18

Genetic Basis of Inherited Bone Marrow Failure Syndromes

Yigal Dror
The Hospital for Sick Children and The University of Toronto, Toronto Canada

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 10^6 child births.(Tsangaris, Klaassen et al. 2011)

In some IBMFSs (e.g. Fanconi anemia) pancytopenia ($\geq$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	*FANCA*	FANCA	16q24.3	AR	(Lo Ten Foe, Rooimans et al. 1996)
	FANCB	FANCB	Xp22.31	XLR	(Meetei, Levitus et al. 2004)
	FANCC	FANCC	9q22.3	AR	(Strathdee, Gavish et al. 1992)
	FANCD1/ BRCA2	FANCD1/ BRCA2	13q12.3	AR	(Howlett, Taniguchi et al. 2002)
	FANCD2	FANCD2	3p25.3	AR	(Timmers, Taniguchi et al. 2001)
	FANCE	FANCE	6p21.3	AR	(de Winter, Leveille et al. 2000)
	FANCF	FANCF	11p15	AR	(de Winter, Rooimans et al. 2000)
	FANCG/ XRCC9	FANCG	9p13	AR	(de Winter, Waisfisz et al. 1998)
	FANCI	FANCI	15q25-q26	AR	(Levitus, Rooimans et al. 2004)
	FANCJ/ BRIP1	FANCJ/ BRIP1	17q22	AR	(Levitus, Rooimans et al. 2004)
	FANCL/ PHF9	FANCL/ PHF9	2p16.1	AR	(Meetei, de Winter et al. 2003)
	FANCM	FANCM	14q21.3	AR	(Meetei, Medhurst et al. 2005)
	FANCN/ PALB2	FANCN/ PALB2	16p12	AR	(Reid, Schindler et al. 2007)
	FANCP/ SLX4	FANCP/ SLX4	16p13.3	AR	(Stoepker, Hain et al.)
	FANCO/ RAD51C	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	*SBDS*	7q11.2	7q11	AR	(Boocock, Morrison et al. 2003)
Dyskeratosis congenita	*DKC1*	Dyskerin	Xq28	XLR	(Heiss, Knight et al. 1998)
	TINF2	TIN2	14q12	AD	(Savage, Giri et al. 2008)
	TERC	TERC	3q21-q28	AD	(Vulliamy, Marrone et al. 2001)
	TERT	Telomerase	5p15.33	AD	(Vulliamy, Walne et al. 2005)
	NOP10	NOP10	15q14-q15	AR	(Walne, Vulliamy et al. 2007)
	NHP2	NHP2	5q35.3	AR	(Vulliamy, Beswick et al. 2008)
	TCAB1	*TCAB1*	17p13	AR	(Zhong, Savage et al. 2011)
Congenital amegakaryocytic thrombocytopenia	*MPL*	Thrombo-poietin receptor	1p34	AR	(van den Oudenrijn, Bruin et al. 2000)
Reticular dysgenesis	*AK2*	Adenylate kinase 2	1p34	AR	(Lagresle-Peyrou, Six et al. 2009; Pannicke, Honig et al. 2009)
Pearson's syndrome	*mDNA*	Variable	Mito-chondrial DNA	Maternal	(Rotig, Cormier et al. 1990)
Lig4-associated aplastic anemia	*LIG4*	DNA Ligase IV	1q22-q34		(O'Driscoll, Cerosaletti et al. 2001)

Disorder	Gene	Protein	Gene Locus	Inheritance	Reference
Diamond-Blackfan anemia	*RPS19*	RPS19	19q13.3	AD	(Draptchinskaia, Gustavsson et al. 1999)
	RPL5	RPL5	1p22.1	AD	(Gazda, Sheen et al. 2008)
	RPS26	RPS26	12q	AD	(Doherty, Sheen et al. 2010)
	RPL11	RPL11	1p35-p36.1	AD	(Gazda, Sheen et al. 2008)
	RPS24	RPS24	10q22-q23	AD	(Gazda, Grabowska et al. 2006)
	RPL35a	RPL35a	3q29	AD	(Farrar, Nater et al. 2008)
	RPS7	RPS7	15q	AD	(Doherty, Sheen et al. 2010)
	RPS17	RPS17	15q	AD	(Doherty, Sheen et al. 2010)
	RPS10	RPS10	6p	AD	(Doherty, Sheen et al. 2010)
Inherited sideroblastic anemia	*ALAS2*	ALAS	Xp11.21	XL	(Cotter, Baumann et al. 1992)
	ABC7	ATP-binding cassette transporter 7	Xq13.1-q13.3	XL	(Allikmets, Raskind et al. 1999)
	SLC19A2	thiamine transporter 2	1q23.3	AR	(Fleming, Tartaglini et al. 1999)
	PUS1	Pseudo-uridine synthase 1	2p16.1	AR	(Zeharia, Fischel-Ghodsian et al. 2005)
	SLC25A38	SLC25A38	3p22.1	AR	(Guernsey, Jiang et al. 2009)

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

Disorder	Gene	Protein	Gene Locus	Inheritance	Reference
Poikiloderma with neutropenia	*C16orf57*	Not-determined	16q13	AR	(Volpi, Roversi et al.)
Thrombocytopenia absent radii	*UK*	UK	UK	AR	
Epstein/Fechtner/ Sebastian/May-Hegglin/ Alport syndrome	*MYH9*	nonmuscle myosin heavy chain IIA	22q11-q13	AD	(Seri, Pecci et al. 2003)
Mediterranean platelet disorder	*GPIBA*	GPIb	17pter-p12	AD	(Savoia, Balduini et al. 2001)
Familial autosomal dominant non-syndromic thrombocytopenia	*MASTL*	microtubule-associated serine/threonine-like kinase	10p11-12	AD	(Gandhi, Cummings et al. 2003)
	ACBD5	ACBD5	10p12.1	AD	(Punzo, Mientjes et al. 2010)
	ANKRD26	ANKRD26	10q22.1	AD	(Pippucci, Savoia et al.)
Thrombocytopenia with dyserythropoiesis	*GATA1*	GATA1	Xp11.23	XL	(Nichols, Crispino et al. 2000)
Thrombocytopenia with associated myeloid malignancies	*CBFA2*	CBFA2	21q22.1-22.2	AD	(Song, Sullivan et al. 1999)
X-linked thrombocytopenia	*WASP*	WASP	Xp11.23	XL	(Devriendt, Kim et al. 2001)
Thrombocytopenia with radio-ulnar synostosis	*HOXA11*	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. *FANCJ* 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 monoubiquination of two downstream FA proteins, FANCD2 and FANCI, through the E3 ubiquiten ligase domain of FANCL and by the E2 conjugating enzyme UBE2T. There is evidence that FANCI phosphorylation promotes FAND2 monoubiquination in an ATR-dependent manner and functions as a molecular switch to turn on the FA pathway.(Ishiai, Katao et al. 2008) Once ubiquinated, 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 FANC 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 FAND2 monoubiquination.

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, Saadatzadeh et al. 2005) Abnormal p38 MAPK and JNK activation was shown to partially contribute to lipopolysaccaride-induced *Fancc*$^{-/-}$ hematopoietic suppression. Saadatzadeh et al(Saadatzadeh, 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 G_2-phase cell cycle arrest.(Sabatier and Dutrillaux 1988) A small number of monoubiquinated 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.

