OncoGeneDx: Familial Cutaneous Malignant Melanoma

Also known as: Dysplastic Nevus Syndrome, Familial Atypical Multiple Mole Melanoma Syndrome

Panel Gene List: CDK4, CDKN2A

Clinical Features:
In the general population, approximately 1 in 50 individuals (2%) will develop malignant melanoma (MM) in their lifetime (SEER). Several individual factors and exposures, such as fair skin, light hair, freckling, multiple moles, a history of sunburn, excessive ultraviolet light exposure, and sun sensitivity, are important risk factors. While most cases of MM develop sporadically with no family history, approximately 10% of individuals diagnosed with MM have at least one first- or second-degree relative with a history of the disease (Hayward 2003). Of those individuals with familial MM, 10 to 40% are thought to be due to pathogenic germline variants in the CDKN2A gene depending on inclusion criteria (Hayward 2003, Goldstein 2004, Goldstein 2007, Sekulic 2008, Puntervoll 2013). The prevalence of pathogenic germline variants in the CDK4 among familial MM cases is currently unknown, but it is considered to be very low as less than 20 families have been reported in the literature (Puntervoll 2013). It is likely that other, not yet identified, genes are responsible for familial MM in a large proportion of families.

Germline pathogenic variants in CDKN2A are associated with a 20 to 76% lifetime risk for melanoma and approximately a 17% lifetime risk for pancreatic cancer, while germline CDK4 pathogenic variants have been shown to confer a 74% risk of melanoma by the age of 50 (Puntervoll 2013, Begg 2005, Rulyak 2003, Bishop 2002, Vasen 2000). Other cancers also have been reported in individuals with CDKN2A pathogenic variants, including CNS tumors (typically astrocytoma), non-melanoma skin cancers, uveal melanoma, and head and neck cancers (de Snoo 2008, Randerson-Moor 2001), while pancreatic cancer, non-melanoma skin cancer, and breast cancer have recently been observed in families with CDK4 pathogenic variants (Puntervoll 2013). However, the specific risk for developing these cancers in individuals with a CDK4 pathogenic variant has not been established.

Features of familial MM due to CDKN2A and CDK4 pathogenic variants may include, but are not limited to, early onset of disease, increased risk of developing clinically atypical nevi, and multiple primary melanomas (Puntervoll 2013, van der Ree 2011). Individuals with germline pathogenic variants in CDKN2A and CDK4 are often referred to as having Familial Atypical Multiple Mole Melanoma syndrome (FAMMM) due to the presence of one or more first-degree or second-degree relatives with melanoma plus numerous (generally >50) atypical nevi.
CDKN2A encodes two overlapping but distinct proteins, p16 and p14-ARF, both of which act as tumor suppressors involved in cell cycle inhibition through different pathways (Sekulic 2008, Puntervoll 2013). In a series of 466 MM families with CDKN2A pathogenic variants, Goldstein et al. (2006) found that the p16 transcript was much more commonly altered than the p14-ARF transcript. A variety of pathogenic variants have been identified in the CDKN2A gene, including regulatory, splicing and small deletions/insertions, with missense and nonsense pathogenic variants being the most commonly reported. Two to three percent of individuals with familial MM harbor a large gene deletion involving CDKN2A (Lesueur 2008, Goldstein 2006, Mistry 2005). To date, only two pathogenic missense variants, Arg24Cys and Arg24His, have been described in the CDK4 gene; large gene deletions or duplications have not been reported.

Begg et al. (2005) found that individuals who test negative for a previously identified familial CDKN2A pathogenic variant may still have an increased risk for melanoma likely due to multifactorial effects, although their risk is lower compared to individuals with the familial germline pathogenic variant. Additionally, as many cases of familial melanoma will not be explained by a germline pathogenic variant in CDKN2A or CDK4, a negative test cannot be used as reassurance.

**Inheritance Pattern:**
Pathogenic variants in CDKN2A and CDK4 are associated with an autosomal dominant cancer risk.

**Test Methods:**
Genomic DNA extracted from the submitted specimen was PCR amplified and capillary sequencing was performed. The sequencing panel includes analysis of exons 1-3 of the CDKN2A gene (including both the primary (p16) and alternate (p14-ARF) isoforms) and the relevant coding region (exon 2) of the CDK4 gene and their respective flanking splice sites. Bidirectional sequence was obtained and DNA sequence was analyzed and compared to the published reference gene sequence. Concurrent deletion/duplication testing was performed on both genes using either exon-level array CGH or MLPA. Data analysis was performed using gene-specific filtering. The array was designed to detect most single-exon deletions and duplications. Capillary sequencing, MLPA, qPCR, or repeat array CGH analysis was used to confirm any variants with clinical or uncertain significance. If present, apparently homozygous variants were confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. Sequence and copy number analysis are based on human genome build GRCh37/UCSC hg19. Array CGH alterations were reported according to the International System for Human Cytogenetic Nomenclature (ISCN) guidelines. All sequence alterations are described according to the Human Genome Variation Society (HGVS) nomenclature.
guidelines. Benign and likely benign variants, if present, are not reported but are available upon request.

**Test Sensitivity:**
The clinical sensitivity of sequencing and deletion/duplication analysis of the 2 genes included in this test depends in part on the patient’s clinical phenotype and family history. In general, the sensitivity is highest for individuals with features suggestive of hereditary predisposition to malignant melanoma as outlined above. DNA sequencing will detect nucleotide substitutions and small insertions and deletions, while array CGH will detect exon-level deletions and duplications. These methods are expected to be greater than 99% sensitive in detecting pathogenic variants identifiable by sequencing or array CGH. The likelihood of a false positive result is expected to be <1%.

Technical Limitations: Neither sequencing nor exon-level aCGH can reliably detect mosaicism, and cannot detect chromosomal aberrations. Deletions or duplications of less than 250bp are not reliably detected by array CGH. Regions of certain genes have inherent sequence properties that yield suboptimal data, potentially impairing accuracy of the results. False negatives may occur in the setting of bone marrow transplantation, recent blood transfusion, or suboptimal DNA quality. In individuals with active leukemia or lymphoma or with known chronic myeloid or lymphoid neoplasms (such as low grade MDS, CML, ET, P. vera, PMF, CLL), there is a possibility that testing of specimens containing leukocytes may detect an acquired somatic variant, resulting in a false positive result. In this situation, please contact one of our genetic counselors to discuss the utility of submitting an alternate specimen. Additionally, rare false negatives may occur when testing for a variant identified at a laboratory other than GeneDx, if a positive control is not provided. Based on the specific array design and technology used, the reported coordinates of duplications and deletions at the exon or gene level can slightly differ among family members tested but, in general, relatives are expected to have the same copy number variant. The ability to detect genetic variants and naming conventions can differ among laboratories.

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<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Inheritance</th>
<th>Disease Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDK4</td>
<td>CYCLIN-DEPENDENT KINASE 4</td>
<td>AD</td>
<td>Melanoma, Non-Melanoma skin &amp; Pancreatic cancer</td>
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<td>CDKN2A</td>
<td>CYCLIN-DEPENDENT KINASE INHIBITOR 2A, TUMOR SUPPRESSOR ARF</td>
<td>AD</td>
<td>Familial atypical multiple mole melanoma (FAMMM) syndrome: Melanoma &amp; Pancreatic cancer</td>
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</tbody>
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Because of evolving and expanding phenotypes, this list of cancer/tumor types is not exhaustive. Gene-specific risk for some of the cancers and other features listed are not well-defined.

**Abbreviations:**

AD – Autosomal Dominant  
CGH – Comparative genomic hybridization  
MLPA – Multiplex ligation-dependent probe amplification

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References: