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Test Information Sheet

CDKN2A (p16) and CDK4 Gene Analysis in Familial Melanoma

Also known as: Hereditary dysplastic nevus syndrome; Familial atypical mole-malignant melanoma syndrome (FAMMM); Cutaneous malignant melanoma (CMM); Cutaneous malignant melanoma 1 (CMM1); B-K Mole syndrome

Mendelian Inheritance in Man Number: 155600 (Familial Melanoma); 600160 (CDKN2A gene; also known as p16); 123829 (CDK4 gene)

***Clinical features*:**

It is estimated that about 10% of melanoma is hereditary. Individuals with familial melanoma have a genetic predisposition to develop multiple clinically abnormal, histologically dysplastic, pigmented nevi distributed over both sun-exposed and sun-protected areas of the body. The age of onset tends to be earlier than in individuals with sporadic (non-hereditary) melanoma. Affected individuals also have an increased risk to develop ocular melanoma, and some families show a predisposition to pancreatic cancer.

***Inheritance pattern*:** Autosomal dominant

***Reasons for referral*:**

1. Identification of a hereditary susceptibility to melanoma
2. Development of a clinical surveillance plan to detect suspicious lesions early
3. Genetic counseling
4. Identification of at-risk family members
5. Prenatal diagnosis

***Test method*:**

For genetic testing of the CDKN2A (p16) gene, analysis is performed by bi-directional sequencing of the three coding exons (1-3) and the intron/exon boundaries including the g.-34T promoter mutation. For an additional fee, bi-directional sequence analysis of exon 2 of the CDK4 gene can be performed. Mutations found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

***Test sensitivity*:**

Approximately 20-40% of patients with a hereditary form of malignant melanoma have disease-causing mutations in the CDKN2A (p16) gene (Hayward, 2003; Goldstein et al., 2006). A handful of melanoma patients (~1%) have been identified with mutations in the CDK4 gene (Berwick et al., 2006). Thus, it is very likely that other genes (not yet identified) account for the remaining familial melanoma cases. The testing methodology used by GeneDx is expected to identify >99% of existing small intragenic mutations in the coding exons and promoter region of the CDKN2A (p16) gene and exon 2 of the CDK4 gene.

Mutation spectrum:

Mutations reported in the CDKN2A gene include nonsense and missense mutations, small deletions and insertions. Large deletions of one or more exons of the CDKN2A gene have been reported in association

with familial malignant melanoma (FMM) (Lesueur et al., 2008; Helsing et al., 2008). However, a large study of 124 families with FMM, who were not found to have a mutation in the CDKN2A and CKD4 genes by sequence analysis, failed to identify a large deletion or duplication of the CDKN2A gene by Multi-plex Ligation-dependent Probe Amplification (MLPA) (Vignoli et al., 2008), indicating that large deletions of the CKDN2A gene appear to be a rare cause of familial malignant melanoma. Only a small number of mutations have been reported in the CDK4 gene and all occur in exon 2 (Lesueur et al., 2008).

Specimen Requirements and Shipping/Handling:

- *Blood*: A single tube with 1-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- *Buccal Brushes*: As an alternative to blood, use a GeneDx buccal kit (others not accepted). Submit by mail. Buccal brushes are not accepted on children less than 6 months of age.
- *Prenatal Diagnosis:* For prenatal testing for a known mutation in the CDKN2A and CDK4 genes, please refer to the specimen requirements table on our website at: http://www.genedx.com/test-catalog/prenatal/. Ship specimen overnight at ambient temperature, using a cool pack in hot weather.

Required Forms:

- Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions

For test codes, prices, CPT codes, and turn-around-times, please refer to the "Familial Melanoma" page on our website: www.genedx.com

References Cited:

Hayward NK (2003) Oncogene 22:3053-3062; Goldstein et al., (2006) Cancer Res 66:9818-9828; Berwick et al., (2006) Cancer Epidemiolo Biomarkers Prev 15: 1520-1525; Lesueur et al., (2008) Brit J of Cancer 99:364-370; Helsing et al., (2008) Genes Chromosomes & Cancer 47:175-184; Vignoli et al., (2008) Melanoma Research 18:431-437