Hereditary melanoma: Update on syndromes and management

Genetics of familial atypical multiple mole melanoma syndrome

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Learning objectives
After completing this learning activity, participants should be able to describe algorithms used to assess patients with possible familial atypical mole melanoma syndrome (FAMM); explain the genetic basis of FAMM predisposition, in light of novel susceptibility genes identified recently in genomic studies; discuss the current role of genetic counseling in patients with FAMM and their relatives; and determine when patient referral to other specialists for FAMM is appropriate.

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Malignant melanoma is considered the most lethal skin cancer if it is not detected and treated during its early stages. About 10% of melanoma patients report a family history of melanoma; however, individuals with features of true hereditary melanoma (ie, unilateral lineage, multigenerational, multiple primary lesions, and early onset of disease) are in fact quite rare. Although many new loci have been implicated in hereditary melanoma, *CDKN2A* mutations remain the most common. Familial melanoma in the presence of multiple atypical nevi should raise suspicion for a germline *CDKN2A* mutation. These patients have a high risk of developing multiple primary melanomas and internal organ malignancies, especially pancreatic cancer; therefore, a multidisciplinary approach is necessary in many cases. The value of dermoscopic examination and total body photography performed at regular intervals has been suggested by a number of studies, and should therefore be considered for these patients and their first-degree relatives. In addition, genetic counseling with the possibility of testing can be a valuable adjunct for familial melanoma patients. This must be performed with care, however, and only by qualified individuals trained in cancer risk analysis. (J Am Acad Dermatol 2016;74:395-407.)

Key words: *CDK4*; *CDKN2A*; familial melanoma syndromes; FAMMM; melanoma genetics; mixed cancer syndromes.

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GENERAL CONSIDERATIONS FOR HEREDITARY MELANOMA

Key point

- **Hereditary melanomas can appear as part of a familial melanoma syndrome or a mixed cancer syndrome**

Cutaneous malignant melanoma (CMM) can be highly lethal if it is not detected and treated during its early stages. The incidence of melanoma has increased in the past several decades. In developed countries, CMM is the sixth most common cancer, accounting for >47,000 deaths worldwide annually (45% occurring in Europe). The rise in incidence affects both young and older populations, while the global projected incidence of melanoma for the year 2025 is estimated to be 317,000 new cases compared to the 200,000 cases reported in 2008.[1]

About 7% to 15% of melanoma cases occur in patients with a family history of melanoma; however, this does not necessarily indicate that a single genetic mutation is being transmitted in those kindreds.[2] Most cases of familial melanoma are caused by shared sun exposure experiences among family members with susceptible skin types.[2] In aggregate, about 45% of familial melanomas are actually associated with germline mutations in *CDKN2A* or *CDK4*. There does not appear to be another major locus beyond *CDKN2A*, because the prevalence of the new melanoma predisposition genes are quite rare (see part II of this continuing medical education article). Although great strides have been made in identifying other novel cosegregating variants within melanoma kindreds, it is likely that many rare disease—causing mutations remain undiscovered.[3] The term mixed cancer syndrome (MCS) can be applied to familial conditions for which there is a high incidence of various cancers in general, including melanoma. In the past few years, melanomas have also been found to arise in families that are generally prone to specific patterns of malignancies. The term melanoma tumor syndrome might be more appropriate to discriminate it from hereditary melanoma, where the dominant cancer phenotype is that of CMM.

FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA (OMIM 155601) AND FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA—PANCREATIC CANCER (OMIM 606719) SYNDROMES

Key point

- **A positive association between melanoma, multiple nevi, pancreatic cancer, and *CDKN2A* mutations is now well established**

The first documented case of familial melanoma was reported by Norris[4] in 1820; his patient was a 59-year-old man with melanoma, a high total body nevus count, and a family history of melanoma. More than a century after Norris made his observations, Lynch and Krush[5] described familial atypical multiple mole melanoma (FAMMM) syndrome, which comprised an association between pancreatic cancer (PC), multiple nevi, and melanoma. Contemporaneously, Clark described a similar phenotype, B-K mole syndrome, consisting of familial melanoma in the setting of numerous atypical nevi.[6] In the early 1990s, several groups reported germline mutations in the cell cycle gene *p16* (now *CDKN2A*) among a subset of FAMMM kindreds.[7,8]

CLINICAL FEATURES OF FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA SYNDROME

Key points

- **Patients suspected to have FAMMM present with multiple atypical nevi (>50) and have a positive personal or family history of melanoma**
- **Patients with FAMMM present with melanomas at a younger age and are at a higher risk to develop a second primary melanoma compared to the general population**
- **Patients with FAMMM may also develop cutaneous melanomas on normal skin in spite of the large number of atypical nevi at presentation**

FAMMM is a clinical phenotype comprised of numerous nevi (Fig 1, *A*), some atypical, and a family history of melanoma; some diagnostic elements of the FAMMM phenotype are outlined in Table I. Documenting a thorough family history of cancer, particularly melanoma, is of utmost importance because it is a critical element of FAMMM syndrome. Particular attention should be paid to the age at which CMM and other cancers (Table II) have been diagnosed in family members—as well as family skin phototype (ie, red hair and fair skin)—because these traits may be associated with higher disease risk.[9] In patients suspected of having FAMMM, careful examination of all nevi should be performed not only on the patient of interest but also their first- and second-degree relatives.

Nevi in patients with FAMMM are phenotypically diverse (Fig 1, *A*). It is not unusual to observe multiple nevi with marked atypia, some bearing a striking resemblance to melanoma, interspersed between numerous benign-looking nevi. Atypical nevi