

Genetic Testing for Inherited Predisposition To Melanoma: Has the Time Come?

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Inherited, or germline, mutations in either *CDKN2A* or *CDK4*, the two major melanoma susceptibility genes identified to date, confer an increased risk of cutaneous melanoma in carriers. However, only a very small proportion of all melanomas are related to germline mutations in either of these two genes.^{1,2} The majority of individuals within the general population who are predisposed to melanoma are at increased risk for other reasons well established in epidemiologic studies, such as: a family history of melanoma; a personal history of previous melanoma or nonmelanoma skin cancer; an increased number of nevi (common or atypical/dysplastic); immunosuppression; fair skin that burns easily; freckles; blue eyes; red hair, and/or a history of blistering sunburns.

Nonetheless, DNA testing to identify carriers of *CDKN2A* or *CDK4* mutations could ultimately be used for significant clinical care applications, including improved surveillance and increased motivation for sun protection. The question is whether such testing should be adopted yet.

The High-risk Susceptibility Genes: What We Know

Thus far, the most intensely studied variants are mutations in the *CDKN2A* gene, which encodes two cell-cycle regulatory proteins (p16INK4A and p14ARF). Several hundred families with *CDKN2A* mutations have been identified worldwide. The frequency of these mutations varies considerably in different geographic areas around the world, which illustrates the complexity and heterogeneity of melanoma.

Overall, germline mutations in the *CDKN2A* gene have been detected in approximately 20 percent of families from North America, Europe, and Australia with three or more cases of melanoma.^{1,2} The frequency of *CDKN2A* mutations detected is directly related to the number of melanoma patients per family; the frequency increases as the number of melanoma cases in the family increases. For example, for families with only two members who have melanoma, the frequency of mutations detected is <5 percent; for families with three to five affected members, the frequency is 20–40 percent; for families with more than six melanoma cases, the frequency is more than 50 percent.^{2,3}

In contrast, inherited mutations co-segregated with melanoma in the *CDK4* gene are quite rare. Mutations have been reported to date in only three melanoma-prone families worldwide. Thus, although *CDK4* is a melanoma susceptibility gene, it is thought to play an extremely minor role in hereditary melanoma.^{1,2}

Genetic Testing Issues

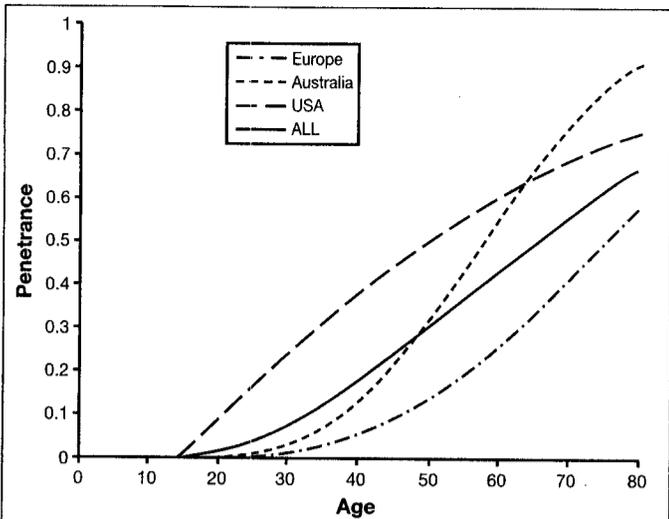
Nonetheless, the identification of these two melanoma susceptibility genes has generated considerable interest in the potential for genetic testing to identify individuals and families that need close surveillance. In 1999, the Melanoma Genetics Consortium, comprised of familial melanoma researchers from North America, Europe, and Australia (accounting for most of the major research groups that have published data on germline mutations in melanoma families), published a consensus statement regarding genetic testing in melanoma-prone families.³ The Consortium's recommendation was that, since the results of such testing could not yet be interpreted adequately, DNA mutation testing for melanoma susceptibility should be performed only in the context of clinical research, and the results should not influence the medical management of a patient or family member.³ The Consortium's recommendation was consistent with the American Society of Clinical Oncology's consensus statement regarding cancer predisposition testing.⁴

In 2002, the Consortium published a study of the penetrance (the proportion of individuals of a particular genotype that express its phenotypic effect over time) of *CDKN2A* mutations in 80 families from Australia, U.S., and Europe, providing the most informed estimates of melanoma risk available.⁵ The families all had *CDKN2A* mutations and at least two cases of melanoma. Overall, *CDKN2A* mutation penetrance reached 30 percent by age 50 and 67 percent by age 80. (See figure.) Due to the availability of this new penetrance data,⁵ and the active promotion of commercially available DNA testing for *CDKN2A* mutations, the Consortium reevaluated its recommended guidelines.⁶ It concluded once again that genetic testing for melanoma susceptibility remains of limited clinical utility, for the following reasons:

- Most melanoma families will not have a *CDKN2A* mutation detected;
- The estimates of lifetime penetrance of *CDKN2A* mutations vary widely by locality (see figure), consistent with the variation in general population rates, suggesting that factors affecting general population rates (e.g., ambient ultraviolet radiation and the influence of other genetic and/or environmental factors) also affect risk in mutation carriers;
- Individuals from families with *CDKN2A* mutations who test negative for *CDKN2A* mutations may feel a false sense of security related to their melanoma risk, since there is evidence suggesting that even non-carriers in families with *CDKN2A* mutations may have a higher incidence of melanoma than the general population does.

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Estimated Age-Specific Penetrance Estimates For CDKN2A Mutations. Penetrances are shown for the total set of 80 families studied by the Melanoma Genetics Consortium, assuming the same penetrance of mutations in: all geographic locations (ALL); families living in Australia (Australia); families living in France, Italy, the Netherlands, or the United Kingdom (Europe); and families living in the United States (USA). Reproduced with permission.⁵

Genetic Testing Recommendations

In summary, after reevaluating current information, the Melanoma Genetics Consortium concluded that until significant advances are made in our understanding of the phenotypic expression of melanoma susceptibility genes both in families and in the general population, it is premature to offer DNA testing for *CDKN2A* mutations in families, or in individuals with multiple primary melanomas, outside of well-defined clinical research protocols. DNA testing should be offered for clinical care purposes only in exceptionally rare circumstances, and only after careful genetic counseling that adequately addresses the low likelihood of finding mutations, the current uncertainties about the penetrance of mutations, the potential benefits and risks of positive and negative results of genetic testing, and the lack of evidence-based melanoma prevention and surveillance strategies, even for mutation carriers.^{1-3, 5-7}

Genetic testing for clinical care purposes might potentially be offered in government-funded health care systems outside of the U.S., where different issues and approaches to care delivery arise. For example, in countries of low melanoma incidence, or in those where founder mutations (whose carriers are all descendants of a single ancestor or founder) are prevalent and thus contribute substantially to the familial clusters,^{8,9} DNA testing to identify mutation carriers may improve compliance (in those identified) with practicing sun protection and undergoing surveillance.

Currently, the gold standard for determining melanoma risk

is through clinical evaluation.⁶ Thus, all individuals considered to be at high risk of melanoma should be managed based on their individual melanoma risk factors well established through clinical and epidemiologic studies.

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disease suggest that melanoma is an important early target for the investigation of novel BRAF-based therapies.

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