Familial skin cancer syndromes

Increased melanoma risk

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Learning objectives
After completing this learning activity, participants should be able to describe the appropriate screening of patients at risk for inherited melanoma risk; list resources for ordering genetic tests for patients who are at increased risk for melanoma; and develop an appropriate management plan for patients with a germline predisposition to melanoma.

Disclosures
Editors
The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Authors
The authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Planners
The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Phenotypic traits, such as red hair and freckling, increase melanoma risk by 2- to 3-fold. In addition, approximately 10% of melanomas are caused by inherited germline mutations that increase melanoma risk from 4- to >1000-fold. This review highlights the key genes responsible for inherited melanoma, with an emphasis on when a patient should undergo genetic testing. Many genetic syndromes associated with increased melanoma risk are also associated with an increased risk of other cancers. Identification of these high-risk patients is essential for preventive behavior reinforcement, genetic counseling, and ensuring other required cancer screenings. (J Am Acad Dermatol 2016;74:423-34.)

Key words: genetics; genetic syndromes; inherited cancer risk; melanoma; oncogenes; skin cancer; tumor suppressor.

INTRODUCTION

Key points

- **Hereditary melanomas account for 5% to 12% of all melanoma cases**
- **Individuals with hereditary melanoma may have an increased risk of internal cancers, such as pancreatic cancer or central nervous system tumors**
- **Clinical criteria for genetic testing include both individual and family factors**
- **Individuals with a strong family history of melanoma are still at increased risk of melanoma regardless of whether they are found to carry a known melanoma-associated mutation**

Malignant melanoma (MM) represents only 5% of all new skin cancer diagnoses but accounts for the majority of skin cancer deaths.[1] MM incidence is rising worldwide, contributing to a significant

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Funding sources: Supported by a Stanford University Medical Scholars Research Fellowship (Ms Jaju) and the Howard Hughes Medical Institute (Ms Ransohoff).
Dr Leachman has collaborated with Myriad Genetics Laboratory. All other authors have no conflicts of interest to declare.

Accepted for publication September 19, 2015.

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0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2015.09.070
Date of release: March 2016
Expiration date: March 2019

Abbreviations used:

ACD:	adrenocortical dysplasia homologue
BAP1:	BRCA1-associated protein-1 (ubiquitin carboxy-terminal hydrolase)
CDKN2A:	cyclin-dependent kinase inhibitor 2A
CDK4:	cyclin-dependent kinase 4
LFS:	Li–Fraumeni syndrome
MM:	malignant melanoma
MCR1:	melanocortin 1 receptor
MITF:	microphthalmia-associated transcription factor
POT1:	protection of telomeres 1
PTEN:	phosphatase and tensin homolog
TERT:	telomerase reverse transcriptase
TERF2IP:	telomeric repeat binding factor 2, interacting protein
UV:	ultraviolet
XP:	xeroderma pigmentosum

health care burden.[1] In addition to environmental exposures and phenotypic traits, such as nevus count, red hair, and freckling, heritable genetic risk factors can contribute significantly to MM risk in affected individuals.[2] An estimated 5% to 12% of all worldwide melanomas are estimated to be caused by inherited, high-penetrance, germline mutations, each with distinct clinical hallmarks (Table I).[3]

Genetic alterations typically increase cancer risk via 3 major mechanisms: the activation of oncogenes, the loss of tumor suppressor genes, or increased chromosomal instability.[4] In oncogene activation, a mutation in 1 copy of a gene creates a constitutively active protein, promoting cell proliferation.[4] Most oncogene-related cancer syndromes are inherited in an autosomal dominant manner or occur sporadically, as is the case with gain of function mutations in the proto-oncogene *RET*, which leads to development of the multiple endocrine neoplasia syndromes.[5]

Tumor suppressor genes encode proteins that function normally to limit cellular growth. The inactivation of tumor suppressors via epigenetic silencing or genetic alterations leads to misregulation of the cell cycle.[4] Many patients with inherited cancer risk harbor a germline mutation (ie, an embryonic mutation present in all cells of the body) leading to the loss of a tumor suppressor gene. If a second mutation occurs in the remaining wild type allele (ie, the normally functioning second copy of the gene), or if the mutation creates a dominant negative (ie, nonfunctional competitor) protein, cell growth is uninhibited and can therefore drive tumor development. Examples of tumor suppressors that lead to cancer risk syndromes include *CDKN2A* (Fig 1) and *CDK4* (inherited melanoma; Fig 2). In the case of *CDKN2A*, the downstream products control the transition between the growth (G_1) and synthesis (S) phases of the cell cycle, during which DNA replication occurs and a cell continues to grow and divide.

The third category of inherited genetic cancer risk factors is those involved in DNA repair and stability. Inactivation of these genes, such as *BRCA1* or *BRCA2*, increases the mutational rate of a cell and predisposes an individual to breast and other cancers.[6] This article focuses on genetic syndromes that increase the risk of cutaneous MM, with mention of those that also increase ocular melanoma. The second article in this series focuses on genetic syndromes that increase the risk of nonmelanoma skin cancer.

MELANOMA-PREDOMINANT SYNDROMES

Key points

- **Hereditary melanoma is an autosomal dominant group of disorders**
- **Inherited mutations in *CDKN2A*, *CDK4*, *POT1*, and *TERT* confer a 60% to 90% lifetime risk of melanoma**
- **Testing criteria in areas of high melanoma incidence, such as Australia or the United States, include individuals with ≥3 primary MMs or a family history of ≥2 MMs or pancreatic cancer**
- **In areas of low/moderate incidence, such as the United Kingdom, testing is indicated in individuals with ≥2 primary melanomas or a family history of ≥3 MMs or pancreatic cancer**

Hereditary melanoma

Hereditary melanoma (also called familial atypical multiple mole syndrome) is an autosomal dominant group of disorders characterized by the presence of hundreds of dysplastic nevi and an increased risk of melanoma. Genetic alterations associated with hereditary melanoma syndrome include the tumor suppressors *CDKN2A* and *CDK4* and the telomerase complex proteins telomerase reverse transcriptase (*TERT*), and protection of telomeres 1 (*POT1*; Table I).

Epidemiology and evaluation. Familial clusters of melanoma have been identified worlwide.[7] In individuals with a strong personal or family history of melanoma (ie, ≥3 individual melanomas in different blood relatives), the likelihood of finding a mutation associated with MM can be as high as 30% to 40%. In contrast, the likelihood of finding a germline mutation in families with a single melanoma is ≤1%.[7-10] Unlike breast cancer, the young age of onset of melanoma is not considered a reliable criterion for