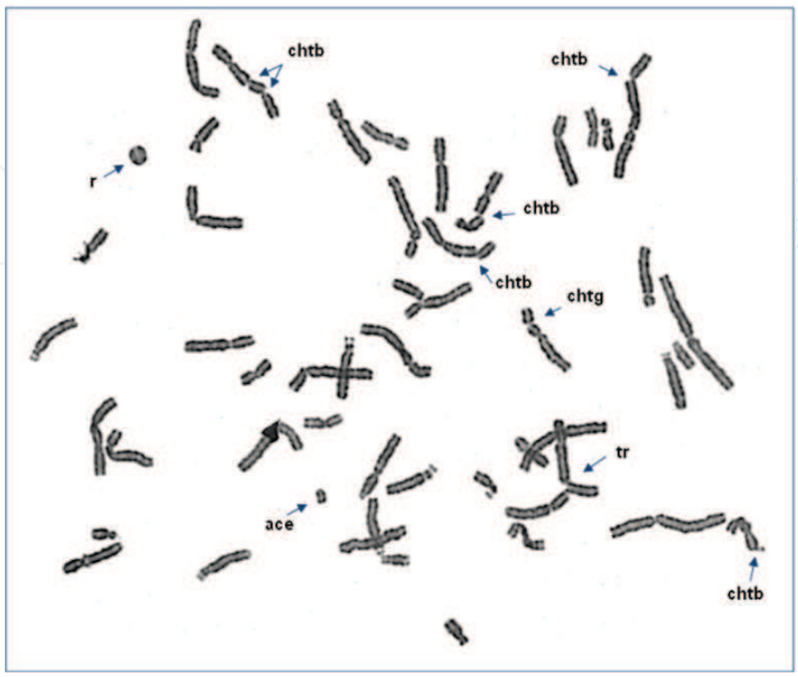


Fig. 1. Characteristic chromosome fragility seen in Fanconi anemia (chtb, chromatid break; chtg, chromatid gap; r, ring; ace, acentric fragment; tr, tri-radial figure)

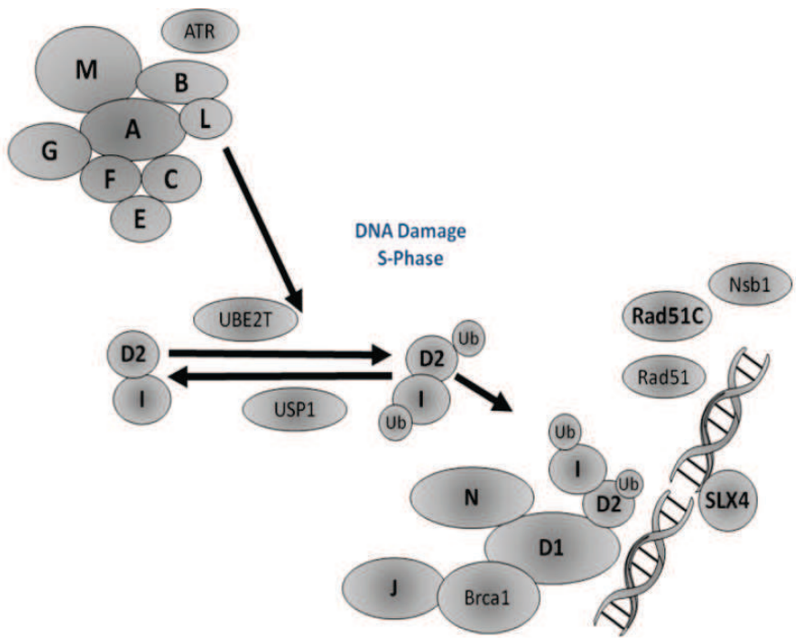


Fig. 2. The Fanconi anemia gene pathway and its reaction to DNA damage. The genes encoding for the proteins in bold are mutated in Fanconi anemia

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 syaplasia.(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 microtubles 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)

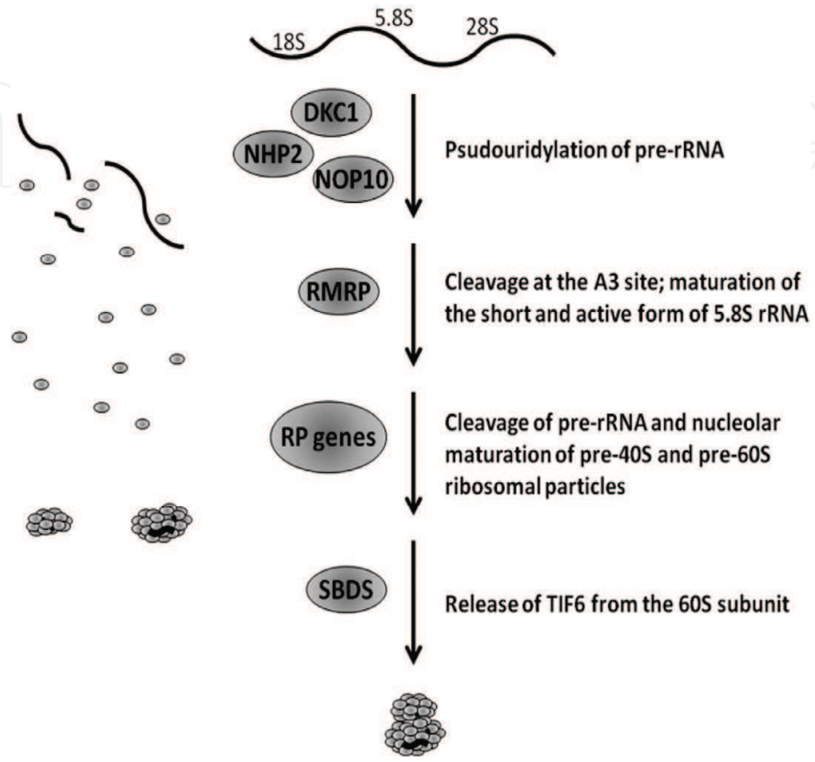


Fig. 3. Ribosome biogenesis and the steps where the inherited bone marrow failure syndrome proteins that are known or hypothesized to function

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 is 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 congenital (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 gastrointestingal 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 peudouridine 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 prevent their recognition as DNA breaks by DNA repair proteins. In the complex, TIN2 binds to TRF1, TRF2, POT1, TPP1 and RAP1.

Heterozygous mutations in *TERT* results 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 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 is 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, tricentric 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)

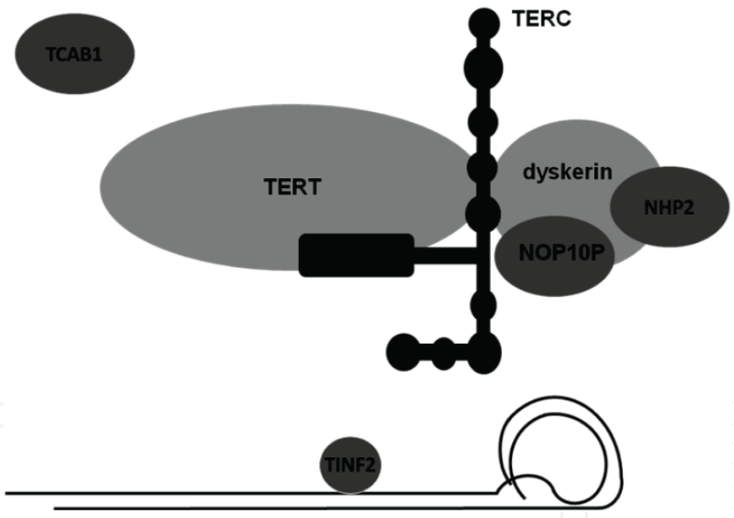


Fig. 4. Telomeres and the dyskeratosis congenita proteins

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, Kutyavin 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 neutroepnia"

2.5.3 Genotype phenotype correlation

ELA2 mutations are associated with severe and early onset neutropenia with differentiation arrest at the stage of promyelocyte-meylocyte. 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-meylocyte. They also have a high risk of MDS/AML, but no know 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. Nonesense 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, Levoye 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. CDAI 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 HP1α. Mutant codanin-1 results in abnormal accumulation of HP1α 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 CDAII 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-β1 and β3 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-assocaited familial macrothrombocytopenia comprises an array of several syndromes; Alport, Fetchner, Ebstein, Sabastian and May-Hegglin, which have traditionally been classified according to their non-hematologtical 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 moderated 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 (10-40 10^9/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.

4. Acknowledgment

The author thanks Dr. Mary Shago, the Hospital for Sick Children, Toronto, for kindly providing Figure. Elena Tsangaris and Santhosh Dhanraj for preparation of data and to Philippa McCaffrey for assistance in preparing the chapter.

