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Genetic Basis of Inherited Bone Marrow Failure Syndromes

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1. Introduction

Inherited bone marrow failure syndromes (IBMFSs) are multi-system disorders with varying degrees of defective production of erythrocytes, granulocytes and platelets in the bone marrow, leading to single-lineage or multilineage cytopenia (Table 1). (Dror 2006) The term IBMFSs is reserved for disorders that are caused by mutations, which are either inherited from the parents or occurred de-novo. (Alter 2003; Dokal and Vulliamy 2008) Based on the transmission patterns of the diseases (e.g. dominant or recessive autosomal or X-linked) and the segregation of known IBMFSs genes within multiplex families, the IBMFSs are considered as monogenic (Mendelian) diseases. (Alter 2003; Shimamura 2006; Dokal and Vulliamy 2008) The incidence of establishing a diagnosis of IBMFSs is about two new cases per a general population of million people per year and 65 cases per 10⁶ child births. (Tsangaris, Klaassen et al. 2011)

In some IBMFSs (e.g. Fanconi anemia) pancytopenia (≥ 2 lineages affected) usually evolves. In others, one lineage is predominantly affected (e.g. neutropenia in Kostmann/severe congenital neutropenia, anemia in Diamond Blackfan anemia or thrombocytopenia in thrombocytopenia absent radii).

The bone marrow failure often causes substantial morbidity and mortality, and many patients require life-long blood transfusions, treatment for infections, growth factors and hematopoietic stem cell transplantation (HSCT). Due to hematological and non-hematological problems, high risk of cancer and major treatment-related toxicity, the life expectancy of the patients is substantially reduced. (Dror 2006; Alter 2007)

IBMFSs have both unique and common features. The clinical manifestations could not always discriminate between the various IBMFSs or between IBMFSs from acquired bone marrow failure syndromes. The associations of bone marrow failure with either congenital malformations or presentation during the first year of life or an affected first-degree relative are important diagnostic features. (Teo, Klaassen et al. 2008) A wide range of physical anomalies (e.g. craniofacial, skeletal, cardiovascular, gastrointestinal, renal, neurological and dermatological) are associated with IBMFSs and may help to establish a diagnosis. However, substantial phenotypic overlap exists among the disorders, which frequently limits the ability to establish a diagnosis based solely on clinical manifestations. Further, some of the disorders are not associated with physical anomalies, or the malformations develop later in life; for example, nail dystrophy in dyskeratosis congenita and metaphyseal dysplasia in Shwachman-Diamond syndrome. Therefore, genetic testing is critical for establishing a diagnosis and provides family counseling and management.

Disorder	Gene	Protein	Gene Locus	Inheritance	Reference
Fanconi anemia	<i>FANCA</i>	FANCA	16q24.3	AR	(Lo Ten Foe, Rooimans et al. 1996)
	<i>FANCB</i>	FANCB	Xp22.31	XLR	(Meetei, Levitus et al. 2004)
	<i>FANCC</i>	FANCC	9q22.3	AR	(Strathdee, Gavish et al. 1992)
	<i>FANCD1/BRCA2</i>	FANCD1/BRCA2	13q12.3	AR	(Howlett, Taniguchi et al. 2002)
	<i>FANCD2</i>	FANCD2	3p25.3	AR	(Timmers, Taniguchi et al. 2001)
	<i>FANCE</i>	FANCE	6p21.3	AR	(de Winter, Leveille et al. 2000)
	<i>FANCF</i>	FANCF	11p15	AR	(de Winter, Rooimans et al. 2000)
	<i>FANCG/XRCC9</i>	FANCG	9p13	AR	(de Winter, Waisfisz et al. 1998)
	<i>FANCI</i>	FANCI	15q25-q26	AR	(Levitus, Rooimans et al. 2004)
	<i>FANCI/BRIP1</i>	FANCI/BRIP1	17q22	AR	(Levitus, Rooimans et al. 2004)
	<i>FANCL/PHF9</i>	FANCL/PHF9	2p16.1	AR	(Meetei, de Winter et al. 2003)
	<i>FANCM</i>	FANCM	14q21.3	AR	(Meetei, Medhurst et al. 2005)
	<i>FANCN/PALB2</i>	FANCN/PALB2	16p12	AR	(Reid, Schindler et al. 2007)
	<i>FANCP/SLX4</i>	FANCP/SLX4	16p13.3	AR	(Stoepker, Hain et al.)
	<i>FANCO/RAD51C</i>	FANCO/RAD51C	17q22	AR	(Vaz, Hanenberg et al.)

Disorder	Gene	Protein	Gene Locus	Inheritance	Reference
	Mono-somy 21q22.11- q22.13	UK	UK	UK	(Byrd, Zwerdling et al.)
Shwachman- Diamond syndrome	<i>SBDS</i>	7q11.2	7q11	AR	(Boocock, Morrison et al. 2003)
Dyskeratosis congenita	<i>DKC1</i>	Dyskerin	Xq28	XLR	(Heiss, Knight et al. 1998)
	<i>TINF2</i>	TIN2	14q12	AD	(Savage, Giri et al. 2008)
	<i>TERC</i>	TERC	3q21-q28	AD	(Vulliamy, Marrone et al. 2001)
	<i>TERT</i>	Telomerase	5p15.33	AD	(Vulliamy, Walne et al. 2005)
	<i>NOP10</i>	NOP10	15q14-q15	AR	(Walne, Vulliamy et al. 2007)
	<i>NHP2</i>	NHP2	5q35.3	AR	(Vulliamy, Beswick et al. 2008)
	<i>TCAB1</i>	<i>TCAB1</i>	17p13	AR	(Zhong, Savage et al. 2011)
Congenital amegakaryocytic thrombocytopenia	<i>MPL</i>	Thrombo- poietin receptor	1p34	AR	(van den Oudenrijn, Bruin et al. 2000)
Reticular dysgenesis	<i>AK2</i>	Adenylate kinase 2	1p34	AR	(Lagresle- Peyrou, Six et al. 2009; Pannicke, Honig et al. 2009)
Pearson's syndrome	<i>mDNA</i>	Variable	Mito- chondrial DNA	Maternal	(Rotig, Cormier et al. 1990)
Lig4-associated aplastic anemia	<i>LIG4</i>	DNA Ligase IV	1q22-q34		(O'Driscoll, Cerosaletti et al. 2001)

Disorder	Gene	Protein	Gene Locus	Inheritance	Reference
Diamond-Blackfan anemia	<i>RPS19</i>	RPS19	19q13.3	AD	(Draptchinskaia, Gustavsson et al. 1999)
	<i>RPL5</i>	RPL5	1p22.1	AD	(Gazda, Sheen et al. 2008)
	<i>RPS26</i>	RPS26	12q	AD	(Doherty, Sheen et al. 2010)
	<i>RPL11</i>	RPL11	1p35-p36.1	AD	(Gazda, Sheen et al. 2008)
	<i>RPS24</i>	RPS24	10q22-q23	AD	(Gazda, Grabowska et al. 2006)
	<i>RPL35a</i>	RPL35a	3q29	AD	(Farrar, Nater et al. 2008)
	<i>RPS7</i>	RPS7	15q	AD	(Doherty, Sheen et al. 2010)
	<i>RPS17</i>	RPS17	15q	AD	(Doherty, Sheen et al. 2010)
	<i>RPS10</i>	RPS10	6p	AD	(Doherty, Sheen et al. 2010)
	Inherited sideroblastic anemia	<i>ALAS2</i>	ALAS	Xp11.21	XL
<i>ABC7</i>		ATP-binding cassette transporter 7	Xq13.1-q13.3	XL	(Allikmets, Raskind et al. 1999)
<i>SLC19A2</i>		thiamine transporter 2	1q23.3	AR	(Fleming, Tartaglioni et al. 1999)
<i>PUS1</i>		Pseudo-uridine synthase 1	2p16.1	AR	(Zeharia, Fischel-Ghodsian et al. 2005)
<i>SLC25A38</i>		SLC25A38	3p22.1	AR	(Guernsey, Jiang et al. 2009)

Disorder	Gene	Protein	Gene Locus	Inheritance	Reference
Congenital dyserythropoietic anemia type I	<i>CDAN1</i>	Codanin-1	15q15	AR	(Dgany, Avidan et al. 2002)
Congenital dyserythropoietic anemia type II	<i>SEC23B</i>	SEC23B	20p11.2	AR	(Bianchi, Fermo et al. 2009; Schwarz, Iolascon et al. 2009)
Congenital dyserythropoietic anemia type III	<i>UK</i>	UK	UN	AR	
Congenital dyserythropoietic anemia - unclassified	<i>KLF1</i>	KLF1	19p13.12-p13.13	AR	(Arnaud, Saison et al.)
Kostmann/Severe congenital neutropenia	<i>ELA2</i>	Neutrophil Elastase	19p13.3	AD	(Dale, Person et al. 2000)
	<i>HAX1</i>	HAX1	1q21.3	AR	(Klein, Grudzien et al. 2007)
	<i>GLI1</i>	GFI1	1p22	AD	(Person, Li et al. 2003)
	<i>WASP</i>	WASP	Xp11.23-p11.22	XLR	(Devriendt, Kim et al. 2001)
Dursun syndrome	<i>G6PC3</i>	Glucose-6-phosphatase catalytic unit 3	17q21		(Banka, Newman et al. ; Boztug, Appaswamy et al. 2009)
Cyclic neutropenia	<i>ELA2</i>	Neutrophil Elastase	19p13.3	AD	(Horowitz, Benson et al. 1999)
WHIM syndrome	<i>CXCR4</i>	CXCR4	2q21	AD	(Hernandez, Gorlin et al. 2003)
Glycogen storage diseases Ib	<i>G6PT</i>	G6PT	11q23	AR	(Annabi, Hiraiwa et al. 1998)
Barth syndrome	<i>TAZ</i>	Taffazin	Xq28	XL	(Bione, D'Adamo et al. 1996)

