts as a TSG. Its heterozygous mutation causes glioma, medulloblastoma, osteosarcoma, B-lineage acute lymphoblastic leukemia, and Ewing sarcoma (Kline et al., 2016).

Nibrin (NBN) gene (Tab. 4) is a component of the MRE11A/RAD50/NBN trimeric protein complex and participates in genome stability maintenance by assisting in DNA DSB repair, cell cycle controlling, HR, and telomere preservation (Maurer et al., 2010).

Biallelic germline mutation in the NBN gene is responsible for the classical autosomal recessive Nijmegen breakage syndrome (NBS). This DNA repair disorder presents with early childhood malignancies, mostly hematological, immunodeficiency, and typical dysmorphic features {bird-like face, microcephaly, microgenia (Walsh et al., 2017), syndactyly,

clinodactyly, and polydactyly}, dermatological manifestations, to some extent CNS malformation, hypoplastic kidney, anal atresia, gonadal failure, and an isolated case with juvenile idiopathic arthritis (Pasic et al., 2013). There are overlapping findings in NBS cases with A-T cases regarding similar laboratory assessments, immunodeficiency, increased ionizing radiation sensitivity, chromosome 7 and 14 structural aberrations (Walsh et al., 2017), skin demonstrations like CAL lesions and telangiectasia (Pasic et al., 2013). This can be interpreted through the close interaction between NBN and ATM gene during DNA DSBs induced by ionizing irradiation, in the view of the fact that MRE11/RAD50/NBN protein complex is requisite for ATM monomerization and autophosphorylation after DNA DSB damage (Chrzanowska et al., 2012).

Approximately 90% of NBS patients carry the homozygous Slavic founder mutation 657del5 in exon 6 (Chrzanowska et al., 2012; Maleva Kostovska et al., 2015; Pasic et al., 2013), the heterozygous frequency of this variant is estimated to be 0.5%-1% for Ukraine, Poland, Sorbs in Germany, Bulgaria, and for Czech Republic/Slovakia (Seemanova et al., 2016).

The displayed case showed Juvenile idiopathic arthritis-like chronic polyarthritis analogous to rheumatoid arthritis, which is rarely observed in the primary immune deficiency disorders. This leads to the conclusion that autoimmune features can also be expected in NBS patients (Pasic et al., 2013).

NBN is a TSG (J.H. Kim et al., 2019), and mutated in breast cancer, melanoma, ovarian cancer, sarcoma, lung cancer, bladder carcinoma, leukemia, basal cell carcinoma, colorectal carcinoma, medulloblastoma, head and neck carcinoma (Berardinelli, Masi and Antoccia, 2013).

NTH like DNA glycosylase 1 (NTHL1) gene (Tab. 4) is another gene in the BER pathway (Groves, Gleeson and Spigelman, 2019). NTHL1 gene codifies a DNA glycosylase protein, which excises the N-glycosidic bond of mispaired or damaged nucleotide, and catalyzes the BER process (Shinmura et al., 2019).

Adenomatous polyposis syndrome contributes to 2% of colorectal cancer (CRC) cases. Lately, in trials to uncover other genes contributing to unexplained adenomatous polyposis cases, which lack mutations in the known genes, NTHL1 biallelic mutations were detected. NTHL1-associated syndrome manifested by multiple adenomatous polyps (range 8-50) and display a high risk for CRC development, and developing other additional malignancies such as endometrial, breast and bladder cancer, meningiomas, basal cell carcinomas (Fostira et al., 2018), and head and neck squamous cell carcinomas (Belhadj et al., 2019).

Regarding the number of polyps and the site at diagnosis, NTHL1-associated polyposis is parallel to APC- and MUTYH-associated polyposis. However, a more complex clinical presentation might be linked to NTHL1-associated polyposis (Fostira et al., 2018).

From all 33 patients with biallelic NTHL1 mutation been reported to have NTHL1-associated adenomatous polyposis to date (Fostira et al., 2018; Groves, Gleeson and Spigelman, 2019; Grolleman et al., 2018), 21 patients harbored homozygous (c.268C>T) variant, seven patients had compound heterozygous variants of (c.268C>T) in combination with (c.709+1G>A), (c.859C>T), (c.806G>A), (c.733dup), (c.235_236insG), and (c.390>A) variants, four patients carried homozygous (c.545G>A) variant, and one patient had compound heterozygous (c.806G>A/c.859C>T) variants.

Terradas et al. (2019) had contributed the prevalence of NTHL1 biallelic mutations among unexplained adenomatous polyposis cases to ~2% within European populations.

NTHL1 acts as a TSG (Limpose et al., 2018). The correlation of heterozygous NTHL1 mutation with the risk of colorectal cancer is not clear and can be better estimated by identifying further NTHL1 mutation carriers (Valle et al., 2019). However, germline heterozygous NTHL1 mutation has been reported to cause breast cancer (Campbell et al., 2018).

Paired like homeobox 2B (PHOX2B) gene (Tab. 4) is a highly conserved transcription factor of the paired-type homeodomain and contained in a complex plexus of transcription factors. Its expression era includes sympathetic, parasympathetic and enteric ganglia of the developing peripheral nervous system (van Limpt et al., 2005).

PHOX2B has the same amino acid combination of the homeobox domain as its homolog, PHOX2A, though in the C- and N-terminal parts of the protein shows a different constitution. Both could initiate the transcription of one another, and both could individually activate Dopamine Beta Hydroxylase (DBH) gene transcription, a gene in the noradrenalin synthesis passage (van Limpt et al., 2005).

PHOX2B is involved in the development of the peripheral nervous system and related to the TrkA (the high-affinity receptor for nerve growth factor) signaling route, the (nor)adrenalin synthesis passage, and the Delta-Notch pathway. The latter makes a significant contribution to the embryonic development and concerned with the sympathetic nervous system differentiation (van Limpt et al., 2005).

Heterozygous germline PHOX2B mutation causes congenital central hypoventilation syndrome (CCHS), a rare and life-threatening disease by virtue of sympathetic nervous

system-mediated respiratory direction deficiency. The disease could be accompanied by other afflictions of neural crest-derived tissues, such as neuroblastoma or Hirschsprung disease (Raabe et al., 2007). The underlying pathomechanism is brainstem hypoxia and diminished hypercapnia sensitivity, resulting in hypoventilation in non-REM sleep or even during awakeness. CCHS patients usually require ventilation support because of carbon dioxide retention (Szymońska et al., 2015).

Familial CCHS is transmitted as an autosomal dominant disease. The most common found mutations are polyalanine expansion (+5 to +13 alanines), frameshift, and missense mutations in the PHOX2B gene. Polyalanine expansion is not associated with the tumors of the sympathetic nervous system. Polyalanine range of {-5, -7, -13, +1, and (+2 in three Japanese individuals)} have been detected in control population (Trochet et al., 2008). The number of polyalanine repeats (genotypes 20/24-20/33) determines the severity of hypoventilation, the overall phenotype, and occurrence of autonomic extra-respiratory manifestations. The most severe phenotype like continuous hypoventilation, Hirschsprung disease, neuroblastoma is associated with non polyalanine repeat mutations, which occur mostly de novo and are novel mutations (Sivan et al., 2019).

Homopolymeric tracts are primary derivations of phenotypic variation. In about 500 human proteins, mostly among transcriptional factors, variable length from 5-20 repeats of polyalanine has been anticipated, which are resulted from DNA loop formation during meiosis and mitosis and/or unbalanced allelic HR, which lead to alanine compression and expansion. Disease induction mechanism of the alanine expansion could subsume a dominant-negative effect, a pathogenic GOF, or a LOF (Trochet et al., 2008).

Trochet et al. (2008) reported a homozygous germline PHOX2B mutation {c.741_752dup12, (p.A247_A250dup)} of expanded alanine type in a patient with CCHS. The +4 alanine expansion acted as a recessive allele and did not reach the dominant phenotypic threshold (+5 alanine is dominant with incomplete penetrance, +6 alanine is fully dominant) for CCHS manifestation, considering the heterozygous states of the proband's healthy parents.

Sivan et al. (2019) reported a male infant with CCHS, who had compound heterozygous mutations in the PHOX2 {polyalanine repeat expansion (24 alanine repeats) and a c.785G-T (p.gly262val)}. All family members, who were carriers, were phenotypically normal. The author concluded that neither variant alone was sufficient to cause the disease in the family members, thus the mutations went unrecognized despite their dominant inheritance. The author highlighted the importance of PHOX2B testing in parents of all CCHS probands to

identify mosaicism in a parent, confirm allele pathogenicity, determine inheritance, and provide information for future pregnancy planning.

For PHOX2B, a role in differentiation promotion and another one in differentiation prevention have been advocated. Similarly, a bi-directional role of PHOX2B in cancer has been discussed, as a TSG and as an OCG (van Limpt et al., 2005).

PHOX2B heterozygous mutation has been identified in sporadic and hereditary neuroblastoma cases. Neuroblastoma (congenital or inherited) is an embryonal tumor that manifests in early pediatric age, with the possibility of multiple primary tumors. Its development is referred to mutations in genes that manage normal neural crest cell lineage specification and cell maturation (Raabe et al., 2007).

DNA polymerase epsilon, catalytic subunit (POLE) gene (Tab. 4) codifies the catalytic subunit of leading-strand DNA Pol Ɛ (POLE1) (Logan et al., 2018). DNA replication is achieved by the interaction of polymerases α, δ, and Ɛ. POLα–primase complex initiates DNA replication and synthesizes short, primed templates, followed by binding of POLƐ and POLδ to primed templates to replicate the leading and lagging strands, respectively (Pachlopnik Schmid et al., 2012).

LOF mutation in DNA polymerases might result in early embryonal or fetal lethality, whereas partial LOF mutation is associated with either multisystem, organ-specific, or cell lineage-specific developmental defects or the early exhaustion of continuously replicating cell lineages (Pachlopnik Schmid et al., 2012).

Pachlopnik Schmid et al. (2012) presented the phenotype of biallelic mutation in the POLE1 gene (polymerase Ɛ 1) in 11 patients with mild facial dysmorphism, immunodeficiency, livedo, and short stature and referred it as "FILS syndrome." FILS syndrome did not predispose to malignancies. Further, the FILS phenotype overlaps with Bloom disease but without sister chromatid exchange defects.

In the displayed mutations, the WT POLE transcript in T-lymphoblast was reduced up to 90% compared with controls, while the second transcript was affected by alternative splicing in the conserved region of intron 34, this led to profound POLE1 protein expression reduction. The mutation resulted in proliferation and G1- to S-phase cell cycle progression impairment in patients' T-lymphocytes, B-lymphocytes, chondrocytes, and osteoblasts. This highlights the requirement of POLE for cell proliferation and early phase of cell cycle progression (Pachlopnik Schmid et al., 2012).

Apart from FILS syndrome, another clinical presentation has also been linked to the biallelic mutation of POLE, which is IMAGe syndrome (Logan et al., 2018).
Microcephalic primordial dwarfism includes a group of prenatal-onset severe growth disturbances and manifests as IUGR, microcephaly, and short stature. IMAGe syndrome is the abbreviation of Intrauterine growth restriction, Metaphyseal dysplasia, Adrenal hypoplasia congenita, and Genitourinary anomalies in males. It is an autosomal dominant disease and caused by heterozygous GOF mutation in the CDKN1C gene (Logan et al., 2018).

Logan et al. (2018) identified biallelic mutations of the POLE gene as an autosomal-recessive cause of the IMAGe syndrome in 15 individuals, as a result of DNA replication deficiency. The patients presented with phenotypes closely resembled IMAGe syndrome, with distinctive facial manifestations and immunodeficiency. The overall growth failure and the immunodeficiency in the patients had been related to replication stress and p53-mediated cell death.
The transcript from c.1686+32C>G variant, which was shared by all patients, was non-functional given its occurrence at the start of the polymerase catalytic domain, together with LOF mutation on the second allele leads to significant declining in POLE1 protein (Logan et al., 2018).
POLE is a TSG (Smith et al., 2013). However, lack of the second hits or other inactivating mutations in the majority of tumors with POLE mutations points to the fact that it may not act as a classical TSG. Contrarily, mouse models showed that only homozygous POLE mutations resulted in increased risk for tumor formations (Heitzer and Tomlinson, 2014).
However, mutations in the POLE exonuclease domain are responsible for 1%-2% of sporadic colorectal carcinoma and 7%-12% of endometrial cancers, and they also predispose to brain, breast, ovary, pancreas, and stomach tumors. The tumors are of hypermutated phenotype and microsatellite-stable (Lorca and Garre, 2019). POLE1 deficiency may increase the risk of lymphoma (Logan et al., 2018).

RAD50 double strand break repair protein (RAD50) gene (Tab. 4) encodes a large coiled-coil ATP-binding cassette ATPase, which binds to MRE11A nuclease and together with checkpoint mediator, NBN establishes the highly conserved MRN complex (Tommiska et al., 2006) (See MRE11A).
As mentioned earlier, biallelic hypomorphic germline mutation in the RAD50 gene results in NBS-LD. Based on the two reported NBS-LD cases, the clinical features of biallelic RAD50

mutation could be defined as NBS similar dysmorphic features, severe IUGR and persistent postnatal growth disturbance, congenital microcephaly, mild to borderline intellectual disability, and radioresistant DNA synthesis, yet normal sexual development and no immunodeficiency, or early neurodegeneration, or myelodysplasia. Unlike A-TLD patients, NBS-LD patients do not display severe neurological signs, and there is no sign of neurodegeneration, apart from a mild degree of learning difficulties (Ragamin et al., 2020).
In humans, the cancer predisposition of biallelic RAD50 mutation has not been studied yet due to the few numbers of reported biallelic RAD50 mutant cases (Damiola et al., 2014).
RAD50 is a TSG (Rupnik, Grenon and Lowndes, 2008). RAD50 acts as an intermediate-risk breast cancer susceptibility gene and has been hypothesized to act also as an intermediate-risk pancreatic cancer susceptibility gene (Damiola et al., 2014).

RecQ like helicase 4 (RECQL4) gene (Tab. 4) is a subunit in the highly conserved RECQ helicase family protein, which comprises of RECQL1, RECQL4, RECQL5, WRN and BLM homologs. All RecQ helicases, inclusive RECQL4, function in multiple biochemical steps, including DNA strand annealing, DNA binding, the classic 3' to 5' unwinding helicase, and DNA-stimulated ATPase activities. These activities are part of essential cellular processes in humans like DNA replication, DNA repair, and recombination, and transcription of RNA. Therefore, these activities play collectively an imperative role in maintaining genome integrity (Croteau et al., 2012).
Germline biallelic mutation in the RECQL4 gene evokes Rothmund-Thomson type II, RAPADILINO, and Baller-Gerold syndromes. These syndromes are explicit and affiliated at the same time, labeled with bone deformities (commonly radial ray defects) and growth retardation. All are uncommon and autosomal recessively inherited. A fully understandable mechanism to declare the ambiguity behind developing three different syndromes from biallelic germline mutation in the RECQL4 gene does not currently exist (Croteau et al., 2012).
Rothmund-Thomson syndrome type II (RTS) is referred as one of the premature aging and cancer-predisposing syndromes and featured characteristically by infantile dermatological rash, poikiloderma, growth retardation, alopecia, cataracts, skeletal deformities, an increased tendency for malignancy development, mostly osteosarcoma (Kellermayer et al., 2005), and chronic wounds. As early as six months of age, clinical findings could be apparent. As an autosomal recessive disease, familial clustering due to consanguinity has been demonstrated

(Moelleken, Jockenhöfer, and Dissemond, 2019). Both exonic and intronic RECQL4 gene mutations could induce the disease (Kellermayer et al., 2005).

The term type II is for those RTS cases with a proven molecular mutation in the RECQL4 gene, whereas RTS cases with no detectable RECQL4 gene mutation are termed type I (Croteau et al., 2012).

The second one, RAPADILINO syndrome, is an abbreviation for RAdial hypoplasia/aplasia, PAtellar hypoplasia/aplasia, cleft, or highly arched PAlate, DIarrhea and DIslocated joints, LIttle size and LImb malformation, and slender NOse and NOrmal intelligence, observed in the affected patients. A biallelic splice site mutation in the intron 7 of the RECQL4 gene is the most common disease-causing one (Kellermayer et al., 2005). It is of Finnish descent and on molecular level homozygous {c. 1390+2delT (p.Ala420-Ala463del)}, which produces a protein lacking ATPase and helicase activity, saving only the strand annealing activity (Croteau et al., 2012). Although overlapping between the two above mentioned syndromes has been reported regarding the collective clinical findings and malignancy predisposition, this syndrome is to be differentiated from RTS by a unique clinical feature which is lacking of poikiloderma. Despite that, the possibility of both syndromes been subtypes of a single disease has been discussed (Kellermayer et al., 2005).

Immunodeficiency in the displayed case of RAPADILINO syndrome in Tab. 4 and other reported cases points to the mandatory standardization of immunological screening in RAPADILINO patients. A plausible explanation for this association is to be investigated, however, it could only be partly proposed by thymic downsizing as a result of RECQL4 protein deficiency, which is normally highly expressed in the thymus (Vollebregt et al., 2015).

The third disease, Baller-Gerold syndrome, also embodies skeletal abnormalities (brachycephaly, prominent forehead, ocular proptosis, oligodactyly as a result of radial ray defect, radius aplasia/hypoplasia and/or thumb aplasia/hypoplasia) with similar features like RTS syndrome including poikiloderma and growth retardation (Cao et al., 2015). Cardiac involvement with ventricular and atrial septal defect, ostium secondum, and subaortic stenosis has also been documented (Gupta et al., 2011).

RECQL4 acts as a TSG, but in breast cancer, as an OCG (Arora et al., 2016). Further, RECQL4 is mutated in sporadic osteoblastoma, gastric, and prostatic cancer (Mo et al., 2016).

RAD50-interacting protein 1 (RINT1) gene (Tab. 4) is part of the tethering NRZ complex of Golgi to endoplasmic reticulum retrograde trafficking of vesicles, and functions in many facets of Golgi apparatus dynamics as well (Park et al., 2014).

Cousin et al. (2019) described biallelic germline mutations in RINT1 in 3 patients presented with unique skeletal abnormalities similar to lysosomal storage disorders, and fever-dependent recurrent episodes of acute liver failure (RALF) in infancy and childhood similar to NBAS deficiency. Recurrent RALF is characterized by repeated events of serious liver damage with the total restoration of hepatic function between the attacks. The skeletal phenotype of the RINT1-mutated patients overlapped with mucopolysaccharidosis and lysosomal storage diseases of dysostosis multiplex disorder.

The constant manifestations of the affected patients were infection/fever combined RALF presentation with disease onset at three years of age or younger, indeterminate findings of liver damage on biopsy, fully or partially restoration of hepatic function between the attacks, skeletal abnormalities including hypoplasia, discrepancy, and anterior beaking of vertebral bodies, femoral head epiphyses abnormalities with or without acetabular involvement (Cousin et al., 2019).

RINT1 is involved in cellular regulation after DNA damage, as truncation of the N-terminal of RINT1 results in an aberrant controlling of radiation-induced G2-M checkpoint. The retrograde vesicle transport from Golgi to endoplasmic reticulum is promoted by the interaction of RINT1 with neuroblastoma-amplified sequence (NBAS) and UVRAG gene. However, this transport is repressed by infection and reduced nutritional supply. The regulation of UVRAG by the mTOR pathway controls the autophagy process. Autophagy is an integral part of post-natal bone growth. Skeletal abnormalities similar to RINT1-mutant patients combined with liver diseases have been described to be associated with aberrant autophagy. Deregulation of autophagy induction or disrupted vesicle trafficking is behind the aberrant autophagy induced by RINT1 deficiency. The hepatic phenotype similarity observed in RINT1- and NBAS-mutated patients is linked to the interaction between RINT1 and NBAS. Further, it has been noticed that loss of cellular RINT1 or NBAS is associated with the collagen VII anterograde transport impairment. This could deliver an explanation for the development of the skeletal phenotypes in both RINT1- and NBAS-related disorders (Cousin et al., 2019).

NBAS and RINT1 are temperature sensitive genes. Biallelic mutations in NBAS have been reported to cause RALF. NBAS-induced RALF has been fever-dependent and overlaps with RALF of biallelic RINT1 mutation. In addition to fever, both present with early age (infancy or early childhood) first RALF episode, improvement with age, impaired mental condition and vomiting preceding the presentation, elevated AST and ALT level, hyperbilirubinemia, and severe coagulopathy. However, they show different liver biopsies, and in NBAS-

associated RALF, the liver function is quickly restored in some of the patients (Cousin et al., 2019).

In the displayed cases, the splice variant had induced nonsense-mediated decay of the transcript. The fibroblast showed reduced RINT1 protein, a defective flux of the autophagic process, and abnormal Golgi morphology. The missense and in-frame deletion variants are thought to be hypomorphic combined with a LOF splice variant, as the total loss of RINT1 in mice is lethal in the early embryonic phase (Cousin et al., 2019).

RINT1 maintains centrosome integrity and acts as a TSG (X. Lin et al., 2007). Its mutation induces breast cancer and cancers of the Lynch syndrome-like spectrum (Park et al., 2014).

SDHA - succinate dehydrogenase complex flavoprotein subunit A

SDHAF2 - succinate dehydrogenase complex assembly factor 2

SDHB - succinate dehydrogenase complex iron sulfur subunit B

SDHC - succinate dehydrogenase complex subunit C

SDHD - succinate dehydrogenase complex subunit D

(Tab. 4, Tab. 6 and Tab. 7)

These five Complexes operate in synergy to produce ATP through oxidation of NADH and FADH2, combined with the reduction of oxygen in the oxidative phosphorylation system. Coenzyme Q 10 (ubiquinone) and cytochrome C, which act as electron carriers, promote electron transfer through the Complexes. Electrons are handed over to Complex I via NADH, which in turn transfers it to Complex III over CoQ10. Complex II incur electrons through FADH2 and transfers it to Complex III over CoQ10 as well. Cytochrome C would then transport electrons to Complex IV, where the reaction with oxygen occurs. The resulted transmembrane proton gradient in the inner mitochondrial membrane is used by an ATPase (Complex V) for the conversion of ADP to ATP (Jain-Ghai et al., 2013).

The succinate dehydrogenase (SDH) protein (also Complex II) subsumes four nuclear-encoded subunits with a protein structure having a hydrophilic head striking out into the mitochondrial matrix, and a hydrophobic tail anchoring the protein to the mitochondrial inner membrane. The head domain, which acts as the catalytic core, involves the flavoprotein SDHA, which contains the binding site for succinate, and the iron-sulfur (Fe-S) containing protein SDHB that mediate electron transfer to ubiquinone. The membrane domain acts as an anchor unit that embraces the SDHC and SDHD subunits and contains a bound haeme component and a ubiquinone binding site. The SDHA subunit confines the cofactor FAD and the succinate binding site. The SDHB subunit encompasses three Fe-S clusters. The binding

of succinate to SDHA triggers a domain change, annexing it to FAD, where the succinate is oxidized to fumarate. This leads to the generation of free electrons, which are then forwarded to SDHB. The electrons are carried between the Fe-S clusters up to the 3Fe-4S cluster. At that point, they are routed to the ubiquinone molecule. The anchoring subunits (SDHC and SDHD) not only anchor the complex to the inner mitochondrial membrane but also provide a binding site for ubiquinone (bound to SDHD), which is then reduced to ubiquinol. Post-translational phosphorylation and acetylation of SDHA and site inhibition by binding of citric acid cycle intermediate adjust the catalytic activity of SDHs. The two newly described assembly factors of the SDH group are the SDHAF1 and SDHAF2 genes. SDHAF1 encodes a small soluble protein, which incorporates Fe-S residue into SDHB and is found in the mitochondrial matrix. The SDHAF2 (SDH5) gene, with its important role in Complex II formation, encodes a soluble mitochondrial protein responsible for the flavination (covalent insertion of FAD into SDHA subunit) of SDHA (Aldera and Govender, 2017; Courage et al., 2016).

Unlike other mitochondrial respiratory chain Complexes, the entire Complex II subunits are encoded by the nucleus. It is distinguished furthermore through its contribution to both the Krebs cycle and the respiratory chain cycle (electron transport chain). The rareness of Krebs cycle enzyme deficient cases is in agreement with the life incompatibility of its total germline deficiency, relying on the fact that the reported cases are of isolated SDH, isocitrate dehydrogenase and fumarate hydratase deficiencies, with fatal outcomes (Alston et al., 2012).

The four mentioned SDH subunits, in addition to the newly described assembly factors, are products of autosomal genes: SDHA, SDHB, SDHC, SDHD, SDHAF1, and SDHAF2. Biallelic germline mutation of most of them (majority by SDHA mutations) results in the autosomal recessively inherited isolated Complex II deficiency with various clinical manifestations like cardiomyopathy and leukodystrophy (Alston et al., 2015).
However, Courage et al. (2016) described two patients with Complex II deficiency due to a heterozygous SDHA mutation with dominant transmission.
Defects in any of the explained Complexes in the oxidative phosphorylation system or their electron carriers lead to defective ATP production, and this results in clinical findings that would be observed in high energy-demanding body systems, namely, muscle, heart, central nervous system, renal, eye, and hematological system (Jain-Ghai et al., 2013). This justifies the phenotypes of patients with mitochondrial enzyme deficiency, such as (cardio)myopathy,

leukoencephaly, optic atrophy, or Leigh syndrome. The latter defines a pathognomonic neurodegenerative pathology with focal, bilateral single or multiple lesions in basal ganglia, thalamus, cerebellum, and spinal cord of the central nervous system with early and progressive onset (Renkema et al., 2014).

Monoallelic mutations in the SDH genes and their subsequent loss of heterozygosity are identified in tumorigenesis as well (Alston et al., 2015). Mutations in SDH genes apart from their effect on OXPHOS also induce a stream of molecular events leading to abnormal stabilization of hypoxia-inducible factors (HIFs), allowing upgrading of cell proliferation, angiogenesis, and tumorigenesis (Renkema et al., 2014). All 5 SDH genes are TSGs (Alston et al., 2012), and their germline mutations predispose to paragangliomas (adrenal and extra-adrenal), gastrointestinal stromal tumor (GIST), renal cell carcinoma, medullary, and papillary thyroid carcinoma. Carney-Stratakis syndrome has been newly related to the mutation in SDHB, SDHC, and SDHD genes (Aldera and Govender, 2017).

Biallelic germline SDHAF2 has not been reported in humans. Mice with SDHAF2 knockout are not compatible with life and show lethality prior to organogenesis. The embryo exhibits decreased size, a rudimentary egg cylinder, failure of primitive streak formation, absence of primitive node and head folds, and gastrulation failure (Cheong et al., 2020).

Serine peptidase inhibitor, Kazal type 1 (SPINK1) gene (Tab. 4) codifies a pancreatitis secretory trypsin inhibitor, produced during inflammation by pancreatic acinar cells. Pancreatitis occurs as a result of premature trypsinogen activation induced by SPINK1 mutation.

Hereditary pancreatitis is described as chronic pancreatitis (CP) or recurrent acute pancreatitis with the onset of the disease before the age of 20, manifested by epigastric pain radiating to the back, steatorrhea secondary to malabsorption, and islet cell damage induced pancreatic diabetes. The patients have a 40% lifetime risk for pancreatic cancer development, which mandates screening (Patel et al., 2017).

The common causes of hereditary pancreatitis are mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR) (Patel et al., 2017), cationic trypsinogen (PRSS1) gene, and its natural intrapancreatic antagonist SPINK1 gene. PRSS1-associated CP is autosomal dominantly inherited and manifests typically with periodic attacks of acute or CP within the affected family (Kühn et al., 2005). It is contributed to 80% of CP cases (Patel et al., 2017). SPINK1-associated CP is considerably correlated with tropical, idiopathic, or

alcoholic CP in 50, 20, and 6% of cases, respectively (Kühn et al., 2005). SPINK1-associated CP is autosomal recessively inherited, and carriers are usually unaffected, with only ~1% of them who develop pancreatitis (Patel et al., 2017). The commonest mutation in SPINK1 regarded as a risk factor for CP is the N34S-mutation, which has 1-2% heterozygosis prevalence in the normal population (Kühn et al., 2005).

SPINK1 N34S-mutation is unlikely to be deleterious (Mehner and Radisky, 2019), hence represents a disease modifier in individuals, who have a genetic propensity to develop pancreatitis, like CFTR mutations carriers or by the existence of CP-inducing environmental factors (Patel et al., 2017).

Venet et al. (2017) had recently reported two severe cases of early manifesting biallelic SPINK1 total LOF mutation in infancy with a distinct phenotype of isolated exocrine pancreatic insufficiency, who presented with diffuse pancreatic lipomatosis.

SPINK1 acts as an OCG that provides the tumor cells the oncogenic characteristics of cell proliferation and cell invasion through interaction with multiple signal pathways, and it is a poor prognostic factor in breast, pancreas, prostate, colon, ovary, and bladder cancer (Soon et al., 2011).

Suppressor of Fused (SUFU) gene (Tab. 4) is the main negative regulator of the SHH pathway. It regulates GLI2 and GLI3 transcription effectors and prompts transcriptional repression through proteasomal-mediated proteolysis and formation of GLI3R and to a lesser extent, GLI2R repressors (De Mori et al., 2017).

Cell configuration and differentiation of the central nervous system (CNS) and the limbs are regulated by an important signal pathway during embryogenesis, known as the Sonic Hedgehog (SHH) pathway. SHH guides the specification of ventral fate, axonal direction, and cerebellar development in CNS. In the extremity formation process, like in CNS, SHH plays a similarly crucial role in chondrogenic progenitor cell survival and expansions, and specification of digit identities along the anterior-posterior axis. SHH signal pathway is closely dependant on organelles known as primary cilium, and hence, intact primary ciliary genes are essential for the proper function of the SHH signal pathway (De Mori et al., 2017).

SHH signaling impairment leads to congenital defects of the CNS, midline facial anomalies, and polydactyly, resulting in a spectrum of disorders known as ciliopathies such as oral-facial-digital syndromes, acrocallosal syndrome, and Joubert syndrome, which all share common manifestations (De Mori et al., 2017).

Joubert syndrome (JS) is caused by a biallelic mutation in the SUFU gene. It is associated with congenital brainstem and cerebellar vermis anomalies, ataxia, episodic hyperpnea, and developmental delay. The characteristic brain MRI finding is Molar Tooth Sign (MTS) resulting from cerebellar vermis hypoplasia, deepened interpeduncular fossa, and thickened and elongated superior cerebellar peduncles. JS is a rare heterogeneous autosomal recessive ciliopathy with many subtypes depending on the brain, limb, eye, liver or kidney involvement (S.F. Wang et al., 2018).

De Mori et al. (2017) described the first (and to our knowledge the only reported) four viable individuals with biallelic SUFU mutations. The patients had features of SHH signaling deregulation, like CNS malformation, facial dysmorphia, and limb developmental defects. This spectrum of recessive phenotypes is related to both SHH-associated disorders and ciliopathies. The described hypomorphic mutations resulted in truncated SUFU proteins, which were unstable, rapidly degradable, and showed impaired GLI3 binding with diminished SHH signal pathway repression activity, which in turn had led to expression level alteration in several SHH target genes.

SUFU is a TSG (Lage et al., 2008). Its monoallelic germline mutation results in Gorlin syndrome, a complex of multiple nevoid basal cell carcinoma and additional malignancies that occur at an early age. Gorlin syndrome is associated mostly with childhood medulloblastoma (Smith, 2015).

Telomerase reverse transcriptase (TERT) gene (Tab. 4) enciphers one element of the telomerase, the reverse transcriptase catalytic subunit that along with an RNA component, TERC, elongate telomeres. TERT is decisive for the telomerase activity (Heidenreich et al., 2014).

In contrast to the embryonic period in which telomerase is normally expressed, there is a restricted expression of telomerase subsequent to somatic cell differentiation. Deleterious biallelic germline TERT mutation is causative in telomeric disorders like dyskeratosis congenita and pulmonary fibrosis (Colebatch, Dobrovic and Cooper, 2019). (See ACD gene).

TERT is an OCG (Trybek et al., 2020). In about 90% of human cancers, there is a clear sign of telomerase up-regulation. Cellular transformation requires overexpression of TERT. TERT mutations have been found in many diverse malignancies including melanoma, glioma, squamous cell carcinoma, skin basal cell carcinoma, liver carcinoma, bladder carcinoma, thyroid carcinoma, ovarian carcinoma, endometrial carcinoma, osteosarcoma, fibrosarcoma,

liposarcoma, pleomorphic dermal sarcomas, medulloblastoma, neuroblastoma, dysembryoplastic neuroepithelial tumor, and others (Heidenreich et al., 2014).
Further, telomerase mutations in TERC and TERT genes have been correlated to an increased incidence of liver cirrhosis (Hartmann et al., 2011).