5. References

Aggett, P. J., N. P. Cavanagh, et al. (1980). Shwachman's syndrome. A review of 21 cases. *Archives of Disease in Childhood* 55(5): 331-347.

Allikmets, R., W. H. Raskind, et al. (1999). Mutation of a putative mitochondrial iron transporter gene (ABC7) in X-linked sideroblastic anemia and ataxia (XLSA/A). *Hum Mol Genet* 8(5): 743-749.

Alter, B. P. (2003). Inherited bone marrow failure syndromes. Hematology of Infancy and Childhood. D. G. Nathan, Orkin S.H., Ginsberg, D., Look, A.T. Philadelphia, W.B. Saunders: 280-365.

Alter, B. P. (2007). Diagnosis, genetics, and management of inherited bone marrow failure syndromes. *Hematology Am Soc Hematol Educ Program 2007: 29-39.*

*Ancliff, P., R. Gale, et al. (2002). Paternal mosaicism proves t*he pathogenic nature of mutations in neutrophil elastase in severe congenital neutropenia. *Blood* 100(2): 707-709.

Ancliff, P. J., R. E. Gale, et al. (2001). Mutations in the ELA2 gene encoding neutrophil elastase are present in most patients with sporadic severe congenital neutropenia but only in some patients with the familial form of the disease. *Blood* 98(9): 2645-2650.

Annabi, B., H. Hiraiwa, et al. (1998). The gene for glycogen-storage disease type 1b maps to chromosome 11q23. *Am J Hum Genet* 62: 400-405.

Antonio Casado, J., E. Callen, et al. (2007). A comprehensive strategy for the subtyping of patients with Fanconi anaemia: conclusions from the Spanish Fanconi Anemia Research Network. *J Med Genet* 44(4): 241-249.

Aprikyan, A. A., T. Kutyavin, et al. (2003). Cellular and molecular abnormalities in severe congenital neutropenia predisposing to leukemia. *Exp Hematol* 31(5): 372-381.

Aprikyan, A. A., W. C. Liles, et al. (2000). Myelokathexis, a congenital disorder of severe neutropenia characterized by accelerated apoptosis and defective expression of bcl-x in neutrophil precursors. *Blood* 95(1): 320-327.

Arai, F., H. Yoshihara, et al. (2009). Niche regulation of hematopoietic stem cells in the endosteum. *Ann N Y Acad Sci* 1176: 36-46.

Arnaud, L., C. Saison, et al. A dominant mutation in the gene encoding the erythroid transcription factor KLF1 causes a congenital dyserythropoietic anemia. *Am J Hum Genet* 87(5): 721-727.

Aubert, G. and P. M. Lansdorp (2008). Telomeres and aging. *Physiol Rev* 88(2): 557-579.

Auerbach, A. D., A. Rogatko, et al. (1989). International Fanconi Anemia Registry: relation of clinical symptoms to diepoxybutane sensitivity. *Blood* 73(2): 391-396.

Austin, K. M., M. L. Gupta, et al. (2008). Mitotic spindle destabilization and genomic instability in Shwachman-Diamond syndrome. *J Clin Invest* 118(4): 1511-1518.

Austin, K. M., R. J. Leary, et al. (2005). The Shwachman-Diamond SBDS protein localizes to the nucleolus. *Blood* 106(4): 1253-1258.

Bagnara, G. P., G. Zauli, et al. (1991). In vitro growth and regulation of bone marrow enriched CD34+ hematopoietic progenitors in Diamond-Blackfan anemia. *Blood* 78(9): 2203-2210.

Balabanian, K., A. Levoye, et al. (2008). Leukocyte analysis from WHIM syndrome patients reveals a pivotal role for GRK3 in CXCR4 signaling. *J Clin Invest* 118(3): 1074-1084.

Ballmaier, M. and M. Germeshausen (2009). Advances in the understanding of congenital amegakaryocytic thrombocytopenia. *Br J Haematol* 146(1): 3-16.

Ballmaier, M., M. Germeshausen, et al. (2003). Thrombopoietin is essential for the maintenance of normal hematopoiesis in humans: development of aplastic anemia in patients with congenital amegakaryocytic thrombocytopenia. *Ann N Y Acad Sci* 996: 17-25.

Ballmaier, M., M. Germeshausen, et al. (2001). c-mpl mutations are the cause of congenital amegakaryocytic thrombocytopenia. *Blood* 97(1): 139-146.

Balmain, A., J. Gray, et al. (2003). The genetics and genomics of cancer. *Nat Genet* 33 Suppl: 238-244.

Banka, S., W. G. Newman, et al. Mutations in the G6PC3 gene cause Dursun syndrome. Am *J Med Genet A* 152A(10): 2609-2611.

Barrios, N., D. Kirkpatrick, et al. (1991). Bone marrow transplant in Shwachman Diamond syndrome. *Br J Haematol* 79(2): 337-338.

Baumann, C., R. Korner, et al. (2007). PICH, a centromere-associated SNF2 family ATPase, is regulated by Plk1 and required for the spindle checkpoint. *Cell* 128(1): 101-114.

Belaaouaj, A., R. McCarthy, et al. (1998). Mice lacking neutrophil elastase reveal impaired host defense against gram negative bacterial sepsis. *Nat Med* 4(5): 615-618.

Benson, K. F., F. Q. Li, et al. (2003). Mutations associated with neutropenia in dogs and humans disrupt intracellular transport of neutrophil elastase. *Nat Genet* 35(1): 90-96.

Bianchi, P., E. Fermo, et al. (2009). Congenital dyserythropoietic anemia type II (CDAII) is caused by mutations in the SEC23B gene. *Hum Mutat* 30(9): 1292-1298.

Bijangi-Vishehsaraei, K., M. R. Saadatzadeh, et al. (2005). Enhanced TNF-alpha-induced apoptosis in Fanconi anemia type C-deficient cells is dependent on apoptosis signal-regulating kinase 1. *Blood* 106(13): 4124-4130.

Bione, S., P. D'Adamo, et al. (1996). A novel x-linked gene, G4.5 is responsible for Barth syndrome. *Nat Genet* 12(4): 385-389.

Birney, E., S. Kumar, et al. (1993). Analysis of the RNA-recognition motif and RS and RGG domains: conservation in metazoan pre-mRNA splicing factors. *Nucleic Acids Res* 21(25): 5803-5816.

Bonsi, L., C. Marchionni, et al. (2009). Thrombocytopenia with absent radii (TAR) syndrome: from hemopoietic progenitor to mesenchymal stromal cell disease? *Exp Hematol* 37(1): 1-7.

Boocock, G. R., J. A. Morrison, et al. (2003). Mutations in SBDS are associated with Shwachman-Diamond syndrome. *Nature Genetics* 33(1): 97-101.

Boria, I., E. Garelli, et al. (2010). The ribosomal basis of Diamond-Blackfan Anemia: mutation and database update. *Hum Mutat* 31(12): 1269-1279.

Boztug, K., G. Appaswamy, et al. (2009). A syndrome with congenital neutropenia and mutations in G6PC3. *N Engl J Med* 360(1): 32-43.

Byrd, R. S., T. Zwerdling, et al. Monosomy 21q22.11-q22.13 presenting as a Fanconi anemia phenotype. *Am J Med Genet A* 155A(1): 120-125.

Calderwood, S., L. Kilpatrick, et al. (2001). Recombinant human granulocyte colony-stimulating factor therapy for patients with neutropenia and/or neutrophil dysfunction secondary to glycogen storage disease type 1b. *Blood* 97(2): 376-382.

Castella, M., R. Pujol, et al. (2011). Chromosome fragility in patients with Fanconi anaemia: diagnostic implications and clinical impact. *J Med Genet.*

Castillo-Caro, P., S. Dhanraj, et al. Proximal radio-ulnar synostosis with bone marrow failure syndrome in an infant without a HOXA11 mutation. *J Pediatr Hematol Oncol* 32(6): 479-485.

Chan, H. S., E. F. Saunders, et al. (1982). Diamond-Blackfan syndrome. I. Erythropoiesis in prednisone responsive and resistant disease. *Pediatr Res* 16(6): 474-476.

Chan, K. L., P. S. North, et al. (2007). BLM is required for faithful chromosome segregation and its localization defines a class of ultrafine anaphase bridges. *Embo J* 26(14): 3397-3409.

Chan, K. L., T. Palmai-Pallag, et al. (2009). Replication stress induces sister-chromatid bridging at fragile site loci in mitosis. *Nat Cell Biol* 11(6): 753-760.

Cheung, Y. Y., S. Y. Kim, et al. (2007). Impaired neutrophil activity and increased susceptibility to bacterial infection in mice lacking glucose-6-phosphatase-beta. *J Clin Invest* 117(3): 784-793.

Choesmel, V., D. Bacqueville, et al. (2007). Impaired ribosome biogenesis in Diamond-Blackfan anemia. *Blood* 109(3): 1275-1283.

Cmejla, R., J. Cmejlova, et al. (2009). Identification of mutations in the ribosomal protein L5 (RPL5) and ribosomal protein L11 (RPL11) genes in Czech patients with Diamond-Blackfan anemia. *Hum Mutat* 30(3): 321-327.

Cohn, M. A. and A. D. D'Andrea (2008). Chromatin recruitment of DNA repair proteins: lessons from the fanconi anemia and double-strand break repair pathways. *Mol Cell* 32(3): 306-312.

Cole, H., J. Rauschkolb, et al. (1920). Dyskeratosis congenita with pigmentation, dystrophia unguis and leukokeratosis oris. *Arch Dermatol Syphiligraph* 21: 71-95.

Cotter, P. D., M. Baumann, et al. (1992). Enzymatic defect in X-linked sideroblastic anemia: molecular evidence for erythroid delta-aminolevulinate synthase deficiency. *Proc Natl Acad Sci U S A* 89(9): 4028-4032.

Cowland, J. and N. Borregaard (1999). The individual regulation of granule protein mRNA levels during neutrophil maturation explains the heterogeneity of neutrophil granules. *J Leukoc Biol* 66(6): 989-995.

Cumming, R. C., J. Lightfoot, et al. (2001). Fanconi anemia group C protein prevents apoptosis in hematopoietic cells through redox regulation of GSTP1. *Nat Med* 7(7): 814-820.

Da Costa, L., G. Narla, et al. (2003). Ribosomal protein S19 expression during erythroid differentiation. *Blood* 101(1): 318-324.

Da Costa, L., G. Tchernia, et al. (2003). Nucleolar localization of RPS19 protein in normal cells and mislocalization due t mutations in the nucleolar localization signals in 2 Diamond-Blackfan anemia patients: potential insights into pathophysiology. *Blood* 101(12): 5039-5045.

Dale, D. C., A. A. Bolyard, et al. (2002). Cyclic neutropenia. *Seminars in Hematology* 39(2): 89-94.

Dale, D. C., R. E. Person, et al. (2000). Mutations in the gene encoding neutrophil elastase in congenital and cyclic neutropenia.[see comment]. Blood 96(7): 2317-2322.

de Oliveira, J. F., M. L. Sforca, et al. Structure, Dynamics, and RNA Interaction Analysis of the Human SBDS Protein. *J Mol Biol*.

de Winter, J. P. and H. Joenje (2008). The genetic and molecular basis of Fanconi anemia. *Mutat Res*.

de Winter, J. P., F. Leveille, et al. (2000). Isolation of a cDNA representing the Fanconi anemia complementation group E gene. *Am J Hum Genet* 67(5): 1306-1308.

de Winter, J. P., M. A. Rooimans, et al. (2000). The Fanconi anaemia gene FANCF encodes a novel protein with homology to ROM. *Nat Genet* 24(1): 15-16.

de Winter, J. P., Q. Waisfisz, et al. (1998). The Fanconi anaemia group G gene FANCG is identical with XRCC9. *Nat Genet* 20(3): 281-283.

Devriendt, K., A. S. Kim, et al. (2001). Constitutively activating mutation in WASP causes X-linked severe congenital neutropenia. *Nature Genetics* 27(3): 313-317.

Dgany, O., N. Avidan, et al. (2002). Congenital dyserythropoietic anemia type I is caused by mutations in codanin-1. *Am J Hum Genet* 71(6): 1467-1474.

Diamond, L. and K. Blackfan (1938). Hypoplastic anemia. *Am J Dis Child* 56(464-467).

Doherty, L., M. R. Sheen, et al. Ribosomal protein genes RPS10 and RPS26 are commonly mutated in Diamond-Blackfan anemia. *Am J Hum Genet* 86(2): 222-228.

Doherty, L., M. R. Sheen, et al. (2010). Ribosomal protein genes RPS10 and RPS26 are commonly mutated in Diamond-Blackfan anemia. *Am J Hum Genet* 86(2): 222-228.

Dokal, I. (2000). Dyskeratosis congenita in all its forms. *Br J Haematol* 110(4): 768-779.

Dokal, I. and T. Vulliamy (2008). Inherited aplastic anaemias/bone marrow failure syndromes. *Blood Rev* 22(3): 141-153.

Donadieu, J., T. Leblanc, et al. (2005). Analysis of risk factors for myelodysplasias, leukemias and death from infection among patients with congenital neutropenia. Experience of the French Severe Chronic Neutropenia Study Group. *Haematologica* 90(1): 45-53.

Donadieu, J., G. Michel, et al. (2005). Hematopoietic stem cell transplantation for Shwachman-Diamond syndrome: experience of the French neutropenia registry. *Bone Marrow Transplant* 36(9): 787-792.

Dong, F., R. K. Brynes, et al. (1995). Mutations in the gene for the granulocyte colony-stimulating-factor receptor in patients with acute myeloid leukemia preceded by severe congenital neutropenia. *N Engl J Med* 333(8): 487-493.

Drachman, J. G. (2004). Inherited thrombocytopenia: when a low platelet count does not mean ITP. *Blood* 103(2): 390-398.

Drachman, J. G., G. P. Jarvik, et al. (2000). Autosomal dominant thrombocytopenia: incomplete megakaryocyte differentiation and linkage to human chromosome 10. *Blood* 96(1): 118-125.

Draptchinskaia, N., P. Gustavsson, et al. (1999). The gene encoding ribosomal protein S19 is mutated in Diamond-Blackfan anaemia. *Nat Genet* 21(2): 169-175.

Dror, Y. (2006). Inherited Bone Marrow Failure Syndromes. Oxford, Blackwell Publishing.

Dror, Y. and M. H. Freedman (1999). Shwachman-Diamond syndrome: An inherited preleukemic bone marrow failure disorder with aberrant hematopoietic progenitors and faulty marrow microenvironment. *Blood* 94(9): 3048-3054.

Dror, Y. and M. H. Freedman (2001). Shwachman-Diamond syndrome marrow cells show abnormally increased apoptosis mediated through the Fas pathway. *Blood* 97(10): 3011-3016.

Dror, Y., H. Ginzberg, et al. (2001). Immune function in patients with Shwachman-Diamond syndrome. *British Journal of Haematology* 114(3): 712-717.

Duckworth-Rysiecki, G., K. Cornish, et al. (1985). Identification of two complementation groups in Fanconi anemia. *Somat Cell Mol Genet* 11(1): 35-41.

Dufour, C., A. Corcione, et al. (2003). TNF-alpha and IFN-gamma are overexpressed in the bone marrow of Fanconi anemia patients and TNF-alpha suppresses erythropoiesis in vitro. *Blood* 102(6): 2053-2059.

Dursun, A., R. K. Ozgul, et al. (2009). Familial pulmonary arterial hypertension, leucopenia, and atrial septal defect: a probable new familial syndrome with multisystem involvement. *Clin Dysmorphol* 18(1): 19-23.

Faivre, L., P. Guardiola, et al. (2000). Association of complementation group and mutation type with clinical outcome in fanconi anemia. European Fanconi Anemia Research Group. *Blood* 96(13): 4064-4070.

Fanconi, G. (1927). Familiäre infantile perniziosaartige Anämie (perniziöses Blutbild and Konstitution). *Jahrbuch Kinder* 117(257): 258.

Farrar, J. E., M. Nater, et al. (2008). Abnormalities of the large ribosomal subunit protein, Rpl35a, in Diamond-Blackfan anemia. *Blood* 112(5): 1582-1592.

Fekairi, S., S. Scaglione, et al. (2009). Human SLX4 is a Holliday junction resolvase subunit that binds multiple DNA repair/recombination endonucleases. *Cell* 138(1): 78-89.

Fleming, J. C., E. Tartaglini, et al. (1999). The gene mutated in thiamine-responsive anaemia with diabetes and deafness (TRMA) encodes a functional thiamine transporter. *Nat Genet* 22(3): 305-308.

Flygare, J., A. Aspesi, et al. (2007). Human RPS19, the gene mutated in Diamond-Blackfan anemia, encodes a ribosomal protein required for the maturation of 40S ribosomal subunits. *Blood* 109(3): 980-986.

Flygare, J., T. Kiefer, et al. (2005). Deficiency of ribosomal protein S19 in CD34+ cells generated by siRNA blocks erythroid development and mimics defects seen in Diamond-Blackfan anemia. *Blood* 105(12): 4627-4634.

Fouret, P., R. M. du Bois, et al. (1989). Expression of the neutrophil elastase gene during human bone marrow cell differentiation. *J Exp Med* 169(3): 833-845.

Freedman, M. H. and Z. Estrov (1990). Congenital amegakaryocytic thrombocytopenia: an intrinsic hematopoietic stem cell defect. *Am J Pediatr Hematol Oncol* 12(2): 225-230.

Freson, K., K. Devriendt, et al. (2001). Platelet characteristics in patients with X-linked macrothrombocytopenia because of a novel GATA1 mutation. *Blood* 98(1): 85-92.

Friedenson, B. (2007). The BRCA1/2 pathway prevents hematologic cancers in addition to breast and ovarian cancers. *BMC Cancer* 7: 152.

Futaki, M., T. Yamashita, et al. (2000). The IVS4 + 4 A to T mutation of the fanconi anemia gene FANCC is not associated with a severe phenotype in Japanese patients. *Blood* 95(4): 1493-1498.

Ganapathi, K. A., K. M. Austin, et al. (2007). The human Shwachman-Diamond syndrome protein, SBDS, associates with ribosomal RNA. *Blood* 110(5): 1458-1465.

Gandhi, M. J., C. L. Cummings, et al. (2003). FLJ14813 missense mutation: a candidate for autosomal dominant thrombocytopenia on human chromosome 10. *Hum Hered* 55(1): 66-70.

Garcia-Higuera, I., T. Taniguchi, et al. (2001). Interaction of the Fanconi anemia proteins and BRCA1 in a common pathway. *Mol Cell* 7(2): 249-262.

Gari, K., C. Decaillet, et al. (2008). Remodeling of DNA replication structures by the branch point translocase FANCM. *Proc Natl Acad Sci U S A* 105(42): 16107-16112.

Gazda, H. T., A. Grabowska, et al. (2006). Ribosomal protein S24 gene is mutated in Diamond-Blackfan anemia. *Am J Hum Genet* 79(6): 1110-1118.

Gazda, H. T., M. R. Sheen, et al. (2008). Ribosomal protein L5 and L11 mutations are associated with cleft palate and abnormal thumbs in Diamond-Blackfan anemia patients. *Am J Hum Genet* 83(6): 769-780.

Geddis, A. E. and K. Kaushansky (2004). Inherited thrombocytopenias: toward a molecular understanding of disorders of platelet production. *Curr Opin Pediatr* 16(1): 15-22.

Germeshausen, M., H. Schulze, et al. (2001). Mutations in the gene encoding neutrophil elastase (ELA2) are not sufficient to cause the phenotype of congenital neutropenia. *Br J Haematol* 115(1): 222-224.

Germeshausen, M., C. Zeidler, et al. (2010). Digenic mutations in severe congenital neutropenia. *Haematologica* 95(7): 1207-1210.

Gillio, A. P., P. C. Verlander, et al. (1997). Phenotypic consequences of mutations in the Fanconi anemia FAC gene: an International Fanconi Anemia Registry study. *Blood* 90(1): 105-110.

Giri, N., E. Kang, et al. (2000). Clinical and laboratory evidence for a trilineage haematopoietic defect in patients with refractory Diamond-Blackfan anaemia. *Br J Haematol* 108(1): 167-175.

Godthelp, B. C., F. Artwert, et al. (2002). Impaired DNA damage-induced nuclear Rad51 foci formation uniquely characterizes Fanconi anemia group D1. *Oncogene* 21(32): 5002-5005.

Greenwald, H. and I. Sherman (1929). Congenital essential thrombocytopenia. *Am J Dis Child* 38: 1245-1251.

Grenda, D. S., M. Murakami, et al. (2007). Mutations of the ELA2 gene found in patients with severe congenital neutropenia induce the unfolded protein response and cellular apoptosis. *Blood* 110(13): 4179-4187.

Guernsey, D. L., H. Jiang, et al. (2009). Mutations in mitochondrial carrier family gene SLC25A38 cause nonsyndromic autosomal recessive congenital sideroblastic anemia. *Nat Genet* 41(6): 651-653.

Guinan, E. C., Y. S. Lee, et al. (1993). Effects of interleukin-3 and granulocyte-macrophage colony-stimulating factor on thrombopoiesis in congenital amegakaryocytic thrombocytopenia. *Blood* 81(7): 1691-1698.

Gulino, A. V., D. Moratto, et al. (2004). Altered leukocyte response to CXCL12 in patients with warts hypogammaglobulinemia, infections, myelokathexis (WHIM) syndrome. *Blood* 104(2): 444-452.

Hall, J. G., J. Levin, et al. (1969). Thrombocytopenia with absent radius (TAR). *Medicine* (Baltimore) 48(6): 411-439.

Halperin, D. S. and M. H. Freedman (1989). Diamond-blackfan anemia: etiology, pathophysiology, and treatment. *Am J Pediatr Hematol Oncol* 11(4): 380-394.

Hamaguchi, I., A. Ooka, et al. (2002). Gene transfer improves erythroid development in ribosomal protein S19-deficient Diamond-Blackfan anemia. *Blood* 100(8): 2724-2731.

Hashmi, S., C. Allen, et al. (2010). Comparative analysis of Shwachman-Diamond syndrome to other inherited bone marrow failure syndromes and genotype-phenotype correlation. *Clinical Genetics*.

Heiss, N. S., S. W. Knight, et al. (1998). X-linked dyskeratosis congenita is caused by mutations in a highly conserved gene with putative nucleolar functions. *Nat Genet* 19(1): 32-38.

Heller, P. G., A. C. Glembotsky, et al. (2005). Low Mpl receptor expression in a pedigree with familial platelet disorder with predisposition to acute myelogenous leukemia and a novel AML1 mutation. *Blood* 105(12): 4664-4670.

Hernandez, P. A., R. J. Gorlin, et al. (2003). Mutations in the chemokine receptor gene CXCR4 are associated with WHIM syndrome, a combined immunodeficiency disease. *Nat Genet* 34(1): 70-74.

Horowitz, M., K. F. Benson, et al. (1999). Mutations in ELA2, encoding neutrophil elastase, define a 21-day biological clock in cyclic haematopoiesis. *Nat Genet* 23(4): 433-436.

Horwitz, M., K. Benson, et al. (2003). Role of neutrophil elastase in bone marrow failure syndromes: molecular genetic revival of the chalone hypothesis. *Curr Opin Hematol* 10(1): 49-54.

Horwitz, M., K. F. Benson, et al. (1999). Mutations in ELA2, encoding neutrophil elastase, define a 21-day biological clock in cyclic haematopoiesis. *Nat Genet* 23(4): 433-436.

Howlett, N. G., T. Taniguchi, et al. (2002). Biallelic inactivation of BRCA2 in Fanconi anemia. *Science* 297(5581): 606-609.

Huang, K. (2010). The FANCM/FAAP24 complex is required for the DNA interstrand crosslink-induced checkpoint response. *Mol Cell* 39(2): 259-268.

Hudson, E. and T. Aldor (1970). Pancreatic insufficiency and neutropenia with associated immunoglobulin deficit. *Arch Intern Med* 125(2): 314-316.

Ihara, K., E. Ishii, et al. (1999). Identification of mutations in the c-mpl gene in congenital amegakaryocytic thrombocytopenia. *Proc Natl Acad Sci U S A* 96(6): 3132-3136.

Ishiai, M., H. Katao, et al. (2008). FANCI phosphorylation functions as a molecular switch to turn on the Fanconi anemia pathway. *Mol Biol* 15(11): 1138-1146.

Johnson, H. J., M. J. Gandhi, et al. (2009). In vivo inactivation of MASTL kinase results in thrombocytopenia. *Exp Hemato*l 37(8): 901-908.

Jonsson, O. G. and G. R. Buchanan (1991). Chronic neutropenia during childhood. A 13-year experience in a single institution. *Am J Dis Child* 145(2): 232-235.

Jun, H. S., Y. M. Lee, et al. Lack of glucose recycling between endoplasmic reticulum and cytoplasm underlies cellular dysfunction in glucose-6-phosphatase-beta-deficient neutrophils in a congenital neutropenia syndrome. *Blood* 116(15): 2783-2792.

Karsunky, H., H. Zeng, et al. (2002). Inflammatory reactions and severe neutropenia in mice lacking the transcriptional repressor Gfi1. *Nat Genet* 30(3): 295-300.

King, S., M. Germeshausen, et al. (2005). Congenital amegakaryocytic thrombocytopenia: a retrospective clinical analysis of 20 patients. *Br J Haematol* 131(5): 636-644.

Klein, C., M. Grudzien, et al. (2007). HAX1 deficiency causes autosomal recessive severe congenital neutropenia (Kostmann disease). *Nat Genet* 39(1): 86-92.

Klopocki, E., H. Schulze, et al. (2007). Complex inheritance pattern resembling autosomal recessive inheritance involving a microdeletion in thrombocytopenia-absent radius syndrome. *Am J Hum Genet* 80(2): 232-240.

Kostmann, R. (1956). Infantile genetic agranulocytosis: A new recessive lethal disease in man. . *Acta Paediatr Scand* 45((suppl 105)): 361-368.

Kuijpers, T. W., N. A. Maianski, et al. (2004). Neutrophils in Barth syndrome (BTHS) avidly bind annexin-V in the absence of apoptosis. *Blood* 103(10): 3915-3923.

Kutler, D. I., B. Singh, et al. (2003). A 20-year perspective on the International Fanconi Anemia Registry (IFAR). *Blood* 101(4): 1249-1256.

Lagresle-Peyrou, C., E. M. Six, et al. (2009). Human adenylate kinase 2 deficiency causes a profound hematopoietic defect associated with sensorineural deafness. *Nat Genet* 41(1): 106-111.

Lai, C. H., C. Y. Chou, et al. (2000). Identification of novel human genes evolutionarily conserved in Caenorhabditis elegans by comparative proteomics. *Genome Research* 10(5): 703-713.

Lau, Y. L., S. Y. Ha, et al. (1999). Bone marrow transplant for dyskeratosis congenita. *Br J Haematol* 105(2): 571.

Levitus, M., M. A. Rooimans, et al. (2004). Heterogeneity in Fanconi anemia: evidence for 2 new genetic subtypes. *Blood* 103(7): 2498-2503.

Lipton, J. M., E. Atsidaftos, et al. (2006). Improving clinical care and elucidating the pathophysiology of Diamond Blackfan anemia: an update from the Diamond Blackfan Anemia Registry. *Pediatr Blood Cancer* 46(5): 558-564.

Lipton, J. M. and S. R. Ellis (2009). Diamond-Blackfan anemia: diagnosis, treatment, and molecular pathogenesis. *Hematol Oncol Clin North Am* 23(2): 261-282.

Lo Ten Foe, J. R., M. A. Rooimans, et al. (1996). Expression cloning of a cDNA for the major Fanconi anaemia gene, FAA. *Nat Genet* 14(3): 320-323.

Londono-Vallejo, J. A. (2008). Telomere instability and cancer. *Biochimie* 90(1): 73-82.

Luke-Glaser, S., B. Luke, et al. (2010). FANCM regulates DNA chain elongation and is stabilized by S-phase checkpoint signalling. *Embo J* 29(4): 795-805.

Luscombe, N. M., S. E. Austin, et al. (2000). An overview of the structures of protein-DNA complexes. *Genome Biol* 1(1): 1-37.

Majeed, F., S. Jadko, et al. (2005). Mutation analysis of SBDS in pediatric acute myeloblastic leukemia. *Pediatr Blood Cancer* 45(7): 920-924.

Makitie, O., L. Ellis, et al. (2004). Skeletal phenotype in patients with Shwachman-Diamond syndrome and mutations in SBDS. *Clinical Genetics* 65(2): 101-112.

Marrone, A., A. Walne, et al. (2007). Telomerase reverse-transcriptase homozygous mutations in autosomal recessive dyskeratosis congenita and Hoyeraal-Hreidarsson syndrome. *Blood* 110(13): 4198-4205.

Marsh, J. C., A. J. Will, et al. (1992). Stem cell origin of the hematopoietic defect in dyskeratosis congenita. *Blood* 79(12): 3138-3144.

Massullo, P., L. J. Druhan, et al. (2005). Aberrant subcellular targeting of the G185R neutrophil elastase mutant associated with severe congenital neutropenia induces premature apoptosis of differentiating promyelocytes. *Blood* 105(9): 3397-3404.

Mavaddat, N., P. D. Pharoah, et al. (2010). Familial relative risks for breast cancer by pathological subtype: a population-based cohort study. *Breast Cancer Res* 12(1): R10.

McGowan, K. A., J. Z. Li, et al. (2008). Ribosomal mutations cause p53-mediated dark skin and pleiotropic effects. *Nat Genet* 40(8): 963-970.

Meetei, A. R., J. P. de Winter, et al. (2003). A novel ubiquitin ligase is deficient in Fanconi anemia. *Nat Genet* 35(2): 165-170.

Meetei, A. R., M. Levitus, et al. (2004). X-linked inheritance of Fanconi anemia complementation group B. *Nat Genet* 36(11): 1219-1224.

Meetei, A. R., A. L. Medhurst, et al. (2005). A human ortholog of archaeal DNA repair protein Hef is defective in Fanconi anemia complementation group M. *Nat Genet* 37(9): 958-963.

Mehaffey, M. G., A. L. Newton, et al. (2001). X-linked thrombocytopenia caused by a novel mutation of GATA-1. *Blood* 98(9): 2681-2688.

Menne, T. F., B. Goyenechea, et al. (2007). The Shwachman-Bodian-Diamond syndrome protein mediates translational activation of ribosomes in yeast. *Nat Genet* 39(4): 486-495.

Michaud, J., F. Wu, et al. (2002). In vitro analyses of known and novel RUNX1/AML1 mutations in dominant familial platelet disorder with predisposition to acute myelogenous leukemia: implications for mechanisms of pathogenesis. *Blood* 99(4): 1364-1372.

Miyake, K., J. Flygare, et al. (2005). Development of cellular models for ribosomal protein S19 (RPS19)-deficient diamond-blackfan anemia using inducible expression of siRNA against RPS19. *Molecular Therapy: the Journal of the American Society of Gene Therapy* 11(4): 627-637.

Miyake, K., T. Utsugisawa, et al. (2008). Ribosomal protein S19 deficiency leads to reduced proliferation and increased apoptosis but does not affect terminal erythroid differentiation in a cell line model of Diamond-Blackfan anemia. *Stem Cells* 26(2): 323-329.

Muraoka, K., E. Ishii, et al. (1997). Defective response to thrombopoietin and impaired expression of c-mpl mRNA of bone marrow cells in congenital amegakaryocytic thrombocytopenia. *Br J Haematol* 96(2): 287-292.

