Hereditary Myeloid Neoplasms Panel, Sequencing

Last Literature Review: December 2020 Last Update: September 2023

While the majority of myelodysplastic syndromes (MDSs), myeloid neoplasms, and malignancies occur sporadically due to somatic mutations, a portion are due to inherited or hereditary predispositions. Identification of an inherited predisposition can affect therapy options and surveillance strategies, as well as lead to testing of biological relatives, and inform stem cell transplant donor selection. Individuals with an inherited predisposition to myeloid neoplasms may present at a younger age, have more than one first-degree relative with MDS/acute myeloid leukemia (AML), and/or a family history of physical findings associated with a known cancer predisposition syndrome. The preferred specimen type to assess the germline status of patients suspected of, or at risk for, a hereditary predisposition to myeloid neoplasms is cultured skin fibroblasts in order to exclude somatic variants and to avoid false negatives due to peripheral blood somatic mosaicism. ARUP will perform culturing services for skin samples at an additional charge.

Featured ARUP Testing

Hereditary Myeloid Neoplasms Panel, Sequencing 3001842

Method: Massively Parallel Sequencing

- Use to assess for inherited/germline DNA variants associated with familial myeloid dysplasias and malignancies.
- NOT intended to detect somatic variants; for test options to assess somatic DNA variants of diagnostic, prognostic, and/or therapeutic significance, refer to the Laboratory Test Directory.
- Cultured skin fibroblasts are the preferred sample type to assess the germline status of patients suspected of a hereditary predisposition to myeloid neoplasms.
- Regions of low coverage and reported variants are confirmed by Sanger sequencing as necessary.
- ARUP will perform culturing services for skin samples at an additional charge.

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Disease Overview

Symptoms/Associated Disorders

- Pathogenic germline variants in several genes have been associated with familial MDS and acute leukemias.
  - Inherited myeloid neoplasm predisposition genes included in this panel that often do NOT present with cytopenia, dysplasia, or other organ dysfunction prior to myeloid malignancy:
    - *CEBPA*
    - *DDX41*
  - Inherited myeloid neoplasm predisposition genes included in this panel that often DO present with preexisting cytopenia(s) or other organ dysfunction prior to myeloid malignancy:
    - *ANKRD26*
    - *ETV6*
    - *GATA2*
    - *RUNX1*
    - *SAMD9*
    - *SAMD9L*
    - *SRP72*
  - Inherited myeloid neoplasm predisposition genes that also predispose to other solid tumors/cancers or syndromic findings:
    - *ATM*
    - *BLM*
    - *CBL*
    - *GATA1*
    - *KRAS*
    - *NBN*
    - *PTPN11*
    - *TP53*
  - Inherited bone marrow failure genes:
    - *ELANE*
    - *TERC*
    - *TERT*
- For a complete list of genes and associated disorders, please refer to the Genes Tested table.

Epidemiology

- In the general population, MDS and AML occur in approximately 4.5 and 3.7 per 100,000 individuals, respectively.[1]
- MDS is rare in children and young adults; approximately 50% of childhood MDS is associated with an inherited cause.[2]

Inheritance

Variable, refer to the Genes Tested table

Test Description

Refer to the Genes Tested table for genes included in this panel.

Clinical Sensitivity

Variable, dependent on phenotype/condition

- Pathogenic germline genetic variants have been identified in approximately 18% of families with hereditary MDS/acute leukemia or other hematologic malignancy.[3,4]

Contraindications for Ordering

- Should not be ordered to detect somatic variants associated with malignancy because sensitivity for mosaic variants is low with methodology used for germline assays.
- Individuals with hematological malignancy and/or a previous allogenic bone marrow transplant should not undergo molecular genetic testing on a peripheral blood specimen. Testing of cultured skin fibroblasts is required for accurate interpretation of test results.

Limitations

- A negative result does not exclude a diagnosis of cancer nor a heritable form of myeloid neoplasm.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of the test result may be impacted if the patient has had an allogeneic stem cell transplantation.
- This assay is not intended to detect somatic variants associated with hematologic malignancy, although such variants may be detected.
- This assay cannot definitively distinguish the germline or somatic origin of detected variants when the patient has a hematologic malignancy, and the assay was performed on blood or other tissue that may be contaminated by malignant cells. In such instances, confirmation of germline variant status by testing of cultured skin fibroblasts is strongly recommended.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted gene(s)
  - Regulatory region and deep intronic variants, unless specifically targeted for their clinical relevance
  - Large deletions/duplications in the targeted genes
  - Noncoding transcripts
  - The following exons are not sequenced due to technical limitations of the assay:
    - *ANKRD26* (NM_014915) exon 19
    - *PTPN11* (NM_002834) exon 9
    - *SRP72* (NM_006947) exon 19
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, or repetitive or homologous regions
  - Low-level somatic variants, including those that have undergone somatic reversion

Analytic Sensitivity

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%)	Analytic Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

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

Genes Tested

Gene	MIM Number	Inherited Disorder, Hematologic Disease Associations, Cancer Predispositions	Inheritance
ANKRD26[5]	610855	*ANKRD26*-related thrombocytopenia MDS Leukemia	AD
ATM[6,7]	607585	Ataxia-telangiectasia Leukemia Lymphoma	AR
		Breast cancer Pancreatic cancer	AD
BLM[8]	604610	Bloom syndrome Leukemia Lymphoma Increased frequency of sister-chromatid exchanges (SCEs)	AR
CBL	165360	Juvenile myelomonocytic leukemia (JMML) Noonan syndrome-like disorder	AD
CEBPA[9]	116897	*CEBPA*-associated AML	AD
DDX41[10]	608170	Adult onset MDS/AML, with or without macrocytosis or other cytopenias Chronic myeloid leukemia (CML) Non-Hodgkin or Hodgkin lymphoma	AD
ELANE[11]	130130	*ELANE*-related neutropenia Congenital or cyclic neutropenia Severe or recurrent infections	AD
ETV6[12,13]	600618	MDS/AML Thrombocytopenia	AD

AD, autosomal dominant; AR, autosomal recessive; X-LR, X-linked recessive

Gene	MIM Number	Inherited Disorder, Hematologic Disease Associations, Cancer Predispositions	Inheritance
		Red cell macrocytosis	
GATA1[14]	305371	*GATA1*-related x-linked cytopenia Thrombocytopenia and/or platelet dysfunction Anemia Mild beta thalassemia Neutropenia Congenital erythropoietic porphyria (CEP)	X-LR
GATA2[15,16]	137295	MDS/AML Cytopenias Chronic myelomonocytic leukemia (CMML) Frequent infections/immunodeficiency Pulmonary alveolar proteinosis Lymphedema Sensorineural hearing loss	AD
KRAS[17,18]	190070	Noonan syndrome Cardiofaciocutaneous (CFC) syndrome Costello syndrome JMML	AD
NBN[7,19]	602667	Nijmegen breakage syndrome (NBS) Aplastic anemia Acute lymphoblastic leukemia (ALL)	AR
		Breast cancer	AD
PTPN11[18]	176876	Noonan syndrome LEOPARD syndrome JMML Metachondromatosis	AD
RUNX1	151385	Familial platelet disorder with associated myeloid malignancy (FPDMM) MDS/AML Thrombocytopenia	AD
SAMD9	610456	MIRAGE Syndrome MDS sometimes accompanied by loss of chromosome 7	AD
		Normophosphatemic familial tumoral calcinosis (NFTC)	AR
SAMD9L[20,21]	611170	*SAMD9L*-related ataxia-pancytopenia syndrome (ATXPC) MDS/leukemia associated with monosomy 7 Somatic revertant mosaicism associated with milder disease Cerebellar ataxia Immunodeficiency	AD

AD, autosomal dominant; AR, autosomal recessive; X-LR, X-linked recessive

Gene	MIM Number	Inherited Disorder, Hematologic Disease Associations, Cancer Predispositions	Inheritance
SRP72	602122	MDS Aplastic anemia/bone marrow failure Hearing loss	AD
TERC[22]	602322	Dyskeratosis congenita Aplastic anemia/bone marrow failure Shortened telomeres Pulmonary fibrosis Somatic revertant mosaicism reported	AD
TERT[22]	187270	Dyskeratosis congenita MDS/AML Aplastic anemia/bone marrow failure Shortened telomeres Cutaneous malignant melanoma Pulmonary fibrosis	AD
		Dyskeratosis congenita (severe)	AR
TP53[7,23]	191170	Li-Fraumeni syndrome (LFS) Leukemia Multiple solid tumors (sarcoma, breast, brain)	AD

AD, autosomal dominant; AR, autosomal recessive; X-LR, X-linked recessive

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Related Information

Acute Myeloid Leukemia - AML
Myelodysplastic Syndromes

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