Von Hippel-Lindau tumor suppressor (VHL) gene (Tab. 4) is part of the cellular signaling pathway. It codifies pVHL protein, which displays a vital role in hypoxia pathway regulation by interaction with a transcriptional factor known as a hypoxia-inducible factor (HIF), which is a heterodimer with alpha and beta subunits with notorious effect on pro-tumorigenic molecules. Degradation of HIF has been proposed to be behind the tumor suppression impact of a normally functioning pVHL. The latter is a part of the VCB-CUL2 complex, which binds in a normoxic circumstance to HIF-α and resulting in its polyubiquitination and subsequent degradation. Reasonably, the absence of a normal pVHL function or hypoxic conditions leads to sustained expression of HIF-α and its stabilization, which in turn results in up-regulation of target factors such as platelet-derived growth factor (PDGF), erythropoietin, transforming growth factor-alpha (TGF-α) and vascular endothelial growth factor (VEGF). The latter are the driving forces for accelerated proliferation, angiogenesis, and tumorigenesis (Varshney et al., 2017).
Biallelic (homozygous and compound heterozygous) germline mutations in the VHL gene have been identified to be the underlying cause of the autosomal recessive congenital polycythemia with the most common mutation being homozygous c.598C<T (p.R200W94), a founder mutation in the Chuvash Autonomous Republic of the Russian Federation and endemic on the Italian island of Ischia. The genomic constellation of the 3′ region of VHL exon 3 (C-terminal domain) has been linked to erythropoiesis promotion (Gossage, Eisen, and Maher, 2014). However, polycythemia inducing mutations have been recognized in all three exons (Bento et al., 2013). In contrast to heterozygous Von Hippel-Lindau disease, patients with congenital polycythemia and obligate carriers of the mutations associated with congenital polycythemia are mostly not prone to tumor development, and Von Hippel-Lindau disease, unlike congenital polycythemia do not present with polycythemia except secondarily to development of paraneoplastic syndromes like pheochromocytoma (PCC), haemangioblastoma and clear cell renal cell carcinoma (Gossage, Eisen and Maher, 2014).
The two head opinions in trials to clarify the mechanism behind developing the above two different phenotypes by VHL mutation propose that polycythemia-associated VHL mutation induces a comparatively slight deficiency in oxygen sensing, not severe enough to up-regulate

all HIF target genes required for tumorigenesis promotion, the second one suggests the participation of diverse molecular pathways with different VHL targets (Gossage, Eisen and Maher, 2014).

Polycythemia points to an elevated number of circulating red blood cells. The primary form is due to an acquired or inherited defect in the hematopoietic progenitor cells and increased sensitivity to circulating cytokines. The secondary form is associated with normal progenitor cells but increased circulating cytokines, mostly Erythropoietin (EPO) (Pastore et al., 2003b).

There is a variety in the presentation of congenital polycythemia depending on the underlying mutations ranging from very mild diagnosed incidentally (Pastore et al., 2003a) to severe form with fatal pulmonary hypertension (Perrotta et al., 2020).

Chuvash polycythemia is complicated mostly with peripheral thrombosis, cerebrovascular events, and hemorrhagic crises contributing to increased mortality (Cario, 2004).

VHL is a TSG (Varshney et al., 2017). Its heterozygous germline mutation is inherited autosomal dominantly and implicated in the progressive and highly penetrant Von Hippel-Lindau disease, which manifests as multiple organ cyst formation and development of numerous tumors (benign and malignant) mostly in the retina and CNS (hemangioblastoma) affecting cerebellar, brainstem, nerve root, and spinal cord. Further, pheochromocytoma, neuroendocrine tumors, pancreatic lesion, endolymphatic sac tumors, clear cell renal carcinoma, and epididymal cystadenoma are among the common findings (Lonser et al., 2003).

Genes	TSG/ OCG/ Dual	Gen-location	OMIM-syndrome or disease name/mode of inheritance	Mutation/aberrant transcription	Biallelic loss/consanguinty or common ancestor	Phenotype in humans/ symptoms/ references	Prevalence in 100,000/no. of cases or families on OW/EBD/ individually calculated
ACD	**OCG**	**16q22.1**	Dyskeratosis congenita–like phenotype (DC)/ AD,AR	Index I: c.280C>T , (p.V94I) Index II: c.284T>A , (p.L95Q)	Homo./Cons	Identification of homozygous ACD variant by whole-exome sequencing in a series of genetically uncharacterized patients presented with DC or constitutional BMF from the DC registry. The index patient of family 1: a 38-year-old ♂ with thrombocytopenia, short stature, pulmonary abnormalities, and LSCD. His older sister is heterozygous for the variant, had short stature, pulmonary abnormalities, and LSCD but no hematopoietic defect. The index patient of family 2: a 12-year-old ♂ presented with leukoplakia and subsequently developed BMF and immunodeficiency. His older brother had died of aplastic anemia. No mutation in BMF-causing genes was identified in these 2 cases. Telomere length measurement by MMQ-PCR revealed short telomeres in the index 1, just below the tenth centile compared with his heterozygous sister and controls. Index 2 had very short telomeres, below the first centile measured by MMQ-PCR and a flow fluorescence in situ hybridization method. PC, had also short telomeres but were asymptomatic (Tummala et al., 2018).	0.1 P in Europe [1]
APC	**TSG**	**5q22.2**	Cenani–Lenz syndrome/ AR	c.423-5_423 3delAAT upstream of exon 5, (p.Arg141Serfs*8)	Homo./Cons	Four limbs syndactaly (including approximation of metacarpals/metatarsals and bony fusion of the phalanges, but no radio-ulnar synostosis), scoliosis, facial dysmorphism (broad forehead, prominent upper incisors, hypertelorism, broad forehead, and depressed nasal bridge). No polyps (Patel et al., 2015).	4 cases (3 siblings,1st cousin)
ATM	**TSG**	**11q22.3**	Ataxia-telangiectasia/ AR	1346G>C , (p.Gly449Ala) in exon 11. ♂ 610G>T , (p.Gly204Stop) in exon 6 + 6679C>T, (p.Arg2227Cys) in exon 47. ♀	Homo./Cons Comp.Hete./ Cons.	15-year-old unrelated ♂ & ♀ with ocular telangiectasias, progressive cerebellar ataxia, cerebellar atrophy, severe disability, elevated AFP level, IgA deficiency, T-cell defect, chromosome 7 and 14 rearrangements, ♀ had relatively milder manifestation (Jiang et al., 2006).	0.49 P in Europe
BLM	**TSG**	**15q26.1**	Bloom syndrome/ AR	Paternal c.2603C>T in exon 13 (alters	Comp.Hete/- -	A 12-year-old Chinese ♀ was apparently healthy until 3 months of age when her parents noticed an erythematous eruption with blisters on the face. Exacerbation	300 Cases

				proline residue with leucine residue at 868) + maternal c.3961G>A in exon 21 (alters valine residue with isoleucine residue at 1321)		after exposure to sunlight. Gradually, progressive extending of the skin lesions to the forehead, nose, and ears, with oozing, crusting, atrophy, and telangiectases development on the face despite treatment (Tx). In the last 3 years, no blisters on the patient's face because of her efforts to avoid sun exposure. On physical examination: short stature (Wt 26 kg, Ht 122 cm), telangiectatic erythema and slight scaling on the face (simulated lupus erythematosus), additionally, alopecia areata, eyebrow hair loss, flat nose, reticular pigmentation on the forehead and trunk, finger swelling, short and sharpened distal phalanges, wide fingernails, less constant dolichocephaly. No microcephaly. Normal intelligence. No Hx of recurrent infection (Jian-Bing et al., 2016).	
BRCA2	**TSG**	**13q13.1**	WILMS2 tumor without typical FA features	Paternal c.886delGT , (p.V220fsX233) in exon 8 + maternal c.5873C→A , (p.S1882X) in exon 11	Comp.Hete./ non-Cons.	The elder ♂ sibling with Wilms tumor (WT) detected during cryptorchidism correction at 2 years of age. On physical examination: hypo- and hyperpigmented skin areas, a few CAL spots, Wt, Ht, and Hc <3rd SD. At 3.5 years of age, a stage III WT was surgically removed, received radiotherapy, chemotherapy. Seizures with 9 years, two intracerebral lesions (glioblastoma multiforme). Died 13 months later. Second ♂, with three CAL spots, many small depigmented and hyperpigmented spots. At 7 months of age, a stage 1 WT was surgically removed, received chemotherapy. On brain MRI screening at 5 years of age, a cerebellar lesion (grade IV medulloblastoma), received radiotherapy. At the age of 10 years, detection of spontaneous breakage of chromosomes and development of pre B-cell acute lymphoblastic leukemia, received chemotherapy, cerebral hemorrhage due to asparaginase. Died at 12 years of age from diffuse relapse of the medulloblastoma. No Hx of Ca in family. After the death of the children, the mother and aunt parental site diagnosed with breast Ca. PC (Reid, 2005).	--
CASR	**Dual**	**3q13.33-q21.1**	Neonatal severe hyperparathyroidism/ AR	Homozygous c.222-226delGATAT , (p.M74Ifs*24) (if expressed) + homozygous c.740C>T , (p.S247F)	Homo./Cons	A ♀ newborn with BWt (50th SD) born by spontaneous vaginal delivery at term. The neonate required ventilatory support for RD on day 2 of life. Admission to NICU because of pneumonia and hypercalcemia on day 23. At presentation, Wt (10th SD), length (50th SD) and HC (50th SD). Normal blood pressure and heart rate. She had generalized hypotonia, coarse facial features, a bell-shaped chest and signs of RD. On lab. investigations: serum calcium, 4.75 mmol/l (normal: 2.10–2.62); phosphate, 0.83 mmol/l (1.55–2.64); PTH, 1096 pg/ml (9–52); alkaline phosphatase (ALP), 577 IU/L (neonate: 145–420); 25-hydroxyvitamin D, 88 nmol/L (>75); and urinary calcium/creatinine ratio, 0.5 mg/mg (<0.8). On X-rays: evidence of parathyroid bone disease, under mineralized skeleton, cyst-like structures at distal ends of both humeri along with destruction of distal clavicles,	100 cases [2]

						distorted barely visible scapulae and bell-shaped rib cage with patchy lytic destruction of upper ribs. Severe generalized bone demineralization and osteopenia with coarse trabeculation and subperiosteal resorption. Biochemical profiles for the father were consistent with FHH with serum calcium, 2.8 mmol/l; phosphate, 0.8 mmol/l (0.87–1.45); PTH, 36 pg/ml; ALP, 64 IU/L (adult: 50–270); and urinary calcium/creatinine ratio (mg/mg), 0.08. The mother had serum calcium, 2.42 mmol/l; phosphate, 1.09 mmol/l; PTH, 52 pg/ml; and urinary calcium/creatinine ratio (mg/mg), 0.01. PC. Maternal uncle and parental aunt were also carriers for frameshift deletion and missense variant (Atay et al., 2014).	
CDKN2A	**TSG**	**9p21.3**	(p16-Leiden): adenocarcinoma with unknown primary site	218-237del of exon 2 leading to frameshift beyond codon 66, introducing a stop codon 64 residues downstream	Homo./ common ancestor	54-year-old ♀ from an endogamous dutch family with no sign of FAMMM apart from the presence of three very mildly atypical nevi. No melanomas. Died of adenocarcinoma at the age of 55 years (Gruis et al., 1995).	2 patients from the same family [3]
			Atypical naevi with malignant melanoma			A 33-year-old ♂ patient with phototype II skin, had Hx of jaundice at 3 years of age. Diagnosed with G6PD deficiency. At the age of 5 years, appearance of several fast-growing papules on the buttocks and right arm (juvenile xanthogranuloma). At 15 years of age had a remarkable number of naevi spread all over the body, excision of two striking asymmetrical lesions from his back 1 year later, both diagnosed as melanoma in situ. 6 months later, lesion with melanoma in situ, superficial spreading melanoma and naevus with severe dysplasia excised on the forehead, back, and left shoulder, respectively. In 10 years, development of more than 200 atypical moles from the scalp to the feet, with different sizes, shapes, and pigmentation. The elder brother also had G6PD deficiency and was heterozygous carrier with several dysplastic lesions and Hx of 1 melanoma treated at 17. The father, with several dysplastic naevi, treated for 1 melanoma at the age of 43, no G6PD deficiency. The mother also carrier but without lesions, she was G6PD mutation carrier (Pavel et al., 2003).	
DIS3L2	**Dual**	**2q37.1**	Perlman syndrome/ AR	c.367-2A>G , (p.Val123Leufs*15) + c.1328T>A , (p.Met443Lys)	Comp.Hete./ non-Cons.	A ♀ infant, the first child of healthy Japanese parents, born after 39 GWs. Her BWt (+3.15 SD), length (3.3 SD), HC (+1.75 SD). On physical examination: a prominent forehead, broad depressed nasal bridge, low-set ears, everted V-shaped upper lip, hypoplastic thorax, abdominal distension, and muscle hypotonia. On abdominal U/S: mild bilateral enlargement of the kidneys and hydronephrosis, no other organomegaly. Requirement of glucose infusions for several days due to	30 cases

						mild hypoglycemia and nasogastric tube feeding due to poor sucking. Severe psychomotor and neurological DD from infancy (head control at 6 months of age, sitting alone without support at 20 months of age, and speaking at 24 months of age). Generalized myoclonic seizures and electroencephalogram abnormalities noted at 8 months of age. On MRI: mild cerebral atrophy. At the age of 4 years and 6 months, Wt 16.3 kg (0 SD), Ht (−1.3 SD), HC (+1.9 SD), developed severe scoliosis, was not able to walk alone, her speech was limited to a small number of words. At 6 years of age, developed a left renal tumor. Histopathological examination after resection showed stage III Wilms tumor with no dissemination. Treated with chemotherapy, as well as abdominal radiation therapy. Normal ♀ karyotype. PC (Soma et al., 2017).	
EPCAM	**OCG**	**2p21**	Congenital tufting enteropathy/ AR	Novel c.227 C>G , (p.Ser76X) a premature stop codon in exon 3	Homo./Cons	A 3-month-old ♀ with FTT and congenital chronic diarrhea. Severe watery diarrhea at the age of 10 days. On investigation: mild thrombocytosis and coagulopathy, low albumin, mildly decreased cholesterol levels, markedly decreased vitamin A & D. Cystic fibrosis and gastrointestinal inflammatory diseases were excluded. The patient remained total parenteral nutrition–dependent, her last follow up Wt was at the 3rd SD, Ht at 5th SD. PC (Thoeni et al., 2014).	0.5 BP in Europe
ERCC1	**TSG**	**19q13.32**	Cerebro-Oculo-Facio-Skeletal syndrome (COFS), with NER deficiency and severe developmental failure/ AR	C<T transition converted codon Gln158 into an amber translational stop signal + a C<G transversion (Phe231leucine)	Comp.Hete/ non-Cons.	The 1st Patient diagnosed with ERCC1 deficiency, born at 37 GWs. The pregnancy was complicated by IUGR. No karyotypic abnormality on amniocyte analysis. Patient's BWt, length, HC were <3rd percentile, microcephaly with premature closure of fontanels, bilateral microphthalmia, blepharophimosis, high nasal bridge, short filtrum, micrognathia, low-set, and posterior-rotated ears, arthrogryposis with rocker-bottom feet, flexion contractures of the hands and bilateral DDH. On x-rays: no evidence for spine abnormalities. On nuclear MRI: a simplified gyral pattern and cerebellar hypoplasia. Mild kidney hypoplasia with normal structure and function. Persistent FTT, tube feeding, and severe DD. No congenital heart defects. No genital abnormalities and retinopathy. Cause of death: RF due to bilateral pneumonia at 14 months. A postmortem study was not performed. +ve UV testing of DNA. PC (Jaspers et al., 2007).	20 cases [4]
FANCM	**TSG**	**14q21.2**	Spermatogenic failure/ AR	c.1946_1958del , (p.P648Lfs*16) in exon 11	Homo./Cons	The first FANCM deficiency-induced spermatogenesis impairment cases in humans, three infertile brothers in a Pakistani family, IV:I, IV:2, and IV:3 had at least two semen analyses, respectively. A single routine blood test was obtained from IV:1, whereas 2 tests were performed for IV:2 and IV:3 at 2-year intervals. Two of the affected brothers, IV:1 (married for 21 years) and IV:3 (single)	7 cases [5]

						diagnosed with mild and severe oligoasthenospermia, respectively. Both had largely normal plasma levels of testosterone and pituitary hormones. The third affected brother IV:2 (married for 9 years) was azoospermic and diagnosed with primary valvular heart disease in his teens, had two open-heart surgeries for artificial valve replacements, one at 17 years old and the second at 37 years old, and he died of an acute heart attack caused by thrombosis in the heart valves at 42 years old. The youngest brother IV:4 (single) died of primary valvular heart disease at 34 years of age before semen analysis could be performed, was heterozygous carrier of the variant. Increased ICL sensitivity in blood lymphocytes of patients IV:2 and IV:3 (IV:1 refused the test). No Hx of tumors, smoking or drinking. No sign of BMF. Normal 46, XY karyotype. PC (Yin et al., 2018).	
			Non-syndromic primary ovarian insufficiency (POI)/ AR	c.5101C>T , (p.Gln1701Ter) in exon 20	Homo./Cons	The first Mendelian phenotype due to a biallelic FANCM mutation, two sisters with POI, normal pilosity, breast and external genitalia, normal blood counts and liver balance, and normal high-resolution karyotype and FMR1 gene. No abnormal skin pigmentation or skeletal deformities. Proband had menarche at 12 years of age, with irregular cycles (20–60 days). Hormonal contraception was started at the age of 16 years for menorrhagia and stopped four years later, after which menstrual cycles became highly irregular (21–140 days). At 24 years, had hot flushes for about one year and spaniomenorrhea. Blood hormonal assays and ultrasonographic studies of the ovaries are reported in the study. High FSH level (41 IU/l) and low AMH level. At the age of 26 years, hormonal stimulation was attempted with no response. Soon after, FSH increased to 120 IU/l, hormonal replacement was initiated. Her sister had menarche at 12 years of age, with regular menses (23 days). Hot flushes started at the age of 20 years. At age of 22 years, she consulted for hot flushes and spaniomenorrhea, had elevated FSH (16 IU/l) and low E2 levels. Elevated prolactin and a suspected 3 mm adenoma on brain MRI indicated Tx with Parlodel. FSH remained elevated and AMH low. At the age of 23, hormonal stimulation was initiated with poor results. However, about 6 months later, she became spontaneously pregnant and gave birth to a healthy child. Both showed increased ICL sensitivity in blood lymphocytes. No Hx of Ca in the family. Parents and 20 years old brother were carriers and were reported as healthy. Mother with regular menses at 47 years (Fouquet et al., 2017).	2 cases [6]
FH	**TSG**	**1q43**	Fumarase deficiency (fumaric	c.844G>C , (p.Gly282Arg) +	Comp.Hete./ non-Cons.	First child in the family with dilated cerebral ventricles on antenatal ultrasound (U/S). Had Hx of jaundice, seizures at 3 months of age, hypotonia, visual inattentiveness, and DD. On examination: plagiocephalic, with alternating	40 cases

			aciduria)/ AR	c.1127A>C , (p.Gln376Pro)		divergent strabismus, a wide mouth with tented upper lip, and some facial coarsening. On MRI scan: a delay in myelination and evidence of poor white matter bulk. Urinary organic acid analysis by gas-chromatography mass spectrometry showed raised fumarate (4790 µmol/ mmol creatinine) with mildly raised succinate and 2-oxoglutarate levels. Functional enzyme analysis in fibroblasts showed a fumarate hydratase activity of 20% of the control level. Delayed developmental progress. Significant central visual impairment limited to the perception of light, episodes of status epilepticus, abnormal posturing, and dystonia. FFT, Wt <0.4th SD. She died at 4 years of age. PC. An U/S of the 30-year-old asymptomatic father showed a cystic lesion at the lower pole of the left kidney (M.M.Y. Chan et al., 2017).	
GPC3	**TSG**	**Xq26.2**	Simpson-Golabi-Behmel syndrome type1/ XLR	Exon 2–4 tandem duplication causes a frame shift from position 1,170 and a premature stop codon at position 1,194, resulting in change of 8 AA from residue 390 to 397, followed by truncation of the protein at codon 397	Hemizygous /non-Cons.	A ♂ born at 40 GWs age after a pregnancy complicated with polyhydramnios. At birth, patient presented with macrosomia, coarse facial features, macroglossia and midline groove in the tongue, hepatosplenomegaly, ostium secundum-type ASD, accessory hemiazygos vein, three pairs of nipples, and generalized hypotonia. No genital or skeletal anomalies. The mother gave previous Hx of abortion because of intrauterine Dx of cystic hygroma and multiple hepatic masses in a male fetus. At the age of 9 months, patient developed an epithelial hepatoblastoma and treated. Two months after Dx of the tumor in the index case, the mother gave birth to another male, genetic testing of the mother and the newborn exhibited the same mutation. Three years after, the index case had not developed any other tumor and his brother was also included in a Ca surveillance program, which included serial measurement of serum AFP, beta human chorionic gonadotropin, neuron-specific enolase concentrations, with abdominal U/S. The father, the three maternal uncles, the maternal aunt, and the maternal grandmother were -ve for the mutation (Mateos et al., 2013).	250 cases
LZTR1	**TSG**	**22q11.21**	Noonan syndrome (NS)/ AD,AR	c.2074T>C , (p.Phe692Leu) predicted to alter the exonic splicing enhancer (ESE) site.	Homo./--	A 4-year-old ♂ with short stature. Hx of unremarkable pregnancy and term delivery. BWt (+1.4 SD), length (–0.2 SD), and an Apgar score of 9/10. Diagnosed with mild pulmonary valve stenosis and Von Willebrand disease. Normal neonatal screening. Right testicle cryptorchidism was noted and orchidopexy followed at 2 years of life. Normal psychomotor development. On examination, at 4 years of age, Wt (–2.1 SD), Ht (–3.2 SD). Distinctive phenotype: hypertelorism, downward slanting palpebral fissures, a low posterior hairline, low-set ears, an ogival palate, and a thin upper lip. Normal 46,XY karyotype. His bone age was 12 months delayed. IGF-1 and IGFBP-3 were on the lower limit of the normal range (IGF-1: 72 ng/mL, RR 72–392; IGFBP-3: 2.36	--

						µg/dL, RR 1.99–4.90). Growth hormone (GH) peak after a clonidine stimulation test was 7.24 ng/ mL (RR >7 ng/mL) and it was 8.40 ng/mL after an insulin hypoglycemia stimulation test. No variants in other NS-causing genes on sanger sequencing. At the age of 13 years and 4 months, Wt (–2.1 SD), Ht (–3.1 SD) (target Ht: –1.46 SD), and had initiated Tanner stage II of puberty. Parents were healthy, non-Cons., have an elderly healthy child (Güemes et al., 2019).	
MET	**OCG**	**7q31**	Non-syndromic autosomal recessive deafness/ AR	c.948A>G , (p.Ile316Met)	Homo./Cons	A 7-year-old ♀ presented with total bilateral hearing loss revealed by the brain auditory-evoked potential test, which had been performed at the age of 3 years and 9 months. Cochlear implantation at 4 years of age. Temporal bone CT-Scan and MRI revealed no detectable abnormalities in the inner ear or in the cochleovestibular nerves. Absence of other symptoms or malformation suggesting syndromic deafness. Normal clinical investigations. Parents and the older brother were heterozygous carriers with normal hearing (Bousfiha et al., 2019).	10 cases [7]
MITF	**OCG**	**3p13**	COMMAD syndrome/ AR	Paternal c.952_954delAGA , (p.Arg318del) + maternal c.921G>C , (p.Lys307Asn)	Comp.Hete./ non-Cons.	A 5-year-old ♂ with colobomatous, microphthalmia and microcornea with pannus, dense bilateral cataracts, translucent irides, profound congenital sensorineural hearing loss, and lack of visible pigment in the hair, skin, and eyes. Microphthalmia first detected on prenatal U/S. HC (>3 SD) for age, consistent with macrocephaly, and Wt (-0.5 SD) and Ht 110.0 cm (0.0 SD). Facial dysmorphisms including frontal bossing, shallow orbits, preauricular pits, and posteriorly rotated ears. Skeletal features included a prominent frontal bone, diffuse expansion of the anterior ends of the ribs, and bilateral fifth-finger clinodactyly. A radiographic skeletal survey performed at 13 months of age showed osteopetrosis. On axial MRI of the brain: small eyes (~7–8 mm), optic nerves, and chiasm with mild prominence of ventricles, but no other structural abnormalities. He was delivered at term after an uneventful pregnancy. Both parents had congenital sensorineural hearing loss, blue irides, fair skin, and premature graying of the hair (both had WS2A) and were in their third or fourth decade. One male sibling was affected similarly to his parents, and one sister was unaffected (George et al., 2016).	2 cases [8]
			Waardenburg syndrome type 2A (WS2A)/ AD	Intronic c.33+5G>C , affects 5′ss sequence at the exon-1M boundary, reducing/ abolishing splicing	Homo./Cons parents were siblings	The first reported homozygous MITF mutation. A 6-month-old ♂ from Argentina with complete depigmentation of the skin except for some scattered pigmented macules (unlikely to be true CAL macules) in conjunction with congenital bilateral hearing loss, which led to deaf-mutism in later course. On medical examination: bilateral sapphire blue eyes (hypoisochromia iridis), total absence of hair pigmentation (hair, eyebrows, eyelashes), mild epicanthic folds, skin redness	0.37 BP in Europe [9]

				efficiency of the Melanocyte specific transcript variant		on face and occiput due to UV sensitivity. No significant change in the number, size, and position of pigmented macules since birth, but an increase in pigmentation was notable. Intensified pigmentation on hands and feet in otherwise depigmented background. +ve family Hx of generalized skin depigmentation. Clinical examination of the family revealed at least six further affected and yet undiagnosed individuals across three generations, presenting with different degrees of pigmentation anomalies and hearing impairment. Family members generally presented with dark hair color, dark irides, and medium skin tone. None of the family members reported unusual hair pigmentation or premature greying. The mother presented with bilateral brilliant blue eyes and congenital bilateral hearing loss. On dermatological evaluation: a large pigment anomaly on her upper abdomen. Three family members presented sectorial iris heterochromia and four individuals were affected by hearing loss (unilateral or bilateral). The index's father revealed neither obvious skin nor eye pigmentary anomalies, but only distinctive freckles in the face which we already observed to much greater extent for the mother and grandmother. The hearing test was not undertaken for the father. The index's sister showed no freckling yet. Affected family members meet major diagnostic criteria of WS2A as proposed by the Waardenburg Consortium, but none were previously diagnosed with WS (Rauschendorf et al., 2018).	
MRE11A	**TSG**	**11q21**	Ataxa-telangiectasia-like disorder (A-TLD)/ AR	Paternal c.727 T> C in exon 8 , (W243R) + maternal (g.24994 G>A) in intron 10 , a single nucleotide substitution in an intron near a splice donor site	Comp.Hete./ --	Two brothers with A-TLD had characteristic short stature, pointy nose, small jaw, atrophy of the lower legs, and equinus foot deformities. Both had cerebellar ataxia, slurred and explosive speech, and ocular apraxia, but no signs of dystonia or dyskinesia. Ataxic gait noted when they were 2 years old. The boys had progressive cerebellar ataxia with atrophy of the cerebellum and mental retardation. The degree of cerebellar ataxia and atrophy was more severe in the elder brother, who became a wheelchair user at 6 years of age. The patients started to speak at the age of 2 years. One brother's IQ score was 43, and the other's was 75. No Hx of serious infection or skin or conjunctival telangiectasia. The elder brother diagnosed with renal Fanconi syndrome. On renal biopsy: vacuolar degeneration of the renal tubules. In 2007, when they were 15 and 9 years old, stage 4 non-small-cell lung Ca (poorly differentiated lung adenocarcinoma with multiple bone metastases) was diagnosed in both boys. Lab. examination: elevation of serum CA125 levels (956.4U/ml and 1449.8U/ml, respectively) and polycythemia. Normal serum AFP and immunoglobulin levels. Cytogenetic analysis performed on PHA-stimulated peripheral blood revealed an increased number of chromosome aberrations, but no specific or particular chromosome abnormalities. Both of the patients received chemotherapy before	--

						the Dx was made. The elder brother died 11 months after the Dx of lung adenocarcinoma. The younger brother died 8 months after the Dx. Radiation-induced esophagitis was observed in autopsy samples. No ATM deficiency on Western blot analysis. No NBN gene mutation was detected. Parents and the eldest son (who had g.24994 G>A variant) were carriers and showed no sign of Ca. Non-Cons. Parents had Hx of DM and smoking. No family Hx of malignancy (Hartlerode, Regal and Ferguson, 2018; Uchisaka et al., 2009).	
MSH3	**TSG**	**5q14.1**	Colorectal adenomatous polyposis/ AR	Individual 1: c.1148delA , (p.Lys383Argfs*32) + c.3001-2A>C in intron 21	Comp.Hete./ --	During exome sequencing of DNA from 102 unrelated individuals with unexplained colorectal adenomatous polyposis with no mutation in APC and MUTYH genes, two unrelated patients revealed biallelic MSH3 mutations. Individual 1 is ♀, diagnosed with colorectal adenomatous polyposis at age of 36 years, underwent a preventive sigmoidectomy at age of 48 years and a right hemicolectomy at age of 53 years. Histology results of >40 polyps were tubular or tubulovillous adenomas with low to intermediate dysplasia, often accompanied by inflammatory infiltration. Three distal hyperplastic polyps also documented. In addition, she had Hx of proliferative disorders in other organs: thyroid adenoma at age of 35 years, a small polyp of the corpus uteri and uterine leiomyomas at age of 44 years, multiple small intraductal papillomas of (peripheral) mammary glands at age of 44 years, and multiple adenomatous polyps in the duodenum at age of 50 years. Exclusion of hypertrophy of the retinal pigment epithelium by ophthalmological examination at age of 50 years.	2 cases [10]
				Individual 2: c.2760delC , (p.Tyr921Metfs*36) + c.2319-1G>A in intron 16		Individual 2 is ♀, diagnosed at age of 32 years with colorectal tubular and tubulovillous adenomas with low-grade intraepithelial neoplasia. At age of 42 years, underwent proctocolectomy and excision of large duodenal adenomas. She had a striking past medical Hx: at age of 26 years, a grade II astrocytoma was diagnosed and surgically treated. At age of 27 years, underwent oophorectomy for the presence of ovarian cysts, including one dermoid cyst. Hysterectomy performed for a myoma at age of 34 years, and thyroidectomy performed for follicular adenomas at age of 42 years. At age of 43 years, showed a cutaneous fibrolipoma, and at age of 46 years, a flat epithelial atypia, multiple peripheral small intraductal papillomas, usual ductal hyperplasias, and cysts with apocrine metaplasia detected in the mammary glands. Both index persons had one affected sibling, their respective PC and had no reported Hx of malignant gastrointestinal disease. A sister of individual 1,	

						diagnosed with a rectal adenocarcinoma at age of 56 years and with a signet cell gastric carcinoma at age of 59 years. The available histology reports described multiple tubulovillous adenomas of the entire colon and proximal duodenum, with up to high-grade intraepithelial neoplasia, and two hyperplastic polyps of the transverse colon. Small bilateral renal cysts reported as a secondary finding. The brother of individual 2 diagnosed with colorectal polyps at age of 33 years and underwent colectomy at age of 37 years. On immunohistochemical staining: complete nuclear loss of MSH3 in normal colon mucosa of individual 1 and in adenomas of both index persons. On tumor tissue analysis of the diseased individuals: high MSI of di- and tetranucleotides (EMAST). No mutation is detected in FAP-related genes, EPCAM, or MMR genes (Adam et al., 2016).	
MUTYH	**TSG**	**1p34.1**	MUTYH-associated polyposis/ AR	c.1186-1187insGG, frameshift mutation with a premature stop codon at position 438 of the AA sequence	Homo./Cons	A ♂ patient diagnosed with low-grade rectal adenocarcinoma and two polyps of the ascending colon at the age of 32 years. Polyps were endoscopically resected. At the age of 10 years, removal of a pilomatricoma located on the left arm and a facial sweat gland adenoma. On colonoscopic examination of his sister, four polyps at the age of 29 years: two tubular adenomas in the caecum, one tubulovillous adenoma in the transverse colon, and a rectal polyp. She had Hx of pilomatricomas diagnosed at 4 years of age. Overall, eight lesions, located on the face, arms, and shoulder. A tubular adenoma and a hyperplastic polyp were detected in their 63-year-old father (Baglioni et al., 2005).	6.0 P in Europe [11]
NBN	**TSG**	**8q21.3**	Nijmegen breakage syndrome/ AR	Typical Slavic founder mutation: 5 base-pair deletion (657del5)	Homo./non-Cons.	A 12-year-old ♀ with Hx of IUGR and microcephaly (HC<3rd SD) suffered from recurrent lung infections since infancy. At 18 months of age, developed bacterial meningitis. At 8 years of age, severe varicella complicated with pneumonia and episode of hip pain diagnosed as transitory synovitis. On physical examination at 9 years of age: normal growth parameter apart from HC<3rd SD, typical facial features with prominent midface, large ears, hypertelorism, an upward slant of the palpebral fissures, hypopigmented spots on trunk and extremities, bilateral clinodactyly and syndactyly of the second and third toe. On chest examination: bilateral basilar crackles due to bronchiectasis. Lab. results confirmed immunodeficiency. On the karyotype of peripheral blood lymphocytes: typical chromosomal rearrangements involving chromosomes 7 and 14. At 10 years of age developed pain, morning stiffness, and bilateral swelling of her proximal interphalangeal, wrist, and knee joints. Affected joints were hot, swollen, and tender on passive or active motion. Elevated ESR, CRP, complement component C3, and C4 level. Knee joint puncture was –ve. Several relapses of arthritis over	1.0 BP worldwide

						months. At the age of 15 years developed T-cell lymphoblastic leukemia/lymphoma (TLBL/ALL). Parent asymptomatic (Pasic et al., 2013).	
NTHL1	**TSG**		Adenomatous polyposis syndrome/ AR	c.268C>T , (p.Gln90*)	Homo./--	Two, apparently unrelated ♂s, previously tested -ve for APC and MUTYH mutations. Both patients originated from the same village. Proband I presented with rectal bleeding and diagnosed endoscopically with approximately 150 colonic adenomas of the right colon, at the age of 49 years. Of the adenomas, approximately 100 were very small of average size of 1.5 mm, while approximately 50 were of average size of 1 cm, one serrated polyp with no dysplasia was also histologically confirmed. Polyps had features of low-grade dysplasia and their resection was performed in three subsequent endoscopies. Proband II was diagnosed with caecal Ca, followed by Ca at the site of anastomosis, at the age of 31 and 65 years, respectively. On abdominal CT-Scan: presence of multiple small intestinal polyps, located both in the duodenum and jejunum, which were further confirmed by upper gastrointestinal endoscopy and were characterized histologically, as adenomas with high-grade dysplasia. Proband's sister was diagnosed with colorectal Ca at the age of 59 years, but did not consent to genetic testing (Fostira et al., 2018).	33 cases [12]
PHOX2B	**Dual**	**4p13**	Congenital central hypoventilation syndrome (CCHS)/ AD	PARM with 24 alanines on one allele (genotype 20/24, PARM) + NPARM missense variant on the other allele (c.785G>T , p.Gly262Val) in exon 3	Comp.Hete./ --	A full-term ♂ infant, the firstborn child to Caucasian Ashkenazi Jewish parents developed soon after birth central apneas and bradypneas with hemoglobin desaturations to a nadir <75% and hypoventilation with paCO2 of 60 mmHg during sleep, necessitating assisted ventilatory support during sleep. No hypoventilation during awakeness except during bottle feedings, when he became hypoxemic (nadir saturation 75%) and hypercarbic (peak end tidal carbon dioxide level 60 mmHg). No identifiable causes for respiratory failure. Normal head MRI and diaphragm movement. –ve drug screening. After an ineffective trial of non-invasive ventilation, a tracheostomy was performed and assisted ventilation was provided during sleep and feeding. At the age of 3 years: proband required artificial ventilation during sleep and with an intercurrent illness, but breathed adequately with eating and on exertion. No suggestive symptoms of Hirschsprung disease or overt symptoms of ANSD (though not formally tested due to young age), and no neural crest tumors on chest radiography, abdominal and pelvic U/S. No arrhythmias on 72-hr Holter monitoring and no abnormality on pupillometry on close routine follow-up. Normal echocardiogram. Exogenous ventilatory challenge testing of peripheral and central chemoreceptors has not been performed. Family genetic investigation identified one of the two PHOX2B mutations in	2 cases [13]

						several members of the two families. In the father's family, the 20/24 genotype was found in the father, the paternal grandfather and 2 out of 5 of the father's siblings. In the mother's family, the NPARM variant was found in the mother, the maternal grandfather and 3 out of 9 of the mother's siblings. One brother was not tested because he died of SCID before the family screening and one sister who had BM transplantation for SCID was found to be -ve by skin fibroblast whole exome study. The proband's parents, their respective brothers and sisters and the grandfathers carrying the PHOX2B variants were all asymptomatic at the time of publication. The patient's mother underwent several surgical procedures under general anesthesia including repair of an inguinal hernia as an infant and gynecological procedures during recent years, and all were uneventful with rapid recovery. More recently, both parents underwent polysomnography and neither had documented apneas, hypoxemia, or hypercarbia. Normal medical investigations of the parents (Sivan et al., 2019).	
POLE	**TSG**	**12q24.33**	FILS syndrome	(g.G4444+3 A>G) at position 3 in intron 34, with two major transcripts: WT, and exon 34 deleted, which leads to a subsequent frameshift and a premature stop codon at position 1561 in the new protein.	Homo./Cons	11 members of a large French kindred displayed mild facial dysmorphism, immunodeficiency, livedo, and short stature. Three additional members displayed two or three of these four features. The patients had mild facial dysmorphism with malar hypoplasia, and a high forehead. Livedo on the cheeks, forearms, and/or legs was present in all but one patient and noticed since birth in numbers of them. No ulceration. Telangiectasia observed on the cheeks with increasing age. Term delivery of all the patients with normal BWt and length. Growth impairment was observed during early childhood and resulted in short stature in adulthood. The mean Ht of the unaffected siblings was around the 50^{th} SD. Normal GH production and response tested in three patients. Normal HC in all but one patient. Bone dysplasia and pain in the extremities with lacunar bone lesions, cortical thickening, and modeling defects at the long bone diaphyses found in the three patients. Striae in the metaphyses observed in 1 patient only. All but two of the patients suffered from immunodeficiency. Since their first year of life, patients had recurrent upper and lower respiratory tract infections, recurrent pulmonary infections resulting in two patients in bronchiectasis, and recurrent meningitis caused by Streptococcus pneumonia. 1 patient died of pulmonary infection at the age of 2 years. Immunological analysis of the patients: decreased IgM and IgG2 levels, reduced isohemagglutinin titers, and a predominant lack of antibodies to polysaccharide antigens. Patients had low memory (CD27+) B-cell counts, but equally affected proportion of switched B-cells (μ-δ-) and non-switched memory B-cells. The IgM, IgG, and IgA B-cell repertoires in blood lymphocytes performed in one patient showed a normal distribution of VH family usage.	15 cases [14]

						Normal B-cell proliferation and switch to IgE production upon stimulation with IL-4 and CD40 ligand in vitro. Several patients had low naive T-cell counts and decreased T-cell proliferation. T-cell immunoscope analysis in one patient showed a normally diversified TCR Vß repertoire. Allergies, autoimmunity, opportunistic infections, and malignancies not observed in any patients. Normal sister chromatid exchange. One affected individual has four children (no association of the syndrome with (male) infertility). PC and healthy (Pachlopnik Schmid et al., 2012).	
		IMAGe syndrome with immunodeficiency/ AR	c.1686+32C>G , (p.Asn563Valfs*16) + c.2091dupC , (p.Phe699Valfs*11) / c.62+1G>A essential splice site intron 1 / c.5940G>A , (p.Trp1980*) / c.4728+1G>T essential splice site intron 36 / c.3264_3275+13del essential splice site intron 26 / c.1A>T p.? / c.3019G>C , (p.Ala1007Pro) / c.5265delG , (Ile1756Serfs*5) / c.2049C>G , (p.Tyr683*) / c.6518_6519delCT, (p.Ser2173Phefs*1 30) / c.801+2T>C essential splice site intron 8	Comp.Hete./ --	In trials to identify other genes underlying microcephalic primordial dwarfism, whole-genome sequencing (WGS) of 48 individuals with microcephalic primordial dwarfism and targeted sequencing of POLE and interrogation of existing WES data in additional cases of primordial dwarfism was undertaken. Cases with IMAGe syndrome without an existing molecular Dx (-ve CDKN1C mutation) were drawn from other cohorts for investigation. 15 patients from 12 families with biallelic POLE were identified. Phenotypically, affected individuals had severe GR of prenatal onset. IUGR was present in all case subjects (BWt 3.0 ± 0.8 SD) with significant short stature evident postnatally (Ht 8.1 ± 2.4 SD). HC was also significantly reduced (OFC 5.4 ± 1.5 SD), but this was less severe, resulting in a relative macrocephaly. The affected case subjects had a common facial appearance with micrognathia, crowded dentition, long thin nose, short wide neck, and small, low-set and posteriorly rotated ears. 12 individuals had adrenal insufficiency and all affected males had genitourinary abnormalities including bilateral cryptorchidism and/or hypospadias, with the majority of case subjects fulfilling clinical criteria for IMAGe syndrome. Osteopenia and DDH were frequently observed. CAL patches were notably present in a third of individuals. One patient died at 22 months of HSV infection. One patient developed a T-cell lymphoma at the age of 11 and the other one developed Hodgkin's lymphoma at the age of 28 years (Logan et al., 2018).	15 cases [15]

RAD50	**TSG**	**5q31.1**	Nijmegen breakage syndrome-like disorder	c.2524G>A in exon 15, with 2 transcripts: (p.Met800Phefs*7) + (p.Val842Ala)	Homo./Cons	The index patient, a 15-year-old ♀, the first child of Turkish parents. The family Hx revealed that the paternal aunt, who was married to a fourth-degree relative, had a daughter diagnosed with Seckel syndrome, presented with GR. No medical record of this girl could be retrieved, however, pictures made available by the family showed overlapping facial features to the index patient. IUGR during pregnancy. The ♀ was born at 37 GWs with a BWt (−3.5 SD) and HC (−3.5 SD). At birth, dysmorphic features were noted. On physical examination at 10 months of age: a broad nose with depressed nasal bridge, hypertelorism, mild upslanting eyelids with epicanthus inversus, a small lower lip, micrognathia, low implanted and rotated ears, a short neck, wide-spaced nipples, bilateral clinodactyly of fingers and toes, bilateral transverse palmar crease, bilateral brachydactyly, a sandal gap, multiple CAL macules, and high pitched cry. Neonatal screening revealed hypothyroidism due to transient hypothyroxinemia as a result of dysmaturity. Normal female karyotype and no spontaneous chromosomal breakages. Normal metabolic and infectious screenings. During her first year of age: feeding difficulties, gastroesophageal reflux, low tolerance for oral intake, and persistent low growth parameter <3rd SD. Temporarily fed with gastrostomy tube. On X-rays of hands and feet at the age of 6 months and a complete skeletal survey at the age of 2 years: hypoplasia of the second and terminal phalanges of the fifth digit, mild valgus shape of both acetabula and normal proportion of long bones. Normal GH production and full endocrine screening. Normal total level of immunoglobulins and the subclasses screening on two occasions. After some improvement in her Wt/Ht ratio, but not in Ht (continued to follow the −6 SD), discontinuation of the tube feeding. On follow-up examinations showed delay in speech and motoric functions. At the age of 2 years, an auditory brainstem response test showed bilateral sensorineural hearing loss of 90 dB, received hearing aids. Normal neurological evaluation apart from high-pitched voice and nasal speech, slightly brisk reflexes of the lower extremities and a slightly unstable straight-line walk, were not observed at later examinations. On brain MRI at the age of 13 years: a narrow foramen magnum with mild herniation of the cerebellar tonsils. Normal EEG. Identification of Wolff–Parkinson–White anomaly without supraventricular tachycardia after complaints of fatigue. At the last examination at the age of 15 years, Ht (−5.8 SD) and HC (−3.9 SD). A prominent nose bridge with a long nose point, a sloping forehead, telecanthus, a short neck, and thoracic kyphosis were noted. Normal puberty and secondary sexual characteristic development. Her TIQ estimated to be 85. She lived with her parents, attended a special school for children with hearing loss. No decline of intellectual or motor functions, had good communication skills, with no severe or	2 cases [16]

						recurrent infections, or malignancies. The variant had induced radioresistant DNA synthesis after Gamma radiation, similar to A-T cases (Ragamin et al., 2020).	
RECQL4	**Dual**	**8q24.3**	Rothmund-Thomson syndrome type II + all features of RAPADILINO/ AR	g.2886delT causes a frameshift, and early stop codon, 97 codon downstream + g.5435C→T transversion , (R1021W)	Comp.Hete./ --	A ♂ patient was born at 37 GWs, 2nd pregnancy of a mother with multiple sclerosis. Body measures were all at 3rd SD, bilateral radial aplasia, absence of the thumbs, hypospadias, bilateral inguinal hernia, prominent anterior fontanelle, slender nose, and micrognathia. Persistent FFT with loose voluminous stools. At age 2 years developed a progressive light-sensitive skin rash. Bilateral absence of the patellae, subluxation of the femoral heads, prominent osteoporosis. On abdominal U/S: localization of the spleen at the upper pole of the left kidney. Lactose intolerance and fat malabsorption. The patient's diarrhea resolved by the age of 4 years. The subsequent dermatological evaluation revealed poikiloderma. At 9 years of age, a mildly hoarse voice, sparse eyebrows and hair with areas of alopecia, no learning difficulties, with persistent GR. Prominent, diffuse dermatosis on all parts of the body, with variegated cutaneous pigmentation, atrophy, and telangiectasia. Extreme sun exposure sensitivity. PC (Kellermayer et al., 2005).	200 cases
			RAPADILINO syndrome(RS)/ AR	Mutation type not mentioned.	--/--	2-year-old ♀ diagnosed with RS at birth. She was admitted with severe lymphadenopathies. A biopsy excluded malignancy. She was admitted later that year for cough, fever, and dyspnea requiring oxygen. Persistent generalized lymphadenopathies in all body regions. On chest X-ray and CT-Scan: mediastinal enlargement, and bilateral infiltrates. –ve bacterial cultures from bronchoalveolar lavage, -ve PCR for viruses (CMV, EBV), and mycoplasma. Slight lymphopenia and hypogammaglobulinemia. –ve antibodies against the received childhood vaccinations. Revaccination with Pneumo 23 led not to an increase in the antibody titers. Low T-cell numbers with a slightly diminished function, a low number of CD4+CD25+FoxP3+ regulatory T-cells Switched memory B-cells. –ve HIV screening. Radiosensitivity was mildly increased. On lymph node biopsy: signs of follicular and interfollicular hyperplasia as well as granulomas. Finally, a culture from the BM became +ve for Mycobacterium lentiflavum. Ionizing radiation was used as little as possible (Vollebregt et al., 2015).	20 cases
			Baller-Gerold syndrome/ AR	Novel c.2059-1G>C disrupted acceptor splice site in intron 12 + c.2141_2142delAG	Comp.Hete./ non-Cons.	A 27-year-old pregnant ♀ and her 31-year-old husband. The pregnancy was at 24 GWs, on U/S: no radius echo detection bilaterally, the left ulna was an "arc" shape, and 25 mm long, the right ulna was 24 mm long. Bilateral "hook" shaped hands. Hx of similar pregnancy before 1.5 years. Pregnancy terminated. PC (Cao et al., 2015).	40 cases

				) a frameshift in exon 13 led to a premature stop at codon 807			
RINT1	**TSG**	**7q22.3**	Infantile-onset recurrent acute liver failure (RALF) and skeletal abnormalities/ AR	Same exon 9 splice donor site (c.1333+1G>A or c.1333+1G>T) + a two-residue deletion c.1853_1858del , (p.Val618_Lys619del) in proband 1, or c.1102G>A , (p.Ala368Thr) in proband 2, or c.1109C>T , (p.Leu370Pro) in proband 3	Comp.Hete./ --	Three unrelated individuals with RALF concurrent with fever and/or infection and skeletal abnormalities. All had unremarkable births, neonatal periods, and family Hx. Two of three affected children have short stature, all have had otherwise normal development and cognition. Onset of ALF ranged from 8 months to 3 years of age. Episodic liver dysfunction was significant with hyperammonemia and coagulopathy that required supportive care. Probands 1 and 2 had abnormal liver transaminase levels that did not recover to normal between early childhood episodes. The liver enzymes of proband 2 did eventually normalize by age 7 years. Proband 3 has had normal liver transaminases between episodes since disease onset; underwent liver transplantation at the age of 8 years. Proband 1 died of acute respiratory failure at 3 years of age. On liver biopsies: no specific abnormalities by light or electron microscopy, but steatosis (probands 1 and 2) and bridging fibrosis. There was mild increase in Kupffer cells indicative of resolving hepatocellular injury and focal hepatocellular cholestasis (proband 3). No identifiable ultrastructural changes, but numerous lipid droplets seen in the hepatocytes. The Golgi could not be clearly observed. Based on skeletal changes observed in some individuals with NBAS deficiency, skeletal surveys were performed for probands 1, 2 and 3: demonstrated vertebral body abnormalities including anterior beaking and irregularity, with at least one hypoplastic vertebral body. Proband 1 had platyspondyly and probands 1 and 2 had acetabular abnormalities. Irregularity of the femoral head epiphyses with asymmetry or decreased spherical contour by all 3 children. The DNA of proband 1 showed no deficiencies in the radiation-induced double-strand break repair pathway. PC (Cousin et al., 2019).	3 cases [17]
SDHA	**TSG**	**5p15.33**	Isolated deficiency of Complex II + leukodystrophy and cardiomyopathy / AR, AD	c.1523C>T , (p.Thr508Ile) + c.1526C>T , (p.Ser509Leu) within the catalytic flavoprotein subunit of complex II in	Comp.Hete./ non-Cons.	A ♂ child born at term following an uncomplicated pregnancy. Smooth neonatal period, but at 3 months of age, increasing dyspnoea, sweating, and difficulty of feeding were noticed. Cardiomegaly on chest radiography, on echocardiogram: ischemia, a dilated and markedly hypertrophied left ventricle, with a degree of non-compaction of the left ventricular myocardium and fractional shortening of only 10%. –ve cardiac catheter investigation of the coronary arteries. Diagnosed with dilated cardiomyopathy. At 18 months of age, the motor delay was noted. A review at 2.5 years: knees and hips in flexion due to contractures, few single words of speech, generalized	37 cases [18]

				exon 11		hypertonia in all limbs with brisk deep tendon reflexes, and bilateral upgoing plantar response. On cranial and spinal MRI at 2.5 years age: extensive cystic change, abnormal high T2 and FLAIR signal in the central cerebral white matter symmetrically and bilaterally, with scattered peripheral foci of abnormal signal in the frontal lobes, an abnormal signal in the anterior and posterior corpus callosum, ventral pons, medulla and throughout the majority of the grey matter of the spinal cord. Metabolic investigations: Acylcarnitine profile demonstrated increased acetyl and hydroxybutyryl carnitines consistent with ketosis/lactic acidosis, with a normal free carnitine concentration. Urinary amino acids were normal, organic acids demonstrated raised lactate, ketones, 3-hydroxyisovalerate, and elevated tricarboxylic acid cycle metabolites (succinate, fumarate, and 2-ketoglutarate). At 3 years of age, a diagnostic open skeletal muscle biopsy was obtained. PC (Alston et al., 2012).	
SDHB	**TSG**	**1p36.13**	Isolated deficiency of Complex II and leukodystrophy/ AR	c.143A>T , (p.Asp48Val) in exon 2 that predicts a substitution within the catalytic iron-sulfur subunit	Homo./Cons	A ♀ child born at term. Smooth antenatal and perinatal period. At 1 year of age was able to cruise around furniture, but this was lost over 6 weeks, became unsteady, very hypotonic with poor head control, had repeated falls and difficulty feeding. No Hx of head injury or febrile illness. Thereafter no further episodes of developmental regression. By the age of 4 years, could stand briefly with support but remained wheelchair-dependent, developed flexion contractures in both her arms and legs. On initial MRI at 4 years of age: leukodystrophy with extensive signal changes in the deep cerebral white matter, sparing U-fibres, with abnormalities in cerebellum and brainstem. On repeated MRI at 4.5 years of age: cyst formation in the abnormal white matter, and persistent signal abnormalities in the corpus callosum. On short echo time MR spectroscopy of the dystrophic white matter: the presence of a singlet lactate peak at 2.4 ppm, also seen in long echo time but not detected in a control group or the normal-appearing basal ganglia of the patient, confirming the accumulation of succinate in the dystrophic white matter in vivo. The metabolite profile of the white matter revealed significantly decreased glutamine and glutamate, relative preservation of the neuronal marker N-acetyl aspartate and increased myo-inositol. Normal metabolite profile of the unaffected basal ganglia, with no succinate detected. Metabolic investigations demonstrated normal plasma, very-long-chain fatty acids, carnitine profile, amino acids, ammonia, and lactate. Normal urinary organic and amino acids, glycosaminoglycans, oligosaccharides, cerebrospinal fluid glucose, and lactate. At the age of 5 years, a diagnostic open skeletal muscle biopsy was obtained. No Hx of miscarriage in the family. Healthy 2 older siblings. PC (Alston et al., 2012).	1 case [18]

SDHD	**TSG**	**11q23.1**	Severe mitochondrial Complex II deficiency and prenatal cardiomyopathy / AR	c.275A>G , (p.Asp92Gly)	Homo./non-Cons.	The third child, ♂, born to Irish parents. On an anomaly scan at 31 GWs, fetal heart abnormalities were identified. On echocardiography: A normally situated heart, right to left shunting was noted at the patent foramen ovale and ductus arteriosus, consistent with gestational age, severe dilatation of the left ventricle and atrium with moderate-severe mitral regurgitation, severe left ventricular systolic dysfunction but no evidence of pericardial effusion or ascites. Normal sinus rhythm with a fetal heart rate between 100-120 bpm. Cardiac MRI at 32 GWs: marked left ventricular hypertrophy and dilation, clinically diagnosed with dilated cardiomyopathy. The proband was born by elective C/S at 37 + 6 GWs with BWt and HC within normal SD. On delivery: no dysmorphic features, transferred to NICU on 100 % oxygen. On physical examination: An additional heart sound and loud murmur, hepatomegaly without splenomegaly. By 12 hours of age, significant deterioration of his condition, on echocardiogram: dilation of the inferior vena cava, hepatic veins, right atrium, and interatrial septal bowing, moderate tricuspid regurgitation and very poor biventricular function with non-compaction hypertrophy. Died the following evening after the withdrawal of life support with parental consent. At postmortem examination, the heart weighed 43 g (normal = 13.9 ± 5.8 g), enlargement of the right atrium, fibroelastosis of the right atrium and right ventricle endocardium, remarkable underdevelopment of right ventricle, a 7-mm-diameter patent foramen ovale in the right atrium with obvious non-compaction of the hypertrophic left ventricular myocardium. On histopathology: non-compaction of the left ventricular myocardium. Histochemistry of muscle biopsy revealed a global reduction of succinate dehydrogenase (complex II) activity compared to age-matched control samples. Spectrophotometric analysis of respiratory chain function in patient muscle homogenate revealed a marked defect in complex II activity, representing ~30 % residual enzyme activity. Assessment of monolysocardiolipin and cardiolipin levels excluded a Dx of Barth syndrome. Normal other complex functions. PC (Alston et al., 2015).	2 cases [18]
SPINK1	**OCG**	**5q32**	Chronic pancreatitis (with pancreaticolithiasis)/ AR,AD	N34S	Homo./--	A 5-year-old ♂ with a 5-month Hx of epigastric pain, increasing over the preceding weeks and with recurrent nocturnal sweats and pallor, no diarrhea or Wt loss and no Hx of acute pancreatitis. On abdominal U/S: a solid and cystic structure in close contact to the pancreatic tail, suggestive of a pancreatic tumor. On abdominal CT-Scan: a PPC of slightly larger size (5.4·4.5 cm) than was seen on the U/S, connected to the main pancreatic duct, not contained any solid component. The imaging Dx was chronic pancreatitis with pseudocyst formation and confirmed by ERCP. The pancreatic duct showed typical changes and	--

						multiple concretions in the proximal duct. On pancreatography: a communication between the pseudocyst and the main pancreatic duct. On lab. investigation: elevated levels of amylase (8.8 lmol/l; NR NR <1.6 lmol/l) and lipase (10.61 lmol/l; NR <1.0 lmol/l). IgG antibodies were +ve for measles, mumps, varicella-zoster virus and EBV. No mutation in cationic trypsinogen gene sequences. Pancreatic sphincterotomy, partial extraction of the pancreatic concretions, and stent placement in pancreatic duct for transpapillary drainage were performed. On abdominal U/S after 2 and 6 weeks, and ERCP after 3 months: significant decrease in the pancreatic duct dilatation and complete disappearance of the pseudocyst. PC with no Hx of acute or chronic pancreatitis (Kühn et al., 2005).	
SUFU	**TSG**	**10q24.32**	Joubert syndrome with cranio-facial and skeletal defects/ AR	Family 1: c.1217T>C , (p.Ile406Thr) + Family 2: c.527A>G , (p.His176Arg)	Homo./Cons	4 patients of 2 unrelated families in 385 probands of two large combined cohorts with neuroradiologically confirmed JS or related cerebellar and brainstem defects, all presented with peculiar facial dysmorphisms (hypertelorism, broad and depressed nasal bridge, frontal bossing), oculomotor apraxia, DD with mild intellectual impairment, gait ataxia, and dysarthria. Three of them had post-axial polydactyly, and two had global macrosomia with macrocephaly. One patient also showed a few small dyskeratotic pits on the foot soles. No other signs of systemic involvement, except for mild retinopathy in one sibling from family 1. On brain imaging: cerebellar vermis hypoplasia with elongated superior cerebellar peduncles, deepened interpeduncular fossa (mild MTS), and mild lateral ventricular enlargement in all children, the two siblings from family 1 had bilateral polymicrogyria mainly involving the perisylvian regions (De Mori et al., 2017).	1.125 BP worldwide
TERT	**OCG**	**5p15.33**	Dyskeratosis congenita/ AD,AR	c.2110C<T in exon 5 , (p.P704S)	Homo./Cons	A 31-year-old ♂ with short stature, elfin appearance, esophageal stricture, leukoplakia of the buccal mucosa, anus, and penis; abnormal pigmentation of his neck, trunk, and back; hyperkeratosis of his palms, ridged fingernails, avascular necrosis of both hips, tooth loss, chronic diarrhea, learning difficulties, pulmonary infiltrates, and progressive BMF. His 61-year-old father was diagnosed with osteoporosis at the age of 60. His 60-year-old mother was healthy. Normal peripheral blood cell counts of both parents. The paternal grandmother (84 years) had Hx of anemia, osteoporosis, and pulmonary fibrosis. The maternal grandmother was reported to have died at the age of 60 years because of pulmonary fibrosis. PC. The father was carrier for a second TERT mutation in exon 2, C1234T/ p.H412Y (Du et al., 2008).	0.1 P in Europe [1]
VHL	**TSG**	**3p25.3**	Congenital polycythemia/ AR	Paternal c.662A>G, (p. Asn150Ser) +	Comp.Hete./ non-Cons.	A 9-month-old ♀ with plethora and erythrocytosis (RBC count 7.67 million/mm3, hemoglobin 21.5 g/dL, hematocrit 66.2%, MCV 86.3 fL). The erythropoietin level was 48 IU/L (normal 4–27), treated with phlebotomy (5 ml/kg of blood,	--

				a de novo (c.646C>T , (p.Gln145X) in exon 2		progressed to 10 ml/kg of blood with normal saline replacement every 4 weeks). Supplementation of ferrous sulfate till the date of the publication (at age of 9 years) for iron deficiency secondary to phlebotomy. Exclusion of secondary causes like cyanotic congenital heart disease, congenital lung diseases, liver or kidney disease, and masses producing erythropoietin. At the age of 9 years, no signs of tumor manifestations. No thrombotic event in patient or her father (Sidhu, Bhambhani and Callaghan, 2015).	

Table 4: demonstrates the presentation of genes with known biallelic germline mutations and associated clinical manifestations.

Age of the patient corresponds to the time of the original publication. Only relevant normal laboratory investigations are mentioned.

AD: autosomal dominant; ANSD: autonomic nervous system dysregulation; AR: autosomal recessive; BP: birth prevalence; DM: diabetes mellitus; CRP: C-reactive protein; ERCP: endoscopic retrograde cholangiopancreatography; ESR: erythrocyte sedimentation rate; FHH: familial hypocalciuric hypercalcemia; HSV: herpes simplex virus ; LSCD: limbal stem cell deficiency; MMQ-PCR: monochrome multiplex quantitative polymerase chain reaction; MTS: molar tooth sign; NICU: neonatal intensive care unit; NPARM: non-polyalanine repeat expansion mutation; P: prevalence; PARM: polyalanine repeat expansion mutation; PHA: Phytohemagglutinin; PPC: pancreatic pseudocyst; RF: respiratory failure; RR: reference range; SCID: severe combined immune deficiency; TIQ: total Intelligence Quotient.; XLR: X-linked recessive. Dual: the gene acts as TSG and as OCG.

[1]: P is representing DC caused by all DC-causing genes.

[2]: Marx and Sinaii, 2019.

[3]: the only reported two cases (Gruis et al., 1995; Pavel et al., 2003).

[4]: the twenty cases on OW/EBD represent COFS cases caused by all COFS-causing genes, not only ERCC1 gene.

[5]: the only reported cases, three from the publication of Yin et al., 2018 and four from Kasak et al., 2018.

[6]: the only reported two cases by Fouquet et al., 2017.

[7]: the only reported cases, the displayed one is from Bousfiha et al., 2019 and nine cases from the large Pakistani family described by Mujtaba et al., 2015.

[8]: the number is from George et al., 2016, the first and the only two reported COMMAD syndrome cases.

[9]: BP represents all types of Waardenburg syndromes, not only type 2A.

[10]: the number represents the only reported two cases of biallelic germline MSH3 mutation.

[11]: P represents familial adenomatous polyposis caused by all FAP-causing genes.

[12]: the number represents the displayed two cases by Fostira et al., 2018; and twelve cases listed in the publication of Groves, Gleeson and Spigelman, 2019 and nineteen cases identified by Grolleman et al., 2018.

[13]: the only reported two cases of biallelic PHOX2B mutation (Sivan et al., 2019; Trochet et al., 2008).

[14]: the only reported cases in the literature, fourteen cases by Pachlopnik Schmid et al., 2012 and one case by Thiffault et al., 2015.

[15]: the only reported cases in the literature by Logan et al., 2018.

[16]: the only reported two cases: one on OW/EBD (Waltes et al., 2009), the second is from Ragamin et al., 2020.

[17]: the only reported three cases by Cousin et al., 2019.

[18]: based on OW/EBD, there are thirty-seven reported cases in mitochondrial Complex II deficiency (alternative title: Succinate CoQ reductase deficiency), inclusive reported cases in SDHA, SDHD and SDHAF1 subunits. Our research yielded ~ 46 cases; we displayed in Tab. 4 the first reported germline SDHB-induced complex II deficiency (Alston et al., 2012), thirty patients with SDHA mutations, thirteen patients with mutations in SDHAF1 (Alston et al., 2015), and two patients with SDHD mutations (Alston et al., 2015; Jackson et al., 2013). Metabolic presentations in association with SDHC or SDHAF2 biallelic germline mutations have yet to be stated.

4.2 Group 2: Genes with solitary reported cases

The bone morphogenetic protein receptor 1A (BMPR1A) gene (Tab. 5) encodes a protein that consists of three main domains, including an intracellular kinase domain, an intracellular glycine–serine-rich domain near the plasma membrane, and a cysteine-rich extracellular region. BMPR1A is a member of the transforming growth factor-β (TGF-β) superfamily with different mechanisms of action (Howe et al., 2001). It demonstrates several functions after binding to bone morphogenetic proteins (BMP) by inducing activation of intracellular SMADs 1, 5, 8, and the latter control nuclear transcription. Moreover, BMPR1A participates in the stimulation of TAK1 and secondary messengers like p38 (Russell et al., 2019).

The process of endochondral ossification is achieved by the proper function of the BMP pathway (Russell et al., 2019).

Russell et al. (2019) reported the first and the only described phenotype related to the biallelic BMPR1A mutation. Skeletal findings, cartilaginous airway defects, facial dysmorphisms, and cardiac anomalies notified in the displayed case highlight the disturbing performance of the BMP pathway as a result of a total loss of BMPR1A function, since less dramatic features were reported by heterozygous missense variants in the same kinase domain.

Analogous abnormalities, including short stature, cardiac septal defects, developmental delays, scoliosis, and juvenile polyposis have been reported by chromosomal deletions in 10q22-q23 (Breckpot et al., 2012; Dahdaleh et al., 2011), but relating them with certainty to BMPR1A deletion could not be claimed because of the involvement of other genes. However, the reported case of Russell et al. (2019) proposes the involvement of BMPR1A gene loss with development of such a distinct syndrome.

Heterozygous mutation in BMPR1A results in the autosomal dominant juvenile polyposis. Because of imbricating manifestations between heterozygous nonsense variants of polyposis and complete deletion of BMPR1A, which also caused polyposis, finding polyposis in the displayed family after the screening is awaited (Russell et al., 2019).

BMPR1A is a TSG. Its mutation in heterozygous carriers evokes different clinical syndromes, like autosomal dominant juvenile polyposis (JP), hereditary mixed polyposis syndrome (HMPS) (Cao, 2005), and atrioventricular septal defects (D'Alessandro et al., 2015).

The checkpoint kinase2 (CHEK2) gene (Tab. 5) interacts with ATM, BRCA1, and p53 and is tangled in DNA DSB repair pathway and cell cycle control (Adank et al., 2011; Huijts et

al., 2013). CHEK2*1100delC variant is one of the most studied in populations all over the world (Apostolou and Papasotiriou, 2017).

Van Puijenbroek et al. (2005) presented an individual, who was homozygote for CHEK2*1100delC mutation and had no critical phenotype manifestations. The history of polyps in the family without CHEK2*1100delC mutation raises the suspicion of other gene collaboration. CHEK2*1100delC allele frequency is estimated to be 1.1-1.4% in the general European population. Identifying a low percentage of this mutation in the colorectal cancer cases within the study notified that there was no immense companionship between CHEK2*1100delC mutation and familial colorectal cancer, but its low penetrance effect could not be rejected.

An enhanced breast cancer risk has been connected to truncating and some missense mutations in the CHEK2 gene, including the CHEK2*1100delC variant. While a female CHEK2*1100delC carrier has about 20-25% estimated lifetime risk for breast cancer development, a female CHEK2*1100delC carrier with a familial breast cancer background has 37% estimated lifetime risk for breast cancer development (Adank et al., 2011).

Adank et al. (2011) estimated the lifetime risk of breast cancer development by homozygous females to be as more as two-folds of the heterozygous risk, and by a familial background tends to be about six-folds.

Huijts et al. (2013) described the risk to develop a second primary breast cancer in homozygotes for 1100delC variant as comparable or even higher than the odds ratio of 6 related to heterozygotes for 1100delC variant when compared with unselected patients with a first primary breast cancer.

Another mutation, p.R474C, for which no healthy homozygous individual has been unmasked to date, is presumed to produce an unsteady protein by devastating an essential well-conserved salt bridge. The produced protein is poorly activated upon cellular DNA damage (Kukita et al., 2016). The author described an individual with homozygous c.1420C>T, p.R474C mutation with multiple primary carcinomas and did not exclude the prospect of involvement of additional unrevealed autosomal dominant genes, which would correspond better to the given hereditary cancer syndrome history in the displayed case.

CHEK2 acts as a TSG (Huijts et al., 2013). Heterozygous CHEK2 mutations are reported to cause Li–Fraumeni syndrome and Li–Fraumeni-like syndrome. For the mentioned syndromes, four CHEK2 mutations have been recorded to date, including the CHEK2*1100delC variant (Zhuang et al., 2016).

Chymotrypsin C (CTRC) gene (Tab. 5) is a pancreatitis-associated gene, encodes the highly specific trypsin and trypsinogen degrading enzyme, which degrades all human trypsin and trypsinogen isoforms. In this way, CTRC controls the physiological intrapancreatic protease/antiprotease balance (Rosendahl et al., 2007).

CTRC heterozygous mutation leads to chronic pancreatic inflammation, which is outlined with diabetes mellitus and maldigestion resulted from endocrine and exocrine inadequacy following persistent pancreatic parenchyma devastation. Chronic pancreatitis is a heterogeneous disease and occurs by a prolonged imbalance between trypsin inactivation and intrapancreatic trypsinogen activation. Trypsin degrading enzymes decay the digestive protease trypsin, the main pathological driver of pancreatitis, and hence display a protective role. Their loss is therefore associated with an increased incidence of chronic pancreatitis (Rosendahl et al., 2007).
Rosendahl et al. (2007) presented the only reported biallelic CTRC mutation in idiopathic chronic pancreatitis to date, disclosed during CTRC gene sequencing of individuals with idiopathic or hereditary chronic pancreatitis and control subjects within large cohorts of German origin.
CTRC-NTRK gene fusion is approved to have an oncogenic role in pancreatic ductal adenocarcinoma (O'Reilly and Hechtman, 2019).

Gremlin 1 (GREM 1) gene (Tab. 5) is the bone morphogenetic protein (BMP) antagonist that codifies a cysteine knot protein, a member of the CAN family. GERM1 is involved in SHH pathway signaling during limb bud organogenesis and expressed in mesenchymal cells that respond to SHH signaling. Further, GREM1 plays a decisive role in lung and kidney development. In the latter, GREM1 induces ureter growth branching, thereby induces metanephric nephrogenesis through interaction with BMP pathway signaling. Therewith, GERM1 has to install a functional apical ectodermal ridge and the epithelial-mesenchymal feedback signaling, required to spread the sonic hedgehog morphogen (Michos et al., 2004).

Kohl et al. (2014) identified GREM1 as one of the first recessive genes causing isolated Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) in humans, based on the hypothesis of correlation of recessive CAKUT-causing genes in mouse models with genes causing isolated CAKUT phenotype in humans.

CAKUT is with a birth prevalence of 3-6/1000 live births, one of the most pervasive human congenital abnormalities. Isolated CAKUT is the most common form between 200 diverse syndromic CAKUT forms. CAKUT manifestations are defined as renal hypodysplasia, unilateral renal agenesis, vesicoureteral reflux, and ureteropelvic junction obstruction. Thus, the phenotype encompasses not only structural anomalies but functional anomalies as well (Kohl et al., 2014).

There are many identified autosomal dominant CAKUT-causing genes, with further six newly recognized recessive CAKUT-causing genes. The recessive genes operate at the Fraser-protein complex/Integrin alpha-8/Glial cell line-derived neurotrophic factor (GDNF) axis and are demonstrated to act synergistically at the ureteric bud/metanephric mesenchyme, which are the two essential embryonic structures for kidney development, and their disruption results in a clinical presentation of CAKUT (Kohl et al., 2014).

More clearly, the interaction of Integrin alpha-8 with Fraser-protein complex triggers GDNF expression through its canonical receptor RETS in metanephric mesenchyme. This signaling is neutralized by BMP4 expression at the ureteric bud/metanephric mesenchyme interface. GREM1 antagonizes the known CAKUT-causing gene, BMP4 (Kohl et al., 2014).

GREM1 has a tumor suppressor effect, and its downregulation has been detected in different tumor cell lines such as fibrosarcoma, neuroblastoma, breast carcinoma, colon adenocarcinoma, and clear cell renal cell carcinoma (van Vlodrop et al., 2010).

Proto-oncogene, receptor tyrosine kinase (KIT) gene (Tab. 5) is involved in cell survival, melanocytic differentiation, normal testicular germ cells and hippocampal cellular function, normal growth of hematopoietic progenitor cells, breast ductal epithelium, interstitial cells of Cajal and mast cells, and in tumorigenesis. Like platelet-derived growth factor receptor α (PDGFRA) and receptor β (PDGRFB), KIT is a type III tyrosine kinase receptor and codifies a tyrosine kinase protein with three isoforms (Roberts and Govender, 2015).

Stem cell factor (SCF) (mast cell growth factor) is the ligand of the KIT receptor. Autophosphorylation-induced KIT receptor dimerization and subsequent protein kinase activation occur after binding of SCF to KIT monomer (Roberts and Govender, 2015).

Activation of KIT leads to activation of downstream signal transduction pathways such as Ras/ERK (involved in cellular- proliferation, migration and invasion, and angiogenesis), PI3K/AKT (promotes cell survival, angiogenesis, escaping apoptosis, cell cycle control dysregulation and tumorigenesis), phospholipase γ (involved in cell proliferation and

survival), JAK/STAT (engaged in cell proliferation, differentiation, and apoptosis) and Src kinase pathways (involved in cell proliferation and angiogenesis). On the other hand, E3 ubiquitin-protein ligase cbl assists KIT kinase proteasomal degradation, SH2 domain-containing phosphatase 1 dephosphorylates KIT receptor, and protein kinase-C diminishes KIT kinase activity (Roberts and Govender, 2015).

Different KIT mutations engender different clinical presentations. Monoallelic KIT LOF mutation results in an autosomal dominant disease, piebaldism, notable by a white patch on certain body regions due to the absence of melanin. Instead, a GOF mutation has been revealed in acute myeloid leukemia, mastocytoma, gastrointestinal stromal tumors, dysgerminomas, mast cell leukemia, seminomas, and natural killer T-cell lymphomas of the sinonasal tract. Primary small cell lung carcinoma is the result of paracrine KIT activation. While for acral and mucosal melanomas, KIT point mutations are etiological (Roberts and Govender, 2015). Hence, KIT is an OCG (Lage et al., 2008).

The mentioned cutaneous clear cell sarcoma (CCS) of the soft tissue is an aggressive, very rare, and slow-progressing tumor found in only 1% of soft tissue tumors, mostly noticed in females. CCS presents as a painless mass on the lower limb. In view of its morphological (regional nodal metastasis inclination), fine structural (presence of melanin and premelanosomes), and immuno-histochemical (positive S-100 proteins) properties, CCS superposes strongly with the malignant melanoma (MM) of soft parts, yet has different pathogenesis. CCS is distinguished from MM by a hallmark translocation, t(12;22)(q13;q12), which gives rise to a fusion gene, that is absent in other types of melanoma. Further, BRAF and KIT mutations are regularly found in MM, but this is unusual in CSS (Gambichler et al., 2012).

It has been evident that introns embrace a convoluted combination of diverse DNA, which are considerable in cell development and survival, and their alteration is instantly affiliated with cancer development. Intron derivative microRNAs are capable of gene function controlling. Not only intronic KIT variants near exon limits have been recognized in many tumors; however, deep intronic KIT variant far away from splice site of exon 17, which probably influences the enzymatic action of KIT, has been reported in 94% of papillary renal cell carcinoma studies (Gambichler et al., 2012).

Menin 1 (MEN1) gene (Tab. 5) is a TSG and encodes menin, a highly conserved protein primarily located in the nucleus. Menin is part of the TNF-ß signal pathway through its

interaction with Smad3. Monoallelic MEN1 mutation is involved in multiple endocrine neoplasia type 1 (MEN1) syndrome, which covers the formation of two or more endocrine tumors, including pancreas, pituitary, and parathyroid glands (Bertolino et al., 2003). This disorder inherited autosomal dominantly and is highly penetrated in the coming generation (Brandi et al., 1993).

Brandi et al. (1993) presented two siblings with features of MEN1 and unexplained infertility, who were carriers of homozygous germline MEN1 mutation. Non-consanguinity and normal chromosomal analysis did not lifer a possible clarification for the unexplained infertility of the two displayed patients. It remained to speculate that the MEN1 gene gets involved with fertility at the time of conception.

Apart from small intrachromosomal isodisomy, the possibility of non-paternity, recombinant chromosomes, and uniparental disomy was excluded. The potential involvement of other loci in the heterogeneity lacking MEN1 disorder is improbable, but MEN1 function deficiency was probably fulfilled at the cellular level (Brandi et al., 1993).

The mutation in the reported family is expected to be compound heterozygous. Moreover, genomic imprinting should be taken into consideration. This unconventional condition illustrates that MEN1 gene loss is not affecting the process of embryogenesis and that tumor formation in MEN1 syndrome requires more than total MEN1 gene inactivation (Brandi et al., 1993).

Neurofibromin 1 (NF1) gene (Tab. 5) codifies a protein that consists of 2818 amino acids. Neuron's glial and Schwann cells are its main target of expression (Escuder, 2017).

Uncontrolled cell growth provides the basis of every predisposition for tumor formation. Since mutation in NF1 is linked to the development of benign tumors and increased tendency for malignancies, there should be an involvement of NF1 normal biological function with cell proliferation, differentiation, and survival processes. The elementary task of the neurofibromin is the negative regulation of an oncogene, Ras, which codifies a group of Guanosine Triphosphatase (GTPase) implicated in cell propagation, differentiation, and maintenance. An activated Ras is unbound to NF1 and induces cell proliferation and vice versa. NF1 deficiency drives Ras overexpression and uncontrolled cell proliferation (Escuder, 2017).

Not all NF1 deficient manifestations could be explained through this signal pathway. This awakes the suspicion about the involvement of NF1 in other cell's specific functions rather

than Ras regulation, precisely like interaction with pituitary adenylyl cyclase-activating polypeptide 38 (PACAP38) neuropeptide in the adenylyl cyclase/cAMP pathway (Dasgupta and Gutmann, 2003).

Monoallelic germline mutation in the NF1 gene provokes an autosomal dominant inherited disorder named neurofibromatosis type I with fluctuating disease intensity and clinical expressions. It is certified by neurological manifestations, peripheral nervous system benign and malignant tumor development, and demonstrations across most body organs like the skeleton, vessels, skull, eye, brain, and skin. CAL spots belong to its major conclusion. In cancer, NF1 acts as a TSG (Escuder, 2017).

The represented case in Tab. 5 is the only published case with biallelic germline NF1 mutation in humans. The case has not been discussed in detail regarding the carrier status of the mother or if there was a family history of fibromatosis in the other generations. The compatibility of biallelic NF1 mutation with life is surprising; also, the fact that the patient is doing quite well apart from CAL spots despite such a truncating NF1 protein. It remains to speculate about the mechanism of homozygosity in this patient including the possibility of UPD or even intragenic isodisomy. Further follow-up of this case would provide related information that might clarify some ambiguities, including the possibility of species-specific differences in neurofibromatosis susceptibility.
As NF1 knockout in mice is lethal (Dasgupta and Gutmann, 2003).

DNA polymerase delta 1 (POLD1) gene (Tab. 5) encodes the largest catalytic subunit P125 (Pol3) of DNA polymerase delta (Pol δ), which is a highly conserved holoenzyme with multiple domains, imperative for chromosomal DNA replication accuracy. Apart from the P125 subunit, the Pol δ has additional three subunits: the p55 (Pol31), p18 (Cdm1), and p40 (Pol32) (Oh et al., 2020). Pol δ synthesizes the vast majority of the lagging-strand and possibly involved also in the leading-strand synthesis, so it assists the replication of a significant part of the genome (Venkatesan et al., 2007). The catalytic subunit of POLD1 binds to the accessory subunits of POLD2, POLD3, and POLD4 to form a heterodimer, known as polymerase δ complex, which functions in genome maintenance by controlling processes like break-induced replication and HR, apart from its crucial role in DNA replication (Conde et al., 2019).

The dysregulated coordination of polymerase and exonuclease activity of POLD1 prompts different clinical presentations. While heterozygous germline mutations in the exonuclease domain of POLD1 predispose to colorectal cancer and endometrial carcinoma, a multisystem disorder known as MDPL: Mandibular hypoplasia, Deafness, Progeroid features, and Lipodystrophy syndrome with severe insulin resistance, results from heterozygous germline mutations in POLD1 that eliminate the polymerase activity of POLD1 but retains its 3′–5′ exonuclease activity (Oh et al., 2020).

Oh et al. (2020) added non-syndromic sensorineural hearing loss (NS-SNHL) to the phenotypic spectrum of POLD1 mutations and reported that a moderate degree of NS-SNHL is caused by biallelic germline POLD1 mutations with reduced polymerase δ activity. (Pol δ-p.Gly1100Arg) variant in the displayed cases showed 30%-40% polymerase activity reduction compared with the wild-type and showed normal exonuclease activity. On the other hand, (Pol δ-p.Ser197Hisfs*54) lacked nearly every function. The syndromic form of SNHL has been correlated to POLD1 mutations with complete loss of polymerase activity, like (p.Ser605del) variant in MDPL.

The maintenance of normal organ function in the human body requires an intact polymerization and proofreading activity of POLD1. The study of immunohistochemical staining and RNA in situ hybridization was able to demonstrate the localization of the POLD1 expression in neighboring cells of the endolymph in the cochlea. It has been assumed that a high polymerase activity of POLD1 is especially demanded by the cochlea for rapidly replicating cells lining endolymphatic space, which contains extracellular fluid endolymph. Endolymph preserves a highly polarized resting potential and high potassium concentrations, which could be noxious to the surrounding cells. This assumption might explain the presentation with SNHL by mutations affecting the polymerase activity of POLD1 (Oh et al., 2020).

Polymerase proofreading-associated polyposis is an autosomal dominant syndrome caused by heterozygous germline mutations that impact the proofreading (exonuclease) activity of polymerases epsilon (POLE) and delta (POLD1) (Terradas et al., 2019), and predisposes to multiple large colorectal adenomas, early-onset or multiple colorectal carcinomas, and other extracolonic manifestations like endometrial carcinoma (Lorca and Garre, 2019), or possibly breast tumors (Valle, 2017).

Conde et al. (2019) presented a patient with syndromic clinical manifestations of developmental and immune abnormalities with suspicion of an autosomal recessive,

undefined syndromic inborn error of immunity. The mutations were considered to be hypomorphic based on the essentiality of the polymerase δ complex, and affected the polymerase δ complex function, mainly the intrinsic enzymatic activity, but preserved the binding property to other POLDs.

POLD1Gln684His/Ser939Trp allele had an impact on the catalytic domain integrity, relying on the fact that Gln684 residue is located within the catalytic domain of POLD1 protein close to its DNA binding site (polymerase active site). The POLD1Arg1074Trp mutation is positioned at the C-terminal region of the protein, which is missed in the POLD1 structure model, but its proximity to a conserved cysteine, which is required for interaction mediation with POLD2, provokes the possibility of inducing interaction defects (Conde et al., 2019).

The syndromic neurodevelopmental abnormalities and immunodeficiency were replication stress-associated due to the loss of polymerase δ activity; this points to a new emerging role of polymerase δ in neurodevelopment and lymphocyte biology, especially the role of crucial DNA replication factor deficiencies in the development of immunodeficiency (Conde et al., 2019).

Pol δ (POLD1) has a tumor-suppressive effect (Preston, Albertson and Herr, 2010). However, lack of the second hits or other inactivating mutations in the majority of tumors with POLD1 mutation points to the fact that they may not act as classical TSG (Heitzer and Tomlinson, 2014).

Protection of telomeres 1 (POT1) gene (Tab. 5) encodes a unique single-strand DNA binding protein in the shelterin complex required in telomere regulation for repression of DNA damage response. By binding to the single-stranded telomeric overhang, POT1 impedes ataxia telangiectasia and RAD3–related (ATR-related) kinase stimulation. As mentioned, POT1 recruitment necessitates TPP1 protein (Jones et al., 2013).

Coats plus is an autosomal recessive telomeric disease caused by a biallelic mutation in the CTC1 gene that codifies the corresponding protein, telomere maintenance component 1 and is an element in the CST complex (CTC1, STN1, and TEN1), which functions in telomere and genome-wide replication by boosting polymerase α/primase-dependent fill-in process. Coats plus is uncommon and manifested by retinal telangiectasia, exudates, osteopenia, intracranial calcification with leukodystrophy and cyst formations, and vasculature ectasias in the gastrointestinal tract, mostly in the liver, stomach, and small intestine. Coats plus is

complicated by bone healing deficiency, multiple fractures, gastrointestinal bleeding, and portal hypertension (Takai et al., 2016).

There are several diverse pathways with which the CST complex assists in telomere function. However, regarding the role of POT1 in the CST function, it has been suggested that POT1 protein is required for CST complex recruitment to the telomere, either through direct binding of POT1 and CST complex or indirectly via TPP1, the binding partner of POT1 (Takai et al., 2016).

CST complex and POT1 act both as negative telomerase regulators. Their downregulation is parallel with a longer telomere. Here, POT1 might block the 3′ end of the telomere and/or act through a mechanism that involves CST (Takai et al., 2016).

Takai et al. (2016) reported homozygous germline POT1 mutation in 2 siblings with coats disease. The author described the mutation as a recessive "separation-of-function allele" rather than a null allele, in which the mutated POT1 proteins did bind TPP1 and telomere and suppressed ATR kinase activation, but were inefficient in repressing the telomerase-mediated telomere elongation in tissues expressing telomerase. This finding contradicts the short telomeres of the coats plus patients. The mechanism underlying POT1 mutation-induced coats plus was observed to be failure of POT1 to secure the telomeres from sudden deletions, which led to extravagant short telomeres. Mutated POT1 was inadequate in maintaining the POT1/CST-dependent fill-in process of telomeric C-rich strand after DNA replication and caused extended 3′ overhang dysregulations, stochastic telomere truncations in metaphase chromosomes, and proliferation arrest in telomerase lacking cells.

POT1 may act as a TSG (Folini, Gandellini and Zaffaroni, 2009). The cancer spectrum, which is predisposed by POT1 mutation includes glioma, chronic lymphocytic leukemia, angiosarcoma, melanoma, and colorectal carcinoma (Shen et al., 2020).

RET-ret proto-oncogene (Tab. 5) is a tyrosine kinase receptor gene with high expression in neural crest-derived cells and decodes required cell membrane transduction signal molecules for cell growth and differentiation. Two-faced monoallelic germline mutations of the RET gene have been described. The LOF mutation leads to congenital anomaly like Hirschprung disease, whereas the GOF induces no congenital anomaly but predisposes to malignancies (Edery et al., 1994). The identified malignancies include familial medullary thyroid carcinoma (MTC), multiple endocrine neoplasia type 2A (MEN2A), and type 2B (MEN2B).

They are inherited in an autosomal dominant manner (Lecube et al., 2002). In tumors, RET acts as an OCG (Lage et al., 2008).

MTC originates from parafollicular thyroid cells and contributes to 5-10% of all thyroid cancers, of which 20-25% is inherited. The familial form presents either as a single occurring form lacking the association with other endocrine tumors known as familial MTC or as a part of MEN2B, which displays the worse prognosis. Mutation in both extracellular and intracellular RET domains resulting in MTC has been documented (Lecube et al., 2002), but mainly non-cysteine RET mutations are attributed to a less aggressive manifestation (Elisei et al., 2004).

The reported V804M mutation reveals poorly established aggressiveness, various ages of disease onset and expressivity between MTC families, relying on the fact that heterozygous V804M carriers who developed MTC have been announced before, in contrast to the displayed case, in which no heterozygous but only homozygous carriers had developed MTC (Lecube et al., 2002).

About the second presented case, the Ala883Thr mutation is suggested to be of weak transforming activity and thus of low penetrance, based on the evidence that the heterozygous and one homozygous carriers did not develop MTC by the time of publication. However, this is to be tested in the future with a larger number of cases (Elisei et al., 2004).

Lesueur et al. (2005) reported three homozygous patients with V804L and V804M mutations in the codon 804. The comparison between heterozygous carriers and homozygous patients regarding age at the disease onset and severity of the clinical features were not striking; this shifts the scale in favor of low transforming potential of the mutations against the suggestion of their higher aggressiveness. The author concluded that the codon 804 mutations result in MTC when combined with another mutation (germline or somatic).

MEN2 is featured mainly by PCC, MTC, and primary hyperparathyroidism (PHPT). Heterozygous RET K666N mutation has been recorded to induce solitary MTC with reduced penetrance in the absence of PCC or PHPT manifestations, and this is in harmony with K666N heterozygous carriers in the displayed family. The homozygous RET K666N carrier developed MTC and PCC. The development of the MEN2-associated clinical presentations, following the exclusion of other MEN2 provoking gene mutations, is owing possibly to a more RET dose reduction. The likelihood of influence of certain SNP editors between MEN2 families is albeit to be studied. For now, RET K666N mutation could be considered as one of

the pathogenic variants with low disease penetrance tendency, as identified in the literature (Jaber et al., 2018).

Bano et al. (2012) reported another homozygous germline mutation in the RET gene, synonymous variant in exon 14 (p.Ser836Ser) in a 50 years old female with combined findings manifested as a gastrointestinal stromal tumor, renal and liver cysts, Hashimoto hypothyroidism, diverticulitis and lip telangiectasia, intestinal polyps and recurrent parathyroid adenomas. The variant was described in the literature before and found in healthy individuals and was also listed in the SNP database, so the mutation was ruled out as the pathogenic variant responsible for the patient's phenotype.

Transmembrane protein 127 (TMEM127) gene (Tab. 5) is a TSG and enciphers a highly conserved endo-lysosomal membrane protein. Through interaction of TMEM127 protein with other proteins, it inhibits the mammalian target of rapamycin (mTOR) signaling. Its involvement in insulin and glucose metabolism has been disclosed as well. Mutations that destroy the transmembrane domain of TMEM127 could lead to its diffuse cytoplasmic subcellular localization. Heterozygous germline mutation in the TMEM127 gene has been related to 2% of all cases of diagnosed PCCs (Flores et al., 2020).
Germline mutation in the TMEM127 gene inherited autosomal dominantly and show low penetrance, usually leading to the development of bilateral PCC, less frequently, extra-adrenal paraganglioma, head and neck paraganglioma, and renal cell carcinoma. PCC due to TMEM127 mutation is distinguished from PCC caused by other PCC-causing genes by an elderly median age of disease onset, about 44 years of age (Eijkelenkamp et al., 2018).

Eijkelenkamp et al. (2018) reported the first patients with homozygous germline TMEM127 mutation, who had bilateral PCC of a larger size as in heterozygous state and a higher urinary metanephrines excretion. The two reported mutations are thought to be truncating and restricting the normal function of TMEM127 protein. The first case, c.410-2A>G p.(?) mutation, based on its location, is expected to affect the splice site of exon 3, resulting in the deletion of the first eight bases of exon 4 and the subsequent frameshifting, which starts at codon Leu138, ends 11 position downstream with a stop codon. The second case, c.3G>A p.(Met1?) mutation, it affects the translation initiation codon and displaces ATG by ATA in exon 2, resulting in a null allele or a protein with defected N-terminal lacking the first 84 amino acids. Linking mental retardation, with which both cases of Eijkelenkamp et al. and the

other patient of Laboureau et al. (2018) were presented, to the homozygous TMEM127 mutation cannot be stated for certainty.

Tumor protein 53 (TP53) gene (Tab. 5) is known for its indispensable role in genome integrity as the "guardian of the genome." TP53 is involved in multi-tasks like cell cycle arrest, apoptosis, cell senescence, and DNA repair. TP53 mutation is identified in about 50% of human cancers. In cancers in which the Tp53 gene is kept undisturbed, the TP53 function is often weakened (Bang, Kaur and Kurokawa, 2019). The mutation is mostly missense that targets hotspots at extremely mutable CpG motifs, affecting codon 125-300 in the protein, which contains a highly conserved DNA-binding domain (Giacomazzi et al., 2013). Responding to and stimulating other cellular processes like autophagy, metabolic reprogramming, tumor microenvironment signaling, invasion and metastasis, have distended the known tumor suppression function of TP53. It serves further in stem cell development, differentiation, and aging (Bang, Kaur, and Kurokawa, 2019).

TP53 does not only suppress tumor formation, but its restoration also implements a persistent tumor-suppressive force on already established TP53-deficient tumors. This has been shown by using the MDM2 (HMDM) inhibitor molecule, blocking the major TP53 negative regulator, E3 ubiquitin ligase, resulting in tumor regression in preclinical models (Aubrey, Strasser and Kelly, 2016).

The necessity of the normal function of the TP53 gene is observable in families with Li–Fraumeni syndrome (LFS), an autosomal dominant and multi-cancer tendentious disorder with early-onset, which results from the heterozygous germline mutation in the TP53 gene. The cancer spectrum covers mostly breast cancer, brain tumor, soft tissue- and bony sarcoma, leukemia, and adrenal cortical cancer with consideration of a much broader range of malignancies (Aubrey, Strasser and Kelly, 2016), including colorectal, lung, gastric, pancreatic and prostate cancers, as well as melanoma and lymphoma. Within families with classical LFS, there is a subcategory of the disease known as Li-Fraumeni-like (LFL) syndrome, which does not fully fit the precise known criteria of LFS (Giacomazzi et al., 2013).

The overall risk of cancer development in TP53 mutation carriers is assessed to be 41% in men and 84% in women by age of 45 years (Brown et al., 2018).

In the typical form of the disease, adrenal cortical and choroid plexus carcinoma appear primarily in infancy, while leukemia and brain tumors all over childhood and young

adolescence, the soft tissue- and bony sarcoma develop mostly during childhood and adolescence followed by breast cancer in young adults (Giacomazzi et al., 2013).
The displayed mutation, p.R337H (c.1010 G>A), is a missense low penetrant pH-sensitive molecular defect of Tp53 with founder effect and is found in about 0.3% of Brazilian families. It has been classified as a conditional mutation, that in neutral PH forms dimers resembling heterozygous mutation and become dysfunctional by increased intracellular PH level. The latter is expected in the perinatal adrenal cortex cells as they undergo tissue remodeling during apoptosis. Homozygosity of p.R337H variant is estimated to be found in 1 in every 455.000 live births and does not lead to a more severe phenotype than in heterozygous carriers (Giacomazzi et al., 2013).

Giacomazzi et al. (2013) tested the aerobic functional capacity of the patient based on observed impaired cardiorespiratory fitness shown as decreased maximum exercise capacity and low training responsiveness in mice lacking functional TP53. The patient showed preserved functional capacity.

Brown et al. (2018) reported another TP53 deficient case with two synchronous primary malignancies. The family history up to the choriocarcinoma of the mother was compatible with LFS. Newly published evidence shows that inheriting a TP53 mutation from a female carrier or partner of a male carrier to a conceptus can incite choriocarcinoma. This would justify a post-partum screening.

RAD51 paralogue, XRCC2 (Tab. 5 and 1) biallelic mutation had led in the displayed three male cases to meiotic arrest, azoospermia, and infertility, and in the female patient to premature ovarian insufficiency (POI).
An indispensable process in both oogenesis and spermatogenesis is mediated by ubiquitous RAD51 and meiosis-specific DNC1 recombinase systems known as meiotic HR. POI is among common causes of infertility in females and describes ovarian function loss or reduction in < 40 years aged women (Zhang et al., 2018).
The primary cause of male infertility is the azoospermia, with up to 12 causal genes been identified to date. For population adaptation, it requires the generation of new DNA molecule combinations, which in turn demand decent chromosomal segregation in gametogenesis, and this is guaranteed by meiotic HR through DMC1 and RAD51. The latter is tangled in both meiotic and mitotic HR with a yet unclear meiotic mechanism (Yang et al., 2018).

Immunofluorescence analysis showed blocked spermatogenesis in the zygotene stage. Besides, terminal deoxynucleotidyl transferase(TdT)-mediated dUTP nick end labeling (TUNEL) assay revealed a comparable finding in ERCC2 knockout mice, namely a considerably intensified apoptosis in seminiferous tubules (Yang et al., 2018; Zhang et al., 2018).

Findings in XRCC2 c.41T<C knockout female mice revealed bilateral small, fibrotic, and atrophied ovaries, free of identifiable follicles (Yang et al., 2018).

Relying on the fact that the two displayed brothers with non-obstructive azoospermia (NOA) were phenotypically normal (truncating XRCC2 mutation results in FA with congenital anomalies), and lymphocytes did not show increased recombination defects of DNA DSBs after DNA exposure to breakage agent, and XRCC2 c.41T<C knockout mouse escaped embryonic lethality related to XRCC2 gene and had normal phenotypes, it could be assumed that the present mutation (c.41T<C/p.Leu14Pro), which was not found in any of the other 127 patients with NOA, affected only the meiotic HR of XRCC2 and not HR in somatic cells (Yang et al., 2018).

Genes	TSG OCG Dual	Gen-location	Mutation/aberrant transcription	Biallelic loss/consanguinity or common ancestor	Syndromes (diseases)/mode of inheritance	Phenotype in humans/ symptoms/ references	No. of published cases on PubMed
APC	**TSG**	**5q22.2**	Point mutation T3920A AAATAAAA to (A)8 , APC*I1307K	Homo./--	Colorectal carcinoma	Diagnosed during genotyping of patients with colorectal carcinoma in colonoscopy unit (Zauber et al., 2005).	2 cases
				Homo./--	Sporadic desmoid tumor	28-year-old ♀ with acute right lower abdominal pain, fever (diagnosed as appendicitis), gastrointestinal reflux, CT-Scan showed a mesenteric mass. No adenomatous or non-adenomatous polyps on subsequent colonoscopy. One grandfather had colon Ca and one grandmother breast Ca (Zauber et al., 2008).	1 case
BMPR1A	**TSG**	**10q23.2**	c.1217G>T , (p.Arg406Leu)	Homo./Cons.	Syndromic features	A 17-month-old ♂ with Hx of IUGR, premature delivery with RD, significant ASD with bilateral enlargement, diastolic dysfunction, subtle unilateral coronal stenosis, arrhythmia, severe subglottic stenosis, laryngomalacia, brachycephaly, flat facial profile, midface retrusion, sparse eyebrows, largemouth with downturned corners and a thin upper lip, low set-cupped ears with a short neck, hypotonia with poor head control, shortened extremities with brachydactyly. Mild thoracic scoliosis, dysplastic hips, lateral bowing of right femur, humerus and radius, GR, and DD. Died of aspiration pneumonia (Russell et al., 2019).	1 case
BRCA2	**TSG**	**13q13.1**	c.68-1G→C + c.4440T→G , (p.Y1480X) in the sisters + c.8168A→T , (p.D2723V) + c.9697_9700del (p.C3233Wfs*15) in the other woman	Comp.Hete./--	Premature ovarian insufficiency (POI)	Three Chinese patients with POI: two affected sisters and a woman whose immediate family members were unaffected. All patients presented with primary amenorrhea. Neither hematologic abnormalities nor solid tumors were found in these women or their relatives (França and Mendonca, 2019; Turchetti et al., 2019).	3 cases
CHEK2	**TSG**	**22q12.1**	CHEK2∗1100delC	Homo./--	Familial colorectal Ca without severe clinical phenotype	The index case died at the age of 52 years with metastatic disease from a sigmoid carcinoma. Found during a CHEK2 study between families with colorectal tumor. The mother (rectal adenoma at age 69) was heterozygous for the CHEK2*1100delC mutation. The brother (two colon adenomas at age 45) had no CHEK2*1100delC mutation. The father could not be tested. All the tumors tested in this pedigree were MSS with normal +ve nuclear expression for	1 case

						the mismatch repair proteins (MLH1, PMS2, MSH2, and MSH6), no mutational hotspots of MUTYH (Van Puijenbroek et al., 2005).	
			CHEK2*1100delC results in a frameshift, a premature termination at codon 381	Homo./non-Cons.	High-risk breast Ca and thymoma	12 homozygous mutation carriers from 8 breast Ca families from the Netherlands. During CHEK2 mutation screening between dutch independent familial non-BRCA1/2 breast Ca patients. All 10 ♀ 1100delC homozygotes had developed breast Ca. 7 cases had multiple primary tumors and had 4 bilateral breast Ca. Between siblings, a homozygous ♂ had thymoma at age 47 years. PC. The other homozygous ♂ was by the age of 54 years Ca-free (Adank et al., 2011).	12 cases
			CHEK2*1100delC	Homo./--	Breast Ca	During genotyping of a sporadic breast Ca hospital-based cohort (ORIGO) from the South-West region of the Netherlands, a group of previously reported non BRCA1/2 breast Ca families, and breast tissue tumors from Rotterdam medical oncology bank (RMOT), three 1100delC homozygous patients were found in the cohort of 1434 sporadic breast Ca patients with the age of 40, 52 and 55 years at breast Ca Dx. Another 1100delC homozygote was found in 592 individuals from 108 non-BRCA1/2 breast Ca families and was 56 years at Dx, and two more were found after testing 1706 breast tumors and confirming homozygosity on their wild-type DNA, diagnosed with breast Ca at ages of 60 and 62 years, respectively. Histology of the primary breast Ca was invasive ductal carcinoma in five patients, while one patient had an atypical medullary carcinoma. The average size of the tumor was 2.3 cm (range 1.7–3.0 cm). Lymph node status was known for five patients and was +ve in four and -ve in one patient. For three patients, the ER status was known, all being ER +ve. The ER status of the atypical medullary carcinoma was not determined. Follow-up information was available for five out of six patients, with an average follow-up of 8.5 years. Three of these five patients developed an invasive ductal carcinoma in the contralateral breast 3, 7 and 10 years after the first breast Ca Dx, while a fourth patient developed a melanoma located on the skin of the ipsilateral breast 5 years after the breast Ca Dx. The fifth patient died of metastatic disease 2.5 years after the initial breast Ca Dx. All three of the 1100delC homozygous breast Ca patients from the ORIGO cohort had one family member with lung Ca (Huijts et al., 2013).	6 cases

			c.1420C>T , (p.R474C)	Homo./Cons.	Multiple primary lung Ca and Ca in other organs	2 siblings, the ♂ patient with Hx of colon Ca and prostate Ca at the age of 59 years. Multiple primary lung Ca without Hx of smoking at the age of 60 years. On histological analysis: minimally invasive adenocarcinoma. His son died at 1 year and 10 months because of neuroblastoma. The elder ♀ patient, at the age of 38 diagnosed with uterine myoma, developed multiple primary lung Ca at the right site (invasive adenocarcinoma and adenocarcinoma in situ) at the age of 60 years without Hx of smoking. Subsequently, multiple primary lung Ca in the left lobe and breast Ca at the age of 71 years. The lesions were invasive adenocarcinoma, of either predominantly acinar pattern or papillary pattern. On histological and molecular analysis of the breast Ca: an invasive ductal carcinoma with a predominant ductal component, ER-ve, PR-ve, and HeR2+ve. Their parents suffered from and died of Ca in various organs (Kukita et al., 2016).	2 cases
CTRC	**OCG in fusion**	**1p36.21**	Maternal p.V235I + paternal p.R254W	Comp.Hete./--	Idiopathic chronic pancreatitis/ AD	During CTRC gene sequencing of individuals with idiopathic or hereditary chronic pancreatitis and control subjects within large cohorts of German origin. One individual with idiopathic disease was compound heterozygous. p.R254W mutant expressing cells produced a CTRC protein with only 50% of wild allele activity. CTRC activity secreted by p.V235I variant expressing cells was moderately reduced to ~65 % of the wild type (Rosendahl et al., 2007).	1 case
GREM1	**TSG**	**15q13.3**	c.103C>G , (p.P35A)	Homo./--	Isolated Congenital Anomalies of the Kidney and Urinary Tract (CAKUT)/ AR	A ♀ child from Macedonia with unilateral renal agenesis on the left side, no extrarenal manifestations. Detected during analysis of the coding sequences of 12 recessive murine candidate genes in 672 individuals from 590 families with isolated CAKUT. PC. 1 unaffected sibling was heterozygous carrier (Kohl et al., 2014).	1 case
KIT	**OCG**	**4q12**	Deep intronic mutations in intron 11 (IVS11+156G/A) + intron 16 (IVS16+965T/A , IVS16+994G/A)*	Homo. for all three mutation /--	Cutaneous clear cell sarcoma (CCS)	A 17-year-old ♀ with a 2-cm, bluish-reddish, subcutaneous nodule, had been growing for about 3 months on the left side of her buttock. On histology: a non-encapsulated lesion composed of atypical polymorph spindle cells that extended from the reticular dermis to the subcutis. Neoplastic cells were +ve for S-100 protein and Melan-A; slightly +ve for CD68, factor XIII, and vimentin; and -ve for CD31, CD34, actin, podoplanin, and CD117. Strongly expressed Ki-67 by tumor cells. In situ hybridization revealed the EWSR1-AFT1 type 1 (22q12) gene rearrangement in a formalin-fixed, paraffin-embedded specimen of the tumor. Performance of a wide re-resection of the lesion along with sentinel lymph node biopsy. On lymph node histology: an intracapsular metastasis of the	1 case

						CCS. Normal cranial, thoracic and abdominal CT-Scan, bone scintigraphy, and lymph node U/S. Complete lymph node dissection was performed on the left groin. PC. Both of the patient's brothers were heterozygous carriers for point mutations in intron 16 (IVS16+994G/A) (Gambichler et al., 2012).	
MEN1	**TSG**	**11q13**	Analysis of 12 polymorphic markers tightly linked to the MEN1 locus, at 11q13	Homo./non-Cons.	MEN1 with unexplained infertility	2 siblings with hypercalcemia. The index patient, a 40-year-old ♀ with hypercalcemia and elevated PTH levels, diagnosed as primary hyperparathyroidism, parathyroidectomy showed parathyroid hyperplasia. Peptic ulcer with elevated gastrin levels. Two pancreatic lesions were diagnosed with regular insulin and glucagon levels, mildly elevated GH levels, without clinical signs of acromegaly. On brain CT-Scan: slight slant of the floor of the sella turcica on the right side. On abdominal CT-Scan: adrenocortical adenoma. Unexplained infertility despite regular menstruation. Tx with exogenous gonadotropins without +ve results. Developed premature menopause. Her 35-year-old brother with a 6-year Hx of UTI and kidney stones. Diagnosed with hyperparathyroidism, after parathyroidectomy, parathyroid hyperplasia was confirmed. Normal lab. investigation, no abnormalities on radiography of the sella turcica. Infertility with idiopathic oligospermia and lack of spermatozoa motility. The father had Hx of peptic ulcer, with elevated gastrin levels, elevated serum calcium, and PTH levels. Refused further diagnostic investigation. The mother underwent total parathyroidectomy, parathyroid hyperplasia was confirmed. PC (Brandi et al., 1993).	2 cases
MITF	**OCG**	**3p13**	p.E318K	Homo./--	Multiple primary melanoma (MM)	The first case of the homozygous MITF p.E318K mutation in MM. The first melanoma lesion: on dermoscopy: a peripheral atypical network, areas of -ve pigment network, and different degrees of pinkish and grey pigmentation. At the confocal examination: observation of a severe cyto-architectural atypia, with polymorphous cells and atypical melanocytic nests at the junctional layer. The second melanoma: characterized by an irregular brown network with a widespread -ve pigment network. Confocal examination showed intraepidermal and junctional atypical melanocytic proliferation and architectural disarray. Two main dermoscopic nevus patterns were observed: a hypopigmented type with a predominant dermal-congenital pattern and a pigmented type with a predominant reticular/homogenous pattern. Mutational screening revealed *500C>G polymorphism in CDKN2A, a homozygous p.E318K mutation in MITF and the p.R160W variant in MC1R. No mutations were found in CDK4 and POT1 genes (Bassoli et al., 2017).	1 case

			c.668G>A , (p.R223H)	Homo./--	Waardenburg syndrome type 4/ AR	The proband is an 11-year-old boy with his 3-year-old brother, both presented with congenital bilateral profound hearing loss, bilateral heterochromia irides, premature greying of the hair, white eyebrows, white eyelashes, and excessive freckle on the face and neck area. The younger brother has additional depigmented skin on his left thigh, ankle, and foot. Both of them suffered from severe constipation accompanied with abdominal discomfort, distension, and abdominal pain since infancy, and persistent chronic milder constipation under conservative Tx. No obvious sign of HD on barium enema and anorectal manometry. A rectal biopsy was not performed due to the disagreement of their parents. Parents had normal hearing and milder clinical manifestations, the only pigmentary abnormality was premature greying of the hair starting from approximately 15 years of age for the father and from birth for the mother. No other abnormities such as dystopia canthorum, inner ear malformations, mental and DD, or ophthalmological, skeletal, and muscle deformities. Inner ear malformations were excluded. PC (Pang et al., 2018).	2 cases
MRE11A	**TSG**	**11q21**	Paternal c.658A>C resulted in exon 7 skipping + maternal c.659+1G>A , (p.Ser183ValfsX31)	Comp.Hete./ non-Cons.	Nijmegen breakage syndrome-like severe microcephaly/ AR	A 35-year-old ♀, pregnant at 18 GWs, presented with fetal IUGR. On U/S: a fetus with small femora and a disproportionately small head. C/S performed at 32 GWs, and a ♂ (Patient 1), was delivered. His BWt (−4.8 SD), length (−6.7 SD), and HC (−8.1 SD). On examination: severe microcephaly, a bird-headed facial appearance with receding forehead, and a prominent nose. No palpable anterior fontanel. On brain MRI at the age of 18 months: hypoplasia of the cerebrum, smooth gyri, and enlarged lateral ventricles. He had PDA, corrected surgically at the age of 5 months. Bilateral cryptorchidism was operated on at the age of 3 years. He stood holding onto a chair at the age of 30 months, sat alone with a stoop at the age of 3 years, and walked at age of 3 years. At the age of 3.5 years, Wt (−4.1 SD), Ht (−4.8 SD), and HC (−10.2 SD). Normal male karyotype. No severe or recurrent infections and normal immunoglobulin levels. At the age of 8 years, was toilet trained, spoke several meaningful words, but no two-word-sentence, attended a primary school, and was affable and friendly, was able to run with a slow pitch and kicked a soccer ball. No sign of ocular apraxia or cerebellar ataxia. He was farsighted with astigmatism. PC and healthy. 2 elderly brothers were healthy and carriers for c.659+1G>A variant.	2 cases

			maternal c.658A>C + paternal c.338A>G with 2 transcripts: (p.Asp113Gly), and exon 5 skipping (p.Phe106GlnfsX10)			Patient 2, a ♂, born at 37 GWs after inevitable pregnancy to a 29-year-old mother and a 28-year-old father. BWt (−4.1 SD), length (−5.9 SD), and HC (−6.1 SD). At the age of 30 months, sat alone but could not stand or walk. At age of 5 years, he shuffled while sitting, but was unable to stand. At age of 13 years, Wt (−4.2 SD), Ht (−7.0 SD), and HC (−12.8 SD), displayed severe microcephaly, a bird-like face with sloping forehead, a big nose, large and simple ears, short palpebral fissures, a small mouth, and a small and receding chin. Decreased range of motion in shoulders, elbows, hips, and knees. Scoliosis, subluxation of the left elbow joint, bilateral cryptorchidism, and bilateral talipes equinus. Slight hyperreflexia. Normal male karyotype. Normal immunoglobulin levels. At the age of 33 years, lived in an institution for disabled individuals, did not speak meaningful words, but recognized people, communicated by gesture, and showed fondness by touching, was bedridden, handfed, and unable to roll over. No secondary sexual characteristic development. No sign of ocular apraxia, malignancy, or severe infections. PC and healthy. An elderly brother was healthy, his DNA sample was not available. +ve ionizing radiation hypersensitivity, comparable to A-T and A-TLD (Matsumoto et al., 2011).	
NF1	**TSG**	**17q11.2**	c.2272delA a frame-shift mutation leads to introduction of a premature stop at codon 759, which truncates the encoded protein to 758 AA	Homo./--	Only a giant CAL spot	The 32-year-old son of a 65-year-old Chinese ♂ with increasing CAL spots presented only with a giant CAL spot on his back and extremities with a diameter of 15 cm. The CAL spot was present at birth and extended gradually. Furthermore, no neurological abnormality on examination and CT-Scan in either patient. The sequencing was replicated twice, and the results were identical. Father was a carrier (Yang, Wu, and He, 2017).	1 case
POLD1	**TSG**	**19q13.3**	c.584_585del , (p.Ser197Hisfs*54) + c.3298G>A , (p.Gly1100Arg)	Comp.Hete./--	Non-syndromic sensorineural hearing loss (NS-SNHL)/ AR	Two affected siblings manifested non-progressive moderate degree SNHL. The affected proband (I), ♂, 29-year-old with clearly normal skeletal morphology, facial morphology, fat distributions, and gonadal feature/function, without any anomalous features. Normal results of serum lipid profile, glucose and insulin levels, fasting insulin and triglyceride levels, and the thyroid and liver function. His sister, 45-year-old, had also moderate degree of SNHL. Mother carried (p.Ser197Hisfs*54) and had normal hearing. Another sister was carrier of (p.Gly1100Arg) had also no hearing difficulty. The affected patients in this study did not have any clinical features indicating MDPL syndrome (Oh et al., 2020).	2 cases

POT1	**TSG**	**7q31.33**	c.965C>T , (p.S322L)	Homo./Cons.	Coats plus / AR	Two affected sisters with classical features of coats plus but with earlier onset and more rapid progression of the disease. The older sister (Index1) demonstrated a prenatal onset and died of gastrointestinal bleeding at 3 years of age. Her younger sister (Index II) began to deteriorate rapidly at the age of 4 years. At the age of 7 years, was incontinent, unable to walk or talk, and had difficulty feeding. Sequencing of STN1, TEN1 and CTC1 genes did not reveal any mutation. PC, an unaffected brother with 2 POT1 wild alleles (Takai et al., 2016).	2 cases
RET	**OCG**	**10q11.21**	GTG → ATG in exon 14 , (p.V804M)	Homo./highly Cons.	Familial MTC	A 15-year-old ♀ with a large lymph node (3 cm) on the right side of the neck for 2 years. –ve family Hx of thyroid disease. Thyroid cells with a +ve immunoperoxidase staining for calcitonin by the FNA biopsy specimen of the lymph node. Elevated basal calcitonin concentration (381 pg/mL), no thyroid nodules on cervical U/S. Normal serum PTH level, urinary catecholamines, and metanephrines. Performance of total thyroidectomy, central and two-sided lateral neck node dissection with removal of the scalene and sternocleidomastoid muscles and jugular vein on the right side. Histology of the thyroid gland, a 3-mm MTC in the left lobe without C-cell hyperplasia, right neck lymph and pretracheal metastases, and invasion of the sternocleidomastoid muscle. 2.5 years after thyroidectomy, her follow-up basal calcitonin levels were still high (500-600 pg/mL), but no tumor had been identified. 4 successive generations were studied. 2 of 3 other homozygous family members underwent total thyroidectomy. One with C-cell hyperplasia, the other one neither MTC nor C-cell hyperplasia. The fourth one was her 5-year-old brother with normal pentagastrin provocative test result within the normal range and no U/S finding. Consequently, thyroidectomy was postponed (Lecube et al., 2002).	4 cases
			Novel mutation in exon 15 leads to an AA substitution (Ala>Thr) at codon 883	Homo./Cons.	MTC	A 51-year-old ♂ with a thyroid nodule and calcitonin +ve immunocytochemistry. Elevated basal and pentagastrin stimulated calcitonin levels (183 and 2853 pg/ml, respectively). On neck U/S: a thyroid volume of 20 ml and a small hypoechoic nodule of (10x14x11 mm) in the right lobe. –ve family Hx. On histological examination: the presence of one MTC foci of 12 mm in the right lobe and one MTC microfoci of 0.3 mm in the left lobe. The same investigation was done for a total of eight family members. Mother, 2 sisters and son were heterozygote with no evidence of MTC. 1 brother was homozygote. His biopsy revealed MTC and C-cell hyperplasia (Elisei et al., 2004).	2 cases

			1 homozygous p.V804L + 2 homozygous p.V804M	Homo./Cons.	1 MTC and PCC, 2 MTC	By Ca research campaign in the UK during registering of patients with sporadic MTC and MTC of MEN2 families. From total of 306 individuals with apparently sporadic MTC, nine were found to have a codon 804 mutation, of which three were homozygous. –ve family Hx by all 3 cases. The first case, a ♀ who had a total thyroidectomy at the age of 37 years for MTC and developed PCC at the age of 39 years, was found to be homozygous for V804L. The second patient, a 54-year-old ♀, was homozygous for V804M presented with MTC only. Parental carrier state testing was not possible. However, all parents were clinically disease-free. The third homozygous patient developed MTC at the age of 32 years. PC and asymptomatic (Lesueur et al., 2005).	3 cases
			p.K666N mutations	Homo./non-Cons.	MEN2A phenotype	A 59-year-old ♀ with metastatic MTC. On neck U/S: bilateral thyroid nodules (1.5-cm left and a 2-cm right lobe nodule) were biopsied. Elevated calcitonin and carcinoembryonic antigen levels (1675 pg/mL) and (101.3 ng/mL), respectively. Elevated free metanephrine levels at (2.09 nmol/L) and free normetanephrine levels at (1.14 nmol/L). She had no signs or symptoms suggestive of PCC. On staging scans: presence of hepatic cysts and bilateral adrenal masses. Hx of laparoscopic bilateral adrenalectomy confirmed the presence of bilateral PCC, measuring 5 cm on the right and 4.5 cm on the left. After thyroidectomy, multifocal MTC confirmed. Additional high-risk features included an extrathyroidal extension, minimal capsular invasion, focal lymphovascular invasion, and +ve margins. Four of nine lymph nodes were +ve for metastatic involvement. The PCC was staged as stage III. Biopsy of a liver lesion confirmed metastatic MTC. –ve family Hx for thyroid disease. Her father was deceased; her mother had no evidence of MEN2 (not tested). Proband's two adult children were heterozygous carriers. Her then 32-year-old son had an elevated calcitonin level of 16 pg/mL. Pathology was consistent with a 3-mm unifocal MTC without lymph node involvement. Her then 30-year-old daughter with normal calcitonin level and neck U/S decided for an elective prophylactic thyroidectomy, which revealed C-cell hyperplasia (Jaber et al., 2018).	1 case
TMEM127	**TSG**	**2q11.2**	c.410- 2A>G , p.?	Homo./Cons.	Bilateral PCC	In the year 1997, a mentally disabled Caucasian 31-year-old ♂ presented with hypertension, headache, nausea, and dizziness. On lab. Investigations: high concentrations of urinary metanephrines: metanephrine 10 948 µmol/mol creatinine (reference range: 33-99 µmol/mol creatinine), normetanephrine 19 089 µmol/mol creatinine (reference range: 64-160 µmol/mol creatinine). On abdominal CT-Scan: bilateral adrenal masses (left 4.5 × 3.0 cm, right 7.0 × 6.0 cm). Dx of bilateral PCC. Bilateral adrenalectomy after preoperative Tx with α-	1 case

						and β-antagonists. Pathologic examination confirmed PCC without signs of hyperplasia. Postoperative normalization of urinary metanephrine excretions. In 2008, the patient had a recurrent PCC localized in the area of the right adrenal gland, was successfully operated. In 1998, DNA analysis found no mutation in the RET, VHL, SDHB, or SDHD genes. In 2014, an update of the DNA analysis was -ve for a mutation in the MAX gene but revealed a mutation in the TMEM127. The medical file of the index patient showed that he had distinct dysmorphic features as a child, including microcephaly, hypertelorism, frontal bossing, divergent strabismus, and DD. Since the age of 12 years, short attacks of absence lasting a few seconds, where he turned away his eyes and became pale. Neurologic examinations, including electroencephalograms, did not reveal an explanation. Later, developed complaints of headache and 2 years before the first Dx of bilateral PCC developed hypertension. Father is deceased from an aortic dissection. Mother, 1 sister and 1 brother were heterozygous carriers with no biochemical sign of PCC or PGL, 2 brothers were not tested. –ve family Hx of PCC (Eijkelenkamp et al., 2018).	
		c.3G>A , (p.(Met1?)	Homo./Cons.	Bilateral PCC	A mildly mentally disabled 26-year-old Turkish ♂ presented with bilateral PCC in 2013 with Hx of episodes of headache, dizziness, and profuse perspiration. Severe hypertension (218/127 mm Hg). On lab. Investigation: elevated urinary metanephrines: metanephrine 14 513 µmol/mol creatinine (reference range: 35-150 µmol/mol creatinine), normetanephrine 4749 µmol/mol creatinine (reference range: 60-260 µmol/mol creatinine). On abdominals CT-Scan: a lobulated mass of the left adrenal gland with a maximum size of 11 cm and an enlarged right adrenal gland of 2.5 cm. A left-sided adrenalectomy and right cortex sparing surgery was performed after preoperative Tx with α- and β-antagonists. Bilateral PCC was confirmed histologically. Pathologic examination revealed a multinodular PCC in the left adrenal gland (14.5 × 11.0 × 7.0 cm) and a PCC in the right adrenal gland (2.1 × 1.8 × 1.4 cm) with signs of hyperplasia of the adrenal medulla. Normalization of urinary metanephrines excretion postoperatively. The same mutation found in the tumor. On tumor immunohistochemistry: normal staining of the SDHA and SDHB proteins. Sequencing in tumor tissue for genes involved in PCC and PGL revealed no mutation. Father underwent an operation for parathyroid adenoma at 43 years of age. –ve family Hx for PCC or PGL. PC with no suggestive clinical symptoms, PCC diagnostic analysis not performed (Eijkelenkamp et al., 2018).	1 case

			c.190_191dup , (p.Gln64HisfsX18)	Homo./Cons.	Bilateral PCC	A mentally disabled 56-year-old Caucasian ♀ with acute RD and abdominal pain. Blood pressure (160/80 mm Hg). On Angio-scan: bilateral adrenal masses and lesions of the lung, no pulmonary embolism. On 18F-Fluorodeoxyglucose positron emission tomography scan: peripheral right adrenal hypermetabolism due to the cystic feature (Standard Uptake Value max of 3.1), left adrenal hypermetabolism (Standard Uptake Value max 11.5). Lung lesions and mediastinal adenopathies took up the radiometabolite. 123-I metaiodobenzylguanidine scintigraphy showed uptake in the adrenal masses but not in the pulmonary lesions. On lab. investigations: elevated urinary normetanephrine (3420 nmol/24 h, N: 44-213), urinary metanephrine (2961 nmol/24 h, N: 40-228) and chromogranin A (1441 ng/mL, N: 27-94). The patient underwent bilateral adrenalectomy. Histopathological examination confirmed PCC (right: 11.5 × 9 × 3 cm, and left: 5 × 3.5 × 1.5 cm); Ki67 level was less than 1%. After surgery, normalization of urinary methylated derivatives and chromogranin. A lung biopsy led to the conclusion of B-cell lymphoma. The patient lived in an institution and presented a mental deficit of unknown etiology, since early childhood, also partial blindness and arterial hypertension but no dysmorphic features. No family Hx of endocrine tumors. Father is deceased from old age. Mother died from unknown cause at 40 years of age. The patient was the second born of 3 children. Her 55-year-old brother and 59-year-old sister were heterozygous carriers but in good health with no specific medical Hx. The brother's adrenal CT-Scan was normal. The sister presented a 5 mm adenoma of the left adrenal gland. Their urinary metanephrines tests showed normal results (Laboureau et al., 2018).	1 case
TP53	**TSG**	**17p13.1**	Maternal (R156H/R267Q) + paternal (R290H)	Comp.Hete./--	Rhabdomyosarcoma	The proband was a ♂ child who developed rhabdomyosarcoma in the right neck at the age of 2 years, a brain tumor at the age of 10 and died at the age of 12 years. His mother had bilateral breast Ca at ages of 35 and 43 years, and his father was unaffected. –ve family Hx was available for the father. The maternal grandmother died at 44 years of age with melanoma (Quesnel et al., 1999).	1 case
			P.Arg337His	Homo./Cons.	Adrenal cortical tumor (ACT)	A 1-year-old ♀ child in a study of 55 Brazilian pediatric and adult patients with apparently sporadic ACT, presented with Cushing face and virilization. Developed a large hormone-secreting adrenocortical tumor without signs of tumor invasion or metastases. The patient was afterward healthy and had not developed another Ca at age of 10 years. PC and healthy (Giacomazzi et al., 2013; Latronico et al., 2001).	1 case

		c.1010G>A in exon 10 , (p.R337H)	Homo./Cons.	Anaplastic ACT	A previously healthy ♀ child of Portuguese and Spanish descent presented at 11 months of age with Hx of increased appetite, significant Wt gain in the past three months, signs of virilization. On admission: Wt (> the 95th SD), Ht: 83 cm (> the 95th SD). Blood pressure: 130/90 mmHg. On examination: "moon-like" face, excess facial and body hair, pubarche and clitoromegaly, facial acne, and an abdominal mass on palpation. On lab. evaluations: normal serum sodium, potassium, calcium, phosphorus, and creatinine. Hormonal evaluation: very high levels of androgens: dehydroepiandrosterone sulphate (DHEAS) > 1000 µg/dL (nl: 2-274 µg/dL), dehydroepiandrosterone > 30 ng/ml (nl: < 2.5 ng/ml), testosterone 9.61 ng/dL (nl: < 0.05 ng/dL), androstenedione > 10 ng/dL (nl: < 0.5 ng/ml), 17-alpha hydroxyprogesterone 8.88 ng/ml (nl: < 1.0 ng/ml), progesterone 4803 pg/ml (nl: < 800 pg/ml), morning cortisol 37 µg/dl (nl: 4.3-22.4 µg/dl), and midnight cortisol 32 µg/dl (nl: < 1.0 µg/dl), normal urinary free cortisol, ACTH was undetectable. Bone age assessed using the Greulich-Pyle method, found to be 24 months (SD = 2.4 months) despite a chronological age of 14 months. On Abdominal CT-Scan: a heterogeneous adrenal mass (4.5 × 3.4 × 3.0 cm), excised without disturbing the adrenal capsule. Surgical margins were -ve, histopathology of the tumor tissue confirmed the Dx. The patient was under follow-up with pediatric oncology, endocrinology, and Ca genetics specialists according to the NCCN guidelines. 96 months after the Dx of the ACT (at age 9 years), the patient was healthy, had adequate cognitive and psychomotor development. Currently, no clinical or lab. evidence of endocrine derangements. At age 8 years and 8 months: full body and brain MRI detected no suspicious lesions, and cardiopulmonary exercise test results were within the normal reference for 9-year-old girls. +ve family Hx of second and third-degree relatives with Dx of Ca consistent with a LFL tumor pattern. PC, healthy, no Hx of Ca (Giacomazzi et al., 2013).	1 case
		p.R337H	Homo./--	Anaplastic embryonal rhabdomyosarcoma + choroid plexus carcinoma (CPC)	During newborn screening for the TP53 R337H mutation to estimate the prevalence of heterozygous carriers, offered free at all Paraná hospitals. 171,649 newborns were screened. Three children were homozygous for the R337H allele. Two of them had ACT during the study and experienced local relapse within 1 year of Dx, and one child developed CPC (Custódio et al., 2013).	3 cases

			c.52delA in exon 2 , (p.Thr18Hisfs*26)	Homo./Cons.	ACT + CPC	A 22-month old ♂ proband presented with a 10 day Hx of a rapidly enlarging left infra-orbital mass. On examination: a large, firm, non-tender, fixed mass in the inferior lateral left orbital rim, several pigmented macules on the legs and back. On MRI: two distinct lesions in the left orbit with an additional mass within the posterior left lateral ventricle, and another within the choroid plexus of the right lateral ventricle. Resection of the orbital masses was performed, on histopathology: an anaplastic embryonal rhabdomyosarcoma. Embolization, followed by resection of the choroid plexus mass, was performed. Histopathology confirmed a CPC, confirming two synchronous malignancies. Immunohistochemistry studies of both tumors revealed complete absence of p53. Initial therapy was poorly tolerated. Given the guarded prognosis, Tx focused on the quality of life, with oral chemotherapy and radiotherapy administered. The proband died approximately 14 months after the presentation. +ve family Hx of several relatives with Ca (maternal grandmother with breast Ca at 53 years, the paternal grandmother with breast Ca at 42 years, maternal great-uncle with gastric Ca in his late 30s). The proband's mother treated for metastatic choriocarcinoma following his birth. PC. Both parents were 25 years at presentation. The younger sister was 10 months old, also carrier (Brown et al., 2018).	1 case
XRCC2	**TSG**	**7q36.1**	c.41T>C , (p.Leu14Pro)	Homo./Cons.	Premature ovarian insufficiency (POI)	An infertile 29-year-old ♀, diagnosed with POI at age of 16 years, attained menarche with hypomenorrhea at age of 15 years, experienced amenorrhea in the next year. On transvaginal U/S examination: relatively small uterus (40 × 23 × 37 mm), as were both ovaries (left ovary: 17 × 10 × 14 mm; right ovary: 19 × 11 × 13 mm). Low estradiol level (15 pg/mL; normal range 21-251 pg/mL), high levels of FSH (39.67 mIU/mL; normal range 3.03-8.08 mIU/mL) and LH (12.07 mIU/ mL; normal range 1.80-11.78 mIU/mL), and normal levels of prolactin and TSH, her AMH and inhibin B levels were too low to be detected. Normal karyotype, normal range of FMR1 CGG trinucleotide repeats. Other causes of infertility were excluded (Zhang et al., 2018).	1 case
					Non-obstructive azoospermia (NOA)	Her 31-year-old brother with Hx of infertility for 5 years, complete azoospermia (only primary spermatocytes found in his testicular biopsy). Normal bilateral testicular size and hormone levels, normal karyotype, and no Y-chromosome microdeletion. Other causes of infertility were excluded. PC (Zhang et al., 2018).	1 case

		Homo./Cons.	NOA	A family with 2 infertile ♂ siblings suffering from NOA and 127 sporadic patients with NOA prospectively recruited at Jiahui genetics hospital, state key lab. of medical genetics, central south university, Changsha city, China from Jan. 2008 to Oct. 2016. All azoospermic cases were clinically examined and included were only patients with normal anatomical integrity of the genital system, no Hx of childhood disease, environmental or radiation exposure, prescription drug usage, varicocele, or cryptorchidism. No XRCC2 recessive mutation was detected in the cohort. The 2 patients had small testes detected at 10 and 12 years by routine regular health check-ups at schools. The size of their testes remained small at the ages of 29 and 31 years (about 9–11mL), respectively. No sperm was found: on two separate semen analyses, in two separate percutaneous epididymal sperm aspiration, on testicular biopsy, which showed meiotic arrest. No other inherited disease in this family. PC (Yang et al., 2018).	2 cases

Table 5: demonstrates the presentation of genes with rarely described biallelic germline mutations with related clinical phenotypes.

Age of the patient corresponds to the time of the original publication.

* InterVening Sequence (i.e., an intron). AD: autosomal dominant; AMH: anti-mullerian hormone; AR: autosomal recessive; ER: estrogen receptor; FSH: follicle-stimulating hormone; HD: Hirschsprung's disease; HeR2: human epidermal growth factor receptor 2; LFL: Li Fraumeni like syndrome; LH: luteinizing hormone; MDPL: Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome; MSS: microsatellite stable; NCCN: national comprehensive cancer network guidelines, PGL: paraganglioma; PR: progesterone receptor; UTI: urinary tract infection. Dual: the gene acts as a TSG and as an OCG.

4.3 Group 3: Genes without human case reports but knockout sequela in mouse models

Aryl hydrocarbon receptor interacting protein (AIP) gene (Tab. 6) encodes AIP protein, a member of the immunophilin family of proteins. AIP protein is a Co-chaperone with particular binding partners of xenobiotic receptors in the xenobiotic signal transduction pathway like aryl hydrocarbon receptor (AHR) and the peroxisome proliferator-activated receptor (PPAR), two mammalian client proteins. AIP is further acknowledged as the hepatitis B virus X-associated protein (XAP2) because of its interaction with the hepatitis B viral protein (B.C. Lin et al., 2007).

AIP functions as an OCG in diffuse large B-cell lymphoma (Barry et al., 2019), and as a TSG in pituitary adenoma (Cazabat et al., 2009).

AIP proteins are notably overexpressed in pituitary growth hormone- and prolactin-secreting cells (Daly and Beckers, 2015). Monoallelic germline mutations in the AIP gene cause pituitary adenoma (Bolger et al., 2016). An overwhelming proportion of pituitary adenoma occurs sporadically, only 3% shows a familial background, as an element of MEN1 (AIP maps to the same genomic region as MEN1) or Carney complex (Cazabat et al., 2009). AIP germline mutations are found in 20% of cases with familial isolated pituitary adenoma. The characteristic feature of the AIP mutated pituitary adenoma is an early onset of the disease, adenoma of growth hormone, and/or prolactin-secreting type (Bolger et al., 2016), large adenoma size and extensity at diagnosis (Daly and Beckers, 2015). Intrafamilial differences regarding homogeneous or heterogeneous familial isolated pituitary adenoma have been reported (Cazabat et al., 2009).

The AIP genetically ablated mice were incompatible with life and died around E10.5-E14.5 day, exhibiting a reduction in blood flow to head and limbs, and congenital heart deformities like pericardial edema, VSD and double outlet right ventricle (B.C. Lin et al., 2007).

AKT serine/threonine kinase 1 (AKT1) gene (Tab. 6) encodes AKT1 protein, the predominantly expressed one between the three main isoforms of the serine/threonine kinase (AKT) family. As a downstream effector of phosphatidylinositol three kinases (PI3K), AKT advocates growth factor-dependent survival of various cells and operates in transcription and the metabolism of insulin, protein, lipid, and carbohydrate. There are many mechanisms behind the enhanced AKT activity considered underlyingly in many human cancers including,

mutation/deletion in PTEN: the negative regulator of AKT; PI3K catalytic subunit amplification; AKT genes amplification; Ras activation; and growth factor receptor activation. The 3 AKT isoforms, AKT1, AKT2, and AKT3, are structurally related and show up to >85% sequence homology and have matching or comparable substrate specificity (Chen, 2001).

AKT1 is an OCG, and its GOF mutation has been detected in a broad spectrum of human cancers of various types (Hyman et al., 2017). AKT1 is mutated in 2% and 3% of breast and urinary bladder tumors, respectively. Its mutation has also been identified in endometrial, prostate and lung cancers (Davies et al., 2015). The pathological localization of AKT1 to the plasma membrane induces the constitutive downstream signal pathway stimulation required for carcinogenesis (Hyman et al., 2017).

Unusually, an egregious consequence of AKT1 germline deficiency was not observed as it was to be expected considering its vital multifunction. Mice with knockout AKT1 gene were born alive with reduced survival following genotoxic exposure. Mice were small-sized, and this was conserved across adulthood. They exhibited spontaneous apoptosis in thymi. Female mice were fertile, while male mice displayed attenuated spermatogenesis with increased apoptosis in testes. No diabetes-related findings were observed. These elusive manifestations proposed the possibility of AKT1 partial substitution by AKT2 and AKT3, with the exception in thymus and testes, which are exclusive AKT1-dependent organs (Chen, 2001).

BRCA1-associated protein 1 (BAP1) gene (Tab. 6) enciphers BRCA1-associated protein 1, a ubiquitin C-terminal hydrolase, which cleaves a covalently attached ubiquitin from target substrates through its N-terminal (UCH) domain. It attaches to the RING finger domain of the BRCA1 protein and acts as a TSG. Monitoring several cellular pathways like DNA transcription, cell cycle regulation, cellular growth, response to DNA damage, and chromatin remodeling, including Histone H2A modifications, belong to the main function of BAP1. Detection of BAP1 mutation indicates a poor prognosis in various cancer types, except for mesothelioma, where is assumed to be of good prognostic factor. BAP1 mutations have been correlated to renal cell and high-grade colorectal carcinoma. Contrary to the fact that BAP1 mutation was unusually found in female breast cancer, BAP1 mutations are more common in women (Angèle et al., 2003).

Monoallelic BAP1 germline mutation results in malignant mesothelioma with or without a history of asbestos exposure. Malignant mesothelioma, uveal melanoma and possibly other types of cancers are the main manifestations in the newly defined BAP1 tumor predisposing

syndrome (BAP1-TPDS). Malignant mesothelioma occurs sporadically or is inherited (Testa et al., 2011).
Basal cell carcinoma, meningioma, and cholangiocarcinoma could expand the spectrum of the BAP1-TPDS (Walpole et al., 2018). The most common described BAP1 germline variations include LOF mutations, small deletions and insertions, and non-synonymous SNPs (Repo et al., 2019).

Homozygous deletion of BAP1 in mice causes early ectoderm, mesoderm, and neural crest anomalies (Kuznetsov et al., 2019). Further, placental phenotype study had revealed that BAP1 knockout induces mid-gestational lethality (around E9.5-10.5 day) due to syncytiotrophoblast formation failure and placental vascularization underdevelopment, pointing to the importance of BAP1 in the extra-embryonic mesoderm lineage and its relevance for the regular function of the trophoblast cells (Perez-Garcia et al., 2018).

BRCA1 associated RING domain 1 (BARD1) gene (Tab. 6) codifies a protein that is an essential counterpart to BRCA1 protein in the BRCA1/BARD1 heterodimer. BARD1 functions combined with BRCA1 in heterodimer, or operate proapoptotic autonomously. Both proteins possess an N-terminal RING domain and two C-terminal BRCT motifs. Heterodimerization between the proteins is interceded by their homologous RING domain sequence encompassing in an antiparallel form. This heterodimerization provides the BRCA1/BARD1 a considerably higher ubiquitin E3 ligase activity than BRCA1 and BARD1 does solely. Further, this communication is critical during the DNA damage response for mRNA processing inhibition. Since the BRCA1/BARD1 heterodimer is vital for BRCA1 nuclear retention, its primary enzymatic reaction, and possibly tumor suppression function, BARD1 mutations might induce BRCA1 pathway dysregulation and/or illustrates independently a focus for tumorigenesis (McCarthy et al., 2003).
BARD1 acts in breast and ovarian cancer as a TSG and in neuroblastoma as an OCG. This double role has been related to the full-length BARD1 mRNA and other BARD1 isoforms, in which the full-length BARD1 comports as a TSG and is indispensable for cell cycle controlling and for maintaining genome stability. Instead, in cancer initiation and progression, this role would be counteracted by other isoforms, which antagonize the full-length BARD1 isoform activity and allow unrestrained proliferation (Cimmino, Formicola and Capasso, 2017).

Biallelic germline BARD1 mutation in mice was lethal around E7.5-E8.5 day. BARD1 deficient mice failed to gastrulate and suffered from profound morphological defects and proliferation arrest. Similarly, BRCA1 and double BRCA1/BRAD1 knockout mice were incompatible with life and displayed comparable phenotypes resulted from proliferation arrest rather than from excessive apoptosis upon checkpoint activations subsequent to DNA damage accretion. This observation is compatible with the statement about the requirement of BRCA1/BRAD1 heterodimer for normal BRCA1 functions and arouses the crucial co-dependent functions of BRAD1 and BRCA1 in early embryogenesis (McCarthy et al., 2003).

Cell division cycle 73 (CDC73) gene (Tab. 6) has a dual role in cancer, acts as a TSG and an OCG. CDC73 is a constituent of the Wnt signal pathway and codifies a ubiquitously expressed but predominantly nuclear protein, parafibromin, an extremely conserved element in the polymerase-associated factor 1 (PAF1) complex. The parafibromin/PAF1 complex is a transcriptional regulator and histone modifier that interacts directly with RNA polymerase II and regulates cell growth and cell survival (Newey, Bowl, and Thakker, 2009; Walls et al., 2017). Through cooperation between cytoplasmic CDC73 and actin-binding proteins, actinin-2, and actinin-3, CDC73 participates in the organization of the cytoskeletal structure (Newey, Bowl and Thakker, 2009).

The tumor suppression function of CDC73 has been determined through enhancing G1-phase arrest and induction of apoptosis with a concomitant reduction in S-phase entry, leading to down-regulation of an up-regulated OCG in the parathyroid tumor, cell cycle regulator cyclin D1. In controversy, its oncogenic role resulted in enhanced S-phase entry of the cells that express the SV40 large T-antigen (Newey, Bowl, and Thakker, 2009; Walls et al., 2017).

CDC73 mutation is linked to the development of hereditary and non-hereditary parathyroid carcinomas and another autosomal dominant syndrome, which is accompanied by ossifying maxillary and mandibular fibromas, renal and uterine tumors known as hyperparathyroidism-jaw tumor syndrome (HPT-JT) (Newey, Bowl and Thakker, 2009).

Parathyroid carcinomas occur in the majority of the cases sporadically, with only 20% been inherited. The latter displays an earlier onset of the disease and is categorized to isolated familial hyperparathyroidism, or as a component in complex syndromes like MEN1, MEN2A, and HPT-JT (Newey, Bowl and Thakker, 2009).

CDC73 mutation might be providing the parathyroid cells with growing- and aggressive transformation ability. Hence CDC73 mutations are found in up to 100% of sporadic

parathyroid carcinoma, in contrast, in only 0-4% of the sporadic parathyroid adenomas (Newey, Bowl and Thakker, 2009).
CDC73 null mice died at E6.5 day, during the implantation stage. The CDC73 loss and parafibromin deficiency exposed the embryos to growth retardation and increased apoptosis (Wang et al., 2008).

CDH1 gene (also E-Cadherin) is an imperative element in the calcium-dependent cell adhesion cadherin family. Epithelial differentiation and tissue morphogenesis referred to the main function of its product, E-cadherin, which in turn necessitates Ca+2 ions binding for a straight-laced adhesion function and cytoskeletal change synchronization. Carcinogenesis has been linked to heterozygous germline mutations in the CDH1 gene with a wide spectrum of cancers, including lobular breast cancer, and hereditary diffuse gastric cancer. Further, CDH1 mutations are causative in syndromic and non-syndromic cleft lip with or without cleft palate (Selvanathan et al., 2020). CDH1 acts as a TSG (Fiolka et al., 2013).

During the preimplantation phase, Morula compaction and blastocyst formation demand a proper CDH1 function. Loss of this action would result in a default in trophectoderm development leading to embryonic death within Zona pellucida. In consequence, no breeding without maternal blood vessel access would occur. During embryogenesis, cell-type-specific CDH1 expression assures an integral role in cell-cell adhesion and germ layers cell differentiation in cooperation with other CDH family members. Later on, CDH1 maintains tissue integrity, homeostasis, and organ function (Stemmler and Bedzhov, 2010). Mice with CDH1 knockout were not compatible with life due to lack of implantation (Riethmacher, Brinkmann and Birchmeier, 1995).

Cyclin-dependent kinase 4 (CDK4) gene has a crucial biological function. In mammalian cells, driving a cell through the different phases of the cell cycle, especially the transition from G1 to S phase cell cycle, is controlled by CDK4 and other partners in the CDK family through retinoblastoma (RB) family protein phosphorylation. The function of CDK4 is reflected in normal pancreatic B-cell proliferation, ideal growth of the organism, and spermatogenesis (Mettus and Rane, 2003). The latter is achieved through a meiosis-specific function of CDKs, which is requisite for proper finalization of both reductional meiotic divisions during gametogenesis (Palmer, Talib, and Kaldis, 2019).

CDK4 is a potential OCG (Sabir et al., 2012), and its overexpression is found in melanoma (Aoude et al., 2015), glioma, sarcoma, breast tumor, colorectal carcinoma, head and neck squamous cell carcinoma (Sabir et al., 2012), and highly aggressive lymphomas (Sánchez-Beato, Sánchez-Aguilera and Piris, 2003).

Experiments on mouse embryo fibroblast delineated an S-phase entry delay by inactivation of CDK4. In mice, CDK4 plays a role in B-cell proliferation and function. CDK4 Knockout mouse is viable but suffers from poor weight gain, infertility, and insulin-deficient diabetes (hyperglycemia, polyuria, polydipsia, and reduced serum insulin level). Collectively, these specified features noticed by CDK4 knockout mouse are due to a mixture of cell-type-specific defects and disturbed glucose metabolism (Mettus and Rane, 2003).

The cyclin-dependent kinase (CDK) inhibitor 1B (CDKN1B) gene (Tab. 6) encodes p27 protein and is a part of the kinase inhibitor protein/cyclin inhibitor protein (Kip/Cip) family of CDK inhibitors. It is involved in cell cycle progression controlling by negatively regulating cyclin A/CDK2 activity, which is required for G1-cell cycle progression and S-phase entry. CDKN1B gene has a tumor suppressor effect, and its deficiency in tumors is a negative prognostic factor related to rapid cell cycle entry and a high proliferation index (Grey et al., 2013).

Increased CDKN1B expression level is a response to extracellular anti-proliferative signaling, or cAMP and rapamycin cell exposure, which are known as anti-mitogenic factors (Fero et al., 1996).

Constitutional CDKN1B is associated with familial autosomal dominant multiple endocrine neoplasia (MEN1) syndrome, which is labeled by no less than two endocrine tumors, commonly pituitary and parathyroid tumors (Grey et al., 2013). This could be taken in to account in around 20-25% of patients meeting MEN1 criteria, though without detected MEN1 gene mutation (Georgitsi et al., 2007).

CDKN1B null mice were viable, showed normal morphology and overgrowth. The latter was partially attributed to organomegaly without endocrine abnormalities. Spleen and thymus were unevenly enlarged with increased hematopoietic progenitor cells, steady with splenic and thymic hypercellularity. Further, pituitary and ovary hyperplasia were noticed. After ten weeks, all the CDKN1B knockout mice developed pituitary adenoma in pars intermedia. Females were sterile with ovulation and implantation defects (Fero et al., 1996).

CCAAT enhancer binding protein alpha (CEBPA) gene (Tab. 6) is a founder member of CEBP subclasses of the basic region leucine zipper (bZIP) transcription factors family. CEBPA is quite relevant in maintaining homeostasis of embryonic and adult tissues, and regulates several biological cellular processes, including cellular proliferation and differentiation, cell cycle controlling, cellular metabolism, and inflammation process (Lourenço and Coffer, 2017).

As a broadly expressed gene, CEBPA is expressed in adipose tissues, myeloid cells, liver, lung, skin, small intestine, colon, prostate, adrenal gland, pancreas, mammary gland, and skeletal muscles. However, CEBPA is paramountly described in adipocytes and hematopoietic system. CEBPA and PPARγ supervise a two-staged mesenchymal cell differentiation in the direction of fully mature adipocyte by means of a complex signaling cascade. Analogously, CEBPA, CEBPβ, RUNX1, and PU.1 are mandatory in the hematopoietic stem cell differentiation to hematopoietic progenitors during the process of myeloid lineage maturation (Lourenço and Coffer, 2017).

CEBPA does not possess any intron and encodes a protein with two isoforms. Dimerization is imperative for its DNA binding. Transcription factor function abolishment is mostly induced by mutations (in-frame duplications, deletions, or substitutions) in the highly conserved leucine-rich dimerization domain of the CEBPA (Lourenço and Coffer, 2017).

CEBPA is a TSG (Lourenço and Coffer, 2017). Its heterozygous germline mutation has been described to induce autosomal dominant leukemia predisposing syndrome similar to GATA2 and RUNX1, causing particularly acute myeloid leukemia (Tawana et al., 2015).

Apart from hematopoietic cancers, CEBPA mutations have been noticed in many solid tissue cancers like lung, breast, liver, lung, and skin cancer, suggesting a different mechanism of action of CEBPA in solid tissues as in hematopoietic tissues (Lourenço and Coffer, 2017).

CEBPA knockout mice though born alive but died right after birth. The mice displayed anomalies like lung and liver deformity, profound and fatal hypoglycemia, and deficiency in mature eosinophils and neutrophils (Lourenço and Coffer, 2017). Further, Carmona et al. (2002) reported that CEBPA deficient mouse showed defective adipogenesis, diminished mitochondrial size and number, immature mitochondrial morphology, missing of the mitochondrial protein "uncoupling protein 1" (which allows thermogenic capacity in mammals) expression and reduced thyroid hormone ingredients in the developing brown fat.

Ribonuclease III (DICER 1) gene (Tab. 6) is a crucial RNase III enzyme, which is ubiquitously expressed and needed for miRNA maturation. DICER1 is regulated positively through the SOX4 transcription factor and melanocyte master transcriptional regulator MITF and negatively through many miRNS families, including miRNA-192, miRNA-103/107, and the let-7 miRNA family (Aryal et al., 2018).

DICER1 serves as haploinsufficient TSG (Lambertz et al., 2009) with an exceptional deviation from Knudson's two-hit hypothesis, defined as LOF of the germline allele and disturbed protein function with some residual activity of the wild allele after somatic mutation (Kim et al., 2019). Indeed, theretofore only diminished DICER1 protein has been found in tumors, but no LOF mutation (Lambertz et al., 2009).

Monoallelic germline missense and truncation mutation in DICER1 gene results in DICER1 syndrome, which is manifested by macrocephaly, developmental delay, multinodular goiter, lung cyst, gigantism and multi-cancer predisposition (Aryal et al., 2018) such as pleuropulmonary blastoma, Sertoli-Leydig cell tumors, rhabdomyosarcoma, thyroid cancer, cystic nephroma and pineoblastoma (J. Kim et al., 2019).

DICER1 mRNA and protein amount modifications are not only witnessed in cancers, yet further in infertility, aging, and degenerative macular blindness (Aryal et al., 2018).

In humans, biallelic mutation (combination of a germline and a somatic mutation) of DICER1 has been attributed to a small fraction of Wilms tumors (Wu et al., 2013).

DICER1 deficiency in mice is found to be embryonically lethal at E7.5 day (Liu et al., 2012), as a result of the loss of pluripotent stem cells and inadequate blood vessel development (Albinsson et al., 2010).

FAM175A gene (Tab. 6) codifies an ABRAXAS (FAM175A) protein, which is a coiled-coil domain-containing protein involved in DNA damage repair (DNA end resection during HR) and G2/M checkpoint controlling. Its loss increases cellular single-strand DNA level and subsequently genome instability. ABRAXAS collaborates with BRCA1 BRCT (BRCA1 carboxyl-terminal) domain, inducing BRCA1 recruitment to DNA damage site. Loss of this interaction is behind G2/M checkpoint controlling defects upon exposure to ionizing radiation (Renault et al., 2016).

FAM175A is a TSG (Castillo et al., 2014), and its germline mutations have been reported in breast cancer, ovarian cancer, lymphoma of the throat, pulmonary carcinoma, and upper aerodigestive tract cancers, cutaneous lymphoma, Kaposi sarcoma (Kastnerova et al., 2020), and endometrial cancer (Castillo et al., 2014).

However, in contrast to BRCA1, FAM175A is dispensable during embryogenesis and postnatal development. FAM175A null mice were viable with no developmental defects, though they died within four weeks after radiation exposure. Further, 60% of FAM175A (-/-) mice developed tumors, mostly lymphoma (Castillo et al., 2014).

Foliculin (FLCN) gene is a TSG with not well-understood activity that perhaps collaborates with adenosine monophosphate-activated protein kinase (AMPK), a substantial cell energy sensor that negatively directs the mammalian target of rapamycin (mTOR) signaling pathway, the central regulator of cell growth and proliferation. The consequence of FLCN gene heterozygous germline mutation is the Birt-Hogg-Dube' syndrome, which points to the potential development of clinical manifestations like pulmonary cysts, fibrofolliculomas, spontaneous pneumothorax, and renal cell carcinoma (Baba et al., 2008; Hasumi et al., 2009).

For elucidation of its function, a trial with FLCN knockout mouse models has been undertaken. As early as E5.5-E6.5 day the FLCN knockout mice exhibited embryonic lethality. The described phenotype of null FLCN mice covered the lack of proamniotic cavity and bilayered ectoderm structure configuration with polarity loss of visceral endoderm. The latter may be induced through LKB1/AMPK signaling modification by loss of FLCN function (Hasumi et al., 2009).

GATA binding protein 2 (GATA2) gene (Tab. 6) is a highly conserved and functionally indispensable transcription factor that belongs to the zinc finger family. GATA2 identifies the consensus sequence 5′ (A/G)GATA(A/T) 3′ by its two C4-type zinc fingers, which provides the GATA2 DNA binding activity. GATA2 is extensively expressed with a particularly vital role in hematopoiesis (Hoshino et al., 2008), neural, urogenital, and vascular development. Owing to the frequent presentation of GATA2 mutation in primary lymphedema, the GATA2 role in lymphatic vasculature has been explicitly investigated. Lymphatic vessels are cardinal in maintaining tissue fluid homeostasis, transportation of immune cells, and dietary fat absorption (Kazenwadel et al., 2012).
It has been demonstrated that GATA2 is expressed in lymphatic vessels of embryonic and adult mice with a significantly high level of GATA2 in the leaflets of lymphatic vascular valves. Besides, loss of GATA2 extinguishes the expression of genes that are momentous for valve development like PROX1, FOXC2, ANGPT2, and ITGA9 (Kazenwadel et al., 2012).

GATA2 acts as a TSG (Menendez-Gonzalez et al., 2019). Heterozygous germline GATA2 mutation within the conserved second zinc finger causes various phenotypes ranging from a leukemic predisposition syndrome, namely myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML), to DCML deficiency (syndrome of dendritic cell, monocyte, B and NK lymphoid deficiency), "MonoMAC" syndrome (syndrome of monocytopenia with non-tubercular mycobacterial infection predisposition) (Kazenwadel et al., 2012), and Emberger syndrome (primary lymphedema with myelodysplasia or leukemia). The patients present mostly with immune deficiency, warts, and proneness to recurrent viral and fungal infections, denoted by a later onset than the classical immunodeficiency. Bone marrow hypocellularity and cytopenia might lead to initial diagnosis as aplastic anemia. This necessitates GATA2 mutation screening prior to bone marrow transplantation in aplastic anemia cases and their family donors (Hsu, McReynolds and Holland, 2015).
GATA2 null mouse would not survive the embryonic period and die at E10.5 day from a severe hematopoiesis failure (Hoshino et al., 2008).

Homeobox B13 (HOXB13) gene (Tab. 6) is a member of the homeobox gene family, which codifies homeoprotein transcriptional factors. They are with their activation and suppression effect on their downstream target genes, the major constituents of the master regulatory pathways in organogenesis and oncogenesis. Homeoproteins are in charge of proper embryonic anterior-posterior axis formation during embryogenesis. HOXB13 is a critical androgen receptor-interacting suppressor and one of the widespread mutated genes in solid tumors within the HOX family (Bhatlekar, Fields and Boman, 2014).
HOXB13 is expressed during early embryogenesis at the time of posterior segment development and continues to be expressed in colon and prostate tissues through adulthood (Ostrander and Decker, 2014).
Heterozygous germline HOXB13 mutation is related to an increased risk of non-aggressive prostate cancer at a young age. Development and differentiation of normal and even cancerous prostate are facilitated by the interaction of the HOXB13 gene with androgen receptors. HOXB13 evinces a bi-phasic role in cancers, as a TSG and as an OCG, without a known precise mechanism of action in carcinogenesis (Hussein, Satturwar and Van der Kwast, 2015).

The expression studies in prostatic cancer cell lines have supposed that HOXB13 functions through androgen receptors in both normal and cancerous prostatic tissues. However,

discordant results complicate the separation of its biological roles, as its role in prostatic and other malignancies like colorectal carcinoma is complex and contradictory. The tumor suppression effect of the overexpressed HOXB13 in prostatic cancer cell lines and other cancers were contributed to its suppression of transcription factor T-cell factor 4, which in turn inhibits cell cycle regulator cyclin D1, and c-myc, leading to cell cycle arrest at G1-phase. Persistent growth of the androgen-independent tumors has been interpreted through the statement that HOXB13 inhibits cell cycle within the context of androgen receptor expression and promotes the cell cycle by the absence of androgen receptors through p21 tumor suppressor gene suppression. In prostatic, renal, and colorectal carcinoma, HOXB13 exhibits a tumor-suppressive role (Ostrander and Decker, 2014). Simultaneously, higher prostatic cancer aggressiveness with an unfavorable outcome was manifested by HOXB13 expression (Cardoso et al., 2016). Further, in breast cancer, HOXB13 promoted tumor cell invasion and migration, and tamoxifen resistance (Ostrander and Decker, 2014).

HOXB13 knockout mice were viable and fertile. Phenotypically, they showed longer and thicker tails. Tail bud derived structures like the caudal spinal ganglia, the developing secondary neural tube, and the caudal vertebrae, displayed overgrowth compared to heterozygous and wild type allele mice. These manifestations establish an inhibitory effect of the HOXB13 gene on neural cell proliferation and caudal vertebrae growth, besides, an activating effect on secondary neural tube apoptosis pathways (Economides, Zeltser and Capecchi, 2003).

kinesin family member 1B (KIF1B) gene (Tab. 6) encodes a corresponding protein that is a member of the Kinesin superfamily proteins (KIFs), which mainly function in intracellular transporting of fundamental substances to particular stations by acting as microtubule molecular motors (F. Xu et al., 2018). The cargoes of KIFs involve mitochondria, tubulin oligomers, lysosomes, endocytic vesicles, mRNA complexes, membranous organelles, macromolecular complexes, and intermediate filament proteins (Hirokawa and Takemura, 2003).

KIF1Bβ is one of the splicing isoforms of KIF1B with a requisite function in neuronal function, morphogenesis, and survival (F. Xu et al., 2018). KIF1Bβ is essential for developmental apoptosis upon nerve growth factor (NGF) withdrawal (Chen et al., 2014).

KIF motor proteins contribute significantly to the pathogenesis of various diseases. Mice with a heterozygous mutation in the KIF1B gene developed neuropathy later in life. Further,

hereditary peripheral neuropathy, Charcot Marie Tooth type 2A (CMT2A), has been mapped in a KIF1B-comprising chromosome region (Hirokawa and Takemura, 2003).
KIF1B (−/−) mice manifest defects in both sensory- and motor nerve functions (Hirokawa and Takemura, 2003). The mice were viable and showed brain abnormalities, including reduced volume, hypocellularity and underdevelopment of the brain stem nuclei and commissural fibers, and exhibit neonatal death ascribed to apnea (F. Xu et al., 2018).
KIF1B is a TSG (Alonso et al., 2005). The germline KIF1Bβ mutation predisposes to pheochromocytoma, neuroblastoma, ganglioneuroma, and lung adenocarcinoma (Yeh et al., 2008).

The MYC associated factor X (MAX) gene is the newly identified member of the PCC causing genes. PCC represents a neuroendocrine adrenal medulla tumor with low metastatic potential, resulting in life-threatening hypertension due to catecholamines overproduction. SDHA, SDHB, SDHC, SDHD, SDHAF2, VHL, RET, TMEM127, and NF1 are the recognized genes that their germline heterozygous mutations result in the familial autosomal dominant inherited PCC (Comino-Méndez et al., 2011).

Cell multiplication, differentiation, and programmed cell death are controlled by a network of basic helix-loop-helix leucine zipper transcription factors, MYC-MAX-MXD1, to which belongs a highly conserved unit, MAX protein, that serves DNA binding and protein-protein synergy. Its expression diminishes cell proliferation and its inactivation the contrary; this aids its role as a tumor suppressor (Comino-Méndez et al., 2011).
Reticulation between MYC-MAX-MXD1 network and NRAS-PIK3CA-AKT1-mTOR axis explains, to some extent, PCC development by any modifications in the MYC network (Comino-Méndez et al., 2011).

Monoallelic MAX knockout mouse models were breed to study the role of the MAX gene in embryonic development. No homozygous null MAX mice were produced. Early postimplantation interval (E3.5-E7.5) was critical, and homozygous MAX mice displayed developmental arrest shortly after implantation with no evident embryonic peculiarity or obvious embryonic and extra-embryonic distinct line. The stored maternal MAX and the stable nature of the protein owed to be behind their survival to E5.5-E6.5 day. The developmental arrest might be related to reduced cell proliferation, metabolic failure, and to a

lesser degree, cellular apoptosis. Taking all the facts into account, this validates the vital role of MAX expression in embryogenesis (Shen-Li et al., 2000).

Neurofibromin 2 (NF2) gene (Tab 6) is a TGS with presumed cytoskeletal-associated activity and enciphers merlin protein (Moesin-Ezrin-Radixin-like proteIN), which is referred as schwanommin as well. It provides the ordinary cytoskeletal constitution by operating on transmembrane signaling, actin cytoskeleton, and cell-cell-adhesion junction points. Merlin displays a regulative involvement in many cascade pathways, including the RAS/MEK/ERK and the PI3K/AKT/mTOR pathways (Ruggieri et al., 2016).

Monoallelic mutation in the NF2 gene is known to predispose the autosomal dominant neurofibromatosis 2, with hallmarks of schwannomas formation (vestibular "mostly bilateral," cranial, spinal and cutaneous nerves), meningiomas (spinal, cranial or optic nerve sheath), astrocytomas, ependymomas, hamartomas (retinal or pigment epithelial), cataracts, NF2 plaques and rarely CAL spots. Neurological demonstrations depend on the existence, siting point, and extension of the mentioned lesions. There is a corresponding linkage of genotype to phenotype according to the type and position of the pathogenic variant in the NF2 gene. A severe truncating mutation would understandably induce a disease with earlier onset, more profound manifestations, more tumors, and earlier death (Ruggieri et al., 2016).

Experiments on NF2 null mice showed that the biological NF2 gene function is important in early embryonic development, as NF2 knockout mice displayed developmental arrest at E6.5-E7.0 day, suffering from deficiently structured extraembryonic ectoderm, unsophisticated extraembryonic structure formation, misorientation, and gastrulation failure. This signifies the essential role of merlin in extraembryonic ectoderm organization during embryogenesis, but also the correlation of its loss in tumorigenesis in human (McClatchey et al., 1997).

Nuclear receptor binding SET domain containing protein 1 (NSD1) gene (Tab. 6) is one of the three members of the NSD family. During embryonic development, NSD1 executes an important role in postimplantation development. It is expressed in skeletal muscle, spleen, brain, thymus, bone periosteum, peripheral blood leucocytes, and lungs. NSD1 interacts through its two distinct nuclear receptor-interacting domains (NIDs) with different subsets of nuclear hormone receptors through their ligand-binding domains, so diversely comports as co-repressor or as co-activator on the target gene expression (transcription) (Visser and Matsumoto, 2003).

The highly conserved SET domain of NSD1 has an intrinsic histone methyltransferase activity, which methylates H3-K36 and H4-K20. Impaired histone methylations could lead to the deregulation of developmental-related genes (Rayasam et al., 2003).

Defects like intragenic mutations and submicroscopic microdeletions in the NSD1 gene result in Sotos syndrome (SoS), which is identified by overgrowth, developmental delay, distinctive craniofacial dysmorphic features, and advanced bone age. SoS is inherited autosomal dominantly in familial cases, although the autosomal recessive pattern has been mentioned, but not supported due to lack of convenient data. The relation of SoS with cancer predisposition is disputed. For the overgrowth in SoS is the loss of NSD1 principal co-repressor function on growth-enhancing genes speculated. Infertility, abortion, and stillbirth have been contributed to the small percentage of the familial cases among reported SoS cases (Visser and Matsumoto, 2003).

NSD family members have main functions in cell growth control and cell differentiation (Rayasam et al., 2003). They are aberrant OCGs and have been involved in malignancies (Morishita, Mevius and di Luccio, 2014) like acute myeloid leukemia, multiple myeloma, and lung cancers (Wang et al., 2007). NSD1 gene is identified in acute myeloid leukemia in children as a fusion transcript with the nucleoporin gene (NUP98) in a recurrent translocation, t(5;11)(q35;p15.5) (Rayasam et al., 2003).

Mice heterozygote for NSD1 mutation did not develop SoS. NSD1 genetically-ablated mice were incompatible with life and died before the E10.5 day (Visser and Matsumoto, 2003). They were affected by severe growth retardation due to increased apoptosis, and showed abnormal gastrulation process, and mesodermal defects (Rayasam et al., 2003).

Platelet derived growth factor receptor alpha (PDGFRA) (Tab. 6) is one of the two identified PDGF receptors with a broader specificity for ligand binding as PDGFRB. It binds PDGF-A, PDGF-B, PDGF-C ligand homodimers, and PDGF-AB heterodimers, leading to the activation of various and overlapping intracellular pathways. Mesenchymal cells generally express the PDGF receptors, while epithelial and endothelial cells express PDGF ligands (Brennan, Tilmann and Capel, 2003).

Platelet-derived growth factors (PDGFs) are derived from platelets and involved in vascular biology. They control biological processes such as cell growth and survival, cell morphology and movement, including scattering, chemotaxis or deposition of extracellular matrix (Soriano, 1997).

PDGFRA has a sex-specific role in promoting cord formation, proliferation, endothelial cell migration, and Leydig cell differentiation (Brennan, Tilmann and Capel, 2003). Further, the activity of PDGF-A and its receptor PDGFR-α regulate the proliferation and differentiation of a subset of the mucosal mesenchymal cells required for the villus morphogenesis in the gastrointestinal tract (Karlsson et al., 2000).

Regarding its role in carcinogenesis, PDGFRA acts as an OCG, its heterozygous mutation is identified in glioma (Flavahan et al., 2015), myeloid neoplasms with eosinophilia (Reiter and Gotlib, 2017), sporadic inflammatory fibroid polyps and familial PDGFRA-mutation syndrome. The latter is inherited autosomal dominantly and manifested by a unique phenotype includes coarse skin and faces, broad hands and feet, premature tooth loss, multiple small bowel inflammatory fibroid polyps, and gastrointestinal stromal tumor (Manley et al., 2018).

A targeted PDGFRA null mutation in mice was lethal around E14.5-E16.0 day. The embryos showed severe developmental defects, including growth retardation, anterior-posterior axis turning failure, hemorrhage in head and neural tube, subepidermal blebs, dilated pericardium, defective yolk sac vasculature, edema, bulging of the liver from the abdominal wall musculature, skeletal abnormalities in the skull (incomplete cephalic closure), acromion of the scapula, ribs, sternum and in the vertebral column (mostly cervical and thoracic) resulted in spina bifida (Soriano, 1997), defects in testis cord formation and vascular development (Brennan, Tilmann and Capel, 2003), and abnormal mucosal lining structure of the gastrointestinal tract (Karlsson et al., 2000). The cause of death was linked to the extensive hemorrhage in the embryos (Soriano, 1997).

There was increased apoptosis on pathways followed by migrating neural crest cells. The neural tube defects, the vertebral and rib abnormalities were related to myotome patterning deficiency. This indicates that PDGF signaling is crucial for cranial neural crest development, the survival of other cells, and for the normal patterning of the somites (Soriano, 1997).

Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) gene (Tab. 6) encodes the p110α catalytic subunit of the lipid kinase, phosphatidylinositol 3-kinase (PI3K). The latter is part of the PI3K/AKT pathway and is involved in cell proliferation, cell metabolism, protein synthesis, angiogenesis and apoptosis (Lai, Killingsworth and Lee, 2015). Receptor tyrosine kinases (RTKs) like epidermal growth factor receptor (EGFR), insulin receptor, and G-protein coupled receptor (GPCR) are upstream growth factors that control the class I PI3K activity. Class I PI3K stimulates phosphatidylinositol (3,4,5)-trisphosphate

(PIP3) production by phosphorylating PIP2. PIP3 could be dephosphorylated back to PIP2 through antagonizing the PI3K pathway by PTEN, which acts as an upstream and downstream PI3K activity regulator. An increased concentration of PIP3 at the plasma membrane leads to protein kinase B (PKB, also known as AKT) activation, which regulates cell proliferation and cell apoptosis, and inhibits autophagy (Lai, Killingsworth and Lee, 2015).

PIK3CA mutations and amplifications result in loss of PI3K dependency on growth factor-mediated upstream signaling leading to unrestrained production of PIP3, which could not be dealt with by PTEN inhibition, resulting subsequently in uncontrolled AKT activation. The latter leads to tumor cell proliferation and tumor progression, or cancer cell cycle disruption (Lai, Killingsworth and Lee, 2015).

PIK3CA is an OCG, and its mutation has been identified in a variety of cancers, such as colorectal cancer in (15-20%), breast cancer in (40%), and head and neck squamous cell carcinoma in (6–21%) of the corresponding cases (Lai, Killingsworth and Lee, 2015).

Mice with PI3KCA deletion were not compatible with life and died at E9.5-E10.5 day, which is the period of increased demand for proliferation and differentiation for organogenesis and placentation. The embryos were growth-retarded, showed delayed development, defective angiogenesis and hemorrhage at the forehead, snout, and other parts of the body.

Failure of PIK3CA deleted embryos to proliferate following growth factor signaling has been related to the developmental delay and growth failure of the embryos, rather than increased apoptosis (Bi et al., 1999).

The type 1 regulatory subunit (R1) of cyclic adenosine monophosphate (cAMP) dependent protein kinase (PKA) (PRKAR1A) gene is a serine/threonine kinase activity regulator in the cAMP signaling pathway, a pathway which is included in many cellular processes like, cell proliferation, cell metabolism regulation, cell differentiation and programmed cell death. There is analogous monitoring between the overactivity of the PRKAR1A gene and cancer development of the poor prognostic type. This had led to the declaration of PRKAR1A blockade as a perception in the specific cancer treatment (Bossis and Stratakis, 2004).

A deleterious inactivating mutation in the PRKAR1A gene transmits dominantly and results in a wide spectrum of manifestations known as the Carney complex (CNC), characterized by myxoma, skin pigmentation, schwannomas, and endocrine overactivity. The manifestations could be roughly categorized in endocrine and non-endocrine presentations. The endocrine presentations include hormone-producing pituitary adenoma, ovarian cysts, large cell

calcifying sertoli cell tumor, thyroid carcinoma or adenoma, and adrenocortical disease, whereas the non-endocrine manifestations involve myxoma, schwannoma, trichofolliculo-epitheliomas, rarely osteochondromyxoma and breast ductal adenoma (Bossis and Stratakis, 2004).

Diminished PKA activity is induced by activating PRKAR1A mutations that decrease connection to cAMP (Le Stunff et al., 2016). This is a potential mechanism of the PRKAR1A gene in a distinct autosomal dominant skeletal disorder known as Acrodysostosis, a group of clinical and radiological skeletal manifestations including short stature, nasal hypoplasia, brachydactyly and developmental retardation (Muhn et al., 2013).
PRKAR1A acts as a TSG and as an OCG. Its loss of heterozygosity has been observed in CNC tumor cases and also in sporadic tumors. On the other hand, there are tumor cases with normal PRKAR1A protein level, and this contradicts the two-hit theory of Knudson (Bossis and Stratakis, 2004).
Biallelic knockout of the PRKAR1A gene in mice is lethal (Bossis and Stratakis, 2004; Saloustros et al., 2015) during early embryogenesis resulting from the failure of mesodermal structural development, which is referred to the consequent enhanced and dysregulated PKA activity (Kirschner, 2009).

PATCHED1 (PTCH1) gene is a TSG, suppresses the sonic hedgehog pathway through its encoded transmembrane protein. Gorline syndrome is the product of heterozygous germline mutation in this gene, in which the affected individual exhibits congenital findings like skeletal deformities, odontogenic keratocysts, broad facies, falx cerebri calcification, palmar/plantar epidermal pits and is prone to specific type of carcinomas, such as basal cell carcinoma, fetal rhabdomyoma, ovarian and cardiac fibromas, meningioma and medulloblastoma. Gorline syndrome is an autosomal dominant disorder (Scanlan et al., 2008) and is mostly due to deleterious or inactivating PTCH1 mutation, whereas activating PTCH1 mutation predisposes to another different syndrome named Holoprosencephaly 7 (Derwińska et al., 2008).
PTCH1 is essential during embryogenesis. A mouse model with PTCH1 knockout was not compatible with life and experienced lethality around E9.0-E10.5 day, distressed with inadequate neural tube closure and asymmetrical neural tube hypertrophy in specific regions like the spinal cord, midbrain, and head folds. This emphasizes the role of PTCH1 in growth

control and the direction of the early neural structure development during embryogenesis (Goodrich et al., 1997).

Phosphatase and Tensin homolog (PTEN) gene (Tab. 6) encodes a dual-specificity protein phosphatase. PTEN is a TSG cited as a prominent negative cell growth regulator and cardinal tissue patterning determinant factor. PTEN negatively regulates the phosphoinositide 3-kinase (PI3K) signaling pathway, which concerned with cell growth, cell proliferation, and cell survival, by removing a 3′-phosphate from phosphatidylinositol-(3,4,5)-trisphosphate (PIP3), producing PIP2 (phosphatidylinositol- (4,5)-bisphosphate), thereby modifies the activity of downstream effectors of the PI3K pathway, like deactivation of AKT-mTOR signal pathway (Tachibana et al., 2018).

Heterozygous germline mutation in PTEN is the underlying defect in an autosomal dominantly inherited disorder known as PTEN hamartoma tumor syndrome (PHTS). The latter covers miscellaneous clinical presentations, including autism spectrum disorder, brain patterning defects (Lhermitte–Duclos disease) and cancer predisposition syndromes (Cowden syndrome). In contrast to the phenotypic diversity, there is a common shared manifestation between all PHTS cases, which is hamartoma, an abnormal malformed benign tissue overgrowth containing disorganized normal cellular components arising from entire embryological lineages. Hamartomas are frequently observed in skin, vasculature, connective tissue, retina, gastrointestinal tract, and central nervous system. In the latter, hamartomas could have a calamitous impact on the tissues, inducing neurological manifestations, including epilepsy and ataxia. Along with hyperplasia found in hamartomas, there is an increased tendency for malignant transformation mostly in the breast, endometrium, thyroid gland (Tachibana et al., 2018), brain and prostate gland (Suzuki et al., 1998).

PTEN knockout in mice led to early embryonic lethality, around E9.5 day (Kishimoto et al., 2003; Suzuki et al., 2008), showing morphogenetic defects like failure of a correct specification of the anterior-posterior body axis and aberrant migration of cells of the anterior visceral endoderm, and defects in the migration of mesoderm and/or endoderm (Bloomekatz et al., 2012).

RAD51 paralog B (RAD51B) gene (Tab. 6) is a member of the RAD51 recombination-repair family, which further includes RAD51C, RAD51D, XRCC2, and XRCC3. Subsequent to DNA damage, RAD51 proteins are recruited to the nucleus, where they interact with P53 and regulate cell cycle progression. RAD51B has been classified as a RAD51 ortholog, and it is

an ionized- and UV radiation-induced gene (Shu et al., 1999). A vital role of RAD51B has been related to DNA repair through HR, and its inactivation is involved in tumorigenesis (Wadt et al., 2015).

RAD51B forms a fusion gene upon translocation with the HMGC1 gene, which is found in leiomyoma (Shu et al., 1999). RAD51B germline mutation also predisposes to familial melanoma and early-onset breast cancer (Wadt et al., 2015). In cervical cancer, RAD51B acts as a TSG. However, its overexpression in gastric cancer has been related considerably to invasive differentiation, tumor stage advancement, and lymph node metastasis (Chen et al., 2020).

RAD51B knockout mice were not compatible with life, and they exhibited severe growth retardation and proamniotic cavity formation failure and died around E5.5-E6.5 day. However, parallel to RAD51-, BRCA1-, BRCA2 knockout mice, a P53-null background was able to progress further the embryonic development of the RAD51B (-/-) embryo to E8.5-E9.5 day, this indicates that the role of RAD51B in cell proliferation and early embryonic development is accomplished through its cooperation with P53, and that the connection between these genes is required for essential cellular processes like transcription, DNA repair, and cell cycle regulation (Shu et al., 1999).

RAD51 paralog D (RAD51D) gene settles on the telomere. With its 39% structure and sequence similarity to RAD51 is one of the components of the central RAD51 protein family, which incorporates RAD51B, RAD51C, RAD51D, XRCC2 and XRCC3 with their primary function been concerned in the HR pathway. The latter is chargeable for normal growth and development, meiotic chromosome segregation, genetic variety, and the process of repairing DNA DSBs that arise mainly from DNA replication, after exposure to environmental DNA damaging agents or chemotherapy, and from antigen receptor gene rearrangements. HR sustains genome stability and provides impedance against these DNA damaging factors (Smiraldo et al., 2005).

The significance of RAD51D participation in HR is seen in two facets of the pathway, the first in strand invasion and secondly in the resolution of Holliday junction by its direct interaction with BLM helicase protein (Smiraldo et al., 2005).

Genomic instability (deletions, complex chromosome rearrangements, aneuploidy, enhanced centrosome fragmentation, radiation-induced RAD51D foci formation failure, and hypersensitivity to DNA damaging agents), p53 activation-mediated proliferation failure

(caused by telomere dysfunction) and increased apoptosis had made the RAD51D deficient mouse embryo face lethality at E10.5 day (Smiraldo et al., 2005).

The nature of the lethality was nonspecific in a way that no specific structural defect could be linked to the non-compatibility with life, but proliferation deficiency was suggested. The RAD51D null mouse manifested embryonic turning failure, delayed development, truncation of the caudal tail region, small brain vesicle size, limb bud disorganized tissues, and pericardial swelling, pointing to multiple structure organization inadequacy (Pittman and Schimenti, 2000).

RAD51D is a TSG (Wickramanyake et al., 2012). Heterozygous germline mutation in RAD51D has been observed in clinical cases with breast and ovarian cancer (Pelttari et al., 2012).

RB transcriptional corepressor 1 (RB1) gene is a TSG, based on which the famous Knudson's two-hit hypothesis regarding retinoblastoma formation was suggested. RB1 gene protein is a nuclear phosphoprotein. In G1-cell growth stage and G0-rest stage of the cell cycle stays the protein hypophosphorylated (Clarke et al., 1992).

Mutation in both alleles of the RB1 gene leads to retinoblastoma, an inherited as well as a non-inherited pediatric tumor of the retina. Heterozygous carriers of the RB1 gene mutation are predisposed to a highly penetrant form of retinoblastoma development (Benedict et al., 1990), mostly bilateral and 17-18% unilateral (Foster et al., 2017), with the consequence of 50% risk of inheriting the predisposition. The disease would be detected before the age of 5 years. The RB1 mutation carrier would gain the second somatic mutation prior to the retinoblastoma development, while by sporadic cases, both gene copies are somatically inactivated (Tomar et al., 2017).

Apart from retinoblastoma, RB1 deficiency is the driving force for the development of many other types of malignancies like breast, bladder and lung cancers, soft tissue sarcoma, and osteosarcoma. It is questionable, whether RB1 total inactivation initiates carcinogenesis or is involved in its progression since RB1 deficiency per se is scanty for tumor development (Benedict et al., 1990). While rarely RB1 loss cannot be identified in retinoblastoma patients, thus the involvement of other genes has been presumed (Tomar et al., 2017). Another vagueness regarding the correlation of genotype/phenotype is that a large RB1 gene deletion results either in no tumor development or a tumor with low penetrance. This had led to focusing on further targets that are essential for the survival of retinoblastoma cells, concretely, the highly conserved MED4 gene in the adjacent genomic region to RB1, which

connects the polymerase II machinery with gene-specific transcription factors (Dehainault et al., 2014).

Trials on mice were undertaken to show the role of the RB1 gene in the embryonic development. Mice with heterozygous RB1 mutations were phenotypically indistinguishable from mice with wild alleles and showed no sign of retinoblastoma at a perceptible periodicity, which contrasts the condition in humans. RB1 knockout was lethal during embryogenesis. The knockout embryos experienced many deformities and were tested between E10.5-E12.5 day, and death even before that period could not be excluded. The malformations in mice covered retardation, head deformity (reduced frontal lobe size, remarkable fourth ventricle, and forehead compression), erythropoiesis failure, no apparent blood vessels in the yolk sac with evidence of spinal cord apoptosis, spinal ganglia pontine flexure, myelencephalon, and even prosencephalon; however, eyes were not damaged. This was interpreted through the fact that the RB1 null mice could not come so far in the embryonic development for their retina to be influenced. It could be shown that the RB1 gene is substantial for precursor cell differentiation and to keep the cells in the growth arrest phase of the cell cycle to desensitize the cells against apoptosis (Clarke et al., 1992).

Rhomboid 5 homolog 2 (RHBDF2) gene (Tab. 6) is an inactive member of the rhomboid serine intramembrane protease family. RHBDF2 controls the maturation of ADAM 17 (or TACE), a cell membrane metalloproteinase, and assists its transport from the endoplasmic reticulum to the Golgi and later to the cell surface (Chenxu et al., 2018), which is the TNF cleavage site (Adrain et al., 2012) when the pro-inflammatory cytokine TNF-α is secreted by macrophages (Q. Xu et al., 2019). ADAM 17 is a TNF-α convertase with a variety of substrates like TNF-α, TNFR, epidermal growth factors, and adhesion proteins (Chenxu et al., 2018).

RHBDF2 is concerned with skin wound healing and keratinocyte proliferation. Heterozygous GOF mutation in RHBDF2 subtends the autosomal dominant Tylosis with oesophageal cancer (TOC), resulting in the up-regulation of cytoskeletal stress-associated Keratin 16, with vigorous K6 downregulation, its type II keratin binding partner. TOC highly predisposes to oesophageal carcinoma of squamous cell type and is manifested by a palmoplantar thickening. Conversely, in RHBDF2 deficient mice, there is lack of K16 expression and RHBDF2 null mice show thin footpad epidermis, reduced keratinocyte hyperproliferation, and migration. K16 is highly expressed in the palmoplantar epidermis, and can be induced in

hyperproliferative states like skin inflammation, skin wound healing, and cancer. Further, K16 plays a biomarker role in squamous cell carcinoma in nasopharynx, oesophagus, and cervix. The keratinocyte of TOC revealed an increased ADAM17 activity with enhanced ectodomain shedding of its substrates (Maruthappu et al., 2017).

RHBDF2 deficiency enhances further the Wnt/β-catenin signaling pathway, which plays a leading role in cancer cell proliferation, differentiation, survival, and epithelial-mesenchymal transition (Q. Xu et al., 2019).

An oncogenic activity has been closely tied to many proteins of the iRhom family in specific cancers. Impaired RHBDF2 level in esophageal cancer underlies EGFR signal pathway stimulation, which in turn leads to hyperproliferation. In cervical cancer, RHBDF2 overexpression promoted cancer cell proliferation, consistent with this result, downregulation of RHBDF2 caused increased cancer cell apoptosis and cell cycle arrest at the G1-phase with decreased cell level in the S-phase, comparable to RHBDF2 effect on colorectal carcinoma. These observations point to the oncogenic RHBDF2 activity in cervical cancer (Q. Xu et al., 2019).

Adrain et al. (2012) reported about RHBDF2 (−/−) mice, which were viable, fertile, and showed no phenotypical deformities. However, they displayed very low serum TNF concentration after a bacterial infection emulation by challenging with the lipopolysaccharide.

Runt-related transcription factor (RUNX) family proteins (Tab. 6) with their three RUNX genes are master regulators of embryonic development. They are highly conserved and entangled with almost all necessary cellular processes like proliferation, differentiation, cell lineage specification, and apoptosis. Depending on the biological context, a dual and contrary function of RUNX genes has been discussed, as they act as OCGs when they are over-activated and as TSGs/OCGs during retroviral insertion-induced transcriptional activation, so classifying them within these two groups is difficult. However, RUNX genes are mostly defended to be OCGs relying on some evidence including: the oncogenic lineage-specific property of the fusion proteins which prohibits normal RUNX complex function, the oncogenic property of the RUNX ‘wild type’ genes in transgenic mice, functional amplification relevance of the RUNX1 in hematological diseases, and experimental-based evidence suggesting retroviral insertion-induced RUNX gene expression deregulation in murine lymphoma. Similarly, antagonizing the RUNX1 ‘wild type’ gene function by RUNX1 fusion protein and mutation-induced RUNX3 function reduction aid their LOF in cancer (Otálora Otálora et al., 2019).

RUNX1 plays a role in hematopoietic cell differentiation and hematopoietic stem and progenitor cell regulation during embryogenesis, and during adult life, in lymphocyte and megakaryocyte maturation. Its haploinsufficiency is expected to predispose leukemia, and its overexpression is found in solid tumors like skin, breast, lung, and intestinal cancers (Otálora Otálora et al., 2019).

The RUNX genes have comparable genomic structure and codify an alpha subunit known under many names like DNA binding factor polyomavirus enhancer-binding protein 2αA subunit (PEBP2α) or acute myeloid leukemia (AML) or core-binding factor subunit α (CBFα). The alpha subunit of RUNX (DNA-binding subunit) combines with CBFβ (non-DNA-binding subunit) to forms a heterodimeric transcription complex, PEBP2/CBF, changing the structure of the alpha subunit, unmasking its DNA binding site, and enhancing its DNA binding affection to practice its function as a sequence-specific transactivator.
The target genes of RUNX1 are driving cellular processes like hematopoietic differentiation, ribosomal biogenesis, cell cycle regulation, and controlling of TGF-β and p53 signaling pathways. RUNX1 controls their expression by interacting with coactivators or corepressors through its terminal C-domain (Otálora Otálora et al., 2019).

Somatic chromosomal translocations that occur between RUNX1 and counterpart genes result in chimeric genes deemed to be accountable for leukemogenesis by inhibiting RUNX1 function (Okada et al., 1998), namely, RUNX1-ETO fusion protein which induces acute lymphoid leukemia (ALL), and t(3;21) AML1-Evi1 which instigates acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and chronic myelogenous leukemia blast crisis. Nevertheless, leukemogenesis is promoted by RUNX1 overexpression as well, as it is seen in Down syndrome, in which an additional RUNX1 allele causes megakaryoblastic leukemia in newborn and children (Otálora Otálora et al., 2019).

Monoallelic germline mutation in the RUNX1 gene leads to an autosomal dominant, familial platelet disorder with a propensity to myeloid malignancy (FPD/AML), which exhibits quantitative/qualitative platelet defects with a tendency to progress to primarily myeloid malignancies, such as MDS and AML by additional “subclonal” mutations (Hayashi et al., 2017).
Mice with RUNX1 (-/-) died around E12.5-E13.5 day, displaying hemorrhages mainly in the central nervous system and defective hematopoiesis in fetal liver (Kundu et al., 2005), a

similar finding is observed even in mice heterozygote for an AML1-ETO allele (Yergeau et al., 1997).

SMAD4 - SMAD family member 4 gene (Tab. 6) acts as a cardinal extracellular signal transducer in transforming growth factor-β (TGF-β) and BMP signaling pathways. TGF-β super family embraces a large group of growth factors that function principally in critical biological processes such as cellular growth, proliferation, differentiation, angiogenesis, migration, apoptosis, and tumorigenesis. In the latter process, a biphasic role of TGF-β protein has been reported, initial cell cycle arrest and apoptosis induction as TSG, and later, induction of angiogenesis, invasion, and metastasis as OCG. The TGF-β/SMAD4 pathway is under massive control of a complex of pathway networks like Wnt/β-catenin, PI3K/AKT, and MAPK pathways, and constrains tumorous cell proliferation predominantly by cell cycle arrest and apoptosis induction (Zhao, Mishra and Deng, 2018).

SMAD4 acts as a TSG (Schwarte-Waldhoff et al., 2000). Heterozygous mutation in the SMAD4 gene has been identified in a variety of cancers (about 26 cancer types), mainly in pancreatic, bladder, breast, prostatic, gastric, esophageal cancer, gallbladder carcinoma, colorectal carcinoma, glioblastoma, head and neck squamous cell carcinoma, kidney cell carcinoma, lung adenocarcinoma, sarcoma, mesothelioma, and testicular germ cell cancer (Zhao, Mishra and Deng, 2018).

SMAD4 knockout mouse model experienced lethality around E7.5 day due to non-cell-autonomous gastrulation failure. The mouse embryo showed growth reduction, poorly-defined boundary between embryonic and extraembryonic region, failure of mesoderm formation, and visceral endoderm disorganization (Sirard et al., 1998). This points to the importance of TGF-β/SMAD4 signal pathway in embryonic gastrulation and mesoderm induction (Li et al., 2010).

SWI (SWItch)/SNF (Sucrose Non-Fermenting)-related Matrix-associated, Actin-dependent Regulator of Chromatin, subfamily A, member 4 (SMARCA4) gene (Tab. 6) is active in the process of nucleosome structure remodeling and encodes a protein subunit known as BRG1, and is an essential ATPase subunit of the BRG1 (Brahma-related gene 1 protein)/BRM (Brahma protein) associated-factor (BAF) complex. Within the chromatin network, ATP-dependent chromatin remodeling complexes come into play by DNA damage repairing. The energy for chromatin remodeling is derived from the hydrolysis of ATP by ATPase/helicase

of the SWI2/SNF2 superfamily, which is confined to all chromatin remodeling complexes (Chetty and Serra, 2020).

SWI/SNF chromatin remodeling complexes with up to 28 members manage vital cellular processes like DNA repair, cell cycle progression, cell differentiation, cell apoptosis, and genomic instability. Trials of complex component recomposition revealed multicellular tasks of SWI/SNF complexes in embryonic stem cell differentiation, neural differentiation, glucose and hepatic lipid metabolism, and brain development (Biegel, Busse and Weissman, 2014).

SMARCA4 and SMARCA2 enhance easy access to the chromatins during DNA damage repair (Chetty and Serra, 2020).

SMARCA4 is a TSG (Guerrero-Martínez and Reyes, 2018). Germline mutation or somatic loss of SMARCA4 has been found in highly aggressive malignancies, such as hypercalcaemic ovarian small cell carcinoma, non-small cell lung carcinoma, pulmonary adenocarcinoma, squamous cell carcinoma, undifferentiated thoracic sarcoma, undifferentiated endometrial, gastrointestinal and sinonasal carcinoma, undifferentiated/rhabdoid components like renal cell carcinoma (Chetty and Serra, 2020).

Despite the unclear mechanism of oncogenesis induction, one of the most constant genetic modification in tumorigenesis is related to SW1/SNF mutations and the resultant SW1/SNF complex dysfunctions (Masliah-Planchon et al., 2015).

Several conditional knockout trials have been undertaken to study the developmental role of the SMARCA4 gene in mice embryogenesis. Nevertheless, total SMARCA4 deficient mouse is not compatible with life and faced peri-implantation lethality (Indra et al., 2005; Wiley et al., 2015).

SWI (SWItch)/SNF (Sucrose Non-Fermenting)-related Matrix-associated, Actin-dependent Regulator of Chromatin, subfamily B, member 1 (SMARCB1) gene (Tab. 6), another member of the adenosine triphosphate (ATP)-dependent SWI/SNF chromatin-remodeling complex, is a TSG with an epigenetic transcriptional activity policy. SMARCB1 regulates further cell cycle progression and the interaction between other signaling cascades (Kalimuthu and Chetty, 2016).

The most common tumor linked to SMARCB1 gene mutations is the malignant rhabdoid tumor. Additionally, a diverse strain of other malignant tumors has been further recognized: epithelioid sarcoma, renal medullary carcinoma, medullary carcinoma (pediatric and adult

type), malignant peripheral nerve sheath tumor, extraskeletal myxoid chondrosarcoma, and familial schwannomatosis (Kalimuthu and Chetty, 2016).
Schwannomatosis is a heterogeneous disease. In about 48% of familial cases and 10% of sporadic cases, a mutation in SMARCB1 is identified. The mutations are primarily at the 5′ or 3′ end of the SMARCB1 gene. SMARCB1 mutant schwannomatosis is unlikely to exhibit unilateral vestibular schwannomas, but rather meningiomas (Kehrer-Sawatzki et al., 2016).

Apart from involvement in oncogenesis, heterozygous germline SMARCB1 and other SWI/SNF complex mutations cause a rare syndromal disorder, Coffin-Siris syndrome with dysmorphic features, speech impairment, hypertrichosis, hypoplastic/absent fifth fingernails/toenails, agenesis of the corpus callosum and developmental delay (Kalimuthu and Chetty, 2016).
Similar to SMARCA4 deficient mice, SMARCB1 null mice die around the peri-implantation stage (Sakakura et al., 2019).

Sprouty related EVH1 domain containing 1 (SPRED1) gene (Tab. 6) is a member of the highly conserved family of negative regulators of the RAS/extracellular signal-regulated kinase (ERK) pathway, which is a signal transduction cascade involved in cellular synaptic plasticity and memory development (Denayer et al., 2008).
Learning difficulty or mental retardation in children with neurofibromatosis type 1-like syndrome (NF-LS), which phenotypically overlaps with the neuro-cardio-facial-cutaneous syndrome (NCFCS), has been recently related to germline heterozygous LOF mutations in SPRED1. NCFCS is caused by germline mutations in genes of the Ras/mitogen-activated protein kinase (ERK) pathway (Denayer et al., 2008).
Besides mental retardation, NF-LS (also known as legius syndrome) is presented with skin manifestations like multiple CAL macules with or without axillary or inguinal freckling. The patients do not have an increased risk for the development of NF1 associated tumors, and they also do not exhibit the Lisch nodules and bone findings. Functionally, SPRED1 is involved in neurofibromin recruitment to the plasma membrane, and both act as negative Ras/ERK pathway regulators (Brems and Legius, 2013).
SPRED1 (-/-) mice were viable, however they exhibited slight growth retardation, shortened face (Taniguchi et al., 2007), reduced spatial learning and memory performance in the Morris water maze and visual-discrimination T maze, but no basic neuromotor and sensory defects. Further, short- and long-term synaptic hippocampal plasticity defects have been electro-

physiologically identified. Increased ERK-phosphorylation found in SPRED1 (-/-) mice had been linked to the hippocampus-dependent learning and synaptic plasticity deficiency (Denayer et al., 2008).

In addition, SPRED1 deficient mice demonstrated allergen-induced airway hyperresponsiveness and eosinophilia, as SPRED1 inhibits interleukin 5 (IL-5)-dependent cell proliferation and ERK activation. In this fashion, SPRED1 plays a role in allergic asthma by adjusting IL-5 signaling, which, in turn regulates adversely eosinophil numbers and actions (Inoue et al., 2005).

SPRED1 negatively regulates the hematopoiesis, and its loss of expression has been identified in pediatric acute myeloblastic leukemia, which means that SPRED1 is a TSG (Pasmant et al., 2014).

Serine/Threonine protein Kinase 11 (STK11) gene (Tab. 6) is a TSG with a downregulation effect on mammalian targets for the rapamycin signal pathway (Towler et al., 2008), found in the nucleus and cytoplasm. Its main catalytic kinase domain is encoded by codons 50-337. STK11 is involved in important cellular processes like cell cycle arrest, apoptosis, cell metabolism, cell polarity, and cell proliferation (Launonen, 2005).

For the accomplishment of the cellular functions, STK11 interacts with other proteins from different signal pathways such as p53-dependent apoptosis pathways, BRG1-dependent chromatin remodeling, vascular endothelial growth factor signaling, and AMP-activated protein Kinase (AMPK) signaling pathway (Launonen, 2005).

Monoallelic germline defect in STK11 is associated with the autosomal dominant Peutz-Jeghers syndrome (PJS), which is presented with gastrointestinal hamartomatous polyps, and mucocutaneous melanin pigmentation. PJS patients have significantly increased lifetime cancer risks mainly for gastrointestinal cancers in the stomach, small bowel, and pancreas, and also for extragastrointestinal neoplasms in the breast, ovary, and testis. The identified mutations in PJS are mostly truncating and affecting the catalytic kinase domain of the protein (Launonen, 2005).

An STK11 knockout mouse faced lethality at midgestation (E8.5-E9.5 day), displayed malformed somites, failure of embryonic turning, vascular abnormalities, and growth retardation (Jishage et al., 2002). Homozygotes for a hypomorphic allele survive and apparently healthy, but male mice are sterile, with reduced mature spermatozoa, non-motility, and abnormal spermatozoa morphology (Tang et al., 2018).

TERF2 interacting protein (TERF2IP) gene (Tab. 6) is an element in the telomere-protecting shelterin complex with telomeric and non-telomeric activities in transcriptional regulation of metabolic pathways. TERF2IP binds the telomeric DNA indirectly. For its recruitment, it needs interaction with TRF2. Deficiency of TERF2IP did not result in telomere defects, indicating that TERF2IP plays a role in protecting telomeres indirectly through the regulation of DNA repair activities at telomere ends. On the other hand, it has been shown that TERF2IP directly regulates DNA damage signaling, independent of its association with the telomeres or with its known partner, TRF2. TERF2IP acts as an adaptor and recruits Ligase IV to the chromatin damaged site. It mediates XRCC4/Ligase IV and DNA-protein kinase interaction (Khattar et al., 2019).

TERF2IP increases T-loop formation and so assists in the prevention of aberrant Holliday junction resolution at telomeres, and its loss is associated with the aberrant homologous repair of the telomeres (Khattar et al., 2019).

TERF2IP knockout mice were fertile, with no obvious developmental defects. The mice were obese (predominantly the female mice, which indicates context-dependent functions of TERF2IP), sensitive to radiation, and showed increased apoptosis, but no effect on hematopoietic cell populations in the bone marrow and spleen. After genotoxic exposure, TERF2IP mice developed bone marrow failure, which was related to the inability of TERF2IP null hematopoietic stem and progenitor cells to proliferate and repopulate after irradiation, and indicates the importance of TERF2IP for the survival of hematopoietic cells. Further, TERF2IP loss induced acceleration of tumorigenesis in mice with defects in DNA damage repair signaling (Khattar et al., 2019).

In cancers, TERF2IP acts as a putative OCG (Pascoal-Xavier et al., 2015), and functions in regulating multiple key events in tumor cell migration, invasion, and metastasis. In tumor development, TERF2IP shows several distinct activities which can be interpreted by its diverse roles in the regulation of normal cell growth. As a member of the Ras-like small GTPase family, its activity is modulated by GTPase activating proteins (GAPs) and guanine nucleotide exchange factors (GEFs) (Yi-Lei et al., 2017).

In addition, a crucial effect of TERF2IP signaling has been linked to angiogenesis promotion and maintenance of vascular stability (Chrzanowska-Wodnicka, 2013).

TERF2IP plays diverse roles in tumor metastasis. In bladder, brain, and lung cancer, active TERF2IP prevents tumor invasion and metastasis, while in breast cancer, esophageal squamous cell carcinoma, melanoma, leukemia, head and neck squamous cell carcinoma, non-small cell lung carcinoma, and pancreatic carcinoma, active TERF2IP enhances tumor

progression. In lymphoma, the role of TERF2IP in tumor metastasis is explained by adhesion promotion of lymphoma cells to endothelial cells by TERF2IP activation and its further transmigration into the hematopoietic system, which subsequently results in multi-organ spreading of the tumor cells (Yi-Lei et al., 2017).
Human tumor cells with high TERF2IP level have a better survival rate, as they have a more efficient DNA repair capacity for the chemotherapy-induced DNA damages, and vice versa, low level of TERF2IP in tumor cells induces tumor cell apoptosis and prognoses a better survival of the patient. Therefore, TERF2IP is predictive for patient survival and responsiveness to chemotherapy in breast and colon cancer (Khattar et al., 2019).

TSC complex subunit 1 (TSC1) and 2 (TSC2) genes (Tab. 6) are TSGs. TSC1 gene codifies a non-homologous hydrophilic protein known as hamartin with the main action in cell adhesion regulation. TSC2 gene enciphers tuberin, a GTPase activating protein, consists of a highly conserved hydrophilic N-terminal domain and a C-terminal domain, which is homologous with the Ras superfamily GTPase proteins. TSC2 is involved in the regulation of cell growth, proliferation, and differentiation. The intracellular TSC complex is composed of binding of both proteins at their coiled-coil domain, and it is widely expressed all over the brain. It protects the TSC2 from ubiquitin-mediated degradation and functions in the transduction of signals regulating a Ras homolog enriched in the brain (Rheb). The latter is an mTOR kinase activator, which is active when bound to GTP. MTOR pathway, in turn, controls the translation of a large extent of essential proteins serving in controlling cell growth and proliferation. Loss of normal function of TSC1 or TSC2 is associated with mTOR pathway deregulation and tumorigenesis promotion (Rosset, Netto and Ashton-Prolla, 2017).

Tuberous sclerosis (TS) results from a heterozygous germline mutation in TSC1 or TSC2, and inherited in an autosomal dominant manner. TS is a progressive and a multisystem disorder leading to the development of multiple benign, non-invasive tumors in different organs like the heart, eyes, skin, brain, liver, kidney, and lung. The clinical symptoms show extreme variability. A skin lesion is found in 90% of patients, CNS symptoms in 90%, renal abnormalities in 70-90%, retinal hamartoma in 50% of patients. The diagnosis of TS is based on described major and minor criteria and sometimes can be made as early as antenatal period where cardiac rhabdomayomas and brain lesions could be seen on ultrasound (Curatolo, Bombardieri, and Jozwiak, 2008).

In 85% of TS patients, a germline mutation is found in either TSC1 or TSC2, of which 70% are occurring de novo, indicating that about 15% of patients would have an intact TSC1 and TSC2 with a milder TS presentation. TSC2 is more frequently mutated and associated with more severe clinical manifestations, while TSC1 mutation is noticed twice as much in familial TS as in sporadic TS (Rosset, Netto, and Ashton-Prolla, 2017).

TSC1 deficient mouse did not survive the embryonic period and died around E10.5-E11.5 day. The embryo exhibited a smaller body size, neural tube unclosure at the head region showing some degree of neural lineage differentiation, abnormal myocardial morphology, and liver hypoplasia. The similarity was noticed regarding overall manifestation between TSC1 (-/-) and TSC2 (-/-) mice, which may points to a common biological pathway between hamartin and tuburin during embryogenesis (Kobayashi et al., 2001).

Much like TSC1 deficient mice, TSC2 homozygous mice died around E10.5 day. The viability of some TSC2 deficient mice till E11.5-E12.5 day, and resorption of some at E9.0-E9.5 day points to a significant diversion in the lethal stage. Deficiency of TSC2 resulted in thickened myocardia with increased cell density, narrow ventricular cavities, poorly recognized endocardia (were apparent at a later stage), smaller body size, and non-closure of the neural tube in the head region. Histologically, the embryo showed complete exposure of the subventricular layer to the body surface, with the detection of some positive neural markers that imply cell division, migration, and differentiation in the neural tube of TSC2 deficient embryo (Kobayashi et al., 1999).

WT1 transcription factor (WT1) gene (Tab. 6) is a Wilms tumor-suppressing gene that enciphers a transcription factor concerned with controlling normal urogenital development (Rackley et al., 1993). WT1 codifies a protein with four zinc fingers of the C2H2 type. The protein consists of 10 exons (Moore et al., 1999). The exons are exposed to alternative splicing to introduce either exon five or an extra three amino acids (KTS) between the third and fourth zinc fingers through the use of a cryptic splice donor site, resulting in 4 various isoforms (Perotti et al., 2005). During embryogenesis, WT1 is widely expressed in the kidneys, gonads, coelomic and subcoelomic epithelial mesenchyme, allowing the cell to switch between mesenchymal and epithelial cell states. However, in its main point of action, the kidneys, it is dynamically expressed along several stages of nephrogenesis, predominantly required at an early stage for the formation of the ureteric bud and subsequent metanephric blastema induction by the bud. Even after birth, its expression is required to sustain the differentiated state of the renal cells. WT1 is essential for myocardial development as well.

The heart of a WT1 deficient mouse undergoes malformations such as thin ventricular myocardium and pericardial bleeding, pointing to heart failure (Moore et al., 1999).
WT1 function in transcription regulation is referred to its isoform; for example, only -KTS isoforms operate effectively in the regulation of transcription through their high-affinity DNA binding, while +KTS isoforms are probably involved in RNA metabolism (splicing), also in polysome binding stimulation, translation of an RNA retaining an intron, and in the proliferation of neural progenitor cells (Hohenstein and Hastie, 2006).
Besides its role as a TSG in Wilms tumor (derived from mesenchymal cells), an oncogenic role of WT1 has been discussed, in conformity with the detection of its cytoplasmic expression in many adult tumors with different origin (derived from epithelial cells), in which WT1 is normally not expressed during adolescence, like breast, desmoid, colorectal and brain tumors without an evident WT1 mutation. This bi-phasic function of WT1 could be interpreted relatively through its conspicuous opposing role in provoking cell differentiation facing impeding differentiation, and the context-dependent two-way control of mesenchymal-epithelial destiny (Hohenstein and Hastie, 2006).

Congenital disorders like WAGR (Wilms Tumor, aniridia, genitourinary anomalies, and mental retardation), Frasier syndrome and Denys-Drash syndrome, all share common manifestations of developmental abnormalities of the gonads and kidneys, with minor disparity regarding the phenotype, mirroring disparate nature and localization of the underlying mutation in WT1 gene (Moore et al., 1999).
Wilms tumor arises mostly sporadically, yet around 10% of cases as part of clinically well-defined genetic conditions covering WAGR, Denys-Drash syndrome and Beckwith-Wiedermann syndrome, and only rarely, germline WT1 mutations have been identified in patients with Wilms tumor without congenital defects (Perotti et al., 2005).

Mice with WT1 knockout die at mid-gestation due to multiple anomalies, including multiple organ agenesis (kidneys, spleen, gonads, and nor adrenal glands), heart malformation, liver hypoplasia with defective lobe formation, and stomach mal-positioning (Ijpenberg et al., 2007).

Genes knockout in mice	TSG/ OCG/ Dual	Chromosomal location	Outcome	References
AIP	**Dual**	**11q13.2**	Lethal around E10.5-E14.5 day	(B.C. Lin et al., 2007)
AKT1	**OCG**	**14q32.33**	Viable, growth-retarded, male with attenuated spermatogenesis	(Chen, 2001)
BAP1	**TSG**	**3p21.1**	Lethal around E9.5-10.5 day	(Perez-Garcia et al., 2018)
BARD1	**Dual**	**2q35**	Lethal around E7.5-E8.5 day	(McCarthy et al., 2003)
CDC73	**Dual**	**1q31.2**	Lethal at E6.5 day	(Newey, Bowl and Thakker, 2009; Wang et al., 2008)
CDH1	**TSG**	**16q22.1**	Preimplantation lethality	(Riethmacher et al., 1995)
CDK4	**OCG**	**12q14.1**	Viable, poor Wt. gain, infertility & IDDM	(Mettus and Rane, 2003)
CDKN1B	**TSG**	**12p13.1**	Viable with overgrowth, organomegaly, female mice were sterile	(Fero et al., 1996)
CEBPA	**TSG**	**19q13.11**	Born alive but die soon after birth	(Inoue et al., 2004; Xu et al., 2007)
DICER1	**TSG**	**14q32.13**	Lethal at E7.5 day	(Liu et al., 2012)
FAM175A	**TSG**	**4q21.23**	Viable with no developmental defects, reduced survival post-irradiation, increased tumor incidence	(Castillo et al., 2014)
FLCN	**TSG**	**17p11.2**	Lethal around E5.5-E6.5 day	(Hasumi et al., 2009)
GATA2	**TSG**	**3q21.3**	Lethal at E10.5 day	(Hsu, McReynolds and Holland, 2015)
HOXB13	**Dual**	**17q21.32**	Viable, overgrowth in major structures derived from tail bud	(Economides, Zeltser and Capecchi, 2003)
KIF1B	**TSG**	**1p36.22**	Viable with brain deformities, exhibited neonatal death attributed to apnea	(Xu et al., 2018)
MAX	**TSG**	**14q23.3**	Lethal around E5.5-E6.5 day	(Shen-Li et al., 2000)
NF2	**TSG**	**22q12.2**	Developmental arrest around E6.5-E7.0 day	(McClatchey et al., 1997)
NSD1	**OCG Fusion**	**5q35.3**	Lethal before E10.5 day	(Visser and Matsumoto, 2003)
PDGFRA	**OCG**	**4q12**	Lethal at midgestation, around E14.0-E16.0 day	(Soriano, 1997)
PIK3CA	**OCG**	**3q26.32**	Lethal at E9.5-E10.5 day	(Bi et al., 1999)
PRKAR1A	**Dual**	**17q24.2**	Lethal	(Bossis and Stratakis, 2004; Saloustros et al., 2015)
PTCH1	**TSG**	**9q22.32**	Lethal around E9.0-E10.5 day	(Lecube et al., 2002)
PTEN	**TSG**	**10q23.31**	Lethal around E9.5 day	(Kishimoto et al., 2003; Suzuki et al., 2008)
RAD51B	**Dual**	**14q24.1**	Lethal around E5.5-E6.5 day	(Shu et al., 1999)
RAD51D	**TSG**	**17q12**	Lethal at E10.5 day	(Smiraldo et al., 2005)
RB1	**TSG**	**13q14.2**	Lethal. Around E10.5 day	(Clarke et al., 1992)
RHBDF2	**OCG**	**17q25.3**	Viable, reduced TNF secretion by bacterial infection	(Adrain et al., 2012)
RUNX1	**OCG Fusion**	**21q22.12**	Lethal around E12.5-E13.5 day	(Kundu et al., 2005)
SDHAF2	**TSG**	**11q12.2**	Lethal prior to organogenesis	(Cheong et al., 2020)
SMAD4	**TSG**	**18q21.2**	Lethal at E6.5day*, at E7.5 day**	(Li et al., 2010*; Sirard et al., 1998)**

SMARCA4	**TSG**	**19p13.2**	Lethal at the peri-implantation stage	(Indra et al., 2005; Wiley et al., 2015)
SMARCB1	**TSG**	**22q11.23**	Lethal at the peri-implantation stage	(Sakakura et al., 2019)
SPRED1	**TSG**	**15q14**	Viable with increased airway hyperresponsiveness, eosinophilia, and impaired spatial learning and memory	(Denayer et al., 2008; Inoue et al., 2005)
STK11	**TSG**	**19p13.3**	Lethal around E8.5-E9.5 day	(Jishage et al., 2002)
TERF2IP	**OCG**	**16q23.1**	Viable, fertile, with reduced radiosensitivity, and obesity in female mice	(Khattar et al., 2019)
TSC1	**TSG**	**9q34**	Lethal around E10.5-E11.5 day	(Kobayashi et al., 2001)
TSC2	**TSG**	**16p13.3**	Lethal around E10.5 day	(Kobayashi et al., 1999)
WT1	**TSG**	**11p13**	Lethal at E13.5 day	(Moore et al., 1999)

Table 6: listing genes, for which mouse model knockout were sought. E. day: Embryonic day. IDDM: insulin dependent diabetes mellitus. Dual: the gene acts as a TSG and as an OCG.

	First Timester						Second Timester	Third Timester	
GD	**Fertilization**	**Cleavage**	**Blastocyst stage**	**Implantation**	**Placentogenesis**	**Organogenesis complete**	**Fetal and placental growth**	**Accelerated Fetal Growth**	**Birth**
	**0**	**1-2.5**	**2-4**	**4,5-5**	**6-14**	**14**	**14-17**	**17-Birth**	**19-21**
	**0**	**2-3**	**2-4**	**6-12**	**28-91**	**84-98**	**99-196**	**197-Birth**	**~294**

Figure 3: illustrates the gestational stages of mice in comparison to humans. GD: Gestational Date. The timeline information is based on the publication of Blum, Chen, and Zelikoff (2017).

4.4 Group 4: Genes without available reports, neither in humans nor in mice

Polypeptide N-acetylgalactosaminyltransferase 12 (GALNT12) gene (Tab. 7) is a member of the hexosyltransferase family and functions as a catalytic enzyme in the initial steps of mucin-type O-glycosylation process. Aberrant glycosylation as a result of defects in this process would affect cell growth, differentiation, transformation, adhesion, metastasis, and immune surveillance in cancers (Lorca et al., 2017).

GALNT12 is highly expressed in the digestive tract, and its primary target is MUC1, which shows aberrant glycosylation in tumors (Lorca et al., 2017). GALNT12 is often downregulated in colorectal cancer (CRC), but its correlation to familial adenomatous polyposis is disputed (Lorca and Garre, 2019). In GALNT12-associated CRC, the complete inactivated alleles do not act as oncogenic alleles or alleles with dominant effect, but rather, they act most likely as simple null alleles (Lorca et al., 2017).

SWI (SWItch)/SNF (Sucrose Non-Fermenting)-related Matrix-associated, Actin-dependent Regulator of Chromatin, subfamily E, member 1 (SMARCE1) gene (Tab. 7) is a part of BAF complexes, observed only in high eukaryotes. It functions in the nucleosome remodeling complex SWI/SNF required for transcriptional controlling. Its topological role during entering or exiting of the BAF complex to the nucleosome is related to its 4-way junction DNA binding property. Functionally, SAMRCE1 (BAF57) interacts specifically with other proteins essential for embryonic development like CD4 during the development and maturation of T-cells. It is also engaged in the BAF/nuclear hormone receptor interaction regulation. During steroid hormone responses, SMARCE1, with its direct interaction with the androgen and estrogen receptors, regulates the nuclear receptor function by recruiting BAF complexes to endogenous nuclear receptor targets. SMARCE1 mutation is considered rather as a metastatic factor, prognosis marker, and cancer therapy target but not as a cancer initiator (Lomelí and Castillo-Robles, 2016).

SMARCE1 is a TSG (Gerkes et al., 2016) and considered one of the main meningioma-predisposing genes in meningioma patients with wild type NF2 gene. Further, SMARCE1 mutations have been identified in other malignancies, including breast, ovarian, endometrial, prostatic, pancreatic, and colorectal carcinoma (Lomelí and Castillo-Robles, 2016).

In similarity to SMARCB1, SMARCE1 mutation with gain of function or some function conservation of the mutated protein, results as well in Coffin-Siris syndrome; however, the affected patients do not develop meningioma (Lomelí and Castillo-Robles, 2016).

SMARCE1 genetic ablation in mice has not been reported yet but is expected to be embryonically lethal (Lomelí and Castillo-Robles, 2016).

Genes	TSG/OCG /Dual	Gene location	Our research about their biallelic mutations	Research of others & references
GALNT12	**---**	**9q22.33**	-	-
SDHC	**TSG**	**1q23.3**	-	- (Alston et al., 2015)
SMARCE1	**TSG**	**17q21.2**	-	- In mice not reported yet (Lomelí and Castillo-Robles, 2016)

Table 7: list of genes without available reports, neither in humans nor in mice.

5. Conclusion

In the present work, the described phenotypes, which have been published regarding biallelic germline mutations in TSGs and OCGs, included in the TSC panel were systematically reviewed.

To the best of our knowledge, this is the first work to summarize the phenotypes associated with biallelic mutations in 113 cancer-related genes on a panel. This overview helps to develop a realistic understanding of potential family-planning issues for heterozygous carriers of TSG/OCG mutations, and helps to facilitate the oncogenetic counseling.

We have noticed that different mutations in the same gene can cause different phenotypes than other mutations. This makes a uniform definition of the phenotypes referred to the gene and the disease itself challenging. Nevertheless, characterization of the entire spectrum of phenotypes associated with mutations in these genes is an important contribution to future oncogenetic counseling.

This study highlights the influence of the consanguinity in oncogenetic testing, as the results show that the risk of autosomal recessive diseases induced by biallelic mutation in TSGs and OCGs are peculiarly increased in geographically isolated populations, where consanguineous relationships may occur more frequently with the consequence of potentially unexpected recessive phenotypes.

In our research, we faced different perspectives regarding autosomal dominant diseases. It is known that their biallelic gene mutation is associated with more profound clinical manifestations or earlier onset of the characteristic disease. We noticed that for some dominant genes, biallelic germline mutation is lethal, while for others, homozygous germline mutations lead to phenotypes quite similar to those seen with heterozygous mutations.

It is necessary to inform TSG/OCG mutation carriers about their own cancer risks and the risk of potential biallelic diseases in their offspring and the option of testing their partner for carrier status.

The intact function of at least one allele of most TSGs and OCGs is important for embryonic development. Concerning the genes, for which no biallelic mutated phenotypes have been described yet, it seems that their function is indispensable for the viability of human embryos.

It is worth mentioning that a history of abortion/stillbirth between some carrier partners was observed, which further supports the crucial role of cancer-related genes in embryogenesis (Ben Haj Ali et al., 2019; Courage et al., 2016; Holden, 2006; Kocak et al., 2014; Mateos et al., 2013; Ragamin et al., 2020; Vaz et al., 2010; Visser and Matsumoto, 2003).

There are cases of biallelic mutations as a consequence of UPD, causing autosomal recessive diseases. Zeng et al. (2006) reported a case of fumarase deficiency due to paternal partial isodisomy of chromosome 1 for the locus of a mutant allele of the FH gene. Further, Donovan et al. (2016) reported four cases of FA, three of them resulted from UPD in the FANCA gene, and one in the SLX4 gene.

Despite the rareness of UPD in the described phenotypes, its effect should be considered in genetic counseling, since it can result in clinical presentations of biallelic mutations even when only one parent is a carrier, however, this risk seems to be extremely low.

It remains to be discussed to which extent, the described phenotypes in knockout mouse models and their pathomechanisms are applicable to corresponding situations in humans, as we noticed some differences between the consequences of biallelic mutations in humans and mice {e.g., MET knockout is lethal in mice but causes only autosomal recessive non-syndromic hearing loss in humans (Mujtaba et al., 2015). Similarly, BRCA1 and BRCA2 knockouts are incompatible with embryonic survival in mice but not in humans, where their biallelic loss causes FA (Evers and Jonkers, 2006)}. Such species-specific mechanisms should be considered by future studies to provide a more accurate and comprehensive disease description.

Concerning the legal obligation to provide the individuals seeking genetical advice with information about all relevant consequences of a possible finding prior to a genetic examination, it would be timely not possible to discuss the consequences of biallelic mutation of all TSC-panel genes with known phenotypes in humans. In this context, this work highlights the significance of personal and family history of the individual in selecting the relevant genes from this comprehensive TSC-panel for evaluation.

For more precise estimation of the prevalence of phenotypes induced by biallelic mutations in TSGs and OCGs, more consequent reporting of these cases is mandatory. Furthermore, reporting these cases would assist in the prediction of the survival rate of the affected patients, clarifying the underlying etiology, and planning a competent prenatal/postnatal screening, especially in high-risk communities.

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7. List of the Genes in TSC Panel with Synonyms in Orphanet

APC: DP2, DP2.5, DP3, PPP1R46, protein phosphatase 1, regulatory subunit 46

ATM: TEL1, TEL1, telomere maintenance 1, homolog (S. cerevisiae), TELO1

BAP1: hucep-6, KIAA0272, ubiquitin carboxy-terminal hydrolase, UCHL2

BMPR1A: ALK3, CD292

BRCA1: BRCA1/BRCA2-containing complex, subunit 1, BRCC1, Fanconi anemia, complementation group S, FANCS, PPP1R53, protein phosphatase 1, regulatory subunit 53, RNF53

BRCA2: BRCA1/BRCA2-containing complex, subunit 2, BRCC2, FAD, FAD1, XRCC11

BRIP1: BACH1, BRCA1/BRCA2-associated helicase 1, FANCJ, OF

CDH1: CD324, E-Cadherin, uvomorulin

CDK4: PSK-J3

CDKN2A: ARF, CDK4I, CMM2, INK4, INK4a, MTS1, p14, p14ARF, p16, p16INK4a, p19, p19Arf

CHEK2: bA444G7, CDS1, CHK2, HuCds1, PP1425

EPCAM: 17-1A, 323/A3, CD326, CO-17A, EGP-2, EGP34, EGP40, Ep-CAM, ESA, GA733-2, HEA125, KS1/4, KSA, Ly74, MH99, MK-1, MOC31, TACST-1, TROP1

FH: fumarase

FLCN: BHD, MGC17998, MGC23445

MAX: --

MEN1: MEN1 , Wermer-Syndrom

MLH1: FCC2, HNPCC, HNPCC2

MSH2: DNA mismatch repair protein Msh2, HNPCC, HNPCC1

MSH6: --

MUTYH: MYH

NBN: ATV, AT-V1, AT-V2

NF1: neurofibromatosis, von Recklinghausen disease, Watson disease

NF2: ACN, BANF, Merlin, moesin-ezrin-radixin like, SCH, schwannomin

PALB2: FANCN, Fanconi anemia, complementation group N, FLJ21816

PMS2: H_DJ0042M02.9, HNPCC4, MLH4

PRKAR1A: Carney complex type 1, CNC1

PTCH1: BCNS

RAD51C: FANCO, RAD51L2

RAD51D: DNA repair protein RAD51 homolog 4, HsTRAD, R51H3, Recombination repair protein, Trad

RB1: PPP1R130, prepro-retinoblastoma-associated protein, protein phosphatase 1, regulatory subunit 130, RB

RECQL4: RecQ4

RET: cadherin-related family member 16, CDHF12, CDHR16, PTC, rearranged during transfection, RET51, RET receptor tyrosine kinase

SDHAF2: FLJ20487, SDH5

SDHB: iron-sulfur subunit of complex II, succinate dehydrogenase [ubiquinone] iron-sulfur subunit

SDHC: CYB560, cybL, large subunit of cytochrome b, succinate dehydrgenase cytochrome b, succinate dehydrogenase cytochrome b560 subunit

SDHD: cybS, small subunit of cytochrome b

SMAD4: DPC4

SMARCB1: BAF47, hSNFS, Ini1, integrase interactor 1, malignant rhabdoid tumor suppressor, PPP1R144, protein phosphatase 1, regulatory subunit 144, RDT, Sfh1p, SNF5, Snr1, sucrose nonfermenting, yeast, homolog-like 1

STK11: LKB1, PJS, polarization-related protein LKB1

SUFU: PRO1280, SUFUH, SUFUXL

TMEM127: FLJ20507, FLJ22257

TP53: LFS1, Li-Fraumeni syndrome, P53

TSC1: hamartin, KIAA0243, LAM

TSC2: LAM, PPP1R160, protein phosphatase 1, regulatory subunit 160, tuberin

VHL: VHL1

WT1: AWT1, NPHS4, WAGR, WIT-2

BLM: BS, RECQ2, RECQL3

DDB2: DDBB, DDB p48 subunit, FLJ34321, UV-damaged DNA-binding protein 2, UV-DDB2, xeroderma pigmentosum group E protein, XPE

ERCC2: EM9, excision repair cross-complementing rodent repair deficiency, complementation group 2 protein, MAG, MGC102762, MGC126218, MGC126219, TFIIH, TFIIH basal transcription factor complex helicase XPB subunit

ERCC3: BTF2, GTF2H, RAD25, TFIIH, xeroderma pigmentosum group B complementing, XPB

ERCC4: FANCQ, RAD1, xeroderma pigmentosum, complementation group F

ERCC5: Cockayne syndrome, veraltete Symbole und Gennamen: ERCM2, XPGC, excision repair cross-complementation group 5, excision repair cross-complementing rodent repair deficiency, complementation group 5, xeroderma pigmentosum, complementation group G

FANCM: FAAP250

RUNX1: aml1 oncogene, AMLCR1, PEBP2A2

PTEN: MMAC1, mutated in multiple advanced cancers 1, PTEN1, TEP1

AIP: ARA9, FKBP16, XAP2

CDC73: FIHP, Paf1/RNA polymerase II complex component, parafibromin, HRPT2

DICER1: Dicer, dicer 1, double-stranded RNA-specific endoribonuclease, HERNA, K12H4.8-LIKE, KIAA0928

DIS3L2: FLJ36974, MGC42174

KIT: CD117, C-Kit, mast/stem cell growth factor receptor Kit, SCFR

MET: DFNB97, hepatocyte growth factor receptor, HGFR, RCCP2

CEBPA: C/EBP-alpha

FANCA: FAA, FAH, FA-H

FANCB: FAAP95, FAB, FLJ34064

FANCC: FA3, FAC

FANCD2: FAD, FA-D2

FANCE:

FANCF: FAF

FANCG: DNA repair protein XRCC9, FAG, X-ray repair, complementing defective, in Chinese hamster, 9, X-ray repair complementing defective repair in Chinese hamster cells 9

FANCI: FLJ10719

FANCL: FAAP43, FLJ10335, Pog

GATA2: NFE1B

GPC3: DGSX, glypican proteoglycan 3, OCI-5, SGB, SGBS, SGBS1

HOXB13: --

NSD1: ARA267, FLJ22263, KMT3B

PHOX2B: NBPhox, Phox2b

RHBDF2: FLJ22341, iRhom2, RHBDL5, TOCG

SLX4: Fanconi anemia, complementation group P, FANCP, KIAA1784, KIAA1987

XPA: XP1, XPAC

XPC: RAD4, xeroderma pigmentosum group C protein, XPCC

MITF: bHLHe32, homolog of mouse microphthalmia, MI

ACD: Pip1, POT1 and TIN2 organizing protein, Ptop, TIN2 interacting protein 1, Tint1, Tpp1

AKT1: AKT, PKB, PRKBA, protein kinase B, RAC

BARD1: --

CASR: FHH, GPRC2A, NSHPT, severe neonatal hyperparathyroidism

CDKN1B: KIP1, P27KIP1

CTRC: caldecrin, CLCR, ELA4, elastase 4

ERCC1: RAD10

FAM175A: ABRA1, ABRAXAS, Abraxas protein, FLJ13614

GALNT12: GalNAc-T12, polypeptide GalNAc transferase 12

GREM1: DAND2, DRM, Gremlin, HMPS

KIF1B: HMSNII, KIAA0591, KLP

LZTR1: BTBD29, LZTR-1

MRE11A: ATLD, AT-like disease

MSH3: Divergent upstream protein, DUP, Mismatch repair protein 1, MRP1

NTHL1: NTH1, OCTS3

PDGFRA: CD140a, GAS9, PDGFR2

PIK3CA: PI3K

POLD1: CDC2, CDC2 homolog (S. cerevisiae)

POLE: DNA polymerase epsilon catalytic subunit A, POLE1

POT1: DKFZp586D211, hPot1

RAD50: hRad50, RAD50-2

RAD51: BRCA1/BRCA2-containing complex, subunit 5, BRCC5, FANCR, HsRad51, HsT16930

RAD51B: hREC2, R51H2, REC2

RINT1: FLJ11785, RINT-1

SDHA: flavoprotein subunit of complex II, FP, SDHF, succinate dehydrogenase [ubiquinone] flavoprotein subunit

SMARCA4: ATP-dependent helicase SMARCA4, BAF190, brahma protein-like 1, BRG1, BRM/SWI2-related gene 1, FLJ39786, global transcription activator homologous sequence, homeotic gene regulator, hSNF2b, mitotic growth and transcription activator, nuclear protein GRB1, SNF2, SNF2-BETA, SNF2LB, SNF2-like 4, sucrose nonfermenting-like 4, SWI2

SMARCE1: BAF57

SPINK1: PCTT, PSTI, Spink3, TATI

SPRED1: FLJ33903, PPP1R147, protein phosphatase 1, regulatory subunit 147

TERF2IP: RAP1

TERT: EST2, hEST2, TCS1, TP2, TRT

XRCC2: FANCU, RAD51-like

8. Gene Index

P

R

S

T

V

W

X