Naim, V. and F. Rosselli (2009). The FANC pathway and BLM collaborate during mitosis to prevent micro-nucleation and chromosome abnormalities. *Nat Cell Biol* 11(6): 761-768.

Nichols, K. E., J. D. Crispino, et al. (2000). Familial dyserythropoietic anaemia and thrombocytopenia due to an inherited mutation in GATA1. *Nat Genet* 24(3): 266-270.

Noy-Lotan, S., O. Dgany, et al. (2009). Codanin-1, the protein encoded by the gene mutated in congenital dyserythropoietic anemia type I (CDAN1), is cell cycle-regulated. *Haematologica* 94(5): 629-637.

O'Driscoll, M., K. M. Cerosaletti, et al. (2001). DNA ligase IV mutations identified in patients exhibiting developmental delay and immunodeficiency. *Mol Cell* 8(6): 1175-1185.

Olivieri, N. F., T. Grunberger, et al. (1991). Diamond-Blackfan anemia: heterogenous response of hematopoietic progenitor cells in vitro to the protein product of the steel locus. *Blood* 78(9): 2211-2215.

Page, A. and R. Good (1957). Studies on cyclic neutropenia. *Am J Dis Child* 94: 623.

Pai, G. S., Y. Yan, et al. (1989). Bleomycin hypersensitivity in dyskeratosis congenita fibroblasts, lymphocytes, and transformed lymphoblasts. *Cytogenet Cell Genet* 52(3-4): 186-189.

Pang, Q., W. Keeble, et al. (2001). FANCC interacts with Hsp70 to protect hematopoietic cells from IFN-gamma/TNF-alpha-mediated cytotoxicity. *Embo J* 20(16): 4478-4489.

Pannicke, U., M. Honig, et al. (2009). Reticular dysgenesis (aleukocytosis) is caused by mutations in the gene encoding mitochondrial adenylate kinase 2. *Nat Genet* 41(1): 101-105.

Perdahl, E. B., B. L. Naprstek, et al. (1994). Erythroid failure in Diamond-Blackfan anemia is characterized by apoptosis. *Blood* 83(3): 645-650.

Person, R. E., F. Q. Li, et al. (2003). Mutations in proto-oncogene GFI1 cause human neutropenia and target ELA2. *Nature Genetics* 34(3): 308-312.

Peterson, L. C., K. V. Rao, et al. (1985). Fechtner syndrome--a variant of Alport's syndrome with leukocyte inclusions and macrothrombocytopenia. *Blood* 65(2): 397-406.

Pippucci, T., A. Savoia, et al. Mutations in the 5' UTR of ANKRD26, the ankirin repeat domain 26 gene, cause an autosomal-dominant form of inherited thrombocytopenia, THC2. *Am J Hum Genet* 88(1): 115-120.

Punzo, F., E. J. Mientjes, et al. (2010). A mutation in the acyl-coenzyme A binding domain-containing protein 5 gene (ACBD5) identified in autosomal dominant thrombocytopenia. *J Thromb Haemost* 8(9): 2085-2087.

Reid, S., D. Schindler, et al. (2007). Biallelic mutations in PALB2 cause Fanconi anemia subtype FA-N and predispose to childhood cancer. *Nat Genet* 39(2): 162-164.

Renella, R., N. A. Roberts, et al. Codanin-1 mutations in congenital dyserythropoietic anemia type 1 affect HP1α localization in erythroblasts. *Blood*.

Rotig, A., V. Cormier, et al. (1990). Pearson's marrow-pancreas syndrome. A multisystem mitochondrial disorder in infancy. *J Clin Invest* 86(5): 1601-1608.

Rujkijyanont, P., K. Watanabe, et al. (2008). SBDS-deficient cells undergo accelerated apoptosis through the Fas-pathway. *Haematologica* 93(3): 363-371.

Saadatzadeh, M. R., K. Bijangi-Vishehsaraei, et al. (2009). Distinct roles of stress-activated protein kinases in Fanconi anemia-type C-deficient hematopoiesis. *Blood* 113(12): 2655-2660.

Sabatier, L. and B. Dutrillaux (1988). Effect of caffeine in Fanconi anemia. I. Restoration of a normal duration of G2 phase. *Hum Genet* 79(3): 242-244.

Santucci, M. A., G. P. Bagnara, et al. (1999). Long-term bone marrow cultures in Diamond-Blackfan anemia reveal a defect of both granulomacrophage and erythroid progenitors. *Exp Hematol* 27(1): 9-18.

Saunders, E. F. and M. H. Freedman (1978). Constitutional aplastic anaemia: defective haematopoietic stem cell growth in vitro. *Br J Haematology* 40(2): 277-287.

Savage, S. A., N. Giri, et al. (2008). TINF2, a component of the shelterin telomere protection complex, is mutated in dyskeratosis congenita. *Am J Hum Genet* 82(2): 501-509.

Savchenko, A., N. Krogan, et al. (2005). The Shwachman-Bodian-Diamond syndrome protein family is involved in RNA metabolism. *Journal of Biological Chemistry* 280(19): 19213-19220.

Savoia, A., C. Balduini, et al. (2001). Autosomal dominant macrothrombocytopenia in Italy is most frequently a type of heterozygous Bernard-Soulier syndrome. *Blood* 97(5): 1330-1335.

Schofield, K. P. and D. I. Evans (1991). Diamond-Blackfan syndrome and neutropenia. *J Clin Pathol* 44(9): 742-744.

Schwarz, K., A. Iolascon, et al. (2009). Mutations affecting the secretory COPII coat component SEC23B cause congenital dyserythropoietic anemia type II. *Nat Genet* 41(8): 936-940.

Sejas, D. P., R. Rani, et al. (2007). Inflammatory reactive oxygen species-mediated hemopoietic suppression in Fancc-deficient mice. *J Immunol* 178(8): 5277-5287.

Seri, M., A. Pecci, et al. (2003). MYH9-related disease: May-Hegglin anomaly, Sebastian syndrome, Fechtner syndrome, and Epstein syndrome are not distinct entities but represent a variable expression of a single illness. *Medicine* 82(3): 203-215.

Shammas, C., T. F. Menne, et al. (2005). Structural and mutational analysis of the SBDS protein family. Insight into the leukemia-associated Shwachman-Diamond Syndrome. *J Biol Chem* 280(19): 19221-19229.

Shimamura, A. (2006). Inherited bone marrow failure syndromes: molecular features. *Hematology Am Soc Hematol Educ Program*: 63-71.

Shwachman, H. (1964). The syndrome of pancreatic insufficiency and bone marrow dysfunction. *J Pediatr* 65: 645-663.

Smeenk, G., A. J. de Groot, et al. (2010). Rad51C is essential for embryonic development and haploinsufficiency causes increased DNA damage sensitivity and genomic instability. *Mutat Res* 689(1-2): 50-58.

Song, W. J., M. G. Sullivan, et al. (1999). Haploinsufficiency of CBFA2 causes familial thrombocytopenia with propensity to develop acute myelogenous leukaemia. *Nat Genet* 23(2): 166-175.

Stepanovic, V., D. Wessels, et al. (2004). The chemotaxis defect of Shwachman-Diamond Syndrome leukocytes. *Cell Motil Cytoskeleton* 57(3): 158-174.

Stoepker, C., K. Hain, et al. SLX4, a coordinator of structure-specific endonucleases, is mutated in a new Fanconi anemia subtype. *Nat Genet* 43(2): 138-141.

Strathdee, C., H. Gavish, et al. (1992). Cloning of cDNAs for Fanconi's anaemia by functional complementation. *Nature* 356: 763-767.

Teo, J. T., R. Klaassen, et al. (2008). Clinical and genetic analysis of unclassifiable inherited bone marrow failure syndromes. *Pediatrics* 122(1): 139-148.

Thompson, A. A. and L. T. Nguyen (2000). Amegakaryocytic thrombocytopenia and radio-ulnar synostosis are associated with HOXA11 mutation. *Nat Genet* 26(4): 397-398.

Thompson, A. A., K. Woodruff, et al. (2001). Congenital thrombocytopenia and radio-ulnar synostosis: a new familial syndrome. *Br J Haematol* 113(4): 866-870.

Timmers, C., T. Taniguchi, et al. (2001). Positioning cloning of a novel Fanconi anemia gene, FANCD2. *Mol Cell* 7(2): 241-248.

Trahan, C. and F. Dragon (2009). Dyskeratosis congenita mutations in the H/ACA domain of human telomerase RNA affect its assembly into a pre-RNP. *RNA* 15(2): 235-243.

Trahan, C., C. Martel, et al. (2010). Effects of dyskeratosis congenita mutations in dyskerin, NHP2 and NOP10 on assembly of H/ACA pre-RNPs. *Hum Mol Genet* 19(5): 825-836.

Tsai, P. H., S. Arkin, et al. (1989). An intrinsic progenitor defect in Diamond-Blackfan anaemia. *Br J Haematol* 73(1): 112-120.

Tsai, P. H., I. Sahdev, et al. (1990). Fatal cyclophosphamide-induced congestive heart failure in a 10-year-old boy with Shwachman-Diamond syndrome and severe bone marrow failure treated with allogeneic bone marrow transplantation. *Am J Pediatr Hematol Oncol* 12(4): 472-476.

Tsangaris, E., R. Klaassen, et al. (2011). Genetic analysis of inherited bone marrow failure syndromes from one prospective, comprehensive and population-based cohort and identification of novel mutations. *Journal of Medical Genetics*.

Urban, C., B. Binder, et al. (1992). Congenital sideroblastic anemia successfully treated by allogeneic bone marrow transplantation. *Bone Marrow Transplant* 10(4): 373-375.

Van Den Oudenrijn, S., M. Bruin, et al. (2002). Three parameters, plasma thrombopoietin levels, plasma glycocalicin levels and megakaryocyte culture, distinguish between different causes of congenital thrombocytopenia. *Br J Haematol* 117(2): 390-398.

van den Oudenrijn, S., M. Bruin, et al. (2000). Mutations in the thrombopoietin receptor, Mpl, in children with congenital amegakaryocytic thrombocytopenia. *Br J Haematol* 110(2): 441-448.

Vaz, F., H. Hanenberg, et al. Mutation of the RAD51C gene in a Fanconi anemia-like disorder. *Nat Genet* 42(5): 406-409.

Vinciguerra, P., S. A. Godinho, et al. (2010). Cytokinesis failure occurs in Fanconi anemia pathway-deficient murine and human bone marrow hematopoietic cells. *J Clin Invest* 120(11): 3834-3842.

Vlachos, A., S. Ball, et al. (2008). Diagnosing and treating Diamond Blackfan anaemia: results of an international clinical consensus conference. *Br J Haematol* 142(6): 859-876.

Volpi, L., G. Roversi, et al. Targeted next-generation sequencing appoints c16orf57 as clericuzio-type poikiloderma with neutropenia gene. *Am J Hum Genet* 86(1): 72-76.

Vulliamy, T., R. Beswick, et al. (2008). Mutations in the telomerase component NHP2 cause the premature ageing syndrome dyskeratosis congenita. *Proc Natl Acad Sci* U S A 105(23): 8073-8078.

Vulliamy, T., A. Marrone, et al. (2002). Association between aplastic anaemia and mutations in telomerase RNA. *Lancet* 359(9324): 2168-2170.

Vulliamy, T., A. Marrone, et al. (2001). The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenita. *Nature* 413(6854): 432-435.

Vulliamy, T. J. and I. Dokal (2008). Dyskeratosis congenita: the diverse clinical presentation of mutations in the telomerase complex. *Biochimie* 90(1): 122-130.

Vulliamy, T. J., S. W. Knight, et al. (2001). Very short telomeres in the peripheral blood of patients with X-linked and autosomal dyskeratosis congenita. *Blood Cells Mol Dis* 27(2): 353-357.

Vulliamy, T. J., A. Walne, et al. (2005). Mutations in the reverse transcriptase component of telomerase (TERT) in patients with bone marrow failure. *Blood Cells Mol Dis* 34(3): 257-263.

Walne, A. J., T. Vulliamy, et al. (2008). TINF2 mutations result in very short telomeres: analysis of a large cohort of patients with dyskeratosis congenita and related bone marrow failure syndromes. *Blood* 112(9): 3594-3600.

Walne, A. J., T. Vulliamy, et al. (2007). Genetic heterogeneity in autosomal recessive dyskeratosis congenita with one subtype due to mutations in the telomerase-associated protein NOP10. *Hum Mol Genet* 16(13): 1619-1629.

Watanabe, K., C. Ambekar, et al. (2009). SBDS-deficiency results in specific hypersensitivity to Fas stimulation and accumulation of Fas at the plasma membrane. *Apoptosis* 14(1): 77-89.

Wessels, D., T. Srikantha, et al. (2006). The Shwachman-Bodian-Diamond syndrome gene encodes an RNA-binding protein that localizes to the pseudopod of Dictyostelium amoebae during chemotaxis. *J Cell Sci* 119(Pt 2): 370-379.

Wetzler, M., M. Talpaz, et al. (1992). Myelokathexis: normalization of neutrophil counts and morphology by GM-CSF. *Jama* 267(16): 2179-2180.

Woloszynek, J. R., R. J. Rothbaum, et al. (2004). Mutations of the SBDS gene are present in most patients with Shwachman-Diamond syndrome. *Blood* 104(12): 3588-3590.

Xia, J., A. A. Bolyard, et al. (2009). Prevalence of mutations in ELANE, GFI1, HAX1, SBDS, WAS and G6PC3 in patients with severe congenital neutropenia. *Br J Haematol* 147(4): 535-542.

Yoshida, M. C. (1980). Suppression of spontaneous and mitomycin C-induced chromosome aberrations in Fanconi's anemia by cell fusion with normal human fibroblasts. *Hum Genet* 55(2): 223-226.

Zeharia, A., N. Fischel-Ghodsian, et al. (2005). Mitochondrial myopathy, sideroblastic anemia, and lactic acidosis: an autosomal recessive syndrome in Persian Jews caused by a mutation in the PUS1 gene. *J Child Neurol* 20(5): 449-452.

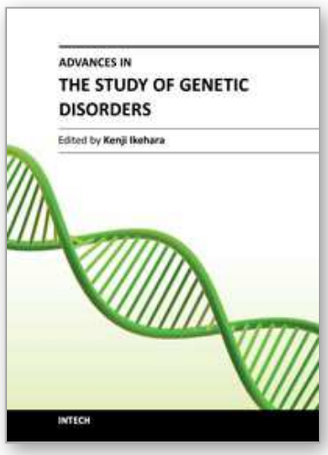
Zhang, S., M. Shi, et al. (2006). Loss of the mouse ortholog of the shwachman-diamond syndrome gene (Sbds) results in early embryonic lethality. *Molecular & Cellular Biology* 26(17): 6656-6663.

Zhang, X., J. Li, et al. (2004). The Fanconi anemia proteins functionally interact with the protein kinase regulated by RNA (PKR). *J Biol Chem* 279(42): 43910-43919.

Zhong, F., S. A. Savage, et al. (2011). Disruption of telomerase trafficking by TCAB1 mutation causes dyskeratosis congenita. *Genes Dev* 25(1): 11-16.

Zinnsser, F. (1906). Atrophia cutis reticularis cum pigmentatione, dystrophia unguium et leukoplakia oris. *Ikonogr Dermatol* (Hyoto) 5: 219-223.

Zuelzer, W. W. (1964). Myelokathexis--a New Form of Chronic Granulocytopenia. Report of a Case. *N Engl J Med* 270: 699-704.



Advances in the Study of Genetic Disorders

Edited by Dr. Kenji Ikehara

ISBN 978-953-307-305-7
Hard cover, 472 pages
Publisher InTech
Published online 21, November, 2011
Published in print edition November, 2011

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.

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen