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Inherited bone marrow failure syndromes

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The inherited bone marrow failure syndromes are a heterogeneous group of disorders characterized by bone marrow failure usually in association with one or more somatic abnormality. The bone marrow failure (which can involve all or a single cell lineage) often presents in childhood but may not do so until adulthood in some cases. Furthermore, some patients initially labeled as having "idiopathic aplastic anemia" actually have cryptic presentations of these genetic syndromes. Over the last two decades there have been considerable advances in the genetics of these syndromes with 33 genes having been identified to date. These advances have provided a better understanding of normal hematopoiesis and how this is disrupted in patients with bone marrow failure. They have also provided important insights into fundamental biological pathways: DNA repair-FA/BRCA pathway; telomere maintenance- dyskeratosis congenita-related genes; ribosome biogenesis-Shwachman Diamond syndrome (SDS) and Diamond-Blackfan anemia (DBA) genes. Additionally, as these disorders are usually associated with developmental abnormalities and an increased risk of cancer they are providing insights into human development and the genesis of cancer.

The features of some of the classical inherited bone marrow syndromes are summarized in Tables 1 and 2. A brief outline of each syndrome is given below.

Table 1. Characteristics of the inherited bone marrow failure syndromes.

	FA	DC	SDS	DBA	CAMT	SCN
Inheritance pattern	AR, XLR AD	XLR, AR	AR	AD AR	AR	AD
Somatic abnormalities	Yes	Yes	Yes	Yes	Rare	Rare
Bone marrow failure	AA (>90%)	AA (~80%)	AA (~20%)	RCA[a]	Meg[b]	Neut[c]
Short telomeres	Yes	Yes	Yes	No	?	?
Cancer	Yes	Yes	Yes	Yes	Yes	Yes
Chromosome instability	Yes	Yes	Yes	?	?	?
Genes identified	13	6	1	9	1	3

FA: Fanconi anemia; DC: dyskeratosis congenita; SDS: Shwachman-Diamond syndrome; DBA: Diamond-Blackfan anemia; CAMT: congenital amegakaryocytic thrombocytopenia; SCN: severe congenital neutropenia; AD: autosomal dominant; AR: autosomal recessive; XLR: X-linked recessive; RCA[a]: Red cell aplasia although some patients can develop global bone marrow failure. Meg[b]: low megakaryocyte count which can progress to global bone marrow failure. Neut[c]:usually low neutrophils count.

Fanconi anemia

Fanconi anemia is usually inherited as an autosomal recessive trait but in a small subset of patients it can be an X-linked recessive disorder. The condition is clinically heterogeneous, but characteristic features include the progressive development of bone marrow failure and an increased predisposition to malignancy.[1] Affected individuals may also have one or more developmental abnormality including skin, skeletal, genitourinary, gastrointestinal and neurological anomalies. Approximately 30% of patients with Fanconi anemia have no overt somatic abnormalities. The majority of patients present towards the end of the first decade of life. However, increasingly some patients are being diagnosed in adulthood and many

Table 2. Inherited bone marrow failure genetic subtypes.

(a) Fanconi anemia (FA) complementation groups/genetic subtypes

Complementation group/gene	Approximate % of FA patients	Chromosome	Gene product	Exons
A (*FANCA*)	65	16q24.3	FANCA	43
B (*FANCB*[a])	<1	Xp22.2	FANCB	10
C (*FANCC*)	12	9q22.3	FANCC	14
D1 (*FANCD1*[b])	<1	13q12.3	FANCD1	27
D2 (*FANCD2*)	<1	3p25.3	FANCD2	44
E (*FANCE*)	4	6p21.3	FANCE	10
F (*FANCF*)	4	11p15	FANCF	1
G (*FANCG*)	12	9p13	FANCG	14
I (*FANCI*)	<1	15q26.1	FANCI	35
J (*FANCJ/BRIP1*[c])	<5	17q23.1	FANCJ	20
L (*FANCL*)	<1	2p16.1	FANCL	14
M (*FANCM*)	<1	14q21.3	FANCM	23
N (*FANCN/PALB2*[d])	<1	16p12.1	FANCN	13

[a]*FANCB is on the X-chromosome;* [b]*FANCD1 is BRCA2;* [c]*FANCJ is BRIP1 (partner of BRCA1);* [d]*FANCN is PALB2 (partner of BRCA2).*

(b) Dyskeratosis congenita (DC) genetic subtypes

DC subtype	Approximate % of DC patients	Chromosome location	Gene product	Exons
X-linked recessive	30	Xq28	dyskerin	15
Autosomal dominant	<5	3q26	TERC	1
	<5	5p15	TERT	16
	10	14q11	TIN2	6
Autosomal recessive	<1	15q14	NOP10	2
	<1	5p15	TERT	16
	<1	5q35	NHP2	4
Uncharacterized*	40-50	?	?	?

**These are likely to represent more than one genetic locus and include the genetically heterogeneous autosomal recessive cases of DC.*

(c) Schwachman-Diamond syndrome (SDS) genetic subtypes.

SDS subtype	Approximate % of SDS patients	Chromosome location	Gene product	Exons
Autosomal recessive	>90	7q11	SBDS	5
Uncharacterized	<10	?	?	?

(d) Diamond-Blackfan anemia (DBA) genetic subtypes.

DBA subtype	Approximate % of DBA patients	Chromosome location	Gene product	Exons
Autosomal dominant	25	19q13.2	RPS19	6
	2	10q22-23	RPS24	7
	1	15q25.2	RPS17	5
	7	1p22.1	RPL5	8
	5	1p35-36.1	RPL11	6
	3	3q29	RPL35A	5
	1	2p	RPS7	7
	7	6	RPS10	6
	3	12	RPS26	4
Uncharacterized*	40-50	?	?	?

**These are likely to represent more than one genetic locus*

(e) Congenital amegakaryocytic thrombocytopenia (CAMT) genetic subtypes.

CAMT subtype	Approximate % of CAMT patients	Chromosome location	Gene product	Exons
Autosomal recessive	?	1p34	MPL	12
Uncharacterized	?	?	?	?

continued in the next page

(f) Severe congenital neutropenia genetic subtypes.

Subtype	Approximate % of patients	Chromosome location	Gene product	Exons
Autosomal dominant	50-60 < 1%	19p13.3 1p22	ELA2 GFI1	5
Autosomal recessive	10-15	1q21.3	HAX1	7
Uncharacterized*	30-40	?	?	?

**This is likely to be a heterogeneous group. Furthermore some patients initially presenting with isolated neutropenia may actually have a cryptic presentation of other syndromes such as Wiskot-Aldrich syndrome and Shwachman-Diamond syndrome*

