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Hereditary Melanoma: Update on Syndromes and Management - Genetics of familial atypical multiple mole melanoma syndrome

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Abstract

Malignant melanoma is considered the most lethal skin cancer if not detected and treated at its early stages. About 10% of melanoma patients report a family history of melanoma; however, individuals with features of true hereditary melanoma (i.e. unilateral lineage, multi-generational, 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. Such patients have a high risk of developing multiple primary melanomas and internal organ malignancies especially pancreatic cancer; thus, a multidisciplinary approach is necessary in many cases. The value of dermoscopy 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. But, this must be performed with care and only by qualified individuals trained in cancer risk analysis.

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1.1. General Considerations for Hereditary Melanoma

Cutaneous malignant melanoma (CMM) can be highly lethal if it is not detected and treated at early stages. The incidence of melanoma has increased during the past several decades. In developed countries, CMM is the 6th most common cancer accounting for more than 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 7–15% 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 due to 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*, as the prevalence of the new melanoma predisposition genes are quite rare (see Part 2). Although great strides have been made in identifying other novel co-segregating variants within melanoma kindreds, it is likely that many rare disease-causing mutations remain undiscovered.[3] The term “mixed cancer syndromes” (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. Thus, the term “melanoma tumor syndromes” might be more appropriate to discriminate it from hereditary melanoma, where the dominant cancer phenotype is that of CMM.

1.2. Familial atypical multiple mole-melanoma (FAMMM; OMIM 155601) and FAMMM-Pancreatic Cancer (FAMMM-PC; OMIM 606719) syndromes

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

1.2.a. Clinical features of FAMMM

FAMMM is a clinical phenotype comprised of numerous nevi (Figure 1a), some atypical, and a family history of melanoma; some diagnostic elements of the FAMMM phenotype are outlined in Table 1. Documenting a thorough family history of cancer, particularly melanoma, is of utmost importance as it is a critical element of the FAMMM syndrome. Particular attention should be paid to the age at which CMM and other cancers (Table 2) have been diagnosed in family members, as well as family skin phototype (i.e. red hair/fair skin) since these traits may be associated with higher disease penetrance.[9] In those 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 (Figure 1a). It is not unusual to observe multiple nevi with marked atypia, some bearing a striking resemblance to melanoma, interspersed between numerous benign-looking nevi. While, atypical nevi are more likely to undergo malignant transformation when compared to banal nevi; melanomas in FAMMM patients, however, often develop on normal skin.[10, 11]

While it is clear that patients with FAMMM syndrome have a dramatically increased risk of melanoma, it is less clear whether there are inherent differences between FAMMM-associated and sporadic melanomas. Patients with FAMMM seem to be more prone to developing superficial spreading and nodular melanomas,[12] which is interesting in light of other findings that suggest *CDKN2A*-mutant CMMs are significantly less invasive (lower Clark levels) than *CDKN2A*-wild-type CMMs.[13] No statistically significant differences in location and Breslow thickness have been reported between sporadic melanoma controls and FAMMM patients. Sargen et al. have recently reported that *CDKN2A* mutation positive CMMs tend to possess histologic features compatible with superficial spreading melanomas, including higher pigmentation (Ptrend = 0.02), increased pagetoid scatter (Ptrend = 0.07) and a non-spindle cell morphology in the vertical growth phase.[14] However, more information is required in order to establish specific histopathologic features indicative of a CMM from a *CDKN2A* mutation positive patient. Gillgren et al. found that familial melanomas have a tendency to occur on the trunk more so than on the head and neck.[15] Recent studies have shown similar rates of somatic *BRAF* and *NRAS* mutations in patients with or without germline *CDKN2A* mutations. Zebary et al. reported that *BRAF* and *NRAS* mutations occurred in 43% and 11% of CMMs, respectively, in *CDKN2A* mutation carriers, compared to 39% and 14% of CMMs in non-*CDKN2A* mutation controls[16]; similar findings are echoed by others.[17] The pattern of metastasis between familial and sporadic melanoma patients does not appear to differ so a distinct post-melanoma follow-up program is probably not necessary for FAMMM patients.[18] However, as will be discussed below, the risk of pancreatic cancer among some patients with FAMMM does warrant special consideration.

An example of a typical FAMMM pedigree is shown in Figure 1b. The proband presented with multiple atypical nevi (>200) and has had more than 10 histologically-confirmed CMMs. Her mother developed pancreatic cancer at age 63 and succumbed to the disease. Genetic testing revealed a single base pair deletion (c.132delC) which was shared by both the proband and the mother. The key elements of FAMMM are embodied in this pedigree-

early age of onset (age 22), multiplicity of CMMs (n=12), family history of melanoma, dysplastic nevi and pancreatic cancer and a documented deleterious co-segregating mutation on one side of the family.

1.2.b. The Genetics of FAMMM

The dominant molecular pathway involved in FAMMM is shown in Figure 2. Xeroderma pigmentosum is an extremely rare condition and as such will only be discussed briefly. The *CDKN2A* gene is located on chromosome 9p21.3 and its alterations are most commonly associated with FAMMM syndrome. Typically, germline mutations of *CDKN2A* seen in CMM and pancreatic cancer (PC)-prone kindreds are missense or nonsense mutations that impair the inhibitory functions of p16 and/or p14ARF. *CDKN2A* is comprised of 4 exons (1α, 1β, 2 and 3) which are used to encode for two proteins- p16 (1α, 2 and 3) and p14ARF (exons 1β, 2 and 3). p16 inhibits cyclin-dependent kinase (CDK) 4 and CDK6, thereby preventing the phosphorylation of retinoblastoma protein (RB1). A hypophosphorylated RB1 molecule sequesters and prevents the transcription factor E2F1 from inducing S-phase genes and triggering G1-to-S transition. On the other hand, p14ARF antagonizes HDM2, which ubiquitinates the tumor suppressor, p53, thereby condemning p53 for proteasomal degradation.[19] Accelerated destruction of p53 abolishes the normal DNA damage and G2 checkpoint responses.[19] Therefore, inactivation of the *CDKN2A* locus enhances proliferation and reduces apoptosis. The prevalence of germline *CDKN2A* mutations has been found to vary with geography and the family context.[3, 20, 21] In a meta-analysis by Goldstein and colleagues, 39% of families (with ≥3 affected) had germline *CDKN2A* mutations, ranging from 20% (32/162) in Australia to 45% (29/65) in North America to 57% (89/157) in Europe.[22] Similarly, in a study of Greek families, Nikolaou et al. reported that 22% of familial melanoma cases and 57% of individuals with multiple primary melanomas carried a *CDKN2A* mutation.[23] When melanoma cases were ascertained independent of family history, there was a much lower rate of mutation. The frequency of *CDKN2A* mutations in patients with a single primary melanoma or multiple primary melanomas were 1.2% and 2.9%, respectively.[24] The likely explanation is that other co-inherited modifiers (e.g. additional risk conferring variants mutations) exist in a pedigree or that select members of some families share extremely high levels of sun exposure histories.

CDKN2A mutation penetrance (or the likelihood of developing melanoma over time) also varies by geography. The estimated penetrance rates are 30–91%, 50–76%, and 13–58% among patients ages 50–80 in Australia, the United States, and Europe, respectively. These broad risk differences could also be attributed to different sun exposure patterns and the presence of other genetic risk factors in the families.[25, 26] For instance, co-inheritance of melanocortin 1 receptor (MC1R) variants and specific interleukin-9 and glutathione S-transferase theta 1 variants have been described as risk modifiers for *CDKN2A*-mutation penetrance.[9, 27, 28] In a population-based study, Begg et al. found that the estimated risks of CMM among *CDKN2A* mutation carriers were 14%, 24% and 28% by ages 50, 70 and 80 years, respectively;[29] the lower risk estimates may reflect the lack of other melanoma-risk variants in these sporadic cases.

Various studies have also demonstrated a much lower median age of onset of CMM in patients from germline *CDKN2A* mutation families (33–45 years) compared to patients without a *CDKN2A* mutation (53–61 years); this trend remains largely consistent irrespective of a geographic region.[3, 30, 31] There are reports of *CDKN2A* kindreds where CMM has occurred in the early teens and twenties.[20] As would be expected, the increased risk of CMM in these patients does not diminish with their first diagnosis as they also have a much higher 5-year cumulative incidence of a second melanoma compared to mutation-negative controls (23.4% and 2.3%, respectively).[32]

Germline *CDK4* mutations have also been described in the FAMMM syndrome, albeit rarely.[33–35] As alluded to above, CDK4, which is the target for p16 inhibition, plays an important role in normal cell cycle progression (Figure 2). The oncogenic CDK4 mutations described in affected families translates into a substitution of arginine-24, which disrupts p16 binding.[35] Puntervoll et al. have reported an increased CMM risk in 17 families from 8 different countries that harbor *CDK4* mutations. Out of 103 patients with one CMM, 41.7% developed a second primary CMM, and 21.1% developed CMM before the age of 30 (median age 39 years). Furthermore, 70–75% of patients exhibited multiple atypical nevi, which was considered to be a modifier for CMM risk, since these patients developed CMMs at a younger age.[36] This study investigated the clinical phenotype of these *CDK4*-mutant melanoma families and determined that it is indistinguishable from the more well characterized *CDKN2A*-mutant melanoma phenotype, i.e. high burden of atypical nevi, early age of disease onset, and predilection for multiple primary melanoma.[36] Since p16 directly interacts with CDK4, it is not surprising that the two phenotypes overlap significantly; in essence, the same biochemical event (increased RB phosphorylation) occurs with either mutation (Figure 2).

1.3. Melanoma-Astrocytoma Syndrome (OMIM 155755)

Melanoma-Astrocytoma Syndrome (MAS) is a variant of FAMMM that may be more linked to the loss of $p14^{ARF}$ function.[37] Larger scale chromosome 9p21 alterations (including deletions involving the *CDKN2A*/*CDKN2B*/*CDKN2BAS* gene cluster up to the MLLT3 gene) have been described in some isolated cases.[38–41] Kaufman et al. described this syndrome in 1993 when they reported concurrent CMMs and multiple types of nervous system tumors (NSTs) in eight members of a family over three generations.[42] Later, Azizi et al. reported that 17 individuals with CMM, among 15 families, had one or more additional relatives with tumors of the nervous system.[43] Conflicting data exist on this very rare syndrome. Generally patients are young (age <30) and can develop CMM either before and after the NSTs.[38–40, 44] A positive association between radiotherapy for the NSTs and the incidence of CMM in these patients has been proposed, but remains unsubstantiated.[41]

1.4. Management of FAMMM patients including *CDKN2A* carriers

The significant risk of melanoma inherent to the FAMMM syndrome means that these patients need heightened dermatologic surveillance. Some general management considerations for patients with hereditary syndromes is presented in Table 3. It must be mentioned that given the rarity of melanoma syndromes, most data regarding follow-up

recommendations are mainly based on small studies or expert opinion. Given the plethora of clinically atypical moles, dermoscopy is an important tool in approaching patients with FAMMM. It is also prudent for children from FAMMM kindreds to undergo routine skin examinations from late adolescence (Level of evidence: IV). This recommendation is supported by observational studies showing that FAMMM patients tend to develop melanomas at much younger ages. Surveillance of FAMMM patients should entail an extensive baseline total body skin examination (TBSE), including the scalp, oral mucosa, genital area, and nails. Most authors suggest that screening performed at 6 month intervals are adequate[10, 20, 45, 46] although formal prospective trials of outcome do not exist (Level of evidence: IV). Haenssle et al. have reported that patients with FAMMM may develop up to 1 new melanoma every 3 years of follow-up and suggest that 3 month interval examinations may be more appropriate.[47] At this point, though, there are no data supporting that 3 month interval examinations may be superior to 6 month interval examinations regarding patient outcomes. (Level of evidence: IV). Nevi should be checked for any changes in morphology (e.g. color or symmetry) and size. Since these patients may have many atypical nevi, lesions that stand out, exhibiting the so called “ugly duckling sign,” may warrant special attention. Beyond a thorough TBSE, the utility of more advanced techniques, such as total body photography (TBP) and sequential digital dermoscopy imaging (SDDI), for patients at extreme risk for melanoma has also been suggested[48] although the adoption of these procedures may be limited by practice logistics. Moloney et al. reported that in 311 high-risk patients evaluated at 6 month intervals, 38% of post-baseline melanomas were detected using TBP and 39% with SDDI. Importantly, these tools allowed for earlier detection and treatment, which are known to impact melanoma outcome.[49] In the Moloney study, most of the excised melanomas were categorized as in situ tumors, and the ratio of benign to malignant excised lesions was reported to be 1.6:1.[49] In addition, Rademaker et al. have reported that the melanomas diagnosed in patients after TBP and SDDI examination where thinner compared to those diagnosed with clinical inspection. (69% <0.75 mm Breslow thickness compared to 52%, p=0.0216).[50] Previous studies have also advocated the benefit of TBP in earlier diagnosis of melanoma.[51, 52] An interesting point, though, is that these studies do not report patient outcomes, and thus their impact on patient survival is unknown. Also, the recommendations supported by those studies depend on the notion that earlier recognition of melanomas may lead to an overall better patient outcome. A small number of studies have reported evidence to support this.[53] However, the exact frequency of follow up (follow up at 3 month, 6 month or 1 year intervals) is not clear. When planning follow up visits for high risk patients, two factors must be weighted: one is the psychological burden of having to be examined at specific intervals and the other is the cost-effectiveness of this process. Risser et al reported that the number of biopsies performed for patients undergoing TBP and clinical inspection was the same. Therefore, the cost-effectiveness of TBP use is questionable.[54] It must be mentioned, though, that patients selected for TBP belong to high risk groups. In addition, the decision to perform a biopsy of a suspicious lesion after TBSE, is taken mostly due to nevus morphology at the time of examination, while TBP relates to morphologic changes over time (i.e. morphology changing from previous examination).[55] Therefore, in theory, melanomas could be diagnosed earlier if TBP is used. In a recent study by Watts et al. a cost analysis of the surveillance of high risk melanoma patients was done. It was concluded that although these patients are indeed more costly to follow-up, it is overall

cheaper to screen than having to later treat a stage IV melanoma. It is important though to find a golden rule where cost and patient benefit are perfectly balanced.[56] Patients must be encouraged and taught to perform self-examination at regular intervals either alone, or with the assistance of a spouse or relative. Furthermore, routine sun protective behaviors must be reinforced at every visit. Screening, of all family members of FAMMM kindreds should be encouraged. Preemptive removal of observable stable or benign-appearing nevi is not recommended since the practice has not been shown to reduce melanoma risk meaningfully and is associated with increased morbidity and costs. (Level of evidence: IV) Isolated lesions which are visually inaccessible to the patient (such as mid lower back or scalp) may be removed prophylactically.

The association between pancreatic cancer (PC) and FAMMM syndrome is well documented, with an estimated risk 13–22 times higher than that of the average population; this risk increases to 38 fold in *CDKN2A*-mutant FAMMM patients.[20, 57, 58] Pancreatic cancer seems to be the second most commonly observed malignancy in FAMMM patients harboring a *CDKN2A* mutation.[3, 59] In a study by Goldstein et al. it was reported that PC was observed in 28% of *CDKN2A*-mutant families compared to only 6% of *CDKN2A*-wild-type families. Conversely, 74% of families with PC harbored a *CDKN2A* mutation compared to 33% of "melanoma only" families.[3] Another study estimated that 17% of *CDKN2A*-mutant patients would develop PC by 75 years of age.[60] In general, the mean age of onset for PC ranges from 65–71 years.[20, 45, 61] It is unclear whether the age of onset for PC is lower for patients with FAMMM compared to sporadic cases. Various studies on this topic have reported mixed data, with only one study by James et al. showing a statistically significant difference in age of PC diagnosis between the two groups. Of note, smoking was a strong confounding factor in this study.[61, 62] Evidence regarding the association of FAMMM and other cancers is more equivocal. Associations with digestive tract, breast, and respiratory tract cancer, among others, have been described; however, *CDKN2A* mutation status does not seem to influence the age of onset in these cancers.[20, 59, 60, 63]

The role of genetic testing for hereditary melanoma has been somewhat controversial since dermatologic management of individuals with familial melanoma (i.e. surveillance, sun protection education) rarely requires knowledge of the patient's *CDKN2A* status. However, as alluded to above, the melanoma phenotype may be a window to a latent PC risk. Thus, a basic understanding of genetic risk assessment and counseling is worthwhile though referral to a genetic counselor for more formal evaluation is preferred especially given the time constraints of a busy dermatologic practice. The following are just a sampling of some fundamental discussion points (also outlined in Figure 3).

[1]. Does my patient have hereditary melanoma?

The individual seeking counseling is known as the "proband." Currently, there are no firm criteria that would allow easy diagnosis of a proband with "hereditary melanoma." Some have adopted the "rule of 3′s,"[64] i.e. one individual with invasive CMM along with 2 additional members with either CMM and/or PC on one side of the family OR one individual with 3 primary CMMs. One caveat is that severely photodamaged patients may develop 3 melanomas especially later in life as sun damage accumulates. One perhaps

slightly more stringent practical criterion would be a “3 by 40” modification where individuals with 3 CMMs diagnosed before age 40 may be more likely to be under genetic influences.

The benefit of formal genetic counseling is the analysis of an in-depth ≥3-generation pedigree. Although dermatologic charts may document a family history of melanoma, other critical information may not be ascertained. For instance, 3 melanoma cases in a small pedigree is different than 3 melanoma cases in a large extensive pedigree. The age of onset, current age and other concurrent non-melanoma cancers all contribute to the final interpretation of hereditary melanoma or mixed cancer syndrome. The presence of pancreatic cancer in a kindred is also important in assessing genetic risk. Formal training is typically required for accurate pedigree acquisition, and a full family history essential to accurate risk assessment.

[2]. What are the possible genes to be tested?

To understand genetic testing, fundamental principles of genetics must first be reviewed. Hereditary melanoma, like nearly all cancer syndromes, with the exception of xeroderma pigmentosum, is autosomal dominant.[19] Thus, there is a 50% chance of sharing a mutation among 1st degree relatives. The major locus to be considered in a patient with FAMMM syndrome is *CDKN2A* although a small percentage (<1%) of FAMMM patients also harbor *CDK4* mutations. In addition, there are likely many other unknown predisposing loci. Therefore, the first important message is that *CDKN2A* will be normal in a majority of individuals suspected of having FAMMM especially in high melanoma incidence areas like the United States. This is because there are environmental factors and other genetic factors (whether they be dominant genes or polygenetic factors) which have yet to be discovered.

[3]. Who is likely to be a carrier?

Phenotypically, the presence of multiple atypical nevi is not enough for the diagnosis of FAMMM though some it has been published that their presence in family members correlates with a three-fold higher likelihood of carrying a genetic mutation.[33] It is important to note, however, that the presence of atypical nevi is not a carrier signature as non-carriers even in *CDKN2A*-mutated families, can exhibit multiple atypical moles. Thus, there is a complex relationship between melanomas and atypical, or dysplastic, nevi. Two statistical models have been developed in order to assist in identifying *CDKN2A*-mutation bearing individuals or families. MELPREDICT is based on logistic regression while MelaPRO (which can be obtained as part of CancerGene-https://www4.utsouthwestern.edu/breasthealth/cagene/) incorporates three different penetrance models (Bayes-Mendel algorithm).[31, 32] These models provide a probability of mutation carriage for any given proband (MELPREDICT) or family member (MelaPRO) based on the family cancer pattern. Cancer risk counselors usually have access to MelaPRO as other similar algorithms, such as BRCAPRO for determining BRCA1/2 carrier risk, have been part of the counseling practice.

[4]. What are the possible results?

The identification of a deleterious *CDKN2A* mutation (“positive result”) establishes a disease-causing mutation in the kindred. First degree relatives (parents, siblings, children)

will have a 50% chance of harboring the same mutation and risk. Since the penetrance is never 100%, there will be carriers in family who may not develop melanoma although the risk will be substantially higher than population rates. If unaffected relatives undergo subsequent testing and are found to have a normal *CDKN2A*, their risks may still elevated because of other risk factors, such as an MC1R variant or excessive sun exposure. However, a non-carrier will have a substantially lower risk of malignancy than a carrier though it may not return to general population risk levels.

In an affected patient with FAMMM who returns a normal *CDKN2A* result ("negative result") or a "variant of unknown significance (VUS)," little advice can be offered. The patient may harbor a high-risk mutation in an undiscovered gene and therefore the risk is incalculable. These patients should continue to undergo the same dermatologic surveillance. For a non-affected member of a FAMMM kindred, there is no role for genetic testing without concomitant evaluation of at least one if not two other affected relatives from the same family. In short, the designation of "carrier" vs "non-carrier" can only be made if the familial mutation can be identified.

[5]. How can I use the results?

CDKN2A mutation carriers should be referred to a healthcare provider familiar with PC screening (Level of evidence: IV)[65] in addition to ongoing intensive dermatologic surveillance at q3–6 month intervals with the possible use of TBP. Relatives of *CDKN2Amutation* carriers, regardless of genetic test results, should continue to be under careful dermatologic surveillance and strict sun protection.

No low-cost, gold standard screening approach exists for PC though studies in high-risk cohorts have demonstrated that early, pre-invasive pancreatic lesions can be detected with screening programs and then treated preemptively.[66] Although PC screening lies outside the purview of dermatologists, familiarity with the available screening modalities is useful. Currently, these include endoscopic retrograde cholangiopancreatography (ERCP), which is able to detect small tumors but has associated complications due to its invasive nature, CT and MRI, which are less sensitive but also less invasive, and endoscopic ultrasound (EUS), which is the most sensitive and safe option at this time.[67] (Level of evidence: IV) Some authors suggest that screening should start at the age of 50 years, or 10 years earlier than the PC age of onset in the family, but no specific consensus exists for a specific protocol in cancer screening of *CDKN2A* mutation carriers.[13] Patients with FAMMM who forego testing, test negative for *CDKN2A* or who have a VUS should remain under careful dermatologic surveillance but PC screening is probably not necessary.

[6]. How will the patient use the results?

Families in general share exposure risks (e.g. sunny vacations together), risk conferring traits (e.g. sun sensitive skin, blue eyes) and disease-causing variants (e.g. *CDKN2A* mutation). The lack of a high-risk mutation in *CDKN2A* should not empower patients to abandon sun protective practices. Parents should also recognize that their children will continue to need strict sun protection even in the face of a normal *CDKN2A*. "True Negatives", however, would not need to undergo PC screening however. There are various

psychological benefits from undergoing genetic testing in *CDKN2A* families, including decreased anxiety.[68]

[7]. Will my patient experience genetic discrimination?

In 2008, the U. S. Government passed the Genetic Information Non-discrimination Act (GINA; http://www.ginahelp.org) which protects all individuals from health and employment discrimination based on genetic information. The Genetic Information Non-discrimination Act (GINA) went into effect in 2009 and provides comprehensive protection against genetic discrimination for all Americans. Under GINA, it is against the law for most health insurers to use genetic test results or family history information as a pre-existing condition. Additionally, under the GINA law, most health insurers cannot use genetic information to make decisions regarding eligibility, premiums, underwriting or coverage. It is also against the law for employers with 15 or more employees to use genetic information in hiring, firing, promotion, or other employment decisions. GINA does not protect against discrimination from life insurance, disability insurance or long-term care insurance companies. GINA's protections do not apply to the US military or employees of the federal government who get care through the Federal Employees Health Benefits Plans, however, these groups have their own policies in place that may protect their members from insurance discrimination. For more information about the protections offered by GINA visit www.ginahelp.org.

1.5 Part 1 Conclusion

Malignant melanoma pathogenesis is multifactorial and complicated. However, hereditary cancer syndromes, such as FAMMM, provide excellent genetic models for studies that may increase early detection rates and improve existing prevention, and management protocols. Patients with a high nevus count and multiple atypical nevi should always be asked about personal or family history of melanoma or other internal organ cancer. Considering the fact that up to 10% of melanomas may be familial, increased physician awareness can lead to faster diagnosis of melanomas and, through patient education, to improved preventive behaviors.

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KEY POINTS

- Hereditary melanomas can appear as part of a Familial Melanoma Syndrome or a Mixed Cancer Syndrome
- A positive association between melanoma, multiple nevi, pancreatic cancer, and *CDKN2A* mutations is now well established
- Patients suspected to have FAMMM present with multiple atypical nevi (>50) and have a positive personal and/ or family history for melanoma
- FAMMM patients 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, despite the large number of atypical nevi that they may present with
- The *CDKN2A* locus is the major recurrent source of germline mutagenesis in hereditary melanoma
- The prevalence of germline *CDKN2A* mutations in melanoma families and *CDKN2A* mutation penetrance vary with geographic location
- Patients that harbor the mutation have a higher risk of developing melanoma, however some evidence suggests that these CMMs may be less invasive than *CDKN2A*-wild-type CMMs
- Patients with FAMMM syndrome should undergo total body skin examination, dermoscopic examination of clinically atypical nevi with possible total body photography every three to six months
- Children from families with FAMMM may begin screening in late adolescence.
- Due to the reported association between *CDKN2A* mutations and internal organ malignancies (specifically pancreatic cancer), all patients suspected to harbor the mutation should be referred to a specialist for appropriate screening

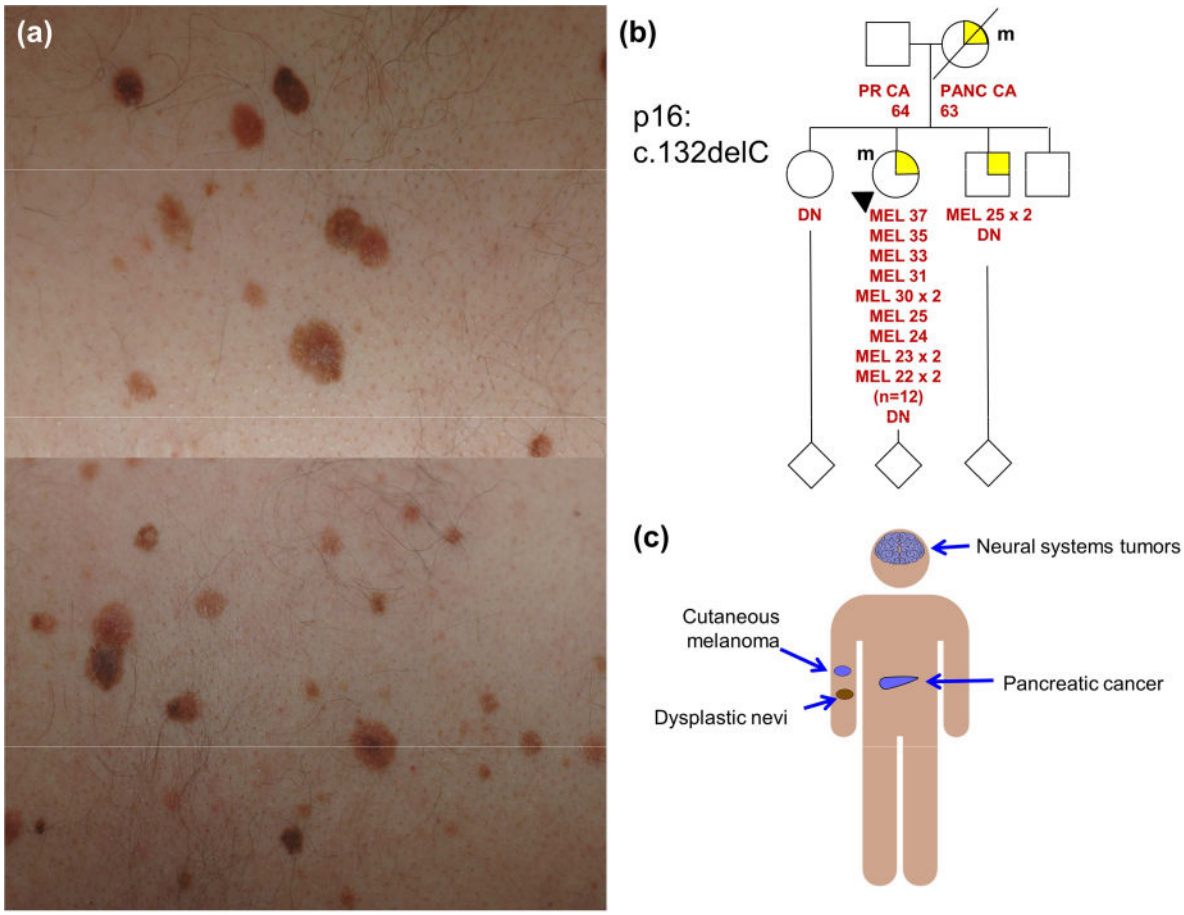

Figure 1. The familial atypical multiple mole-melanoma phenotype

(a) Clinically atypical moles frequently associated with FAMMM syndrome. (b) Pedigree of a FAMMM kindred showing multiple early onset cutaneous melanomas (proband and brother) and pancreatic cancer (PANC CA; mother). The patient and mother are carriers of a p16 mutation (m). (c) Patients with FAMMM syndrome (in particular those with germline *CDKN2A* mutations) are at risk for cutaneous melanoma, pancreatic cancer and neural systems tumors (melanoma-astrocytoma syndrome).

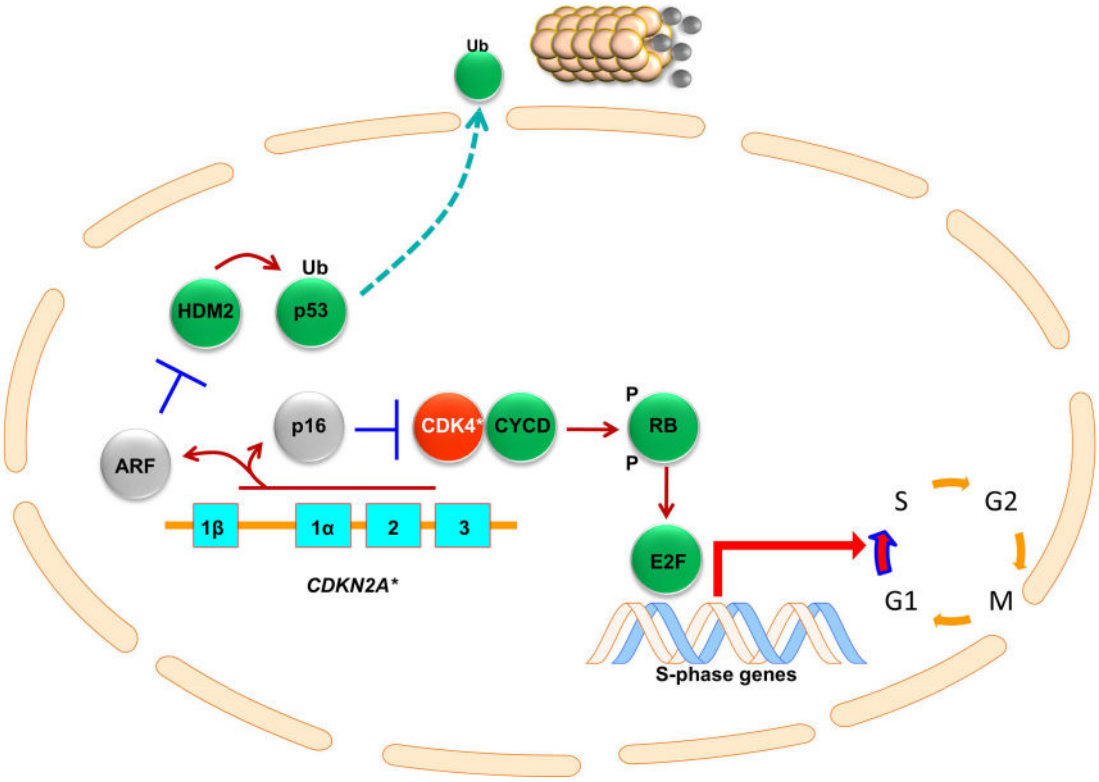

Figure 2. Pathways linked to FAMMM predisposition

CDKN2A is comprised of 4 exons- 1α, 1β, 2 and 3. Exons 1α, 2 and 3 encode for p16 while exons 1β, 2 and 3 encode for p14ARF (ARF). p16 inhibits CDK4, which, without p16, binds cyclin D (CYCD) and phosphorylates (P) the retinoblastoma protein (RB). This in turn releases E2F transcription factors, which induces G1 phase genes and triggers G1-S cell cycle transition. p14ARF inhibits HDM2, which normally ubiquitinates (Ub) p53 condemning it to destruction by the proteasome. Mutations in *CDKN2A* (*CDKN2A**) leads to loss of p14ARF and p16 function (gray color) while mutations in CDK4 (CDK4*) renders CDK4 resistant to p16 inhibition thereby activating CDK4 activity (red color); non-mutated genes are shown in green.

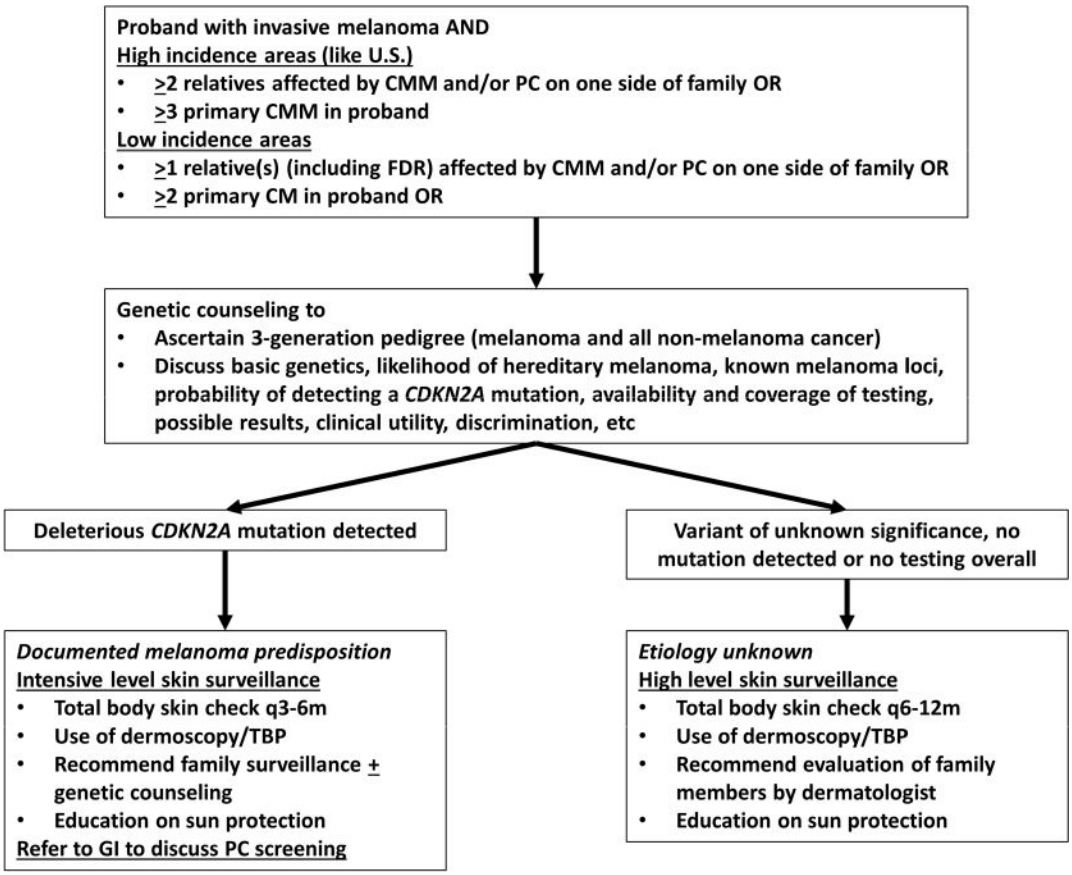

Figure 3. Genetic counseling algorithm for FAMMM patients

Patients with a personal history of melanoma may be considered for genetic counseling if certain criteria from high and low incidence area are met. The United States and Australia would be considered high incidence areas while England and Greece would be considered low incidence areas. A genetic counselor would ascertain a 3-generation pedigree and discuss the likelihood of hereditary melanoma, the molecular genetics related to familial melanoma risk, testing options, costs, risks of discrimination and possible test results. If patient undergoes *CDKN2A* testing and a deleterious mutation is detected, intensive skin surveillance is recommended along with a referral to GI for discussion of pancreatic cancer screening. If testing is not pursued or if a normal or variant of unknown significance result is returned, the etiology of the familial pattern remains unknown. Given the family history, the patient is considered high risk and should undergo high level skin surveillance.

Abbreviations, PC, pancreatic cancer; TBP, total body photography, CMM, cutaneous malignant melanoma.

Table 1

Criteria for the diagnosis of FAMMM. All criteria should be present in order to make a diagnosis.[22]

1	Cutaneous melanoma in one or more first- or second-degree relatives
2	High total body nevi count (>50), multiple atypical nevi
3	Specific histologic features present on nevi (these include: asymmetry, subepidermal fibroplasia, lentiginous melanocytic hyperplasia with spindle or epithelioid melanocytes, variable dermal lymphocyte infiltration and presence of “shouldering” phenomenon)

Table 2

Malignancies (besides melanoma) reported with *CDKN2A* and *CDK4* mutations[3,20,36,49,51,52,62,63,64]

CDKN2A	***CDK4***
Uveal melanoma	–
Breast cancer	Breast cancer (Phyllodes tumor)
Ovarian tumors	Ovarian tumors
Cervical cancer	Cervical cancer
Endometrial cancer	–
Pancreatic cancer	**Pancreatic cancer**
Stomach cancer	Stomach cancer
Esophageal cancer	–
Colon cancer	Colon cancer
Lung cancer	Lung cancer
Leukemia	–
Lymphoma (Hodgkin)	Lymphoma
Brain/CNS tumors	–
Renal cell carcinoma	–
Urinary bladder carcinoma	–
Prostate cancer	Prostate cancer
Hepatic cancer	–
Sarcomas	–
Parotic gland tumors	–
Tonsillar tumors	–
Nasopharyngeal/laryngeal tumors	–
Tongue cancer	–

Table 3

Recommendations for patients with suspected hereditary melanoma[3,63,64,65]

Obtain thorough medical history from patient:

- Sun exposure patterns
- Personal history of MM or other type of skin cancer (age at diagnosis should be noted)
- History of internal organ malignancies
  - Age at diagnosis should be noted
  - Should be updated annually
  - Special interest: pancreatic, renal, breast, or other rare types of cancer
- Family medical history should include:
  - Relatives with multiple and/or atypical nevi
  - Sun exposure patterns
  - Fitzpatrick skin type/clinical phenotype (i.e. red hair etc.)
- Family history of MM (1st and 2nd degree relatives)
  - Number of primary MMs and age at diagnosis should be noted
- Family history of internal organ malignancies (3-generation pedigree)
  - Age at diagnosis should be noted
  - Should be updated annually
  - Special interest: pancreatic, ocular melanoma, mesothelioma, renal, breast, or other rare types of cancer
- In cases of positive personal or family history of MM or other cancer, relevant medical information should be obtained (i.e. histology reports, medical reports etc.)

Physical examination

- Fitzpatrick skin type/clinical phenotype (i.e. red hair etc.)
- Number of banal and atypical nevi (<50 or >50)
- Signs of solar elastosis (lentigos, actinic keratoses etc.)
- Presence of multiple “Spitzoid” nevi or lesions resembling dermal nevi
- Special attention should be given in examining for atypical features in clinical appearance (e.g. presence of trichilemmomas, various types of minor malformations etc.)
- Dermoscopy should be applied to all nevi

Clinical recommendations

- In general, patients and families should be educated in the importance of skin cancer prevention measures (sunscreen, sun avoidance, abstaining from tanning beds, etc.)
- If patient exhibits multiple banal nevi and has negative personal or family history for MM and/or other cancers:
  - Dermoscopic examination should be repeated at least annually
  - Total body photography can be considered
- If patient exhibits multiple and/or atypical nevi or has positive personal or family history for MM and/or other cancers or if patient exhibits lesions resembling MBAITs:
  - Dermoscopic examination should be repeated every 3 to 6 months depending on the clinical phenotype
  - Total body photography can be performed at 6 month intervals
- Recommend dermatologic evaluation all 1st and 2nd degree relatives
- If suspicious lesions present (MBAITs), selection and removal should be made for histopathological examination
- If rapidly changing nevi or new lesions appear, surgical removal and histopathological examination should be recommended to all patients

- If melanoma cancer syndrome suspected, patient should be referred for genetic counseling and possible work up of internal malignancies