THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Next Generation Sequencing Panel for Inherited Bone Marrow Failure Syndromes

Clinical Features:
Inherited bone marrow failure syndromes are a diverse group of rare disorders associated with insufficient production of blood cells and cancer predisposition [1]. Bone marrow failure can affect all three hematopoietic cell lineages, or be restricted to one particular lineage [2]. Aplastic anemia can also be caused by other disorders, including paroxysomal nocturnal hemoglobinuria, myelodysplastic syndrome and acute myeloid leukemia [1].

Our Inherited Bone Marrow Failure Panel includes sequence and deletion/duplication analysis of the 63 genes listed below.

Inherited Bone Marrow Failure Genes					
Dyskeratosis Congenita	**Fanconi Anemia**		**Diamond-Blackfan Anemia**	**Severe Congenital Neutropenia**	**Other**
ACD	BRCA1(FANCS)	RAD51 (FANCR)	GATA1	CSF3R	ALAS2
CTC1	BRCA2 (FANCD1)	RAD51C (FANCO)	RPL5	CXCR4	DDX41
DKC1	BRIP1 (FANCJ)	UBE2T(FANCT)	RPL11	ELANE (ELA2)	DNAJC21
NAF1	ERCC4 (FANCQ)	SLX4 (FANCP)	RPL15	G6PC3	GATA2
NHP2	FANCA		RPL35A	GFI1	MPL
NOP10 (NOLA3)	FANCB		RPL26	HAX1	RBM8A
PARN	FANCC		RPS7	VPS45	RUNX1
POT1	FANCD2		RPS10	WAS	SAMD9
RTEL1	FANCE		RPS19		SAMD9L
TERC	FANCF		RPS24		SBDS
TERT	FANCG		RPS26		SRP72
TINF2	FANCI				TP53
USB1 (C16orf57)	FANCL				
WRAP53 (TCAB1)	PALB2 (FANCN)				

Dyskeratosis Congenita

Dyskeratosis congenita (DC) is a highly heterogeneous disorder characterized by abnormal skin pigmentation, nail dystrophy and oral leukoplakia (mucosal keratosis appearing as white patches in the oral cavity) [3]. This classic triad of findings is present in 80-90% of affected individuals [4]. Bone marrow failure is present in approximately 85% of cases [4]. Other disease manifestations can include epiphora (excessive tear production), intellectual disability, pulmonary fibrosis, abnormal pulmonary vasculature, tooth loss or decay, premature hair loss or greying, liver disease, osteoporosis, and deafness [4]. Dyskeratosis congenita is commonly associated with shortened telomeres [4]. Anticipation may be observed in affected families, and is thought to be due to the inheritance of shortened telomeres from an affected parent [4]. DC can be inherited in either an autosomal dominant, autosomal recessive or X-linked manner, depending on the causative gene.

Gene	Clinical Features
ACD	Guo Y *et al.* (2014) reported germline mutations of *ACD*, the gene encoding telomere protein TPP1 in Inherited bone marrow failure [5]. A pathogenic variant in *ACD* has also been described in a family with chronic lymphocytic leukemia [6]. Hoyeraal-Hreidarsson syndrome can also be caused by a germline mutation in *ACD* [7].
CTC1	Keller *et al.* (2012) identified compound heterozygous mutations in *CTC1* in a patient with DC [8]. The *CTC1* gene is also associated with Coats syndrome, which is characterized by bilateral exudative retinopathy, intracranial calcifications and cysts, premature hair greying, osteoporosis and anemia [9].
DKC1	Mutations in the X-linked *DKC1* gene are the most common cause of DC [10]. Age of onset and severity of symptoms is highly variable, but affected males typically present in the first decade of life, and typically die in their twenties due to complications from bone marrow failure [10]. Many mutations occur *de novo*. Female heterozygous carriers are typically asymptomatic [10].
NAF1	Mutations in *NAF1* have been described in patients with short telomere length, pulmonary fibrosis, low

	telomerase RNA levels, and extrapulmonary manifestations including myelodysplastic syndrome and liver disease [11].
NOP10 (NOLA3)	A homozygous mutation in *NOP10* was identified in 3 individuals with DC in a consanguineous family [12]. All three individuals had the mucocutaneous features of DC, one individual also developed bone marrow failure [12].
NHP2	Biallelic mutations in *NHP2* have been described in two patients with DC [13].
PARN	Biallelic mutations in *PARN* have been reported to be associated with severe aplastic anemia and marked hypomyelination [14,15]. Monoallelic mutations of *PARN* can cause developmental/mental illness [14].
POT1	Germline heterozygous pathogenic variants in *POT1* have been recently reported in thyroid cancer, breast cancer, renal cell carcinoma, colorectal cancer and familial chronic lymphocytic leukemia [6,16]. A *POT1* mutation has been recently reported implicating defective telomere end fill-in and telomere truncations in Coats plus [17].
RTEL1	Both dominant and recessive mutations in the *RTEL1* gene have been associated with Hoyeraal Hreidarsson syndrome, a clinically severe variant of DC with cerebellar hypoplasia, severe immunodeficiency, enteropathy, and intrauterine growth retardation [18]. Anticipation has been described in one family where two affected males inherited a heterozygous mutation from a clinically unaffected female with short telomeres [18]. Heterozygous mutations in *RTEL1* have been reported in patients with bone marrow failure and myelodysplastic syndromes [19,20].
TERC	Heterozygous mutations in the *TERC* gene account for approximately 4% of all cases of DC [10]. Anticipation has been observed in families with *TERC*-associated DC, with increased disease severity and earlier age of onset seen with successive affected generations [10].
TERT	Heterozygous mutations in *TERT* have been associated with DC or aplastic anemia [10]. Penetrance of these mutations appears to be reduced, with some individuals being asymptomatic [10]. Variable expressivity has also been described, with some individuals being mildly affected [10].
TINF2	Dominant mutations in *TINF2* have been described in patients with DC [21]. Both inherited and *de novo* mutations have also been described [21,22].
USB1 (C16orf57)	Walne *et al.* (2010) identified homozygous mutations in the *USB1* (*C16orf57)* gene in 6 out of 132 families with dyskeratosis congenita (DC) [23]. DC has previously been associated with short telomeres, however patients with *USB1* mutations and DC were found to have normal length telomeres [23]. Mutations in the *USB1* gene have also been described in individuals with poikiloderma with neutropenia (PN), which is characterized by poikilodermatous rash (patchy skin discoloration), noncyclical neutropenia, small stature, pachyonychia, and pulmonary disease [24].
WRAP53 (TCAB1)	Biallelic mutations in *TCAB1* have been described in individuals with classical DC from two different families [25].

Fanconi Anemia

Fanconi anemia (FA) is a chromosomal instability disorder associated congenital anomalies, progressive bone marrow failure, and cancer predisposition [26]. The most commonly described anomalies include thumb and radial bone abnormalities, short stature and skin hyperpigmentation [26]. Some patients lack these characteristic physical features and first present with bone marrow failure or cancer [27]. Associated cancers include acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), and solid tumors of the head, neck, skin, gastrointestinal tract and genital tract [26]. The majority of cases of FA are inherited in an autosomal recessive manner. Mutations in the *FANCB* gene are inherited in an X-linked manner.

Gene	**Clinical Features**
BRCA1 (FANCS)	Recently, two cases of individuals harboring biallelic deleterious *BRCA1* mutations were reported [28,29]. Detailed phenotypic and cellular characterization of one patient provided lines of evidence supporting the hypothesis that biallelic BRCA1 mutations cause a new Fanconi anemia subtype associated with increased breast and ovarian cancer susceptibility [28].
BRCA2 (FANCD1)	Homozygous or compound heterozygous mutations in *BRCA2* are associated with FA complementation group D1. *BRCA2* mutations are associated with early-onset leukemia and solid tumors, and a high rate of spontaneous chromosome aberration compared to other types of FA [30,31]. Heterozygous mutations in *BRCA2* are associated with hereditary breast and ovarian cancer [32].
BRIP1 (FANCJ)	FA complementation group J is associated with biallelic mutations in the *BRIP1* gene [33]. There is some evidence that heterozygous BRIP1 mutations may be associated with increased breast cancer susceptibility [34].
ERCC4 (FANCQ)	FA complementation group Q is associated with biallelic *ERCC4* mutations [35]. *ERCC4* mutations can also be associated with xeroderma pigmentosa [36].
FANCA	Biallelic *FANCA* mutations are associated with FA complementation group A [37]. Patients with mutations associated with no FANCA protein production may have earlier onset anemia and higher risk of leukemia, compared with patients with production of an abnormal FANCA protein [37].
FANCB	Mutations in the X-linked *FANCB* are associated with FA complementation group B. Affected patients typically have multiple malformations, including a ventriculomegaly or hydrocephalus, bilateral radial defects, vertebral defects, and renal agenesis [38]. An estimated 50% of affected males do not survive the perinatal period; heterozygous females are typically unaffected and exhibit skewed X-inactivation [38].
FANCC	FA complementation group C is associated with biallelic mutations in *FANCC*. A founder mutation in *FANCC* exists in the Ashkenazi Jewish population, and has a carrier frequency of 1 in 100 [39].

FANCD2	Biallelic mutations in *FANCD2* are associated with FA complementation group D2, and account for approximately 3-6% of all cases of FA [40]. Patients with *FANCD2* mutations frequently have congenital malformations, and have earlier onset hematological manifestations compared FA cases overall [40].
FANCE	Homozygous mutations in *FANCE* have previously been identified in 2 Turkish patients and 1 Bangladeshi patient with FA complementation group E [41].
FANCF	FA complementation group F is caused by homozygous or compound heterozygous mutations in the *FANCF* gene [42].
FANCG	Biallelic *FANCG* mutations are associated with FA complementation group G. FANCG mutations are typically associated with more severe cytopenia and a higher risk of leukemia than is observed with cases of FA in general [37].
FANCI	FA complementation group I is caused by homozygous or compound heterozygous mutations in the *FANCI* gene [43].
FANCL	A patient with FA complementation group L and compound heterozygous mutations in *FANCL* has previously been described [44].
PALB2 (FANCN)	FA complementation group N has been associated with compound heterozygous mutations in *PALB2*. Heterozygous mutations in *PALB2* have been associated with increased susceptibility to breast cancer [45].
RAD51 (FANCR)	Wang *et al.,* 2015, identified a *de novo* heterozygous mutation in *RAD51* in a patient with a FA-like phenotype [46].
RAD51C (FANCO)	A homozygous mutation in *RAD51C* has previously been described in a family with FA complementation group O [47]. Heterozygous mutations in this gene have been associated with breast cancer predisposition [48].
UBE2T (FANCT)	Two unrelated individuals were reported with biallelic *UBE2T* missense mutations that rendered the UBE2T protein unable to interact with FANCL and caused Fanconi anemia [49].
SLX4 (FANCP)	FA complementation group P has been associated with either homozygous or compound heterozygous mutations in the *SLX4* gene [50].

Severe Congenital Neutropenia (SCN)

Severe congenital neutropenia (SCN) is characterized by severe neutropenia at birth [51]. Bone marrow exhibits arrest of neutrophil maturation at the promyelocyte or myelocyte stage of development [51]. By age 6 months, 90% of patients with SCN develop bacterial infections such as skin or deep tissue abscesses, oral ulcers and pneumonia [51]. Despite improvements in therapy there remains a 12% risk of death due to sepsis by age 15 years [51]. Patients with SCN also have an increased risk of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), with a hazard rate of 2% per year [51]. SCN can be inherited in either an autosomal dominant, autosomal recessive or X-linked manner, depending on the causative gene.

Gene	Clinical Features
CSF3R	Biallelic loss-of-function mutations in *CSF3R* have been described in patients with SCN [52]. Plo *et al.* (2009) identified a heterozygous activating mutation in *CSF3R* in a family with dominantly inherited chronic neutropenia [53]. One affected family member also developed MDS.
CXCR4	Heterozygous mutations in the *CXCR4* gene WHIM syndrome is an immunodeficiency disease characterized by neutropenia, hypogammaglobulinemia, and extensive human papillomavirus (HPV) infection [54,55].
ELANE (ELA2)	Heterozygous mutations in the *ELANE* gene are responsible for the majority of cases of SCN [56]. *ELANE* can also be associated with cyclic neutropenia [56]. To clear phenotype-genotype correlations exist, and there is significant overlap between predicted severity of the mutation and the clinical phenotype [56].
G6PC3	Biallelic mutations in *G6PC3* have been associated with SCN type 4 [57]. Patients with *G6PC3* deficiency commonly present with congenital anomalies including cardiac anomalies, urogenital malformations and venous angietasia [57]. Alangari *et al.* (2013) described a consanguineous family where affected individuals presented with either SCN or cyclic neutropenia [57].
GFI1	Dominant-negative mutations in *GFI1* have been associated with SCN [58]. *GFI1* mutations have also been identified in patients with nonimmune chronic idiopathic neutropenia of adults [59].
HAX1	Biallelic mutations in *HAX1* account for 15% of cases of SCN [58]. A proportion of patients with *HAX1*-associated SCN also develop neurological disease such as cognitive impairment, developmental delay, and epilepsy [58].
VPS45	Stepensky *et al.* (2013) identified homozygous mutations in *VPS45* in patients with SCN [60]. Affected individuals developed neutropenia, thrombasthenia, myelofibrosis and progressive bone marrow failure [60].
WAS	Activating mutations in the X-linked *WAS* gene are associated with SCN and lmyphopenia [58]. Loss of function mutations in *WAS* have been associated with Wiskott-Aldrich syndrome, associated with immunodeficiency, eczema, microthromobocytopenia, and susceptibility to malignant lymphoma [58].

Diamond-Blackfan Anemia (DBA)

Diamond-Blackfan anemia (DBA) is an inherited red blood cell aplasia disorder associated with reduced or absent erythroid precursors in bone marrow, macrocytic anemia and reticulocytopenia [51]. Approximately 30% of cases have growth retardation and 50% have congenital anomalies, which may include thumb anomalies, congenital heart defects and midline facial defects such as cleft palate and hypertelorism [51]. Patients have an increased risk of malignancies, including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and solid tumors such as osteogenic sarcoma [51]. The cumulative incidence of solid tumors or leukemia is 22% by age 46 [61]. DBA is a genetically heterogeneous condition, with the currently known genes accounting for 50-70% of cases [51]. All the DBA genes included on this panel are inherited in an autosomal dominant manner.

An estimated 55-60% of cases are caused by *de novo* mutations; DBA has variable expressivity and penetrance is incomplete.

Gene	Clinical Features
GATA1	Patients with inherited thrombocytopenia in a concurrent hemolytic anemia should raise the suspicion of thrombocytopenia caused by *GATA1* mutations or sitosterolemia [62]. Recent exome sequencing has identified a novel splice site mutation in *GATA1* in two siblings with DBA [63].
RPL5	DBA type 6, caused by heterozygous mutations in *RPL5*, is typically associated with multiple physical anomalies, including craniofacial, thumb and cardiac anomalies [64].
RPL11	Heterozygous mutations in *RPL11* are associated with DBA type 7. In terms of observed congenital malformations, mutations in *RPL11* are predominantly associated with isolated thumb defects [64].
RPL15	Deletions of *RPL15* have been identified in patients with Diamond-Blackfan anemia recently [65,66].
RPL35A	Mutations in *RPL35A* have been identified in both familial and sporadic cases of DBA type 5. In one familial case, some individuals were found to have subclinical DBA with macrocytic anemia [67].
RPL26	Gazda HT *et al.* (2012) identified a frameshift mutation in p53 regulator *RPL26* that is associated with multiple physical abnormalities and a specific pre-ribosomal RNA processing defect in diamond-blackfan anemia[68].
RPS7	*RPS7* has been associated with DBA type 8 [69]. At least one individual with no associated physical anomalies has been described [64].
RPS10	*RPS10* mutations are associated with DBA type 6, and are estimated to account for 2.6% of all DBA cases [70].
RPS19	Mutations in the *RPS19* gene account for an estimated 24% of all DBA cases overall [71].
RPS24	*RPS24* mutations are associated with DBA type 3, and account for an estimated 2% of DBA cases [72]. Both sporadic and familial mutations have been described [72].
RPS26	Mutations in *RPS26* are associated with DBA type 10, and account for an estimated 6.4% of DBA cases overall. Based on available data from a limited number of cases, physical malformations appear to be rare in patients with *RPS26* mutations [70].

Other Genetic Causes of Bone Marrow Failure

Gene	Clinical Features
ALAS2	The most common form is X-linked sideroblastic anemia, due to loss-of-function mutations in the erythroid-specific δ-aminolevulinate synthase (ALAS2), which is the first enzyme of the heme biosynthesis pathway in erythroid cells [73]. ALAS2 gain-of-function mutations lead to the increased erythroid protoporphyrin accumulation causing X-linked protoporphyria [74].
ATG2B/ GSKIP	Germline duplication of *ATG2B* and *GSKIP* predisposes to familial myeloid malignancies, including myeloproliferative neoplasms, frequently progressing to leukemia [75].
DDX41	Recurrent mutations in the DEAD/H-box RNA helicase gene *DDX41* have been reported in patients with familial and acquired myelodsyplasia and acute myeloid leukemia [76].
DNAJC21	Biallelic mutations in *DNAJC21* cause Shwachman-Diamond syndrome and bone marrow failure prone to hematological malignancies [77,78].
GATA2	Zhang *et al* (2014) identified germline mutations in *GATA2* in 5 out of 71 subjects with idiopathic bone marrow failure or myelodysplastic syndrome [79]. These patients did not have additional features associated with other *GATA2* disorders, Emberger syndrome and MonoMac.
MPL	Biallelic mutations in the *MPL* gene have been associated with congenital amegakaryocytic thrombocytopenia (CAMT), which typically presents with thrombocytopenia during infancy, but can also present as bone marrow failure without a specific history of thrombocytopenia [26].
RBM8A	The *RBM8A* gene is associated with thrombocytopenia-absent radius (TAR) syndrome, a rare autosomal recessive disorder [80]. Affected individuals have severe thrombocytopenia at birth, and bilateral radial hypoplasia or aplasia, with preservation of thumbs [80]. The majority of patients with TAR are heterozygous for a 200kb deletion at 1q21.1 which encompasses the *RBM8A* gene. In patients who carry the 200kb deletion, the remaining *RBM8A* allele is typically hypomorphic due the presence of 1 of 2 known low frequency SNPs, either in the 5' UTR or in the first intron.
RUNX1	Zhang *et al* (2014) identified a truncating germline mutation in *RUNX1* in a patient with myelodysplastic syndrome, including neutropenia and thrombocytopenia [79]. Additional clinical findings included Chiari I malformation, scoliosis, myopathy, and chronic obstructive pulmonary disease.
SAMD9	Mutations in *SAMD9* cause a multisystem disorder including myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy. Patients carrying a *SAMD9* mutation can develop MDS that was accompanied by loss of the chromosome 7 [81,82].
SAMD9L	Mutations in *SAMD9L* cause ataxia-pancytopenia syndrome which is characterized by cerebellar ataxia, variable hematologic cytopenias, and predisposition to marrow failure, myelodysplastic syndrome and myeloid leukemia, sometimes associated with monosomy 7. Hematopoietic revertant mosaicism has been reported and was associated with milder disease [83,84].

SBDS	Homozygous or compound heterozygous mutations in *SBDS* are associated with Shwachman-Diamond syndrome, which is characterized by short stature, exocrine pancreatic insufficiency, and bone marrow dysfunction [85]. Hematologic findings can include intermittent neutropenia, anemia, increased fetal hemoglobin levels, thrombocytopenia and aplastic anemia [85]. There is an increased risk of malignant transformation, including a risk of AML [85]. Heterozygous mutations in SBDS have been associated with aplastic anemia [86].
SRP72	Kirwan *et al.* (2012) identified a mutation in *SRP72* in a family with autosomal dominant aplastic anemia/myelodysplasia and congenital deafness[87]. An additional mutation was identified in a family with autosomal dominant myelodysplasia [87].
TP53	Toki *et al.* (2018) identified *de novo* variants in *TP53* in two individuals with bone marrow failure, hypogammaglobulinemia, growth retardation, and microcephaly, similar to Diamond Blackfan anemia and dyskeratosis congenita [88]. These variants were located in the C-terminal domain (CTD) and resulted in truncation of the protein with augmented transcriptional activity, whereas typically pathogenic variants associated with Li-Fraumeni syndrome affect the core DNA binding domain. The variants identified by Toki *et al.* were studied in zebrafish and demonstrated abnormal erythrocyte production.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Inherited Bone Marrow Failure Panel (63 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube. NOTE: blood samples are not accepted if patient has a history of MDS or leukemia. Please send 2 T-25 flasks of cultured skin fibroblasts instead. Cultured skin fibroblasts are highly recommended for the testing.
Cost:	$3000
CPT codes:	81216, 81242, 81334, 81345, 81405
Turn-around time:	6 weeks

Note: We cannot bill insurance for the Inherited Bone Marrow Failure Sequencing panel.

Results:

Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. One report will be issued for the entire Inherited Bone Marrow Sequencing Panel. All abnormal results are reported by telephone or email.

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