Familial Melanoma

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Cutaneous malignant melanoma (CMM) shows a rapidly rising incidence in white-skinned populations across the world. It has been estimated that in 2007, approximately 60,000 new cases of invasive CMM were diagnosed in the United States and over 8000 deaths from melanoma occurred [1]. There is thus a need for improved preventive strategies. One essential task is to define those at high-risk for development of melanoma who may then be enrolled in preventive programs to reduce the risk of CMM. A particular high-risk group for melanoma development includes members of families that have hereditary CMM. In this review, the clinical characteristics, genetic aspects, and guidelines for management of familial melanoma are summarized.

Risk factors for melanoma

Environmental risk factors

The major environmental risk factor for melanoma is exposure to UV radiation, both the long wavelength UVA (320–400 nm) and the intermediate wavelength UVB (290–320 nm). The increase in incidence of CMM in white-skinned populations is likely caused to a large degree by changing sun exposure patterns; however, the relationship between sun exposure and CMM is complex. In a recent meta-analysis of the published data, the most consistent relationship to increased risk of CMM was seen between intermittent sun exposure, particularly in early life, and a history of sun-burns [2]. In contrast, increased levels of chronic sun exposure showed no significant association with increased risk of CMM.
Host risk factors

The presence of large numbers of melanocytic nevi is an important risk factor for CMM [3]. In addition to large numbers of common nevi, the presence of atypical moles/dysplastic nevi (DN) is a melanoma risk factor. For the clinical diagnosis of DN, the established ABCD(E) criteria may be used. Nevi are judged DN if they have an asymmetrical form (Asymmetry), irregular borders (Border), composite multicolor pigmentation (Color), and a diameter of more than 6 mm (Diameter) [4]. Elevation of the nevus (Elevation), that is, the simultaneous presence of macular and papular components, is a further criterion [5]. It should be noted that these criteria are also used to identify CMM, indicating the difficulty in the differential diagnosis of DN and CMM. In trained hands, dermatoscopy (epiluminescence microscopy) is a useful technique to increase the diagnostic accuracy [6].

Although DN were originally described in the context of familial melanoma [7], DN are not infrequent in the adult population. In a German study, at least 5% of individuals had at least one DN [8], whereas in a Swedish study, this figure was as high as 19% [9].

Other phenotypic risk factors include skin type with an inability to tan, presence of many freckles, red or blond hair, blue/gray eyes, indicators of actinic skin damage, and a history of a previous premalignant or skin cancer lesions (melanoma or nonmelanoma) [10].

Familial melanoma

There is evidence for familial clustering of cases of CMM. It is estimated that 5% to 10% of all cases of CMM occur in kindreds that have a hereditary predisposition for CMM [11,12]. In population-based studies, 1% to 13% of melanoma cases report melanoma in at least one first-degree relative [13,14]. The risk of melanoma is increased in relatives of CMM patients. Thus, according to a recent report from the Genetic Epidemiology of Melanoma Group, individuals who have a first-degree relative who has CMM have a markedly increased risk of developing melanoma, with a cumulative risk of 6% to 7% at age 80 years [15]. Increased CMM risk in biologic relatives of CMM patients may be caused by genetic factors and by shared environmental exposure. Ultimately, the individual risk is a result of gene–gene and gene–environment interactions, which are just beginning to be elucidated.

The occurrence of families that have increased melanoma risk has been recognized for nearly 2 centuries. In the first description of CMM in the English language in 1820, Norris [16] reported a family in which two members had CMM and several relatives had large moles. In 1978, Clark and colleagues [7] reported six melanoma-prone families in which CMM patients and their relatives had large “funny-looking” nevi, which were designated as potential precursors of CMM. The syndrome was subsequently entitled
dysplastic nevus syndrome (DNS) (Figs. 1 and 2) [14]. In parallel, Lynch and colleagues [17] reported the same syndrome, which was entitled familial atypical multiple-mole melanoma syndrome. The syndrome is also called atypical mole syndrome [18].

Familial melanoma patients tend to have an earlier age at first melanoma diagnosis, thinner tumors, and a higher frequency of multiple primary melanomas (MPMs) than patients who have sporadic melanoma [19]. In some melanoma families, there is also an increased risk of pancreatic carcinoma (see later discussion).

In the original descriptions of melanoma families, there was an association between melanoma risk and the DNS phenotype, and DN were considered precursor lesions of CMM [7]. For instance, in an early study, 14 families that had familial melanoma and DNS were reported [20]. Approximately 95% of the melanoma patients and 50% of the family members had DN. During follow-up, new cases of CMM were diagnosed only in individuals who had DN. It has now become clear that a variation between families exists as to whether they exhibit the DNS phenotype. Moreover, although risk of melanoma is higher in family members who have DNS (and it is clear that DN may be precursor lesions of CMM; see Fig. 2) [21], CMM also develops in individuals who do not have DNS. Therefore, all members of melanoma families should be considered at increased risk for CMM.

Fig. 1. Familial melanoma—DNS phenotype. The back of a young woman belonging to a kindred with familial melanoma who exhibits numerous DN.
Molecular genetics of familial cutaneous melanoma

In recent years, considerable efforts have been made to unravel the genetic alterations responsible for familial CMM. For instance, the Melanoma Genetics Consortium (GenoMEL) has been active as a nonprofit consortium since 1997 in this area. GenoMEL comprises most research groups worldwide working on the genetics of familial CMM. The mission of GenoMEL is to develop and support collaborations between member groups to identify melanoma susceptibility genes, to evaluate gene–environment interactions, and to assess the risk of CMM and other cancers related to variations in these genes. More detailed information on GenoMEL and its activities can be obtained at http://www.genomel.org.

High-risk melanoma genes

*CDKN2A*

In 1994, it was demonstrated that affected members in some kindreds that have familial CMM harbor germline mutations in the *CDKN2A* gene on chromosome 9p21 [22,23]. Remarkably, the *CDKN2A* gene encodes two unrelated proteins, which are tumor suppressors and which play key roles in cell cycle regulation (Fig. 3) (reviewed in Ref. [24]). Thus, the p16INK4 protein is encoded by exons 1a, 2, and 3 and negatively regulates cell cycle progression by inhibiting the cyclin-dependent kinases CDK4 and CDK6. Inhibition of the kinases prevents phosphorylation of the retinoblastoma protein pRb, thereby preventing entry into the S-phase of the cell cycle.
Recently, it was suggested that p16INK4 normally causes senescence in melanocytes and in nevi containing activating BRAF proto-oncogene mutations [25,26]. Germline loss of one CDKN2A allele would thus weaken this protective mechanism against melanoma development and may contribute to the development of increased numbers of nevi later in life in affected individuals compared with healthy persons [27]. The second CDKN2A protein product, p14ARF, is encoded by splicing of an alternative exon 1b to exon 2. This protein is translated in an alternative reading frame (hence the acronym ARF) and therefore shows no amino acid homology to p16INK4. p14ARF blocks HDM2-mediated degradation of p53. Mutations in CDKN2A thus have the capacity to target negative regulators in two key signaling pathways, the pRb and p53 pathways, which have central roles in cell cycle regulation. In addition, p14ARF has been implicated in sumoylation of several of its binding proteins and in inhibiting the transcriptional activator E2F-1 and promoting its degradation [28,29].

A large number of different germline CDKN2A mutations have been identified in members of kindreds that have familial melanoma and in patients who have multiple primary CMM [30–33]. Most mutations are missense mutations and are scattered throughout the gene without any clear hotspots. Mutations in exon 1a alter the p16INK4 protein only; those in exon 1b target the p14 ARF protein. Exon 2 mutations, however, may affect both proteins. Most mutations have been reported in exons 1a and 2, which is consistent with inactivation of the p16INK4 protein as the main predisposing factor for CMM. More recently, however, alterations affecting exon 1b only have been described in melanoma families in which neural system tumors (NSTs) also occur, including deletions, insertions, and splice site mutations [34–38]. Therefore, it seems that mutations affecting either protein may be involved in development of familial CMM.
Worldwide, it has been estimated that approximately 20% to 40% of kindreds that have familial melanoma are related to germline CDKN2A mutations [39]. GenoMEL recently reported a large study that included 466 families (2137 patients) with at least three melanoma patients from 17 centers [40]. Overall, 41% (n = 190) of families had mutations; most involved p16INK4A (n = 178), whereas mutations in CDK4 (n = 5) (see later discussion) and p14ARF (n = 7) occurred at similar frequencies (2%–3%). There were striking differences in mutations across geographic areas. Specific founder CDKN2A mutations have been described in several countries, and the proportion of families that had such mutations differed significantly among geographic regions (P = .0009). Single founder CDKN2A mutations are predominant in Sweden (p.R112_L113insR, 92% of familial mutations) [41], the Netherlands (c.225_243del19, 90% of familial mutations) [42], and Iceland (p.G89D) [43]. France, Spain, and Italy have the same most frequent mutation (p.G101W) [44]. Similarly, Australia and United Kingdom share the same most common mutations (p.M53I, c.IVS2-105A>G, p.R24P, and p.L32P).

In another recent international GenoMEL study of 385 families that had three or more melanoma cases, frequencies of germline CDKN2A mutations in different continents were analyzed [43]. Overall, 39% of families had CDKN2A mutations, ranging from 20% (32/162) in Australia to 45% (29/65) in North America and to 57% (89/157) in Europe. The lower frequencies of CDKN2A mutations in areas with high CMM incidence, such as Australia, may be explained by a higher frequency of clustering of sporadic cases or by cases associated with low-penetrance genes in geographic areas with high environmental UV exposure.

An analysis of factors predictive of germline CDKN2A mutations was performed using the major factors individually reported to be associated with an increased frequency of CDKN2A mutations: increased number of patients who had melanoma in a family, early age at melanoma diagnosis, and family members who had MPMs or pancreatic cancer. All four features in each group, except pancreatic cancer in Australia (P = .38), individually showed significant associations with CDKN2A mutations, but the effects varied widely across continents. Multivariate examination also showed different predictors of mutation risk across continents. In Australian families, the predictors of more than two patients who had MPM, median age at melanoma diagnosis of 40 years or younger, and six or more patients who had melanoma in a family jointly predicted the mutation risk. In European families, all four factors concurrently predicted the risk, but with less stringent criteria than in Australia. In North American families, only 1 or more patient who had MPM and age at diagnosis of 40 years or younger simultaneously predicted the mutation risk. The variation in CDKN2A mutations for the four features across continents is consistent with the lower melanoma incidence rates in Europe and the higher rates of sporadic melanoma in Australia.
**CDK4**

Worldwide, only a small number of kindreds that have familial CMM and germline mutations in the *CDK4* gene encoding a cyclin-dependent kinase, which normally interacts with p16INK4A, have been described (reviewed in Ref. [24]). In all cases, the mutations occur in exon 2 and affect codon 24 (p.R24C, p.R24H), which is essential for binding to p16INK4A. The phenotype of these families seems to be similar to those that have *CDKN2A* mutations.

**Candidate loci for novel genes predisposing to familial cutaneous malignant melanoma**

GenoMEL has performed a genome-wide screen of microsatellite markers in 82 melanoma families, most of who were from Australia. This screen yielded a significant linkage to a marker on chromosome 1p22 [45]. Although loss of heterozygosity studies indicate that a tumor suppressor gene may be present at this locus, so far, no susceptibility gene has been identified, despite considerable efforts [46].

More recently, a linkage analysis of three Danish kindreds that had ocular and cutaneous melanoma yielded a suggested linkage to markers on chromosome 9q21.32, but the putative gene responsible for the syndrome has not been identified [47].

