Melanoma Hereditary Cancer Panel

Indications for Ordering

Confirm suspected hereditary melanoma in individuals with personal or family history of melanoma

Test Description

- Targeted capture of all coding exons and intron/exon junctions followed by massively parallel sequencing
  - Reported mutations are confirmed by Sanger sequencing
- Deletion/duplication analysis by tiled, custom-designed comparative genomic hybridization array

Tests to Consider

Primary test

Melanoma Hereditary Cancer Panel, Sequencing and Deletion/Duplication, 6 Genes 2010209

- Preferred test for individuals at high risk for hereditary melanoma
- Analysis of specific genes included in this panel may be available individually at ARUP
- For test availability and further information, please see ARUP's Genetics site (www.aruplab.com/genetics)

Related test

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Incidence – 77,000 new cases of melanoma diagnosed annually in the U.S.

- ~5-10% hereditary – clusters in families
  - Potential increased risk for additional cancer types, depending on specific gene mutation
  - Individuals with a pathogenic germline mutation have a 50% risk of passing the mutation on to their offspring
- Most melanomas are not caused by germline mutations

Diagnostic issues

- Genetic testing should be offered to individuals with
  - 3 or more diagnoses of melanoma and/or pancreatic cancer in first- or second-degree relatives
  - 3 or more synchronous or metachronous primary melanomas
  - Synchronous or metachronous melanoma and pancreatic cancer

Genetics

Genes – see table for genes tested and for gene-specific information

Inheritance – autosomal dominant for all genes in panel

Mutations

- Large deletions/insertions/duplications account for
  - ~6% of *CDK4* gene mutations
  - ~8% of *PTEN* gene mutations
  - ~18% of *RB1* gene mutations
  - ~3% of *TP53* gene mutations
- These mutations are not identified by sequencing and require deletion/duplication analysis for detection

Test Interpretation

Results

- Positive – one pathogenic gene mutation detected
  - Confirms diagnosis of hereditary melanoma in symptomatic individual
  - Predicts increased risk for hereditary melanoma in asymptomatic individual
- Negative – no pathogenic mutation detected
  - Reduces, but does not exclude, the risk of a hereditary melanoma
- Inconclusive – variants of unknown clinical significance may be identified

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not determined or evaluated
  - Mutations in genes not included on panel
  - Deep intronic and regulatory region mutations
  - Breakpoints for large deletions/duplications
  - Large deletions/duplications in
    - Exon 1 of *BAP1* gene
    - Exon 8 of *PTEN* gene
- Lack of a detectable gene mutation does not exclude a diagnosis of hereditary melanoma
  - Not all predisposing genes are analyzed
- Individuals with hematological malignancy and/or a previous allogenic bone marrow transplant should not undergo molecular genetic testing on peripheral blood specimen
  - Testing of cultured fibroblasts or buccal specimen is required for accurate interpretation of test result

Gene Symbol	Gene Name	NM #	OMIM #	Germline Mutations Increase Risk for the Following Cancer Types (Lifetime Risk as %)	Percentage of Hereditary Melanoma Attributed to this Gene
BAP1	BRCA1-associated protein-1	004656	603089	Mesothelioma; melanoma of the eye	Rare
CDK4	Cyclin-dependent kinase 4	000075	123829	Melanoma	2%
CDKN2A	Cyclin-dependent kinase inhibitor 2A	000077	600160	Melanoma (75%); pancreatic (17%)	20-40%
PTEN	Phosphatase and tensin homologue	000314	601728	Thyroid (35%); breast (85%); renal (35%); colorectal (9%); endometrial (28%); melanoma (>5%)	Rare
RB1	Retinoblastoma	000321	614041	Retinoblastoma; pinealoblastoma; sarcomas; melanoma	Rare
TP53	Tumor protein p53	000546	191170	Li-Fraumeni syndrome; sarcomas; leukemia; breast, brain, adrenocortical, and hepatocellular	Rare