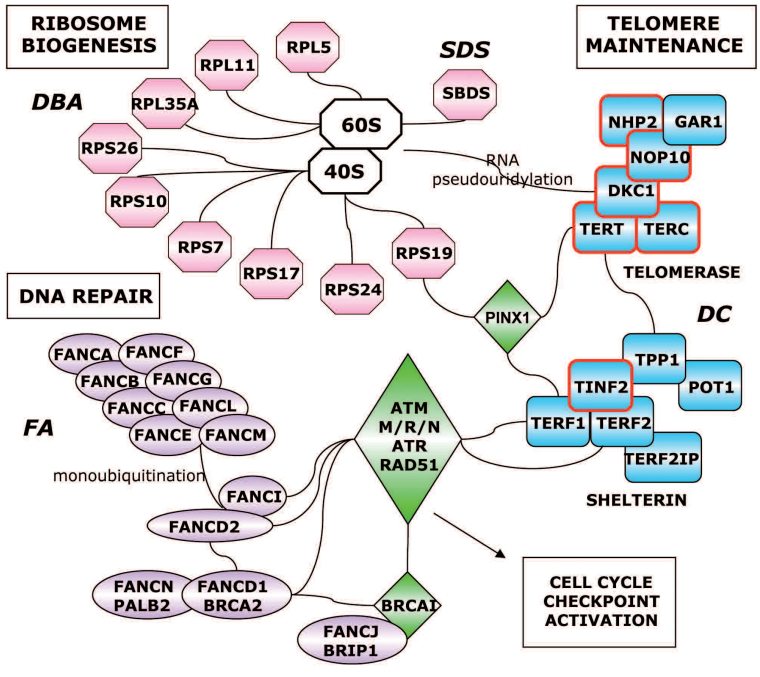

Figure 1. Interconnected pathways that cause bone marrow failure. Genes known to be mutated in three different pathways that lead to bone marrow failure are highlighted. Genes mutated in the telomere maintenance pathway are circled in red. Interactions are as defined in Entrez Gene at *http://www.ncbi.nlm.nih.gov/*. Gene names for those mutated as well as for several key interconnecting proteins are as follows: RP ribosomal protein; FANC, Fanconi anemia complementation group; DKC1, dyskeratosis congenita 1, dyskerin; NOP10, nucleolar protein 10 homolog; NHP2, nonhistone ribonucleoprotein 2 homolog; GAR1, glycine and arginine rich ribonucleoprotein 1 homolog; TERF1, telomeric repeat binding factor 1; TERF2, telomeric repeat binding factor 2; TINF2, TERF1-interacting nuclear factor 2; TERF2IP, TERF2 interacting protein (RAP1); POT1 protection of telomeres 1 homolog; TPP1, TIN2 interacting protein 1 (= ACD, adrenocortical dysplasia homolog); PINX1, PIN2 (=TERF1) interacting protein; ATM, ataxia telangiectasia mutated; M/R/N = MRE11/RAD50/NBS1, meiotic recombination 11 homolog A/radiation resistance 50 homolog/Nijmegen breakage syndrome 1; ATR, ataxia telangiectasia and Rad3 related (Seckel syndrome); BRCA1, breast cancer 1. BRIP1, BRCA1 interacting protein C-terminal helicase 1; PALB2, partner and localizer of BRCA2 (modified from reference 20).

patients diagnosed in childhood are surviving into adulthood.

Fanconi anemia cells display a high frequency of spontaneous chromosomal breakage and hypersensitivity to DNA cross-linking agents such as diepoxybutane. This genomic instability led to the development of a diagnostic test over two decades ago and has facilitated many advances, including elucidation of the genetics with 13 subtypes/complementation groups currently characterized. The proteins encoded by the Fanconi anemia genes (Table 2) participate in a complicated network important in DNA repair (Figure 1).[2-3] Specifically, eight of the Fanconi anemia proteins (FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL and FANCM) interact with each other and form a nuclear complex called the "Fanconi anemia core complex". The Fanconi anemia core complex is required for the activation of the FANCI-FANCD2 protein complex to a monoubiquitinated form (FANCI-FANCD2-Ub). FANCI-FANCD2-Ub then interacts with DNA repair proteins (including BRCA2, BRCA1 and RAD51) leading to the repair of damaged DNA. Patients with Fanconi anemia-D1 have biallelic mutations in BRCA2. These observations have linked the Fanconi anemia proteins with BRCA1 and BRCA2 (FANCD1) in a DNA damage response pathway "the FA/BRCA pathway". The BRCA2 protein is important in the repair of DNA damage by homologous recombination. Cells lacking BRCA2 inaccurately repair damaged DNA and are hypersensitive to DNA cross-linking agents. It has also been observed that FANCJ is BRIP1 (partner of BRCA1) and that FANCN is PALB2 (partner of BRCA2). These findings further strengthen the connection between Fanconi anemia and DNA repair.

Dyskeratosis congenita

Classical dyskeratosis congenita is an inherited bone marrow failure syndrome characterized by the mucocutaneous triad of abnormal skin pigmentation, nail dystrophy and mucosal leucoplakia.[4] A variety of other (dental, gastrointestinal, genitourinary, neurological, ophthalmic, pulmonary and skeletal) abnormalities have also been reported. Bone marrow failure is the major cause of mortality with patients having an additional predisposition to malignancy and fatal pulmonary complications. X-linked recessive, autosomal dominant and autosomal recessive subtypes of dyskeratosis congenita are recognized. Six dyskeratosis congenita genes (*DKC1*, *TERC*, *TERT*, *NOP10*, *NHP2*, *TINF2*) have been identified to date.

