

Hereditary Bone Marrow Failure Panel, Sequencing and Deletion/Duplication

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Bone marrow failure (BMF) encompasses a heterogeneous array of acquired and germline conditions characterized by qualitative or quantitative defects in one or more hematopoietic lineages resulting in cytopenias and hypocellular bone marrow. These include inherited syndromes such as Fanconi anemia (FA), telomere biology disorders (TBD) such as dyskeratosis congenita (DC), Schwachman-Diamond syndrome (SDS), Diamond-Blackfan anemia (DBA), congenital amegakaryocytic thrombocytopenia (CAMT), severe congenital neutropenia (SCN), aplastic anemia, and others.

This panel includes genes causative for hereditary BMF syndromes as well genes associated with hereditary predisposition to myeloid neoplasms, as there is often clinical overlap between these two entities.

Disease Overview

Hereditary BMF syndromes are caused by germline pathogenic variants that disrupt DNA repair, telomere maintenance, ribosome biogenesis, and structural protein pathways. In addition to BMF, these conditions may also be accompanied by syndromic physical findings and predisposition to hematologic and other malignancies. While most patients with hereditary BMF present in childhood, these conditions may manifest at any age.

Genetics

Genes

For a list of genes tested, associated disorders, and inheritance, refer to the [Genes Tested](#) table.

Refer to [Limitations](#) for exons not covered by sequencing and genes for which deletion and/or duplication is not available.

Test Interpretation

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing, or NGS) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for the detection of large deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Featured ARUP Testing

[Hereditary Bone Marrow Failure Panel, Sequencing and Deletion/Duplication 3001615](#)

Method: Massively Parallel Sequencing

- Use to assess for **inherited/germline** DNA variants associated with bone marrow failure or hereditary predisposition to myeloid neoplasms.
- **Preferred sample type is cultured skin fibroblasts; testing whole blood in affected patients may not definitively determine germline status.**
- Not intended to detect somatic variants; refer to the [Laboratory Test Directory](#) for myeloid malignancy panel testing.

Analytic Sensitivity/Specificity

Variant Class	Analytic Sensitivity (PPA) Estimate ^a (%) and 95% Credibility Region	Analytic Specificity (NPA) Estimate (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp ^b	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp ^b	94.8 (86.8-98.5)	>99.9
Exon-level ^c deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [single exon]	>99.9
Exon-level ^c duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

^aPPA values are derived from larger methods-based MPS and/or Sanger validations. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA) unless otherwise indicated.

^bVariants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

^cIn most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Limitations

- A negative result does not exclude a diagnosis of bone marrow failure.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient received an allogeneic stem cell transplant unless the sample analyzed is definitively from the recipient, such as cultured skin fibroblasts.
- The germline or somatic status of a detected variant cannot be definitively determined in patients with hematologic malignancy if the assay is performed on blood or other tissue that may be contaminated by clonal or malignant cells; testing a definitively germline specimen such as cultured fibroblasts may be recommended in such cases.
- The following will not be evaluated:
 - Variants outside the coding regions and intron-exon boundaries of targeted genes
 - *SBDS* gene associated with Schwachman-Diamond syndrome
 - Regulatory region and deep intronic variants
 - SNVs and small insertions/deletions will not be called in the following exons due to technical limitations of the assay:
 - *CXCR4* (NM_001348056) exon 2
 - *CXCR4* (NM_001348059) exon 2
 - *DNAJC21* (NM_001348420) partial exon 9 (Chr5:34945827-34945845)
 - *ERCC6L2* (NM_001375291) exon 19
 - *ERCC6L2* (NM_001375292) exon 19
 - *ERCC6L2* (NM_001375293) exon 18
 - *ERCC6L2* (NM_001375294) exon 18
 - *FANCA* (NM_001018112) exon 11
 - *FANCA* (NM_001351830) exon 10
 - *FANCD2* (NM_033084) exons 14, 17, 21, 22
 - *FANCD2* (NM_001018115) exons 14, 17, 21, 22
 - *FANCD2* (NM_001319984) exons 14, 17, 21, 22
 - *FANCD2* (NM_001374253) exons 14, 17, 20, 21
 - *FANCD2* (NM_001374254) exons 14, 17, 21, 22
 - *FANCD2* (NM_001374255) exon 10
 - *FANCL* (NM_001374615) exon 8

- Deletions/duplications in *CEBPA*, *NOP10*, *RMRP*, and *RPL15* genes
- Duplications in the *TERC* gene
- Breakpoints of large deletions/duplications
- The following may not be detected:
 - Deletions/duplications/insertions of any size by massively parallel sequencing
 - Large duplications less than 3 exons in size
 - Noncoding transcripts
 - Some variants due to technical limitations in the presence of pseudogenes and/or repetitive/homologous regions
 - Low-level somatic variants

Genes Tested

Gene	MIM #	Disorders	Inheritance
<i>ACD</i>	609377	Dyskeratosis congenita	AD, AR
<i>ALAS2</i>	301300	Sideroblastic anemia Erythropoietic protoporphyria	XL
<i>ANKRD26</i>	610855	Thrombocytopenia 2	AD
<i>ATM</i>	607585	Ataxia-telangiectasia	AR
<i>BLM</i>	604610	Bloom syndrome	AR
<i>BRCA1</i>	113705	Fanconi anemia, complementation group S	AR
		Hereditary breast and ovarian cancer syndrome	AD
<i>BRCA2</i>	600185	Fanconi anemia, complementation group D1	AR
		Hereditary breast and ovarian cancer syndrome	AD
<i>BRIP1</i>	605882	Fanconi anemia, complementation group J	AD
<i>CBL</i>	165360	Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia	AD
<i>CEBPA</i>	116897	Familial acute myeloid leukemia	AD
<i>CSF3R</i>	138971	Severe congenital neutropenia 7	AR
<i>CTC1</i>	613129	Dyskeratosis congenita	AR
		Coats plus syndrome	
<i>CXCR4</i>	162643	WHIM syndrome	AD
<i>DDX41</i>	608170	Familial myeloproliferative/lymphoproliferative neoplasms	AD
<i>DKC1</i>	300126	Dyskeratosis congenita	XL
<i>DNAJC21</i>	617048	Bone marrow failure syndrome 3	AR

Gene	MIM #	Disorders	Inheritance
<i>ELANE</i>	130130	Cyclic neutropenia Severe congenital neutropenia 1	AD
<i>ERCC4</i>	133520	Xeroderma pigmentosum, group F Fanconi anemia, complementation group Q	AR
<i>ERCC6L2</i>	615667	Bone marrow failure syndrome 2	AR
<i>ETV6</i>	600618	Thrombocytopenia 5	AD
<i>FANCA</i>	607139	Fanconi anemia, complementation group A	AR
<i>FANCB</i>	300515	Fanconi anemia, complementation group B	XL
<i>FANCC</i>	613899	Fanconi anemia, complementation group C	AR
<i>FANCD2</i>	613984	Fanconi anemia, complementation group D2	AR
<i>FANCE</i>	613976	Fanconi anemia, complementation group E	AR
<i>FANCF</i>	613897	Fanconi anemia, complementation group F	AR
<i>FANCG</i>	602956	Fanconi anemia, complementation group G	AR
<i>FANCI</i>	611360	Fanconi anemia, complementation group I	AR
<i>FANCL</i>	608111	Fanconi anemia, complementation group L	AR
<i>G6PC3</i>	611045	Dursun syndrome Severe congenital neutropenia 4	AR
<i>GATA1</i>	305371	Dyserythropoietic anemia and thrombocytopenia	XL
<i>GATA2</i>	137295	Familial acute myeloid leukemia and myelodysplastic syndrome	AD
<i>GFI1</i>	600871	Severe congenital neutropenia 2	AD
<i>HAX1</i>	605998	Severe congenital neutropenia 3	AR
<i>HOXA11</i>	142958	Radioulnar synostosis with amegakaryocytic thrombocytopenia 1	AD
<i>IKZF1</i>	603023	Common variable immunodeficiency 13	AD
<i>KRAS</i>	190070	Noonan syndrome	AD
<i>MBD4</i>	603574	Susceptibility to acute myeloid leukemia	Unknown

Gene	MIM #	Disorders	Inheritance
<i>MPL</i>	159530	Congenital amegakaryocytic thrombocytopenia (CAMT)	AR
<i>MYH9</i>	160775	Macrothrombocytopenia and granulocyte inclusions with or without nephritis or sensorineural hearing loss	AD
<i>NBN</i>	602667	Aplastic anemia Nijmegen breakage syndrome	AR
<i>NHP2</i>	606470	Dyskeratosis congenita	AR
<i>NOP10</i>	606471	Dyskeratosis congenita	AR
<i>NRAS</i>	164790	Noonan syndrome	AD
<i>PALB2</i>	610355	Fanconi anemia, complementation group N	AR
<i>PARN</i>	604212	Dyskeratosis congenita	AR
		Pulmonary fibrosis and/or bone marrow failure	AD
<i>PTPN11</i>	176876	Noonan syndrome	AD
<i>RAD51C</i>	602774	Fanconi anemia, complementation group O	AR
<i>RMRP</i>	157660	Aplastic anemia	AR
		Cartilage-hair hypoplasia	
<i>RPL11</i>	604175	Diamond-Blackfan anemia 7	AD
<i>RPL15</i>	604174	Diamond-Blackfan anemia 12	AD
<i>RPL26</i>	603704	Diamond-Blackfan anemia 11	AD
<i>RPL35A</i>	180468	Diamond-Blackfan anemia 5	AD
<i>RPL5</i>	603634	Diamond-Blackfan anemia 6	AD
<i>RPS10</i>	603632	Diamond-Blackfan anemia 9	AD
<i>RPS19</i>	603474	Diamond-Blackfan anemia 1	AD
<i>RPS24</i>	602412	Diamond-Blackfan anemia 3	AD
<i>RPS26</i>	603701	Diamond-Blackfan anemia 10	AD
<i>RPS7</i>	603658	Diamond-Blackfan anemia 8	AD
<i>RTEL1</i>	608833	Pulmonary fibrosis and/or bone marrow failure	AD

Gene	MIM #	Disorders	Inheritance
		Dyskeratosis congenita	AD, AR
<i>RUNX1</i>	151385	Familial platelet disorder with associated myeloid malignancy	AD
<i>SAMD9</i>	610456	Monosomy 7 myelodysplasia and leukemia syndrome MIRAGE syndrome	AD
<i>SAMD9L</i>	611170	Monosomy 7 myelodysplasia and leukemia syndrome Ataxia-pancytopenia syndrome	AD
<i>SLX4</i>	613278	Fanconi anemia, complementation group P	AR
<i>SRP72</i>	602122	Bone marrow failure syndrome 1	AD
<i>TERC</i>	602322	Dyskeratosis congenita Pulmonary fibrosis	AD
<i>TERT</i>	187270	Dyskeratosis congenita	AD, AR
<i>TET2</i>	612839	Immunodeficiency	AR
<i>TINF2</i>	604319	Dyskeratosis congenita	AD
<i>TP53</i>	191170	Li-Fraumeni syndrome Bone marrow failure syndrome 5	AD
<i>UBE2T</i>	610538	Fanconi anemia, complementation group T	AR
<i>USB1</i>	613276	Poikiloderma with neutropenia	AR
<i>VPS45</i>	610035	Severe congenital neutropenia	AR
<i>WAS</i>	300392	Wiskott-Aldrich syndrome, Severe congenital neutropenia Thrombocytopenia	XL
<i>WRAP53</i>	612661	Dyskeratosis congenita	AR