Disorder	Gene	Protein	Gene Locus	Inheritance	Reference
Poikiloderma with neutropenia	<i>C16orf57</i>	Not-determined	16q13	AR	(Volpi, Roversi et al.)
Thrombocytopenia absent radii	<i>UK</i>	UK	UK	AR	
Epstein/Fechtner/Sebastian/May-Hegglin/ Alport syndrome	<i>MYH9</i>	nonmuscle myosin heavy chain IIA	22q11-q13	AD	(Seri, Pecci et al. 2003)
Mediterranean platelet disorder	<i>GPIBA</i>	GPIb	17pter-p12	AD	(Savoia, Balduini et al. 2001)
Familial autosomal dominant non-syndromic thrombocytopenia	<i>MASTL</i>	microtubule-associated serine/threonine-like kinase	10p11-12	AD	(Gandhi, Cummings et al. 2003)
	<i>ACBD5</i>	ACBD5	10p12.1	AD	(Punzo, Mientjes et al. 2010)
	<i>ANKRD26</i>	ANKRD26	10q22.1	AD	(Pippucci, Savoia et al.)
Thrombocytopenia with dyserythropoiesis	<i>GATA1</i>	GATA1	Xp11.23	XL	(Nichols, Crispino et al. 2000)
Thrombocytopenia with associated myeloid malignancies	<i>CBFA2</i>	CBFA2	21q22.1-22.2	AD	(Song, Sullivan et al. 1999)
X-linked thrombocytopenia	<i>WASP</i>	WASP	Xp11.23	XL	(Devriendt, Kim et al. 2001)
Thrombocytopenia with radio-ulnar synostosis	<i>HOXA11</i>	HOXA11	7p15-p14.2	AD	(Thompson and Nguyen 2000)

Table 1. The inherited bone marrow failure syndromes

2. The inherited bone marrow failure syndromes and genes

Mutations in IBMFS genes result in high-penetrance alleles; namely alleles that cause Mendelian (monogenic) diseases transmitted in a autosomal dominant, autosomal recessive autosomal or X-linked recessive patterns.(Balmain, Gray et al. 2003) The IBMFS genes are crucial for fundamental cellular processes such as DNA repair,(Cohn and D'Andrea 2008) telomere maintenance,(Vulliamy and Dokal 2008) ribosome biogenesis(Choesmel, Bacqueville et al. 2007; Ganapathi, Austin et al. 2007; Menne, Goyenechea et al. 2007)

microtubule stabilization,(Austin, Gupta et al. 2008) chemotaxis,(Wessels, Srikantha et al. 2006) signaling from hematopoietic growth factor,(Ihara, Ishii et al. 1999) signal transduction related to hematopoietic cell differentiation,(Song, Sullivan et al. 1999; Nichols, Crispino et al. 2000) granulocytic enzymes,(Dale, Person et al. 2000) and cell survival.(Cumming, Lightfoot et al. 2001; Miyake, Flygare et al. 2005; Klein, Grudzien et al. 2007; Rujkijyanont, Watanabe et al. 2008; Watanabe, Ambekar et al. 2009) Although rare, the study of IBMFSs genes made critical contributions to the understanding of not only the pathogenesis of the individual disorders, but also to common health problems such as cancer(Friedenson 2007; Londono-Vallejo 2008) and aging.(Aubert and Lansdorp 2008)

2.1 Fanconi anemia

2.1.1 Clinical features of Fanconi anemia

Fanconi anemia (FA) is an IBMFS with increased chromosome breakage. It has the highest child birth incidence among the IBMFSs.(Tsangaris, Klaassen et al. 2011) It was first described by Professor Fanconi in 1927. (Fanconi 1927) It is a multisystem disorder which commonly affects the bone marrow and the development of other organs.(Auerbach, Rogatko et al. 1989) Hematologically the patients suffer from aplastic anemia, which is characterized by various degrees of single or multilineage cytopenia, red blood cell macrocytosis, high fetal hemoglobin levels and reduced bone marrow cellularity. Common malformations include cafe-au-lait spots, hypopigmented skin patches, hypoplasia/absence of the thumbs, dysplastic/absence kidneys, characteristic delicate faces, microcephaly, developmental delay and various heart defects. Also, the patients have a high predisposition for myelodysplastic syndrome (MDS), leukemia (particularly acute myeloid leukemia, AML) and solid cancer. The cumulative incidence of developing bone marrow failure, MDS/AML and solid neoplasms were estimated at 90%, 33%, and 28% by 40 years of age.(Kutler, Singh et al. 2003) At presentation patients may have an either classic phenotype comprised of both physical anomalies and abnormal hematology, or typical physical anomalies but normal hematology, or normal physical features but abnormal hematology. The disease occurs in all racial and ethnic groups. The treatment for the bone marrow failure includes androgens or hematopoietic stem cell transplantation (HSCT). The later is the only curative therapy for the bone marrow failure. Surgical interventions may be required for some organ malformations or cancer.

2.1.2 Fanconi anemia genes

FA is a genetically heterogeneous disease with 15 genes currently identified (Table 1). Most genetic groups are inherited in an autosomal recessive manner with an estimated overall FA heterozygote frequency of about 1 in 200. This was confirmed with the identification of the FA genes. However, a XL-recessive inheritance characterizes the rare FA group B. The most commonly mutated FA genes are *FANCA*, *FANCC* and *FANCG*. Based on the ability to correct the chromosome fragility phenotype by forming hybrid cells with another genetic group cells(Yoshida 1980; Duckworth-Rysiecki, Cornish et al. 1985) or by vector-mediated gene transduction,(Antonio Casado, Callen et al. 2007) each genetic group is also called complementation group.

DNA Repair

A major finding in FA is abnormal chromosome fragility; this is seen in metaphase preparations of peripheral blood lymphocytes or cultured skin fibroblasts either

spontaneously or after treating the cells with DNA cross linking agents such as mitomycin C, di-epoxybutane and cisplatinum (Fig 1). The FA cellular karyotype shows chromatid breaks, rearrangements, gaps, endoreduplications, and chromatid exchanges. Spontaneous chromosomal breaks are occasionally absent in FA, (Auerbach, Rogatko et al. 1989) but is strikingly enhanced if cross linking agents are added to the cell culture. (Auerbach, Rogatko et al. 1989) It is postulated that the increased chromosomal fragility is caused by a defects in DNA repair. Indeed, some of the FA genes have been previously shown to be tumor suppressor genes related to DNA repair. (Mavaddat, Pharoah et al. 2010) *FANCD1* is *BRCA2*, which is mutated in the germline of 12% of patients with familial breast cancer and also contributes to a risk of ovarian and pancreatic cancer. *FANCI* was identified as BRIP1 or BACH1, which is mutated in 1-2% of familial breast cancer. *FANCN* is *PALB2* which is mutated 1-2% of familial breast cancer.

The FA genes might have variety of functions, but all belong to the FA homologous recombination DNA repair pathway (Reviewed by de Winter & Joenje (de Winter and Joenje 2008)) (Fig 2). During S phase, the replication forks are stalled in areas of DNA interstrand crosslinks. *FANCM* associates with *FAAP24*, which senses the stalled replication forks. *FANCM* then recruits the FA core complex to chromatin at the site of DNA damage. (Huang 2010) The core FA complex is composed of *FANCA, B, C, E, F, G, L, M*, which associate with each other in a stepwise manner. Activation of the FA core complex via phosphorylation of *FANCA, FANCE, FANCD2* and *FNACI* occurs in response to DNA damage in an ATR dependent manner. The complex is required for monoubiquitination of two downstream FA proteins, *FANCD2* and *FANCI*, through the E3 ubiquitin ligase domain of *FANCL* and by the E2 conjugating enzyme *UBE2T*. There is evidence that *FANCI* phosphorylation promotes *FANCD2* monoubiquitination in an ATR-dependent manner and functions as a molecular switch to turn on the FA pathway. (Ishiai, Katao et al. 2008) Once ubiquitinated, *FANCD2* and *FANCI* bind to chromatin at DNA damage foci. Other DNA repair proteins that are recruited to these foci are *FANCD1, BRCA1, RAD51, NSB1, BLM* and *PCNA*. The recruitment of *FANCD2* and *FANCI* to DNA damage foci likely facilitates DNA repair through homologous recombination, nucleotide excision repair and translesion synthesis; however, the exact biochemical functions are still unclear. *FANCO (RAD51C)* protein is critical for formation of *RAD51* foci in response to DNA damage. (Godthelp, Artwert et al. 2002; Smeenk, de Groot et al. 2010) *FANCP (SLX4)* is a regulator of structure-specific endonucleases that repair DNA interstrand crosslinks. (Fekairi, Scaglione et al. 2009) The FA protein-related DNA damage foci are thought to be assembled during S phase and mostly disassembled once the damage is repaired, before the exit from S phase.

Mutations in any member of the core FA protein complex reduces *FANCD2* ubiquitinylation and its recruitment to DNA damage foci. (Garcia-Higuera, Taniguchi et al. 2001) Mutations in downstream FANCC proteins such as *FANCD1* prevent localization of DNA repair proteins such as *RAD51* in damage-induced nuclear foci, (Godthelp, Artwert et al. 2002; Howlett, Taniguchi et al. 2002) but do not affect *FANCD2* monoubiquitination.

Apoptosis

The FA proteins might also be directly involved in protecting cells from apoptosis. Enhanced apoptosis of hematopoietic stem cells progenitors is probably a key cellular mechanism promoting bone marrow failure in FA. Most of apoptosis-related work was done on the FANCC subgroup. First, *FANCC* associates with *HSP70*, upon exposure to either combinations of tumor necrosis factor and interferon-gamma or double-stranded

RNA and interferon-gamma. This interaction facilitates HSP70 binding to and inactivation of double-stranded RNA-dependent protein kinase, thereby protecting from apoptosis.(Pang, Keeble et al. 2001) Mutations in the *FANCA*, *FANCC*, and *FANCG* genes markedly increase the amount of RNA-dependent protein kinase, leading to hypersensitivity of hematopoietic progenitor cells to growth inhibition by interferon- γ and tumor necrosis factor- α .(Zhang, Li et al. 2004) Second, it has been shown that *FANCC* interacts with and enhances the function of *GSTP1*, which detoxifies by-products of redox stress and xenobiotics, whereby it might protect cells from inducers of apoptosis.(Cumming, Lightfoot et al. 2001) Third, it has also been shown that oxidative stress through excess inflammatory cytokines such as tumor necrosis factor- α may contribute to the loss of FA hematopoietic stem cells/early progenitors. High production of inflammatory cytokines including tumor necrosis factor- α was observed in FA patients(Dufour, Corcione et al. 2003) and in *Fancc*^{-/-} mice challenged with lipopolysaccharide.(Sejas, Rani et al. 2007) *Fancc*^{-/-} hematopoietic progenitors are hypersensitive inflammatory mediators such as interferon- γ and lipopolysaccharide with a concomitant increase in tumor necrosis factor- α -dependent apoptosis.(Sejas, Rani et al. 2007) Importantly, the inflammatory-related apoptosis in FA requires the production of reactive oxygen species. It has been shown that enhanced oxidant and tumor necrosis factor- α -induced apoptosis in *Fancc*^{-/-} murine hematopoietic progenitors is dependent on apoptosis signal-regulating kinase 1.(Bijangi-Vishehsaraei, Saadatzaheh et al. 2005) Abnormal p38 MAPK and JNK activation was shown to partially contribute to lipopolysaccharide-induced *Fancc*^{-/-} hematopoietic suppression. Saadatzaheh et al.(Saadatzaheh, Bijangi-Vishehsaraei et al. 2009) showed that p38 MAPK and JNK inhibition protected c-kit⁺ bone marrow cells from tumor necrosis factor- α -induced apoptosis and enhanced *Fancc*^{-/-} hematopoietic colony formation in the presence of tumor necrosis factor- α . However, engraftment and in-vivo hematopoietic reconstitution might be inhibited by p38MAPK rather than JNK.

Replication fork progression

FANCM has been proposed to directly function in DNA replication and repair. It contains ATP-dependent translocase activity, which promotes replication fork reversal(Gari, Decaillet et al. 2008) and has been proven to control replication fork.(Luke-Glaser, Luke et al. 2010)

Cytokinesis

FA cells demonstrate G₂-phase cell cycle arrest.(Sabatier and Dutrillaux 1988) A small number of monoubiquitinated FANCD2/FANCI foci localize to DNA fragile sites, persist into mitosis(Chan, Palmai-Pallag et al. 2009; Naim and Rosselli 2009) and mark the extremities of ultrafine DNA bridges;(Chan, Palmai-Pallag et al. 2009) ssDNA which link the centromeres of sister chromatids during mitosis.(Chan, North et al. 2007) The ultrafine DNA bridges are naturally coated by BLM and Plk-interacting checkpoint helicase (PICH) (Baumann, Korner et al. 2007; Chan, North et al. 2007) The ultrafine DNA bridges which contain PICH and BLM also display FANCD2/FANCI foci at their extremities. They are generated when replication is incomplete, particularly at fragile loci under replication stress, but also in between two replication forks. BLM participates in the resolution of these bridges during mitosis and persistent DNA bridges may lead to micronucleation.(Chan, Palmai-Pallag et al. 2009) Vinciguerra et al.(Vinciguerra, Godinho et al. 2010) demonstrated abnormally high number of ultrafine DNA bridges in cellular

models of FA, which was correlated with a higher rate of cytokinesis failure and formation of binucleated cells.

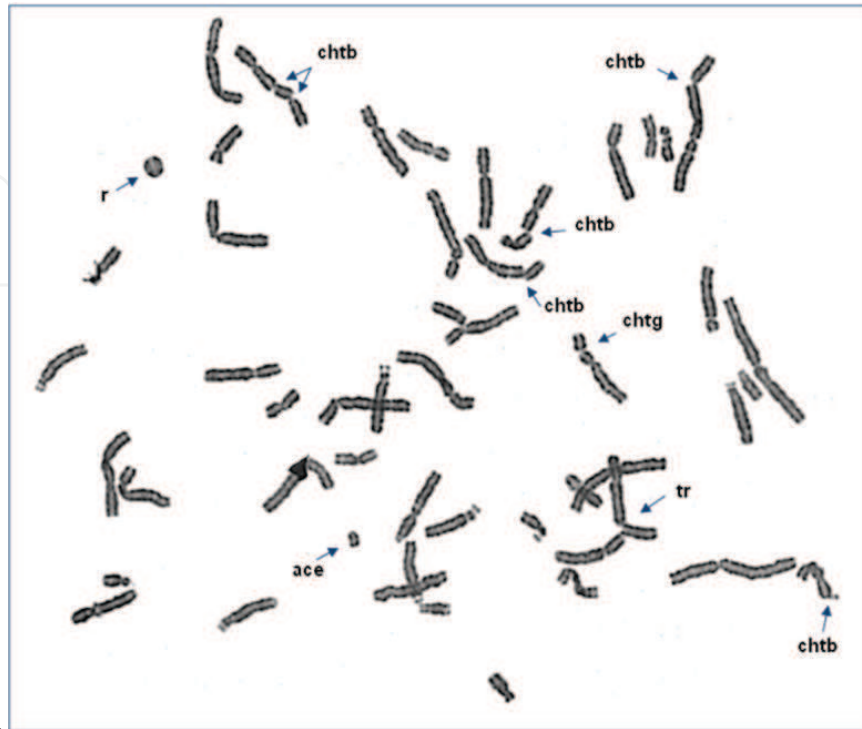


Fig. 1. Characteristic chromosome fragility seen in Fanconi anemia (chtb, chromatid break; chtg, chromatid gap; r, ring; ace, acentric fragment; tr, tri-radial figure)

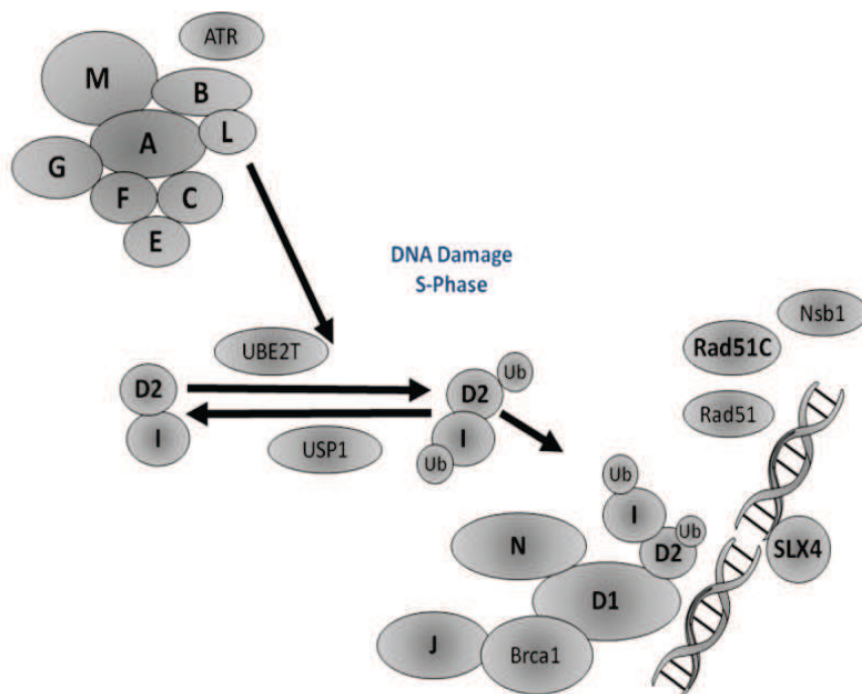


Fig. 2. The Fanconi anemia gene pathway and its reaction to DNA damage. The genes encoding for the proteins in bold are mutated in Fanconi anemia

2.1.3 Genotype phenotype correlation

The abnormal chromosome pattern, number of breaks/cell and variations in proportion of abnormal cells have no direct correlation with the severity of the hematological defects or clinical course of individual patients. (Gillio, Verlander et al. 1997) However, sensitivity to interstrand linking inducing agents may correlate with increased physical malformations. (Castella, Pujol et al. 2011)

A certain degree of correlation exists between genotype and phenotype. FA group A patients with homozygous for null mutations tend to have an earlier onset of anemia and a higher incidence of leukemia than those with mutations producing an altered protein. (Faivre, Guardiola et al. 2000) Also, FA group C patients with IVS4+4A>T or exon 14 mutations usually, (Gillio, Verlander et al. 1997; Faivre, Guardiola et al. 2000) but not always, (Futaki, Yamashita et al. 2000) have more somatic abnormalities and earlier onset of hematological abnormalities and poorer survival compared to patients with other *FANCC* 1 mutation. FA group G patients have severe cytopenia and a higher incidence of leukemia. FA group D1 and N patients may present with solid cancer without apparent bone marrow failure or physical anomalies. Common types of cancer in these groups include medulloblastoma, Wilm's tumor and AML.

2.2 Shwachman-Diamond syndrome

2.2.1 Clinical features of Shwachman-Diamond syndrome

SDS is an autosomal recessive multi-system disorder. (Shwachman 1964) It usually presents in childhood and commonly includes bone marrow failure, exocrine pancreatic insufficiency and bony metaphyseal dysplasia. (Aggett, Cavanagh et al. 1980) The patients have a high risk of leukemia, particularly AML. (Donadieu, Leblanc et al. 2005) The clinical diagnosis of SDS relies on having an evidence of bone marrow dysfunction and exocrine pancreatic dysfunction.

Neutropenia is the most common hematological abnormality, occurring in virtually all patients, followed by reticulocytopenic anemia and thrombocytopenia. Trilineage cytopenias occur in up to 65% of patients. Severe aplastic pancytopenia has occasionally been reported. (Aggett, Cavanagh et al. 1980; Tsai, Sahdev et al. 1990; Barrios, Kirkpatrick et al. 1991) Various degrees of abnormalities in B and T-cell lymphocytes as well as natural killer cells have also been reported in SDS. (Hudson and Aldor 1970; Aggett, Cavanagh et al. 1980; Dror, Ginzberg et al. 2001) Bone marrow biopsy usually shows a hypoplastic specimen. (Aggett, Cavanagh et al. 1980; Dror and Freedman 1999) The only curative therapy for the hematological complications in SDS is HSCT. (Donadieu, Michel et al. 2005)

2.2.2 The Shwachman-Diamond syndrome gene

SBDS is the only gene currently known to be associated with SDS. Mutations in *SBDS* can be identified in 90% of the patients. (Boocock, Morrison et al. 2003) *SBDS* was originally identified by Lai and colleagues (Lai, Chou et al. 2000) in 2000. The protein is 250 amino acids-long, and is highly conserved in evolution. Three structural/functional domains were predicted for the human (de Oliveira, Sforca et al.) and archael (Shammas, Menne et al. 2005) orthologues. The *SBDS* N-terminal domain was postulated to play a role in protein-protein interaction, the central domain is predicted to bind DNA, (Luscombe, Austin et al. 2000) and the C-terminus to bind RNA. (Birney, Kumar et al. 1993)

Data from the Canadian registry showed that *SBDS* is the most commonly mutated gene among the IBMFSs. This is probably because SDS is a common IBMFS and genetically homogenous. (Tsangaris, Klaassen et al. 2011) *SBDS* was mutated in 85%-90% of the SDS

patients.(Boocock, Morrison et al. 2003) The other 10-15% of the patients were diagnosed based on clinical characteristics, and are likely to have mutations in an additional, yet unknown, SDS gene(s).

Ninety six percent of the SBDS mutations are in exon 2.(Boocock, Morrison et al. 2003) The type of mutations include nonsense, splice site mutation, frameshift, missense and complex rearrangements comprising of deletion/insertion. The two common mutations are 183-184TA>CT (nonsense) and 258+2T>C (intronic with predicted alternative splicing & frameshift reading). The mutations are mostly in the N-terminal domain of the protein and cause markedly reduced protein levels.(Woloszynek, Rothbaum et al. 2004)

SBDS mRNA is ubiquitously expressed.(Boocock, Morrison et al. 2003) The protein is essential as no patients with homozygous null mutations have been reported, and residual protein levels can usually be detected in SDS patients.(Woloszynek, Rothbaum et al. 2004; Austin, Leary et al. 2005) Further, a complete loss of the protein in mice causes developmental arrest prior to embryonic day 6.5 and early lethality.(Zhang, Shi et al. 2006) SBDS seems to be multifunctional and play a role in several cellular pathways.

Ribosomal biogenesis

SBDS was found by one group to concentrate in the nucleolus during G1 and G2,(Austin, Leary et al. 2005) and is associated with rRNA.(Ganapathi, Austin et al. 2007) Synthetic genetic arrays of YHR087W, a yeast homolog of the N-terminal domain of SBDS, suggested interactions with several genes involved in RNA and rRNA processing.(Savchenko, Krogan et al. 2005) The loss of the protein in yeast results in a defect in maturation of the 60S ribosomal subunit due to defect in release and recycling of the nucleolar shuttling factor TIF6 from pre-60S ribosomes (Fig 3).(Menne, Goyenechea et al. 2007)

Apoptosis

Bone marrow cells from patients with SDS are characterized by decreased frequency of CD34+ progenitors,(Dror and Freedman 1999) and a reduced ability to generate hematopoietic colonies of all lineages *in vitro*.(Dror and Freedman 1999) Marrow cells(Dror and Freedman 2001) as well as SBDS-knockdown HeLa cells(Rujkijyanont, Watanabe et al. 2008) are characterized by accelerated apoptosis.(Dror and Freedman 2001) The accelerated apoptosis in marrow cells and SBDS-knockdown cells seems to be through the FAS pathway and not through the BAX/BCL-2/BCL-XL pathway.(Dror and Freedman 2001; Rujkijyanont, Watanabe et al. 2008) Depletion of SBDS results in accumulation of FAS at the plasma membrane level and specific overexpression of FAS transcript 1; the main FAS transcript which contains both the transmembrane domain and the death domain.

Chemotaxis

SDS patients have a defect in leukocyte chemotaxis.(Dror, Ginzberg et al. 2001; Stepanovic, Wessels et al. 2004) Consistent with this observation, the SBDS homologue in ameba was found to localize to the pseudopods during chemotaxis.(Wessels, Srikantha et al. 2006) These observations suggest that the SBDS-deficiency in SDS causes the chemotaxis defects in patients.

Mitotic spindle formation

SBDS has been shown to localize to the mitotic spindle, binds microtubules and stabilize them.(Austin, Gupta et al. 2008) Its deficiency results in centrosomal amplification and multipolar spindles.

Bone marrow stromal function

SDS bone marrows are also characterized by a defect in the ability of the stroma to support normal hematopoiesis in cross over experiments of normal CD34+ cells over SDS stroma.(Dror and Freedman 1999)

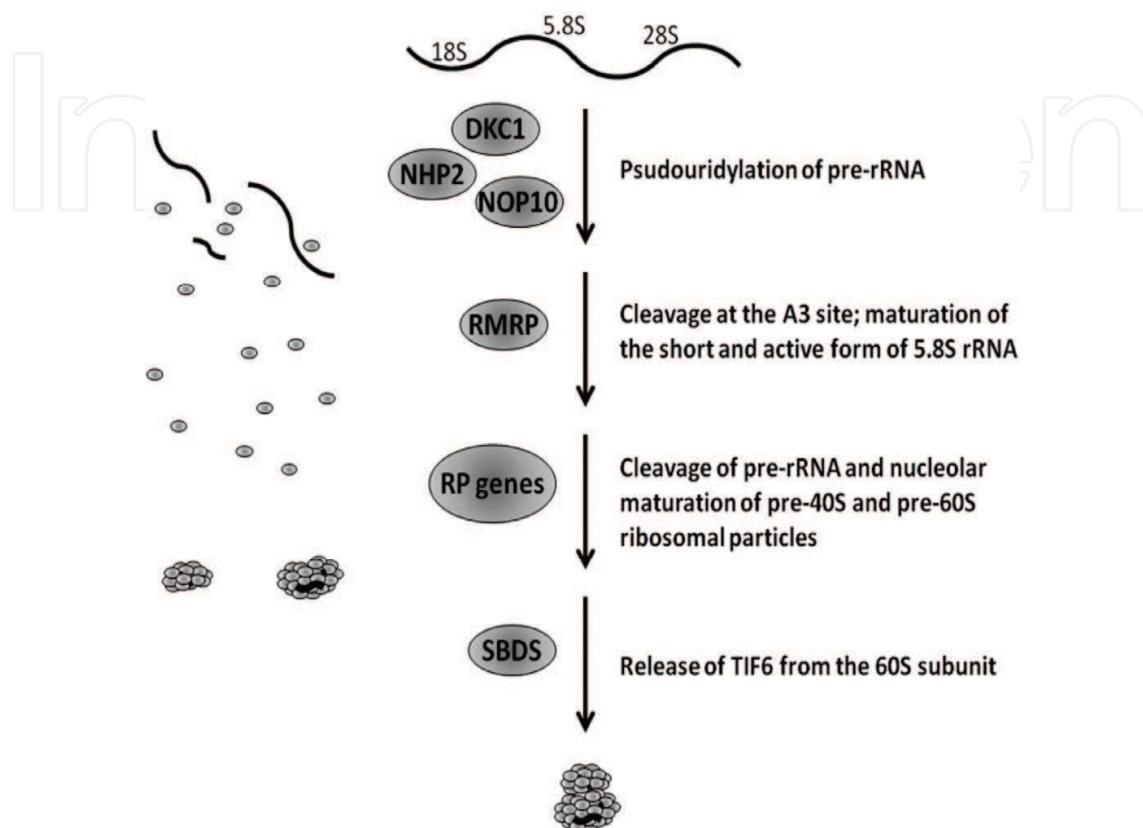


Fig. 3. Ribosome biogenesis and the steps where the inherited bone marrow failure syndrome proteins that are known or hypothesized to function

2.2.3 Genotype phenotype correlation

The study of genotype-phenotype correlation in SDS is difficult since most patients have at least one of the two common mutations. Nevertheless, with regard to the common mutations, patients with severe phenotype including major skeletal abnormalities (Makitie, Ellis et al. 2004) or AML(Majeed, Jadko et al. 2005) have been found to have common mutations.

Based on relatively small numbers it was suggested that SDS patients without mutations in the *SBDS* coding region or flanking intronic regions had more severe hematological disease (lower hemoglobin levels and higher incidence of severe bone marrow failure) but milder pancreatic disease compared to patients with biallelic *SBDS* mutations.(Hashmi, Allen et al. 2010)

2.3 Dyskeratosis Congenita

2.3.1 Clinical features of Dyskeratosis Congenita

Dyskeratosis congenita (DC) is characterized by mucocutaneous abnormalities,(Zinnsser 1906; Cole, Rauschkolb et al. 1920) bone marrow failure,(Dokal 2000) cancer

predisposition (Dokal 2000) and extreme telomere shortening (Vulliamy, Knight et al. 2001). With the recent advances in understanding the molecular basis of the disease, patients with hematological abnormalities without dermatological anomalies have been identified, which changed dramatically the historical definition of the disease (Vulliamy, Marrone et al. 2002). The original diagnostic triad included oral leukoplakia, nail dystrophy and skin hyperpigmentation. Patients may have many other manifestations including immunodeficiency, dacryostenosis, urethral meatal stenosis, pulmonary fibrosis, hepatic fibrosis and gastrointestinal bleeding due to vascular anomalies. The treatment for the bone marrow failure includes androgens or HSCT. Surgical interventions may be required for some organ malformations or solid cancer.

2.3.2 Dyskeratosis Congenita genes

Multiple genes have been associated with DC (Heiss, Knight et al. 1998; Vulliamy, Marrone et al. 2001; Vulliamy, Walne et al. 2005; Marrone, Walne et al. 2007; Walne, Vulliamy et al. 2007; Savage, Giri et al. 2008; Vulliamy, Beswick et al. 2008). All are components of the telomerase complex or shelterin (Fig 4). The X-linked recessive disease is a common form of DC. It was originally estimated as more than 50%, but with the identification of more DC genes and more patients with autosomal dominant inheritance, the true incidence seems lower at approximately 30%. The X-linked disease is caused by mutations in *DKC1* on chromosome Xq28 (Heiss, Knight et al. 1998). *DKC1* encodes for the protein dyskerin. Dyskerin associates with the H/ACA class of RNA. Dyskerin binds to the 3' H/ACA small nucleolar RNA-like domain of the *TERC* component of telomerase. This stimulates telomerase to synthesize telomeric repeats during DNA replication. Dyskerin is also involved in maturation of nascent rRNA. It binds to small nucleolar RNA through their 3' H/ACA domain and catalyzes the isomerization of uridine to pseudouridine through its pseudouridine synthase homology domain. This might be the mechanism for impaired translation from internal ribosome entry sites seen in mice and human DC cells.

There are several genes which are mutated in families with autosomal dominant inheritance. *TINF2* is probably the most commonly mutated gene in this group and accounts for approximately 11-25% of the DC families (Walne, Vulliamy et al. 2008). *TINF2* protein is part of the shelterin protein complex, which binds to telomeres and prevents their recognition as DNA breaks by DNA repair proteins. In the complex, *TINF2* binds to *TRF1*, *TRF2*, *POT1*, *TPP1* and *RAP1*.

Heterozygous mutations in *TERT* result in autosomal dominant disease. *TERT* encodes for the enzyme component of telomerase. Telomerase is a ribonucleoprotein polymerase that maintains telomere ends by synthesis and addition of the telomere repeat TTAGGG at the 3'-hydroxy DNA terminus using the *TERC* RNA as a template.

Heterozygous mutations in the *TERC* gene are another cause of an autosomal dominant form of DC (Vulliamy, Marrone et al. 2001). *TERC* encodes for the RNA component of telomerase and has a 3' H/ACA small nucleolar RNA-like domain.

The autosomal recessive forms of DC are caused by biallelic mutations in *NOP10*, *NHP2*, *TERT* or *TCAB1*. In the telomerase complex, the H/ACA domain of nascent human telomerase RNA forms a pre-ribonucleoprotein with *NAF1*, dyskerin, *NOP10*, and *NHP2*. Initially the core trimer dyskerin-*NOP10*-*NHP2* forms to enable incorporation of *NAF1* (Trahan and Dragon 2009; Trahan, Martel et al. 2010) and efficient reverse transcription of telomere repeats. *NOP10* and *NHP2* also play an essential role in the

assembly and activity of the H/ACA class of small nucleolar ribonucleoproteins, which catalyze the isomerization of uridine to pseudouridine in rRNAs.

TCAB1 facilitates trafficking of telomerase to Cajal bodies. Mutations in this gene lead to misdirection of telomerase RNA to nucleoli and prevent elongation of telomeres by telomerase. (Zhong, Savage et al. 2011)

DC cells are characterized by very short telomeres. In several acquired and inherited marrow failure syndromes, telomere length is reduced. However, since the telomerase function is profoundly impaired in DC, the telomeres in this disease are very short (<1% of the median range for normal). Shortening of telomeres results in senescence, apoptosis ("cellular crisis") or chromosome instability. However, some cells may survive the crisis by harboring compensatory genetic mutations which confer proliferative advantage and neoplastic potential.

DC is a chromosome 'instability' disorder of a different type than Fanconi anemia. (Dokal 2000) Clastogenic stress studies of DC cells are normal. (Pai, Yan et al. 1989; Dokal 2000) However, probably due to the short telomeres, in some patients metaphases in peripheral blood cells, marrow cells and fibroblasts in culture showed numerous spontaneous unbalanced chromosome rearrangements such as dicentric, trisomic and translocations. Clonogenic assays of marrow cells showed a marked reduction or absence of CFU-GEMM, BFU-E, CFU-E and CFU-GM progenitors. (Saunders and Freedman 1978; Marsh, Will et al. 1992)

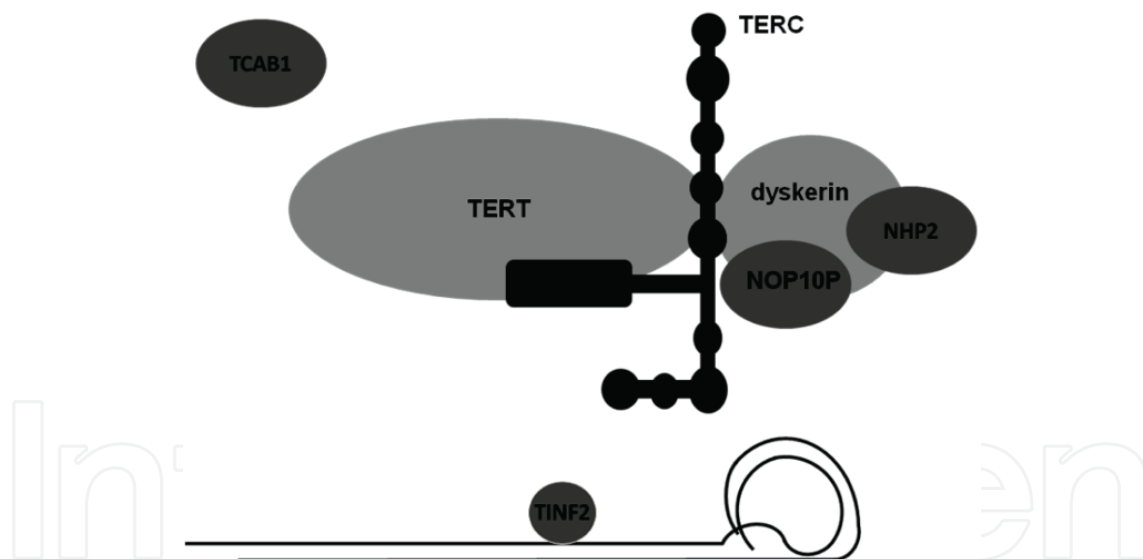


Fig. 4. Telomeres and the dyskeratosis congenita proteins

2.3.3 Genotype phenotype correlation

DC with mutations in the *DKC1*, *TINF2* can result in a severe form of DC called Hoyeraal Hreidarsson syndrome. It is characterized by hematological and dermatological manifestations of dyskeratosis congenita in addition to cerebellar hypoplasia. Immune deficiency is common when the syndrome is caused by *DKC1* mutations. Revez syndrome is a combination of classical manifestations of DC and exudative retinopathy. It is caused by mutations in *TINF2*. Biallelic mutations in *TERT* are also associated with a severe form of DC. However, heterozygosity for mutations in *TERT* is associated with milder

phenotype,(Song, Sullivan et al. 1999) late presentation, severe aplastic anemia without physical malformations, pulmonary fibrosis and hepatic fibrosis. Heterozygosity for mutations in *TERC* is associated milder phenotype, late presentation and severe aplastic anemia without physical malformations. (Song, Sullivan et al. 1999)

2.4 Diamond Blackfan anemia

2.4.1 Clinical features of Diamond Blackfan anemia

Diamond-Blackfan anemia (DBA) is an inherited form of pure red cell aplasia. (Diamond and Blackfan 1938) It is the second most common IBMFSs with incidence of approximately 10 cases/million live births. (Tsangaris, Klaassen et al. (Under Revision)) DBA was first reported in 1936 and later described by Diamond and Blackfan in 1938. It is characterized by varying degrees of red cell aplasia. (Lipton, Atsidaftos et al. 2006; Vlachos, Ball et al. 2008; Lipton and Ellis 2009) Patients may present at birth or become symptomatic after birth with pallor, weakness and cardiac failure. Physical anomalies including short stature, craniofacial dysmorphism, thumb anomalies, among others. (Lipton, Atsidaftos et al. 2006; Vlachos, Ball et al. 2008; Lipton and Ellis 2009) Additionally, patients with DBA carry a high risk of developing malignancies including MDS/AML, osteosarcoma and Hodgkin lymphoma. (Lipton, Atsidaftos et al. 2006; Vlachos, Ball et al. 2008)

Many patients can be diagnosed clinically based on having anemia, low reticulocytes, reduced marrow erythroid progenitors, characteristic physical malformations and high adenosine deaminase levels. (Vlachos, Ball et al. 2008) However, mutations in several genes encoding ribosome proteins have been found mutated in DBA,(Draptchinskaia, Gustavsson et al. 1999; Gazda, Grabowska et al. 2006; Farrar, Nater et al. 2008; Gazda, Sheen et al. 2008; Cmejla, Cmejlova et al. 2009) and can help to establish a diagnosis in many cases when the diagnosis is unclear. (Lipton and Ellis 2009) Standard treatment options include chronic administration of low-dose prednisone (after induction with 2mg/kg/day), chronic red blood cell transfusions and HSCT from a related donor.