The gene mutated in X-linked DC (*DKC1*) encodes a highly conserved nucleolar protein called dyskerin.[5] Dyskerin associates with the H/ACA class of small nucle-

olar RNA in small nucleolar ribonucleoprotein particles (snoRNP), which are important in guiding the conversion of uracil to pseudouracil during the maturation of ribosomal RNA. Dyskerin also associates with the RNA component of telomerase (TERC) where it is important in stabilizing the telomerase complex, which is critical in the maintenance of telomeres.[6] Heterozygous mutations in *TERC* and *TERT* (telomerase reverse transcriptase) have been found in patients with autosomal dominant dyskeratosis congenita and in some patients with aplastic anemia, myelodysplastic syndrome and pulmonary fibrosis.[7-8] A subset of patients with the multi-system disorder Hoyeraal-Hreidarsson syndrome, have been found to have *DKC1* mutations. It has also been established that autosomal recessive dyskeratosis congenita is genetically heterogeneous with three subtypes due to biallelic mutations in *NHP2*, *NOP10* and *TERT*. One subtype of autosomal dominant dyskeratosis congenita was recently found to be due to mutations in *TINF2* which encodes a component of the shelterin complex that protects telomeres and controls access to the telomere. Collectively, these findings have demonstrated that classical dyskeratosis congenita, Hoyeraal-Hreidarsson syndrome, and a subset of aplastic anemia and myelodysplastic syndrome/acute myeloid leukemia are principally due to a defect in telomere maintenance and cells from these patients have very short telomeres.[4] The multi-system abnormalities seen in these patients, including the increased incidence of malignancy, have highlighted the critical role of telomeres and telomerase (Figure 1) in humans.

Shwachman-Diamond syndrome

Shwachman-Diamond syndrome is an autosomal recessive disorder characterized by exocrine pancreatic insufficiency, bone marrow failure and other somatic abnormalities (particularly metaphyseal dysostosis).[9] Features of pancreatic insufficiency are apparent early in infancy. The spectrum of hematologic abnormalities includes neutropenia, pancytopenia (~20%), myelodysplastic syndrome and leukemia (~25%). The majority (>90%) of patients with Shwachman-Diamond syndrome have been found to have mutations in the *SBDS* gene.[10] The *SBDS* gene product (SBDS) has an important role in the maturation of the 60S ribosomal subunit and, therefore, in ribosome biogenesis (Figure 1).[11]

Diamond-Blackfan anemia

Diamond-Blackfan anemia usually presents in early infancy, with features of anemia. The hallmark of classical Diamond-Blackfan anemia is a selective decrease in erythroid precursors and normochromic macrocytic anemia associated with a variable number of somatic abnormalities such as craniofacial, thumb, cardiac and urogenital malformations.[12] Myelodysplastic syndrome and acute myeloid leukemia have been reported in a few patients, suggesting an increased predisposition to hematologic malignancies. There are also cases in which the disease has evolved into aplastic anemia. Thus, although Diamond-Blackfan anemia has been regarded classically as a pure red cell aplasia, a more global hematopoietic defect can be observed.

The first Diamond-Blackfan anemia gene (*RPS19*) was identified in 1999[13] and in western populations accounts for approximately 25% of the cases of the disorder. Subsequently heterozygous mutations in other genes encoding for ribosomal proteins of the small (RPS24, RPS17, RPS7, RPS10, RPS26) and large (RPL5, RPL11, RPL35A) ribosomal subunits have also been reported; collectively the genetic basis of approximately 50-60% of cases of DBA can now be established.[13-14] These observations have demonstrated that Diamond-Blackfan anemia is a disorder of ribosome biogenesis (Figure 1). It is noteworthy that patients with mutations in the *RPL5* gene tend to have multiple physical abnormalities, including craniofacial, thumb and heart anomalies, whereas isolated thumb malformations are seen predominantly in patients with heterozygous *RPL11* mutations.

Among the Japanese, *RPS19* mutations account for only about 13% of the cases of Diamond-Blackfan anemia and there are also some differences in the clinical phenotypes associated with the different Diamond-Blackfan anemia genes in this population compared to those in western populations.[15] This suggests ethnic differences in phenotypic expression; a feature that has been observed previously in other genetic diseases including Fanconi anemia. It also highlights the need to define the clinical-genetic spectrum in different ethnic populations.

Severe congenital neutropenia (including Kostmann syndrome)

Severe congenital neutropenia, as its name indicates, is characterized by profound peripheral neutropenia ($<0.2\times10^9$/L).[16] Patients with the congenital disorder usually present with recurrent, life-threatening infections in infancy. Bone marrow examination usually reveals a maturation arrest in the myeloid lineage. The disease can progress to myelodysplasia and leukemia, usually with acquisition of secondary mutations including mutations in the granulocyte colony-stimulating factor receptor. Heterozygous mutations in the neutrophil elastase gene (*ELA2*) have been demonstrated in the majority of patients.[17] These mutations are thought to lead to the accumulation of a non-functional protein which in turn triggers an unfolded protein response leading to maturational arrest. The original family described by Kostmann, had autosomal recessive severe congenital neutropenia, which has been shown to be associated with biallelic mutations in the *HAX1* gene predicted to lead to defects in cell death. Mutations in other genes (*GFI1*, *WASP*) are also known to be associated with severe congenital neutropenia, demonstrating genetic heterogeneity.[16]

Congenital amegakaryocytic thrombocytopenia

Congenital amegakaryocytic thrombocytopenia usually presents in infancy and is characterized by isolated thrombocytopenia and a reduction or absence of megakaryocytes in the bone marrow, but usually no somatic abnormalities. Approximately 50% of patients develop aplastic anemia, usually by the age of 5 years. Congenital amegakaryocytic thrombocytopenia can also evolve into myelodysplastic syndrome or leukemia. In a subgroup of patients with congenital amegakaryocytic thrombocytopenia biallelic mutations in the gene encoding for the thrombopoietin receptor (*c-MPL*) have been identified.[18]

Epidemiology and natural history

The true incidence and natural history of these congenital bone marrow disorders remains largely unknown. It is generally considered that severe congenital neutropenia and Diamond-Blackfan anemia are among the most prevalent of these disorders; the estimated annual incidence of Diamond-Blackfan anemia is 5 cases per 1,000,000 births. In this issue of Haematologica, Tamary *et al.* report on a retrospective population-based registry of inherited bone marrow failure syndromes in Israel, including 127 patients diagnosed between 1966 and 2007.[19] Of the patients in this registry, 52% had Fanconi anemia, 17% severe congenital neutropenia, 14% Diamond-Blackfan anemia, 6% congenital amegakaryocytic thrombocytopenia, 5% dyskeratosis congenita, 2% Shwachman-Diamond syndrome, and 2% thrombocytopenia with absent radii. This report represents the first comprehensive population-based study evaluating the incidence and complications of the different inherited bone marrow failure syndromes. The commonest disease was Fanconi anemia, which also carried the worst prognosis, with severe bone marrow failure and cancer development. Such data are needed for each country to provide a rational basis for developing treatment programs. It is worth noting that these data are probably only relevant to Israel. For example, based on the data from this registry the annual incidence of Fanconi anemia was calculated to be approximately 2 cases per 100,000 live births. This is 7-fold higher than expected from the world-wide carrier frequency of 1:300 and probably reflects the high rate of consanguinity in Israel.

Concluding remarks

The significant advances in the molecular basis of the inherited bone marrow failure syndromes have provided insights into several biological pathways, such as DNA repair, of importance in human physiology. They have also provided an interesting connection between Diamond-Blackfan anemia, Shwachman-Diamond syndrome, myelodysplastic syndrome (5q– syndrome is associated with haploinsufficiency of ribosomal protein RPS14) and defective ribosome biogenesis.

Clinical similarities (bone marrow failure, developmental anomalies and cancer) between these syndromes have been observed for several years, so it is no surprise that some overlap is also present at the level of molecular pathology. For example, Shwachman-Diamond syndrome and Diamond-Blackfan anemia both appear to be disorders of ribosomal biogenesis and patients with Fanconi anemia, dyskeratosis congenita and Shwachman-Diamond syndrome have short telomeres. It is possible that further overlaps and connections in these pathways will emerge.

The genetic advances have already led to improved diagnosis, particularly for cases in which the presentation is atypical. These advances may also lead to new treatments. In the meantime it is important to obtain accurate information on the incidence and natural history of each disorder in order to provide a more rational basis for the optimal provision of clinical services.

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