Hereditary Bone Marrow Failure Panel, Sequencing and Deletion/Duplication

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Bone marrow failure (BMF) encompasses a heterogenous 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 as genes associated with hereditary predisposition to myeloid neoplasms, as there is often clinical overlap between these two entities.

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.

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.

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

[a]PPA 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.

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In 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
ACD	609377	Dyskeratosis congenita	AD, AR
ALAS2	301300	Sideroblastic anemia Erythropoietic protoporphyria	XL
ANKRD26	610855	Thrombocytopenia 2	AD
ATM	607585	Ataxia-telangiectasia	AR
BLM	604610	Bloom syndrome	AR
BRCA1	113705	Fanconi anemia, complementation group S	AR
		Hereditary breast and ovarian cancer syndrome	AD
BRCA2	600185	Fanconi anemia, complementation group D1	AR
		Hereditary breast and ovarian cancer syndrome	AD
BRIP1	605882	Fanconi anemia, complementation group J	AD
CBL	165360	Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia	AD
CEBPA	116897	Familial acute myeloid leukemia	AD
CSF3R	138971	Severe congenital neutropenia 7	AR
CTC1	613129	Dyskeratosis congenita Coats plus syndrome	AR
CXCR4	162643	WHIM syndrome	AD
DDX41	608170	Familial myeloproliferative/lymphoproliferative neoplasms	AD
DKC1	300126	Dyskeratosis congenita	XL
DNAJC21	617048	Bone marrow failure syndrome 3	AR
ELANE	130130	Cyclic neutropenia Severe congenital neutropenia 1	AD
ERCC4	133520	Xeroderma pigmentosum, group F Fanconi anemia, complementation group Q	AR
ERCC6L2	615667	Bone marrow failure syndrome 2	AR
ETV6	600618	Thrombocytopenia 5	AD
FANCA	607139	Fanconi anemia, complementation group A	AR
FANCB	300515	Fanconi anemia, complementation group B	XL
FANCC	613899	Fanconi anemia, complementation group C	AR
FANCD2	613984	Fanconi anemia, complementation group D2	AR
FANCE	613976	Fanconi anemia, complementation group E	AR

Gene	MIM #	Disorders	Inheritance
FANCF	613897	Fanconi anemia, complementation group F	AR
FANCG	602956	Fanconi anemia, complementation group G	AR
FANCI	611360	Fanconi anemia, complementation group I	AR
FANCL	608111	Fanconi anemia, complementation group L	AR
G6PC3	611045	Dursun syndrome Severe congenital neutropenia 4	AR
GATA1	305371	Dyserythropoietic anemia and thrombocytopenia	XL
GATA2	137295	Familial acute myeloid leukemia and myelodysplastic syndrome	AD
GFI1	600871	Severe congenital neutropenia 2	AD
HAX1	605998	Severe congenital neutropenia 3	AR
HOXA11	142958	Radioulnar synostosis with amegakaryocytic thrombocytopenia 1	AD
IKZF1	603023	Common variable immunodeficiency 13	AD
KRAS	190070	Noonan syndrome	AD
MBD4	603574	Susceptibility to acute myeloid leukemia	Unknown
MPL	159530	Congenital amegakaryocytic thrombocytopenia (CAMT)	AR
MYH9	160775	Macrothrombocytopenia and granulocyte inclusions with or without nephritis or sensorineural hearing loss	AD
NBN	602667	Aplastic anemia Nijmegen breakage syndrome	AR
NHP2	606470	Dyskeratosis congenita	AR
NOP10	606471	Dyskeratosis congenita	AR
NRAS	164790	Noonan syndrome	AD
PALB2	610355	Fanconi anemia, complementation group N	AR
PARN	604212	Dyskeratosis congenita	AR
		Pulmonary fibrosis and/or bone marrow failure	AD
PTPN11	176876	Noonan syndrome	AD
RAD51C	602774	Fanconi anemia, complementation group O	AR
RMRP	157660	Aplastic anemia Cartilage-hair hypoplasia	AR
RPL11	604175	Diamond-Blackfan anemia 7	AD
RPL15	604174	Diamond-Blackfan anemia 12	AD
RPL26	603704	Diamond-Blackfan anemia 11	AD
RPL35A	180468	Diamond-Blackfan anemia 5	AD
RPL5	603634	Diamond-Blackfan anemia 6	AD
RPS10	603632	Diamond-Blackfan anemia 9	AD

Gene	MIM #	Disorders	Inheritance
RPS19	603474	Diamond-Blackfan anemia 1	AD
RPS24	602412	Diamond-Blackfan anemia 3	AD
RPS26	603701	Diamond-Blackfan anemia 10	AD
RPS7	603658	Diamond-Blackfan anemia 8	AD
RTEL1	608833	Pulmonary fibrosis and/or bone marrow failure	AD
		Dyskeratosis congenita	AD, AR
RUNX1	151385	Familial platelet disorder with associated myeloid malignancy	AD
SAMD9	610456	Monosomy 7 myelodysplasia and leukemia syndrome MIRAGE syndrome	AD
SAMD9L	611170	Monosomy 7 myelodysplasia and leukemia syndrome Ataxia-pancytopenia syndrome	AD
SLX4	613278	Fanconi anemia, complementation group P	AR
SRP72	602122	Bone marrow failure syndrome 1	AD
TERC	602322	Dyskeratosis congenita Pulmonary fibrosis	AD
TERT	187270	Dyskeratosis congenita	AD, AR
TET2	612839	Immunodeficiency	AR
TINF2	604319	Dyskeratosis congenita	AD
TP53	191170	Li-Fraumeni syndrome Bone marrow failure syndrome 5	AD
UBE2T	610538	Fanconi anemia, complementation group T	AR
USB1	613276	Poikiloderma with neutropenia	AR
VPS45	610035	Severe congenital neutropenia	AR
WAS	300392	Wiskott-Aldrich syndrome, Severe congenital neutropenia Thrombocytopenia	XL
WRAP53	612661	Dyskeratosis congenita	AR