2.4.2 Diamond Blackfan anemia genes

About 80% of DBA cases are sporadic.(Halperin and Freedman 1989) The discovery of 11 DBA genes demonstrated heterozygosity for mutations in the respective genes; consistent with autosomal dominant inheritance in all currently known genetic groups. All known DBA proteins are structural components of either the small or large ribosomal subunits.(Doherty, Sheen et al. ; Draptchinskaia, Gustavsson et al. 1999; Farrar, Nater et al. 2008; Gazda, Sheen et al. 2008) The most common mutated DBA gene is *RPS19*. It is mutated in about 25% of the patients.(Gazda, Sheen et al. 2008; Cmejla, Cmejlova et al. 2009) *RPS19* encodes for the ribosomal protein S19, which is associated with the ribosomal subunit 40S.(Da Costa, Tchernia et al. 2003) Deficiency in *RPS19* causes defective cleavage of the pre-rRNA at the ITS1 sequence and abnormal maturation of the 40S subunit (Fig 3).(Flygare, Aspesi et al. 2007) Its deficiency leads to apoptosis of erythroid progenitors,(Miyake, Utsugisawa et al. 2008) possible in a p53 dependent manner. (McGowan, Li et al. 2008)

Other ribosomal protein genes that are mutated in DBA are *RPL5* (12-21%),(Doherty, Sheen et al. ; Gazda, Sheen et al. 2008; Cmejla, Cmejlova et al. 2009) *RPL11* (7-9%),(Gazda, Sheen et al. 2008; Cmejla, Cmejlova et al. 2009) *RPS24* (2%),(Gazda, Grabowska et al. 2006; Gazda, Sheen et al. 2008; Cmejla, Cmejlova et al. 2009) *RPL35a*(Farrar, Nater et al. 2008) and other

more rarely mutated (Table 1). Despite the identification of multiple genes, only about 50% of the patients with DBA can now be genotyped, (Gazda, Sheen et al. 2008; Cmejla, Cmejlova et al. 2009) and new DBA genes are still to be discovered.

DBA marrows are characterized by complete or nearly complete absence of erythroid precursors in 90% of the patients. The defect in DBA is intrinsic to the hematopoietic stem cells and selectively limits their ability to differentiate into and expand the erythroid compartment. DBA erythroid progenitors demonstrate subnormal colony growth in response to erythropoietin. (Tsai, Arkin et al. 1989) Clonogenic assays of marrow cells or CD34+ cells typically show absent BFU-E and CFU-E progenitors. Some patients show normal or even increased numbers of both progenitors or a block at the BFU-E stage. The colony growth can be improved *in vitro* by the addition of combinations of glucocorticoids and erythropoietin. (Chan, Saunders et al. 1982) DBA CD34+ cells had impaired ability also to undergo granulocytic-monocytic differentiation in addition to their erythroid differentiation defect. (Santucci, Bagnara et al. 1999) These results underscore a stem cell defect in DBA rather than an isolated erythroid defect. This is in keeping with the clinical observation that in addition to anemia patients can have neutropenia and thrombocytopenia. (Schofield and Evans 1991; Giri, Kang et al. 2000) The exact role of the RP genes such as *RPS19* in erythropoiesis is unclear. *RPS19* expression is highest at the earlier stages of erythropoiesis and decreases with differentiation. (Da Costa, Narla et al. 2003) Gene transfer of the wild type *RPS19* into CD34+ cells from DBA patients with *RPS19* mutations improves erythroid colony growth, (Hamaguchi, Ooka et al. 2002) proving the causative role of mutations in the gene in the pathogenesis of DBA. Studies of CD34+ cells from DBA patients and CD34+ cells in which *RPS19* expression was reduced by approximately 50% showed that *RPS19* promotes cell proliferation as well as differentiation into CFU-E progenitors. (Miyake, Flygare et al. 2005) Intermediate levels of *RPS19* to approximately haploinsufficiency levels does not affect myeloid progenitors (Bagnara, Zauli et al. 1991; Olivieri, Grunberger et al. 1991) or megakaryocytic progenitors. (Bagnara, Zauli et al. 1991) It is likely that the genetic defects in the DBA gene/s accelerates apoptosis of erythroid progenitor cells (Perdahl, Naprstek et al. 1994; Flygare, Kiefer et al. 2005)

2.4.3 Genotype phenotype correlation

Patients with mutations in *RPL5* and *RPL11* are more likely to have multiple physical malformations. (Gazda, Sheen et al. 2008; Boria, Garelli et al. 2010) For example, thumb anomalies are seen in 56% and 39% of the patients with *RPL5* and *RPL11* mutations, respectively compared to 7% in patients who have *RPS19* gene mutations. Interestingly, cleft lip and/or palate were reported in 42% of the patients with *RPL5* mutations compared to 6% and 0% among the patients with *RPL11* and *RPS19* gene mutations.

2.5 Kostmann/Severe congenital neutropenia

2.5.1 Clinical features of Kostmann/severe congenital neutropenia

Kostmann neutropenia and severe congenital neutropenia (K/SCN) comprise a heterogeneous group of disorders. Herein, we will refer to K/SCN as disorders that are characterized by severe subtype of inherited neutropenia with typical onset at early childhood, profound neutropenia (absolute neutrophil count < 200/ml), recurrent life-threatening infections and a maturation arrest of myeloid precursors at the promyelocyte-myelocyte stage of differentiation. The mainstay of treatment is life-long daily injection with granulocyte-colony stimulating factor (G-CSF).

2.5.2 Kostmann/Severe congenital neutropenia genes

The original families described by Dr. Kostmann showed an inheritance typical of an autosomal recessive disorder.(Kostmann 1956) However, patients with severe congenital neutropenia with an autosomal dominant inheritance mode usually have exactly the same clinical phenotype.

The most common K/SCN gene is *ELA2*, which is associated with an autosomal dominant K/SCN.(Dale, Person et al. 2000) The prevalence of *ELA2* mutations seems to be higher in North America than in Europe, and was reported in about 40-80% of the K/SCN patients. (Horwitz, Benson et al. 1999; Xia, Bolyard et al. 2009) Although some healthy family members have been reported to have the same *ELA2* Genotype as their affected family members, (Germeshausen, Schulze et al. 2001) and although there is a lack of neutropenia in homozygous and heterozygous knock-out mice,(Belaaouaj, McCarthy et al. 1998) it is now widely accepted that *ELA2* mutations are causative. (Ancliff, Gale et al. 2002; Horwitz, Benson et al. 2003)

ELA2 encodes for neutrophil elastase, a glycoprotein synthesized in the promyelocyte/myelocyte stages,(Fouret, du Bois et al. 1989) is packed in the azurophilic cytoplasmic granules, and released in response to infection and inflammation.(Cowland and Borregaard 1999) Computerized modeling of neutrophil elastase showed that *ELA2* mutations in K/SCN tend to cluster on the opposite face of the active site of the enzyme in contrast to cyclic neutropenia, where the mutations tend to cluster near the active site. (Dale, Person et al. 2000)

Neutrophil elastase normally localizes diffusely throughout the cytoplasm.(Benson, Li et al. 2003; Massullo, Druhan et al. 2005) The mutations in the protein are predicted to disrupt its AP3 protein recognition sequence, resulting in excessive membrane accumulation of elastase,(Benson, Li et al. 2003; Massullo, Druhan et al. 2005) leading to premature apoptosis of differentiating (myeloblasts and promyelocytes) but not proliferating myeloid progenitor cells.(Aprikyan, Kutuyavin et al. 2003; Massullo, Druhan et al. 2005) Also, there is evidence that unfolded protein response occurs in primary granulocytic precursors from K/SCN patients and that expression of mutant neutrophil elastase induces unfolded protein response and apoptosis.(Grenda, Murakami et al. 2007)

HAX1 was reported to be mutated in 40% of patients with K/SCN in a European study,(Klein, Grudzien et al. 2007) but in none of the patients in the American studies, (Xia, Bolyard et al. 2009) and in none of the patients on the Canadian Inherited Marrow Failure Study.(Tsangaris, Klaassen et al. 2011) *HAX1* localizes to the mitochondria. It contains two domains reminiscent of a BH1 and BH2 of the BCL-2 family. It promotes normal potential of the inner mitochondrial membrane and protects myeloid cells from apoptosis.

Mutations in the gene encoding the transcriptional repressor *GFI1* were also identified in severe congenital neutropenia.(Person, Li et al. 2003) The mutated protein appears to cause overexpression of *ELA2*, and higher neutrophil elastase levels in all subcellular compartments. *GFI1*-deficient mice also exhibit severe neutropenia. (Karsunky, Zeng et al. 2002)

Activating *WASP* gene mutations are another cause of severe congenital neutropenia. (Devriendt, Kim et al. 2001) The mutant protein is constitutively activated due to disruption of the autoinhibitory domain, leading to increased actin polymerization, disruption of mitosis, genomic instability and apoptosis of neutrophils. (Devriendt, Kim et al. 2001)

Germline G-CSFR mutations are a rare cause of K/SCN. One patient in our registry had digenic germ line mutations in *ELA2* and the extracellular domain of the G-CSFR. Others

have also described digenic mutations in patients with K/SCN. (Germeshausen, Zeidler et al. 2010)

Some patients with K/SCN acquire mutations in the intracytoplasmic domain of the G-CSF receptor. The mutations are restricted to the myeloid lineage and a proliferation but not differentiation signal. Alterations are associated with the development of MDS/AML, and are not the cause of the neutropenia. (Dong, Brynes et al. 1995)

Severe other types of inherited neutropenia with more distinct phenotype are discussed in Section 2.7 “Other inherited bone marrow failure syndromes with predominantly neutropenia”

2.5.3 Genotype phenotype correlation

ELA2 mutations are associated with severe and early onset neutropenia with differentiation arrest at the stage of promyelocyte-megakaryocyte. Typically the patients do not have physical malformations. The patients have a high risk of MDS/AML, but no known risk of solid tumors.

Patients with mutations in *HAX1* typically have severe and early onset neutropenia with differentiation arrest at the stage of promyelocyte-megakaryocyte. They also have a high risk of MDS/AML, but no known risk of solid tumors. About 30% of the patients have neurological abnormalities such as seizures, learning disabilities and developmental delay. This is usually due to nonsense mutations that affect both *HAX1* transcripts (e.g. p.Gln155ProfsX14).

Mutations in *WAS* are associated with moderate to severe neutropenia, reduced phagocyte activity; monocytopenia, lymphopenia, reduced NK cells, reduced lymphocyte proliferation and recurrent infections (Usually not as frequent as in the classical K/SCN). MDS/monosomy 7 has also been reported.

GFI mutations are associated with severe to moderate neutropenia, monocytosis, reduced B and T cells with normal lymphocytic function. There is no clear data about the bone marrow findings in this type of neutropenia and the risks of MDS/AML is unknown.

2.6 Congenital amegakaryocytic thrombocytopenia

2.6.1 Clinical feature of congenital amegakaryocytic thrombocytopenia

Congenital amegakaryocytic thrombocytopenia (CAMT) is an IBMFS, which typically presents in infancy with predominantly thrombocytopenia due to reduced or absent marrow megakaryocytes. It commonly progresses to pancytopenia and severe bone marrow failure. In untreated cases, MDS with monosomy 7 and AML can develop at a later stage. (Lau, Ha et al. 1999) Non-hematological manifestations occur in about one fifth of the patients and include cardiac defects, growth abnormalities, psychomotor retardation (King, Germeshausen et al. 2005) and brain structural malformations (Dror, Unpublished Data). The only curative treatment is HSCT and is indicated in patients who persistently manifest severe cytopenia.

2.6.2 Congenital amegakaryocytic thrombocytopenia genes

Biallelic mutations in the *MPL* (thrombopoietic receptor) gene are the cause for the disorder in 94% of the patients with CAMT,²⁶ particularly, (Ballmaier, Germeshausen et al. 2001) but not exclusively, (King, Germeshausen et al. 2005) (Dror, Unpublished Data) in those without physical anomalies. *MPL* mutations cause inactivation of the thrombopoietin receptor. The

compensatory elevated levels of thrombopoietin (van den Oudenrijn, Bruin et al. 2000; Van Den Oudenrijn, Bruin et al. 2002) do not result in transmitting its signaling. (Muraoka, Ishii et al. 1997; Ballmaier, Germeshausen et al. 2003) Thrombopoietin plays a critical role in the proliferation, survival and differentiation of early and late megakaryocytes. This clearly explains the thrombocytopenia. However, *MPL* is highly expressed in hematopoietic stem cells and promotes their quiescence and survival; (Arai, Yoshihara et al. 2009) thus, insufficiency may account to depletion of hematopoietic stem cells and pancytopenia. The number of CFU-Meg progenitors might be normal initially, but declines as the disease progresses (Freedman and Estrov 1990; Guinan, Lee et al. 1993)

2.6.3 Genotype phenotype correlation

Data about genotype-phenotype correlation is scarce. Nonsense or frameshift mutations that entirely abrogate the thrombopoietin receptor signaling are associated with early development of pancytopenia and more severe bone marrow failure. Missense mutations which only partially reduce receptor signaling are associated with relatively milder initial phenotype and slow progression into pancytopenia. (King, Germeshausen et al. 2005; Ballmaier and Germeshausen 2009) However, the overall outcome might not be different. (Ballmaier and Germeshausen 2009)

2.7 Other inherited bone marrow failure syndromes with predominantly neutropenia

Cyclic neutropenia is an autosomal dominant disorder characterized by a regular, repetitive decrease in peripheral blood neutrophils for 3-4 days every 19-23 days. (Page and Good 1957) Between nadirs the patients have normal or nearly normal neutrophil counts. Patients usually present in infancy or childhood, and have a less severe infectious course compared to Kostmann/severe congenital neutropenia. However, life threatening infections have been reported. (Jonsson and Buchanan 1991; Dale, Bolyard et al. 2002) Daily treatment with G-CSF typically improves symptoms in most patients. Cyclic neutropenia is caused by heterozygous mutations in the *ELA2* gene usually at the active site of neutrophil elastase, (Horowitz, Benson et al. 1999; Ancliff, Gale et al. 2001) without disrupting the enzymatic substrate cleavage by the active site. (Ancliff, Gale et al. 2001) The mutations seem to disturb a predicted transmembrane domain, leading to excessive granular accumulation of elastase and defective membrane localization of the enzyme. (Benson, Li et al. 2003) The myeloid precursors are characterized by cyclic increase in apoptosis. (Aprikyan, Kutyavin et al. 2003) However, the precise molecular mechanism of the cycling hematopoiesis in the disease and why the same mutations in *ELA2* are associated with both cyclic and Kostmann/severe congenital neutropenia phenotype are unknown.

Myelokathexis is a rare autosomal dominant disorder with recurrent bacterial infections caused by reduced number and function of neutrophils. (Zuelzer 1964) Neutropenia is typically moderate to severe. Degenerative changes in the granulocytes are characteristic and include pyknotic nuclear lobes, fine chromatin filaments and hypersegmentation. (Zuelzer 1964) Bone marrow specimens are usually hypercellular with granulocytic hyperplasia. The pathophysiology of myelokathexis has been attributed to a defective release of marrow cells into the peripheral blood. (Zuelzer 1964) Neutrophil precursors are characterized by depressed expression of BCL-X and accelerated apoptosis. (Aprikyan, Liles et al. 2000) G-CSF ameliorate the neutropenia and lead to clinical improvement during episodes of bacterial infection. (Zuelzer 1964; Wetzler, Talpaz et al. 1992) WHIM syndrome

refers to an association of myelokatheksis with other features (warts, hypogammaglobulinemia, infections and myelokalthexis). Most cases studied are caused by mutations in the chemokine receptor gene *CXCR4*. (Hernandez, Gorlin et al. 2003) The mutations result in enhanced chemotactic response of neutrophils in response to the *CXCR4* ligand *CXCL12* (stroma-derived factor 1) and pathological retention of neutrophils in the bone marrow. (Gulino, Moratto et al. 2004) Patients with wild type *CXCR4* might have other genetic defects that lead to enhanced interaction between *CXCR4* and *CXCL12* and enhanced chemotactic response, such as reduced inhibition of *CXCL12*-promoted internalization and desensitization of *CXCR4* by GPCR kinase-3 due to decreased transcription of the GPCR kinase-3. (Balabanian, Levoe et al. 2008)

Dursun syndrome is an autosomal recessive disorders with cardiac anomalies (particularly atrial septal defect), urogenital anomalies, vascular anomalies (prominent skin blood vessels), mild immune deficiency and intermittent mild thrombocytopenia. (Dursun, Ozgul et al. 2009) The bone marrow shows either normal maturation or promyelocyte-meylocyte arrest. The risk of MDS/AML is unknown. It is caused by mutation in *G6PC3*, the gene encodes for glucose-6-phosphatase catalytic unit 3. (Banka, Newman et al. ; Boztug, Appaswamy et al. 2009) *G6PC3* is expressed ubiquitously. It is located in the endoplasmic reticulum and hydrolyses glucose-6-phosphate to glucose and phosphate. *G6PC3* function loss causes impaired glucose recycling from the endoplasmic reticulum to the cytoplasm in neutrophils. (Jun, Lee et al.) Neutrophil endoplasmic reticulum stress increases susceptibility of neutrophils and myeloid cells to apoptosis, (Boztug, Appaswamy et al. 2009) possibly due to unfolded protein response as evident by enlarged rough endoplasmic reticulum and overexpression of BiP. (Cheung, Kim et al. 2007)

Other disorders with isolated neutrophil production defects such as glycogen storage disease type Ib. (Annabi, Hiraiwa et al. 1998; Calderwood, Kilpatrick et al. 2001) and Barth syndrome (Bione, D'Adamo et al. 1996; Kuijpers, Maianski et al. 2004) are listed in Table 1.

2.8 Selected other inherited bone marrow failure syndromes with predominantly anemia

Congenital dyserythropoietic anemias (CDAs) are inherited disorders with prominent morphological dyserythropoiesis and ineffective erythropoiesis. Three main types of CDA exist: CDA I, II, and III, which differ in marrow morphology, serologic findings and inheritance patterns (Table 1). The anemia in most patients is not severe and does not mandate chronic therapy. In cases with severe anemia splenectomy, a chronic RBC transfusion program, or HSCT should be considered. Due to ineffective erythropoiesis and multiple transfusions, patients can develop iron overload necessitating iron chelation. CDA I is characterized by megaloblastic appearance of erythroid bone marrow precursors with some binucleated cells and internuclear chromatin bridges. The CDA I gene was identified as *CDA1*, which encodes for codanin-1. (Dgany, Avidan et al. 2002) The protein was shown and was entitled to be during cell cycle; it is localized to heterochromatin in interphase cells, overexpressed during the S phase and phosphorylated at mitosis. (Noy-Lotan, Dgany et al. 2009) Another group found that codanin-1 interacts with HP1 α . Mutant codanin-1 results in abnormal accumulation of HP1 α in the Golgi apparatus. (Renella, Roberts et al.) CDA II is characterized by larger number of binucleated cells and some multinuclear cells. Abnormally high protein, lipid dysglycosylation and endoplasmic reticulum double-membrane remnants are seen in erythroid cells. The gene for CDAAII was identified as

SEC23B. The *SEC23B* protein is an essential component of protein complex II-coated vesicles that transport secretory proteins from the endoplasmic reticulum to the Golgi apparatus. Knockdown of *SEC23B* in zebrafish leads to aberrant erythrocyte development. The gene for CDA III has not been identified.

Inherited sideroblastic anemias are disorders of mitochondrial iron utilization. Iron accumulation occurs in the mitochondria of red blood cell precursors. Perl's Prussian-blue shows iron accumulation in a circular or ringed pattern around the nucleus in greater than 10% of the erythroblasts. Treatment depends on the specific syndrome. Patients with X-linked sideroblastic anemia respond to pyridoxine. Patients with thiamine responsive megaloblastic anemia respond to thiamine. In the other types of inherited sideroblastic anemia RBC transfusions are the mainstay of treatment. HSCT is curative. (Urban, Binder et al. 1992) The genes mutated in sideroblastic anemias are involved in heme biosynthesis, iron-sulfur cluster biogenesis, iron-sulfur cluster transport or mitochondrial metabolism (Table 1).

2.9 Selected other inherited bone marrow failure syndromes with predominantly thrombocytopenia

The syndrome of thrombocytopenia with absent radii (TAR) was first described in 1929, (Greenwald and Sherman 1929) and subsequently defined in 1969, (Hall, Levin et al. 1969) The two features, which are currently essential for the definition of the syndrome are hypomegakaryocytic thrombocytopenia and bilateral radial aplasia. The definition of the syndrome may change once the genetic basis is deciphered, and its inheritance mode may be clarified. Typically, parents of TAR syndrome patients are phenotypically normal, and females with TAR syndrome can conceive and give birth to hematologically and phenotypically normal offspring. Klopocki and colleagues reported deletion on chromosome 1q21.1 in TAR syndrome patients; (Klopocki, Schulze et al. 2007) however, the etiological significance of this finding is still unclear. Another group found that bone marrow adherent stromal cells from patients with TAR syndrome do not express CD105 antigen, a protein component of the transforming growth factor- β 1 and β 3 receptor complex which is normally expressed in mesenchymal cells. (Bonsi, Marchionni et al. 2009) They hypothesized that the clinical phenotype of TAR could derive from damage to a common osteo/chondrogenic and hematopoietic progenitors.

MYH9-associated familial macrothrombocytopenia comprises an array of several syndromes; Alport, Fetchner, Ebstein, Sabastian and May-Hegglin, which have traditionally been classified according to their non-hematological manifestations. (Drachman 2004; Geddis and Kaushansky 2004). *MYH9* encodes for nonmuscle myosin-heavy chain IIA, cytoskeletal contractile protein. (Seri, Pecci et al. 2003) The common features include autosomal dominant inheritance, large platelets, mild to moderate thrombocytopenia, normal numbers of megakaryocytes in the bone marrow and variable platelet aggregation and secretion defects which may rarely cause bleeding, requiring platelet transfusions. (Peterson, Rao et al. 1985) Progression into aplastic anemia or leukemia has not been reported thus far. Myosin-heavy chain IIA normally exists as a large hexamer, comprised of two heavy chains and 4 myosin light chains. The N-terminal head interacts with actin. An intermediate neck domain binds myosin light chains. Phosphorylation of myosin light chains result in activation of myosin and interaction with actin filaments. The C-terminal tail domain is important for filament assembly and cargo binding. Mutations in

the head region directly affect important functions of the motor protein and have a critical effect on function. Mutated myosin-heavy chain IIA light chains forms aggregates in neutrophils, which bind other proteins including normal myosin-heavy chain IIA from the normal allele.

Familial non-syndromic thrombocytopenia is characterized by an autosomal dominant inheritance, mild to moderate thrombocytopenia, normal platelet size and morphology and mild bleeding tendency. There is no known increased risk of progression to leukemia. Bone marrow specimens are of normal cellularity with normal to mildly reduced numbers of megakaryocytes, which can be small and have hypolobulated nuclei. Clonogenic assays show increased megakaryocytic colony growth.(Drachman, Jarvik et al. 2000) Three genes have been reported as mutated in this disease (Table 1). The most common one is *MASTL*, which encodes for a putative kinase.(Gandhi, Cummings et al. 2003) *MASTL* expression is restricted to hematopoietic and cancer cell lines and localizes to the nucleus in overexpression studies.(Johnson, Gandhi et al. 2009) A transient knockdown of *MASTL* in zebrafish reduced platelet counts.

Radioulnar synostosis with bone marrow failure is an autosomal dominant disorder with proximal radio-ulnar synostosis, clinodactyly, syndactyly, congenital hip dysplasia and sensorineural deafness.(Thompson, Woodruff et al. 2001) The thrombocytopenia can be severe and require platelet transfusions. The bone marrow shows absence of megakaryocytes. Progression into pancytopenia is common. If the thrombocytopenia is severe or progresses to aplastic anemia, allogeneic HSCT can be curative.(Thompson, Woodruff et al. 2001),(Castillo-Caro, Dhanraj et al.) Most patients are heterozygous for mutations in the *HOXA11* gene, which lead to truncation of the protein.(Thompson and Nguyen 2000) Some patients with classical presentation are negative for *HOXA11*.(Castillo-Caro, Dhanraj et al.)

Familial platelet disorder with predisposition to AML is an autosomal dominant disease and a striking predisposition for hematological malignancy.(Michaud, Wu et al. 2002) The thrombocytopenia is mild to moderate, and platelets have normal size and morphology. Treatment of the thrombocytopenia is usually not required, but periodic screening for pancytopenia and MDS/AML is advisable. HSCT is potentially curative in the leukemic phase. The disorder is caused by mutations in the *RUNX1* gene.(Song, Sullivan et al. 1999) The thrombocytopenia may result from reduced *MPL* expression possibly by decreased binding of *RUNX1* to the *MPL* promotor.(Heller, Glembotsky et al. 2005) *RUNX1* acts as a tumor suppressor and promotes differentiation.

Familial thrombocytopenia with dyserythropoiesis is an X-linked disease with mild to severe bleeding tendency and mild to moderate dyserythropoiesis.(Nichols, Crispino et al. 2000; Mehaffey, Newton et al. 2001) Platelets are hypogranular and of normal-to large size. Platelet counts are moderately to severely affected ($10\text{-}40 \times 10^9/\text{L}$), have variably low expression of glycoprotein Ib, and their aggregation in response to ristocitin is reduced.(Freson, Devriendt et al. 2001) The anemia is variable in severity. Bone marrow biopsy specimens are hypercellular with dysplastic megakaryocytes having peripheral location of the nucleus and lack of nuclear segmentation or fragmentation. Dysplastic erythroid precursors with mild megaloblastic changes and delayed nuclear maturation are also seen.(Mehaffey, Newton et al. 2001) There are no reports of progression to severe aplastic anemia, MDS or AML. The treatment consists of platelet transfusion in case of bleeding, trauma or preparation for surgery. Severe cases can be cured by allogeneic related

or unrelated HSCT.(Nichols, Crispino et al. 2000) The disorder is caused by missense mutations in the GATA1 protein domain between 205-218 amino acids,(Nichols, Crispino et al. 2000) a transcription factor important for both magakaryopoiesis and erythropoiesis. Other IBMFSs with predominantly thrombocytopenia are listed in Table 1.

3. Conclusion

Multiple genes which function in many different pathways are associated with IBMFSs. However, about 45% of the patients do not have mutations in known genes; thus it is likely that many more genes remained to be identified. Despite accumulation of substantial knowledge about the functions of the IBMFS proteins, the mechanism of bone marrow failure in most of the conditions is still unknown.

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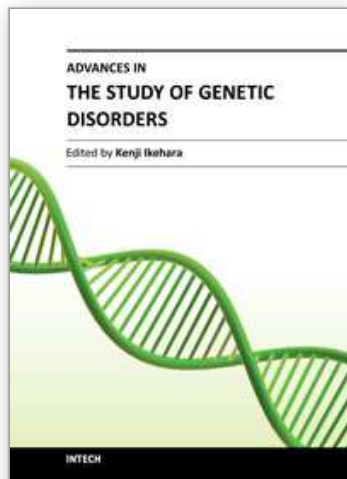
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The studies on genetic disorders have been rapidly advancing in recent years as to be able to understand the reasons why genetic disorders are caused. The first Section of this volume provides readers with background and several methodologies for understanding genetic disorders. Genetic defects, diagnoses and treatments of the respective unifactorial and multifactorial genetic disorders are reviewed in the second and third Sections. Certainly, it is quite difficult or almost impossible to cure a genetic disorder fundamentally at the present time. However, our knowledge of genetic functions has rapidly accumulated since the double-stranded structure of DNA was discovered by Watson and Crick in 1956. Therefore, nowadays it is possible to understand the reasons why genetic disorders are caused. It is probable that the knowledge of genetic disorders described in this book will lead to the discovery of an epoch of new medical treatment and relieve human beings from the genetic disorders of the future.

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