**Risk of melanoma and of other cancers in melanoma families that have germline *CDKN2A* mutations**

For genetic counseling, it is important to obtain an estimate of the penetrance of a certain germline gene mutation, that is, the risk of developing the disease among carriers of the gene mutation. The penetrance of germline *CDKN2A* mutations for melanoma development in kindreds that have familial melanoma has been the subject of a large collaborative study by GenoMEL. In this study, members of 80 kindreds that had familial melanoma from different parts of the world were investigated. Overall, *CDKN2A* mutation penetrance was estimated to be 0.30 (95% confidence interval [CI], 0.12–0.62) by age 50 years and 0.67 (95% CI, 0.31–0.96) by age 80 years. Penetrance with respect to melanoma development was not statistically significantly modified by sex or by whether the *CDKN2A* mutation altered the p14ARF protein; however, there was a statistically significant effect of residing in a location with a high population incidence rate of melanoma ($P = .003$). By age 50 years, *CDKN2A* mutation penetrance reached 0.13 in Europe, 0.50 in the United States, and 0.32 in Australia; by age 80 years, it was 0.58 in Europe, 0.76 in the United States, and 0.91 in Australia. Thus, the same factors that affect population incidence of melanoma may also modulate *CDKN2A* penetrance. These data strongly support an
interaction between the presence of a germline CDKN2A mutation and environmental UV exposure.

The risk of melanoma in carriers of germline CDKN2A mutations in the general population is lower, however, as reported in a recent publication from the Genes, Environment and Melanoma study [48]. This investigation was based on analyses of 3550 population-based melanoma patients and 23,485 of their first-degree relatives. The risk of melanoma in carriers of germline CDKN2A mutations was 14% (95% CI, 8%–22%) by age 50 years, 24% (95% CI, 15%–34%) by age 70 years, and 28% (95% CI, 18%–40%) by age 80 years. Thus, carriers of CDKN2A germline mutations in the general population seem to have a considerably lower melanoma risk than those who belong to kindreds that have familial melanoma. This is most likely due to the influence of other, unknown melanoma predisposing factors in melanoma kindreds that interact with and increase the penetrance of CDKN2A mutations.

Apart from CMM, an increased risk for pancreatic carcinoma has been documented in several families, including families that have the Dutch p16 Leiden mutation and the Mediterranean p.G101W and the Swedish p.112_L113insR founder mutations [42,49–51]. In the recent study from GenoMEL addressing risk of other cancers, there was a strong association between the presence of pancreatic cancer and CDKN2A germline mutations in melanoma families ($P < .0001$); however, this relationship differed between mutations and also between geographic areas because there was no significant association between pancreatic carcinoma and CDKN2A mutations in Australian families, which may reflect a different spectrum of mutations in Australian compared with European or North American families. Although the data indicate a possible relationship between the type of CDKN2A mutation and risk of pancreatic cancer, with more mutations affecting p16 and p14ARF in kindreds that have pancreatic cancer compared with those that do not, further studies are needed to further explore this association. The cumulative risk for development of pancreatic cancer in individuals who have the p16-Leiden deletion was 17%, with a mean age at diagnosis of 58 years [52]. Although the risk of pancreatic cancer is lower than that of melanoma, a study of Dutch melanoma families showed nearly equal mortality rates owing to melanoma and pancreatic cancer in these families [53].

In a small number of families, the incidence of CMM and NSTs has been associated with large deletions of CDKN2A/ARF, mutations that affect p14ARF, or both [34–38]. In the recent GenoMEL study, there was no significant association between CDKN2A mutations and NSTs ($P = .52$) and a marginally significant association of NSTs with mutations affecting the p14ARF transcript ($P = .05$), thus giving some support for the impact of germline ARF alterations, NSTs, and melanoma [40]. This analysis, however, has low power and requires further confirmation. Furthermore, there was no significant association between CDKN2A germline mutations in
families and the occurrence of uveal melanoma \( (P = .25) \). Thus, rare families that have clustering of uveal and cutaneous melanoma may have a different underlying genetic alteration such as the putative chromosome 9q21 gene mentioned earlier [47].

**Gene testing in familial melanoma**

Gene testing for familial melanoma remains controversial. Although it is practised in certain health care systems, it has, until recently, been the view of GenoMEL that testing is premature [54], but this remains under review and family members should be counseled regarding the advantages and disadvantages of genetic testing [55].

There are several arguments against genetic testing. First, many melanoma families that have several affected members still lack identifiable germline mutations in known high-risk genes. Therefore, a negative test result is uninformative. Second, the risk of melanoma and other cancers in individuals who have germline mutations is still insufficiently characterized, making the implications of a positive test result imprecise. Third, because non–gene carriers in CDKN2A-positive families may have DNS and develop CMM, there is an increased risk of CMM in family members who do not have mutations. A negative test result could thus lead to false reassurance and possibly have a negative impact on preventive activities, although there is no evidence for this from genetic testing for other familial cancers [56,57]. Ultimately, in the absence of a validated screening method for pancreatic cancer, a positive CDKN2A test will have little impact on the management of melanoma kindreds.

Arguments in favor of gene testing have been given. First, provided that the limitations of the test are explained to family members, the information obtained may be valuable to them. Second, a positive test result may improve the compliance of some family members in preventive programs. Finally, a negative test result in a member of a high-risk family who has relatives who have died from melanoma or pancreatic cancer is reassuring.

Gene testing for melanoma should be offered only in conjunction with qualified genetic counseling and education and be performed at departments of clinical genetics or equivalent centers. Gene testing for germline CDKN2A mutations should be considered only when there is a reasonable likelihood of finding a positive result. At this time, it is not possible to define the exact criteria for such testing in melanoma. CDKN2A testing is not meaningful in patients who have single sporadic CMM without a family history of melanoma, even if the melanoma has occurred at an early age, due to the low frequency of mutations [58]. For the same reason, testing is not meaningful in patients who have MPMs in the absence of a family history.

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CDKN2A mutations are more prevalent in the setting of familial CMM. As discussed previously, although there are geographic variations, the likelihood of the presence of a CDKN2A mutation increases with (1) the number of affected CMM cases in a family, (2) a lower median age of diagnosis of CMM, (3) the occurrence of MPMs, and (4) an incidence of pancreatic carcinoma. Thus, although testing for germline CDKN2A mutations may be considered in families that have two first- or second-degree relatives who have CMM, the likelihood of a positive test in such kindreds is very low, below 10% in most areas [11]. Thus, the main-candidate families for genetic testing are those that have three or more affected members, particularly when there is a low age of diagnosis of CMM, individuals who have MPMs, and occurrence of pancreatic carcinoma.

Management of familial melanoma

There is a long-standing consensus that members of kindreds that have familial melanoma should be invited to participate in preventive programs [59]. A consensus statement on the management and counseling of such individuals has been published by GenoMEL [60]. In the absence of data from randomized controlled clinical trials, the evidence for these measures is level 4 (Oxford Center for Evidence-Based Medicine Levels of Evidence, www.cebm.net).

To identify kindreds that have familial melanoma, it is important to question all newly diagnosed patients who have CMM regarding family history of melanoma and other malignancies. Verified diagnoses of CMM and other cancers, preferably through histopathology reports, and age at diagnosis should be documented. Such verification of diagnoses is essential because family members often confuse nonmelanoma skin cancers and DN with melanoma. When a family history of melanoma has been established, the health care provider should establish a careful extended pedigree of the family in collaboration with the proband of the family (Fig. 4). The pedigree should be revised annually in collaboration with the proband.

At present, due to the limitations of testing for germline CDKN2A mutations, it is recommended that members of melanoma families be managed in a similar manner regardless of CDKN2A mutation status. It is recommended that in melanoma families, at least all first-degree relatives of patients affected with CMM are offered to participate in a preventive program. This recommendation also applies to members of CDKN2A mutation-negative families with multiple melanoma cases in whom it can be assumed that an unidentified high-penetrance gene is present. First-degree relatives of CMM patients in such families have a 50% likelihood of carrying the unknown melanoma risk gene.

Primary prevention of cutaneous malignant melanoma

An essential part of primary prevention is education of family members regarding sun protection. Support for a role of sun exposure on melanoma
risk in CDKN2A germline mutation carriers comes from the observation that CDKN2A penetrance is higher in Australia than in the United States or Europe [61]. Case-control studies in sporadic melanoma strongly support the role of intermittent sun exposure, particularly in early life and when associated with sunburns [2]. The efforts should aim to reduce sun exposure in all members of melanoma families, particularly in early life. Thus, parents should be educated about sun-protective measures for infants and children [59,62], including the use of sun-protective clothing, hats, and sunglasses; avoidance of sun exposure during peak UV conditions; and absolute avoidance of sunburns. The use of sunscreens remains controversial but may be considered as a complement to other sun-protective measures. If used, it must be ensured that sunscreens have a sufficient level of broad-spectrum protection for UVA and UVB [63].

Secondary prevention of cutaneous malignant melanoma

Because many melanomas develop from precursor lesions such as DN, and because melanomas that are detected and treated early have an excellent prognosis, there is a clear role for monitoring of pigmented skin lesions in members of melanoma families. Family members should be instructed in skin self-examination and be given the opportunity to participate in regular screening by trained health care professionals. Commencing at age 10 years, members of kindreds that have familial CMM should have a baseline whole-skin examination with characterization of moles. The skin examination must include examination of the scalp and the external genitals. The examination should focus on detection and characterization of nevi and any suspicious...
melanoma lesions. Documentation, with overview photographs of the entire skin and close-up pictures of DN, is very useful for follow-up (see Figs. 1 and 2). Melanoma family members should be followed by an appropriately trained health care provider, with skin examinations approximately every 6 months, at least until the nevi are stable and the person is judged competent in self-surveillance. Subsequently, the individual should be examined annually or have prompt access to the health provider as necessary. Individuals who have large numbers of DN and unstable and rapidly changing nevi may require more frequent skin examinations. Such examinations may also be necessary, for instance, during pregnancy, when nevi may be particularly unstable. Skin-surface microscopy (epiluminescence microscopy) using conventional dermatoscopes or digital equipment is helpful during skin examinations [6,64,65].

Any changing nevus should be considered for excision for histopathologic diagnosis. There is, however, no justification for prophylactic removal of nevi because the probability of progression to melanoma is low for every individual lesion and, over time, many nevi mature and disappear. Furthermore, because melanomas may occur on previously normal skin, removal of nevi would not change the guidelines for skin surveillance by the patient or the health care provider [66].

Family members should be taught about routine self-examination of the skin and may be provided with their own set of photographs and be instructed on how to use them in self-examination. A monthly self-examination or examination by a parent, a partner, or another family member is recommended. Information regarding the significance of change in shape and size of pigmented lesions should be given, and instruction on the ABCD(E) rules may be useful [4,5,67]. It should be noted, however, that these criteria do not apply to all melanomas because a considerable fraction of early melanomas have a diameter less than 6 mm [68]. Moreover, because some CMM tumors apparently arise de novo and not by progression of a precursor lesion, the individuals must also be informed to be watchful regarding novel skin lesions [66].

Because no prospective studies of the outcome of preventive programs in high-risk groups for CMM have been reported, the benefits remain unproven. There are reports, however, that indicate that preventive activities may result in early diagnosis of CMM, as indicated by a low tumor thickness of tumors detected during follow-up [69–71]. In a more recent report on long-term follow-up of 844 members of 33 kindreds that had familial melanoma, of which 19 had germline mutations in CDKN2A or CDK4, 86 new CMMs were identified [72]. Of these, 72 were classified as T1a lesions (tumor thickness ≤1.0 mm; Clark level ≤3; no ulceration) with an average thickness of 0.3 mm. Similarly, in an analysis of 2080 family members of 280 Swedish familial CMM kindreds who were followed between 1987 and 2001, 41 CMM tumors were detected during follow-up. Of these, 15 (37%) were in situ tumors, and among the 26 invasive CMMs, 22 were
T1a tumors. Overall, 27 of the 41 CMM tumors (66%) lacked vertical growth phase and thus, by definition, lacked metastatic capacity [73]. The existing data support the hypothesis that preventive programs as previously described can lead to the diagnosis of early melanomas with an excellent prognosis and can efficiently reduce the risk of potentially metastatic CMMs in melanoma families.

**Pancreatic carcinoma surveillance**

At present there are no efficient screening methods to detect pancreatic carcinoma at a curable stage. Surveillance of pancreatic cancer in familial melanoma kindreds affected with this second malignancy is therefore a difficult task [74–76]. Serum markers, such as CA 19-9 are of limited value in asymptomatic individuals. Likewise, noninvasive imaging techniques such as abdominal CT or MRI are inadequate for the detection of pancreatic carcinoma at an early stage. Endoscopic retrograde cholangiopancreatography (ERCP) is considered the gold standard for visualization of pancreatic carcinoma. Due to the risk of serious complications such as bleeding, intestinal perforation, and pancreatitis, however, ERCP cannot be used in routine surveillance. Endoscopic ultrasound is a novel technique that may be able to detect early pancreatic cancer and precursor lesions. More recently, MRI combined with magnetic resonance cholangiopancreatography has been proposed as a screening tool. Parker and colleagues [74] described a pancreatic carcinoma screening algorithm for familial melanoma kindreds affected with pancreatic cancer in which CDKN2A mutation carriers are offered surveillance with endoscopic ultrasound and CA 19-9 beginning at age 50 years, or 10 years before the first diagnosis of pancreatic carcinoma in the family. Individuals who have abnormal findings are further investigated with ERCP. The benefits of such screening programs need to be investigated in prospective studies, and there are a number of research programs in the United States and Europe addressing this. For improved future surveillance, development of improved noninvasive methods such as serum markers would be very useful.

**Other cutaneous malignant melanoma–predisposing genes**

*Low-penetrance risk–modifying genes: MC1R and OCA2*

The melanocortin 1 receptor gene, *MC1R*, encodes the membrane receptor for a-melanocyte-stimulating hormone (a-MSH). On binding of a-MSH to the receptor, the levels of cyclic AMP increase, which in turn results in a shift in melanin synthesis from reddish pheomelanin to brown-black eumelanin [77]. Several variants—single nucleotide polymorphisms (SNPs)—have been described in the *MC1R* gene, and some of these may alter the function of the receptor, thereby shifting melanin synthesis from eumelanin
toward pheomelanin [78–80]. Such variants, which are common in Caucasian populations, are associated with red hair, fair skin, and freckling. Certain SNPs, so-called “RHC alleles,” are associated with a significant, although modest (approximately twofold) increased risk of CMM (these RHC alleles include D84E, R151C, R160W, and D294H) [81]. Other frequent, non–RHC alleles are not associated with significantly increased CMM risk. An independent association between some MC1R SNPs and melanoma risk after adjustment for phenotype has also been reported [81,82]. This association suggests that the α-MSH receptor may have functions apart from its role in pigment metabolism. There are reports that α-MSH, through the receptor, may affect the growth of melanocytic cells and may have immunomodulatory and anti-inflammatory effects, although the role, if any, of such effects for CMM risk remains to be established [83–86]. Although each RHC allele is associated with an approximately twofold risk for CMM, each individual may carry two or more RHC SNPs, which further increases the CMM risk [79]. In the context of familial melanoma with germline CDKN2A mutations, MC1R RHC variants increase the gene penetrance. In conclusion, the MC1R gene is the most commonly altered low-penetrance gene for CMM.

The OCA2 gene, which is a gene of importance for eye color, is mutated in oculo-cutaneous albinism [87,88]. More recently, variants of the OCA2 gene have been implicated as low-risk melanoma genes [89,90]. In a recent report of Icelandic and Dutch individuals, other SNPs in genes of importance for skin pigmentation were reported [91]. Whether these SNPs have an implication for melanoma risk remains to be established.

Other inherited syndromes associated with increased risk for cutaneous malignant melanoma

Familial retinoblastoma is caused by a germline mutation in the RB1 gene and is characterized by early-onset retinoblastoma, which is frequently bilateral. In reported series of retinoblastoma patients, there is an elevated risk for melanoma [79,92–95]. It is likely that the risk of melanoma in RB1 mutation carriers is considerably elevated.

The Li-Fraumeni syndrome is characterized by an increased risk of several tumor types including sarcomas, brain tumors, adenocarcinomas, and childhood tumors [96] and is associated with germline mutations in the TP53 tumor suppressor gene [96]. An association with CMM has been reported in some [97–99], but not other [100,101], Li-Fraumeni kindreds. Thus, the association with CMM remains controversial.

Neurofibromatosis 1 is caused by germline mutations in the NFI gene and is characterized by alterations of cells of neural crest origin, resulting in neurofibromas, café-au-lait spots, freckling in non–sun-exposed areas, and bone lesions. In some affected kindreds, CMM has been reported, and there have been reports of extracutaneous melanomas such as ocular
and mucosal melanomas [102]. The occurrence of melanomas is not unexpected because they represent tumors of neural crest–derived cells.

Xeroderma pigmentosum (XP) is a rare autosomal recessive syndrome associated with hypersensitivity to UV light due to defects in DNA repair. XP is subclassified into seven genetic complementation groups, XPA through XPG, each associated with defects in separate genes involved in nucleotide excision repair [103]. XP patients have more than a 1000-fold increased risk of developing skin cancers, predominantly nonmelanoma skin cancers, and CMM is diagnosed in approximately 5% to 20% of XP patients [103]. Of interest, a large proportion of melanomas in XP patients are lentigo maligna melanomas on chronically sun-exposed sites, indicating that chronic, rather than intermittent, UV radiation damage is the major cause of melanoma in XP.

Werner syndrome is caused by a defect in the WRN gene encoding a DNA helicase with a putative role in DNA repair. The syndrome is characterized by premature aging and by increased cancer incidence, including CMM. In a Japanese study, a large number of acral lentiginous and mucosal melanomas were found [104].

BRCA2-associated familial breast/ovarian carcinoma is characterized by greatly increased risk of breast and ovarian carcinoma. Some of these families are reported to have a modestly increased risk of CMM [105], whereas other groups of families do not [105–107].

**Summary**

Because CMM is rapidly increasing in white-skinned populations, there is a need for improved preventive strategies. Identification of risk groups for CMM is a central task. Familial melanoma represents 5% to 10% of cases of CMM. Such kindreds are characterized by multiple cases of CMM in biologic relatives, an earlier age at diagnosis, and a larger proportion of MPMs in affected individuals compared with sporadic CMM cases. In many families, members exhibit DN, some of which may be precursor lesions for CMM. In approximately 20% to 40% of familial melanoma kindreds, germline mutations in the CDKN2A gene are identified. Intense efforts are ongoing to identify novel melanoma-predisposing genes. The likelihood of CDKN2A mutations is increased in families that have three or more CMM cases, members who have an early onset of melanoma, and members who have MPMs or pancreatic carcinoma. In such families, genetic testing for germline CDKN2A mutations may be considered if combined with adequate information and counseling. Members of melanoma families should be invited to participate in preventive programs, including education regarding sun protection, skin self-examination, and regular skin examinations by trained professionals. There is a need for improved methods for surveillance of pancreatic cancer in families that have germline CDKN2A mutations and occurrence of pancreatic carcinoma. Members of
such families should have the opportunity to be enrolled in research programs aiming to improve such surveillance.

References


