Hereditary Melanoma Panel, Sequencing and Deletion/Duplication

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Pathogenic germline variants in multiple genes have been implicated in hereditary melanoma. Hereditary melanoma is usually characterized by an early age of cancer onset (typically before age 50), multiple primary melanomas, internal organ malignancies, and/or similar cancers in one or more closely related family members.

Featured ARUP Testing

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, refer to the ARUP Hereditary Cancer Panel Comparison table.

Hereditary Melanoma Panel, Sequencing and Deletion/Duplication 3002673

Method: Massively Parallel Sequencing/Sequencing

- Recommended test to confirm a hereditary cause of melanoma in individuals with a personal or family history of melanoma
- Testing minors for adult-onset conditions is not recommended; testing will not be performed in minors without prior approval. For additional information, please contact an ARUP genetic counselor at 800-242-2787 ext. 2141.

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.

Genetics

Genes

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

Etiology

Less than 10% of melanoma is associated with a hereditary cause.

Inheritance

- Typically autosomal dominant (AD)
- Some genes are associated with an autosomal recessive (AR) transmission

Test Interpretation

Contraindications for Ordering

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

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 [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 (single exon-level or larger) 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.
- Bidirectional Sanger sequencing is performed on the following gene and exon:
  - *PTEN* (NM_000314) 9

Sensitivity/Specificity

Clinical Sensitivity

- Pathogenic variants in the *CDKN2A* gene are identified in 20-40% of families affected by hereditary melanoma.[1]
- The prevalence of other gene variants in hereditary melanoma is uncertain.

Analytic Sensitivity

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 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; MLPA, multiplex ligation-dependent probe amplification; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Limitations

- A negative result does not exclude a heritable form of melanoma or another cancer.
- Diagnostic errors can occur due to rare sequence variations.
- The interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- 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
  - Breakpoints of large deletions/duplications
  - The following exons are not sequenced due to technical limitations of the assay:
    - *MITF* (NM_001354607) exon 2
- The following may not be detected:
  - Deletions/duplications/insertions of any size by MPS
  - Large duplications less than 3 exons in size
  - Noncoding transcripts
  - Low-level somatic variants
  - Certain other variants due to technical limitations in the presence of pseudogenes and/or repetitive/homologous regions
  - The following regions may have reduced sequencing sensitivity due to technical limitations of the assay:
    - *RB1* (NM_000321) exon 22
  - Deletions/duplications in the following exons:
    - *CDKN2A* (NM_000077, NM_001195132, NM_001363763, NM_058195) 2
    - *MITF* (NM_001354607) 2
    - *PTEN* (NM_000314, NM_001304718) 9
    - *PTEN* (NM_001304717) 1,10
    - *RB1* (NM_000321) 22

Genes Tested

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, refer to the ARUP Hereditary Cancer Panel Comparison table.

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
BAP1	603089	*BAP1*-TPDS *BAP1*-inactivated melanocytic tumors, basal cell carcinoma, cutaneous melanoma, malignant mesothelioma, renal cell carcinoma, uveal melanoma	AD
BRCA2	600185	HBOC syndrome Breast, fallopian tube, melanoma, ovarian, pancreatic, peritoneal, prostate	AD
		Fanconi anemia, complementation group D1	AR
CDK4	123829	Cutaneous melanoma, pancreatic[a]	AD
CDKN2A	600160	FAMMM syndrome (also known as melanoma-pancreatic cancer syndrome) Cutaneous melanoma, pancreatic	AD
MC1R	155555	Cutaneous melanoma[a]	AD
MITF	156845	Waardenburg syndrome type II Cutaneous melanoma	AD
POT1	606478	*POT1* tumor predisposition syndrome Angiosarcoma, chronic lymphocytic leukemia, cutaneous melanoma, glioma	AD
PTEN	601728	Cowden syndrome/*PTEN* hamartoma tumor syndrome Breast, colorectal, endometrial, Lhermitte-Duclos disease (cerebellar dysplastic gangliocytoma), melanoma,[a] renal cell carcinoma, thyroid, and others	AD
RB1	614041	Hereditary retinoblastoma Melanoma,[a] osteosarcoma, pineoblastoma, retinoblastoma, retinoma, soft tissue sarcoma	AD
TERT	187270	Dyskeratosis congenita Acute myelogenous leukemia, melanoma,[a] pulmonary fibrosis	AD and AR
TP53	191170	LFS Adrenocortical carcinoma, breast, choroid plexus carcinoma, CNS, colorectal, melanoma, osteosarcoma, pancreas, prostate, renal, rhabdomyosarcoma, soft tissue sarcoma, stomach, thyroid, and others	AD

[a]Association is suggested but not well-established at this time.

BAP1-TPDS, *BAP1* tumor predisposition syndrome; CNS, central nervous system; FAMMM, familial atypical multiple mole melanoma; HBOC, hereditary breast and ovarian cancer; LFS, Li-Fraumeni syndrome

References

1. Rossi M, Pellegrini C, Cardelli L, et al. Familial melanoma: diagnostic and management implications. *Dermatol Pract Concept*. 2019;9(1):10-16.