Familial Malignant Melanoma — Overview

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Abstract

Approximately 3–15% of all malignant melanomas (MM) are familial cases. MM is a highly heterogeneous tumour type from a genetic perspective. Pedigrees with disease confined to a single generation of siblings or MM occurring among second- or third-degree relatives suggest multifactorial polygenic inheritance. However, not infrequently, within large families aggregations of MM are consistent with autosomal dominant inheritance, suggesting a hereditary syndrome caused by germline alterations of a single gene. Several different genes are involved in the development of MM. However, even when taken together they are responsible for less than 20% of all MM cases. It is thus necessary to perform association studies focused on genetic markers that could be used in identifying patients with a high risk of MM. Evaluation of aggregations of MM and other malignancies, like breast cancer, could be essential in identifying relatives of MM probands being at high risk of developing malignancies other than MM. The ultimate goal is to apply in these cases prevention recommendations and surveillance protocols to reduce the disease risk.

Epidemiology

Malignant melanoma (MM) is one of the most aggressive human malignancies. The incidence rates differ among Caucasian populations: ~35 per 100 000 in Australia [1], ~10 per 100 000 in the United States [2], ~7-10 per 100 000 in Western Europe [3, 4]. Its incidence has increased dramatically over the past years in Caucasian population worldwide up to a 10-fold increase since 1950s [5].

Risk factors

Sun exposure

Well-established environmental risk factor of MM is ultraviolet radiation (UV), sunburn and overexposure to the sun [6]. Armstrong and Kricker estimated that up to 65% of MM could be related to sunburn [7]. Exposure in childhood seems to be an especially important risk factor [8]. In countries with a growing awareness of MM and public health campaigns to avoid UV a downturn in MM incidence has been observed [9].

Genetic factors

It has been long stated in many different reviews that genetic susceptibility is another major MM risk factor. Recent epidemiological studies confirm these suggestions. Evaluation of over eight thousand Swedish probands with primary MM revealed that the familial risk for offspring of affected parents is about 2.57, and even higher (4.22) when a parent has been diagnosed at an age <50 years [10]. Similar results were obtained during the evaluation of 1505 MM probands recorded in Utah (USA) when the familial risk for first-degree
relatives (both offspring and siblings) was 2.1, and as high as 6.52 when MM cases were diagnosed under 50 years [11]. Hemminki et al reported that the familial MM risk showed a clear age dependence and higher risk in situ melanoma than in its invasive counterpart [12].

Familial clustering of MM has also been studied in twins. A population-based study of cancer risk in twins performed by Swerdlow et al indicated an increased risk of the occurrence of MM in opposite-sex co-twins, however studies performed by Hemminki and Milan did not confirm these results [13, 14, 15].

Familial aggregations of malignancy may be due to either genetic factors, environmental factors shared by family members, or both. In a recent study Czene et al assessed the genetic and environmental components in the main types of cancer by statistical analyses of family pairs. The importance of genetic effects was indicated by a higher correlation among relatives that were more closely related to each other genetically. Structural equation modelling was used to derive estimates of the importance of environmental and genetic effects. A statistically significant proportion of susceptibility to cancer accounted for by genetic effects was obtained for almost all malignancies, including MM. It was estimated that in the case of MM genetic factors constitute 21% of susceptibility, similarly to other neoplasms, such as cancers of breast, colon or stomach [16].

Familial aggregations of MM

There are two distinct ways of defining familial melanoma: 1) occurrence of melanoma in at least two first-degree relatives; or 2) families with at least two melanomas irrespective of the degree of relationship. Approximately 3-15% of all MM are familial cases of any type [17]. In Australia, Holman and Armstrong found a positive family history in 15% of 507 cases (9.9% in first-degree relatives) [18]. In the USA MM was present in first-degree relatives in 4.1% of 116 cases [19], in Denmark among 474 patients 4.7% had a relative with MM (3% in first-degree relatives) [20]. In our center among 405 unselected MM patients 12 cases (3%) had at least one first-degree relative affected.

In several families the co-occurrence of melanoma of the skin and the eye is reported [21]. The question whether ocular melanoma is also part of the familial melanoma syndrome remains unanswered.

Familial MM constitutes most probably a heterogeneous group of disorders characterized by occurrence of MM among relatives. The mode of inheritance is controversial and according to Mao is most likely polygenic [22]. Pedigrees with disease confined to a single generation of siblings or MM occurring among second- or third-degree relatives suggest multifactorial polygenic inheritance. However, not infrequently, within large families aggregations of MM are consistent with autosomal dominant inheritance. Anderson et al described MM in at least 15 members of a three-generation kindred. Early age of onset and a tendency for multiple primary lesions were characteristic features [23]. Lynch and Krush (1968) described two families with malignant melanoma in two generations in one family and three generations in the other [24]. Such pedigrees strongly suggest that part of familial MM constitutes hereditary syndrome caused by single-gene germline alterations. In order to identify such families the first definition of familial melanoma described above should be used.

Familial aggregations of MM and malignancies at different sites of origin

Aggregations of MM and other malignancies have been reported by many authors.

Most significantly a high incidence of pancreatic cancer has been reported in melanoma families, either by itself or in association with breast cancer [25-27]. Weston et al described a case with familial aggregation of melanoma, basal cell carcinoma and gastric cancer [28]. Aggregations of MM and cerebral astrocytoma [29], squamous cell carcinoma (SCC) [30] and kidney [31] were described. Recently, an increased risk of breast cancer among first-degree relatives of MM probands from families with strong cancer familial aggregation (showing features of autosomal dominant pattern of inheritance) has been suggested [32].
Molecular background of familial melanoma

Genes conferring high risk of developing MM

**CDKN2A**

In 1994 the first and so far the most significant high-risk MM susceptibility gene, CDKN2A (9p21, OMIM 600160) was identified [33, 34]. One of the four transcripts coded by this gene is the p16 protein. It inhibits the activity of the complex of cyclin D1 with cyclin-dependent kinase 4 (CDK4) or 6 (CDK6), the function of which is to promote cellular proliferation [35]. Thus CDKN2A acts as a tumour suppressor gene by inhibiting cellular proliferation.

Germline mutation frequencies in CDKN2A among members of melanoma families show considerable variation. Soufir et al showed frequent involvement of CDKN2A in French familial melanoma families (46%) whereas Fitzgerald et al identified 18% of US familial melanoma harboured CDKN2A constitutional mutations [36, 37]. Among Swedish families only 8% of cases were found to harbour alterations in the CDKN2A gene [38, 39]. Germline mutation and large deletion analysis of the CDKN2A/ARF genes in Polish families with multiple melanomas and in families with an aggregation of MM and breast cancer revealed that less than 6% of familial MM can be associated with the CDKN2A/ARF constitutional mutations [40]. In a separate study done by Lamperska et al no CDKN2A mutations have been detected in Polish melanoma-prone families [41].

According to Bressac-de-Paillerets et al the number of CDKN2A alterations correlates with the number of MM cases in the family and a young age at diagnosis (<50) [42]. However, no germline mutations have been reported in childhood melanoma so far [43].

In Dutch melanoma-prone families with a specific recurrent 19bp deletion of exon 2 of the CDKN2A gene, a high frequency of pancreatic cancer was observed [44]. CDKN2A was the first of the melanoma genes and is associated with an increase in the risk of pancreatic cancer as well [45]. Occurrence of multiple MM, pancreatic cancer and also breast cancer has been reported in families with different recurrent CDKN2A constitutional alterations [46].

In a recent study Bishop et al examined 80 families with documented CDKN2A mutations and multiple cases of cutaneous melanoma to establish the penetrance of the CDKN2A germline mutations. The penetrance was 30% by the age of 50 and 67% by the age of 80. It depended on the geographic origin: at 80 years of age, it was 58% in Europe, 76% in North America and 91% in Australia [47]. These data suggest that UV increases the penetrance of the CDKN2A mutations.

There is no doubt that regardless of the geographical origin, inclusion criteria or study methods, CDKN2A constitutional alterations have been found only in the minority of melanoma-prone families. In families with multigenerational inheritance of MM there remains a possibility that non-coding mutations of CDKN2A or alterations in another tumour suppressor gene predispose to familial melanoma.

**ARF**

In 1995 two independent groups discovered that CDKN2A shares exons 2 with another gene, ARF [48, 49]. The transcript, p14ARF is involved in the regulation of the cell cycle and apoptosis [50]. It has also been implicated in the pathogenesis of MM. The first exon of ARF is unique, whereas its second exon is derived from exon 2 of CDKN2A using a different reading frame of the sequence. Up to now mutations in ARF are reported to be present only in a few families worldwide and are characterized by an aggregation of MM and brain tumours [51]. Hewitt et al described a germline mutation of ARF in patients affected with melanoma or breast cancer from a family with multiple melanomas and breast cancers [52], in an independent study performed in our center no constitutional ARF alterations in cases with familial aggregation of MM and breast cancer were detected [40].

**CDK4**

In 1996 Zuo et al identified the CDK4 gene (12q13, OMIM 123829) as a third MM susceptibility gene [48]. CDK4 is an oncogene that codes the cyclin-dependent kinase 4 protein. Alterations in this gene are responsible...
for the occurrence of very small proportions of familial MM. Up to now germline CDK4 mutations have been found in 3 families world-wide [36, 53, 54].

**BRCA2**

Mutations in BRCA2 (13q12, OMIM 600185), acting in DNA repair, predispose to a range of cancer types. The Breast Cancer Linkage Consortium estimates the relative risk of melanoma to be 2.58 in BRCA2 carriers [55]. In 2002 Scott et al examined 71 patients with ocular MM and pedigree and clinical data suggestive of genetic background (bilateral cases, positive family history for occurrence of MM, age at diagnosis <50). He estimated the prevalence of possible loss of function changes in BRCA2 in 3% of patients with familial ocular melanoma [56]. No germline BRCA2 mutations have been found in familial skin MM to date. The penetrance of this gene is unknown. Johannsson et al suggested that apart from breast and ovarian cancer, the incidence of other cancer types did not appear to be greatly increased in BRCA2-associated families and did not warrant specific clinical follow-up in mutation carriers [57].

**NBS1**

In 1998 Varon et al mapped and cloned the gene responsible for Nijmegen breakage syndrome characterized by spontaneous chromosomal instability, immunodeficiency and predisposition to cancer. The NBS1 gene is located on 8q21 (OMIM 602667) [58]. The NBS1 protein product, called nibrin (also referred to as p95), is an integral component of hMRE11/hRAD50/NBS1 nuclease complex, acting in a double-strand break repair of human DNA [59].

Mutations in the NBS1 gene predispose to a range of cancer types. We recently reported a greater than expected prevalence of a founder 657del5 mutation in the NBS1 gene in consecutive MM patients with aggregations of breast cancer but this preliminary finding needs to be confirmed [60]. No germline NBS1 mutations have been found in familial skin MM to date.

**CHK2**

Malignant melanoma has been suggested to belong to the clinical spectrum of Li-Fraumeni syndrome (LFS, OMIM151623). In 1999 Blasina et al and Chaturvedi et al independently identified cell-cycle-checkpoint kinase 2 (CHK2, MIM 604373), one of the key mediators of cellular responses to DNA damage [61, 62]. The germline recurrent mutation in the CHK2 gene (1100delC in exon 10) has been found among two families with a phenotype suggestive of Li-Fraumeni syndrome [63]. The tumour spectrum of one of these families included MM. In a recent study germline 1100delC mutation in the CHK2 gene was reported in a patient with MM of the skin and three metachronous malignancies belonging to LFS tumour spectrum [64]. Thus, it seems that 1100delC of the CHK2 gene may be responsible for occurrence of very small proportions of MM cases, especially in families with Li-Fraumeni syndrome or Li-Fraumeni-like syndrome. No germline CHK2 mutations have been found in familial skin MM to date.

**MLH1, MSH2**

Germline mutations in the MLH1 (3p21, OMIM 120436) and MSH2 (2p22, OMIM 120435) genes can lead to Muire-Torre syndrome, a variant of hereditary non-polyposis colorectal cancer syndrome with an increased frequency of occurrence of skin malignancies, including MM. Both genes participate in mismatch repair system of DNA. There is a report of biallelic somatic inactivation of the MLH1 gene in a primary skin melanoma [65]. It seems that a small proportion of MLH1/MSH2 carriers could be at risk of developing MM. No germline MLH1/MSH2 mutations have been found in familial skin MM to date.

**XP-genres**

MM, as well as a large number of basal cell carcinoma and squamous cell cancer of the skin, is a characteristic feature of xeroderma pigmentosum syndrome (XP). XP is a group of disorders characterized by high sensitivity to sunlight with the development of skin malignancies at an early age. There are several variants of XP caused by different XP susceptibility genes, all of these genes are involved in UV-damaged DNA repair. Three most common forms of XP variants are: XPA (OMIM 278700), XPC (OMIM 278720) and XPD (OMIM 278730). Recently an increased risk of cutaneous melanoma in carriers of XPD polymorphisms has been reported [66, 67].

In the literature we found no data about germline mutations of XPA, XPC and XPD genes in familial melanoma to date.

**MC1R**

The MC1R gene (16q24, OMIM 155555) codes a protein that acts as the receptor for melanocyte-stimulating hormone (MSH). It has been reported that some germline allelic variants of the MC1R gene (Arg151Cys, Arg160Trp, Asp294His) conferred to fair skin/red hair phenotype associated with an increased risk of MM [68-70]. The same allelic variants independently of skin type are associated with an increased MM risk [69]. They also act as modifiers of the
melanoma risk in carriers of the CDKN2A mutations by increasing the penetrance from 50% to 84% in Australia and from 18% to 55% in the Netherlands [71, 72].

**Other factors**

Inherited traits explaining part of the familial risk of MM by modulating the response to UV radiation also include:

1) nevi, the risk of developing a melanoma increases with the number of nevi and their clinically atypical aspects (increase in size, red hue and/or ABCDE criteria: (A) asymmetry, (B) vague border, (C) variegated pigmentation, (D) diameter exceeding 5 mm, (E) elevation) [73, 74]. This risk is especially high in dysplastic nevus syndrome [75]. Recent twin studies indicate the contribution of both genetic factors and sun exposure to the number of nevi [76]. Analysis of familial transmission of nevi suggests a more complex mechanism than a single-gene effect [77]. Atypical nevi, present either in the familial or sporadic setting are regarded by dermatologists as strong indicators of an increased melanoma risk and should be either monitored or excised.

It should be mentioned that MM, especially a nodular type, can arise in apparently healthy skin;

2) skin type (liability to tan), the risk of MM is increased in persons with fair skin (limited capabilities of tanning) and red hair [78].

**Conclusions**

MM is a highly heterogeneous tumour type from a genetic perspective. Pedigree and clinical data of a proportion of familial MM suggest a hereditary syndrome caused by germline alterations of a single gene. Several different genes are involved in the development of MM. However, even when taken together they are responsible for less than 20% of all MM cases. It is thus necessary to perform association studies focused on identifying genetic markers that could be used in identifying patients with a high risk of MM. Evaluation of aggregations of MM and other malignancies, like breast cancer, could be essential in identifying relatives of MM probands being at high risk of developing malignancies other than MM. The ultimate goal is to apply in these cases prevention recommendations and surveillance protocols to reduce the disease risk.

**Prevention recommendations**

The use of higher sun protection factor sunscreens, avoidance of physical trauma of nevi.

**Surveillance protocols**

In the case of familial MM: melanoma patient, his first- and second degree relatives: half-yearly careful skin examination by the dermatologist. In cases with atypical nevi: skin examination should be performed every three months. Random removal of a large number of atypical nevi is not recommended. The removal of lesions in susceptible individuals should be indicated by clinical signs of malignant transformation (increase of size, red hue, bleeding, pruritus, etc.). Additionally the melanoma patient and his relatives should be screened for pancreatic cancer with an annual ultrasonography and computer tomography every three years.

In cases with familial aggregations with MM and malignancies (at least two cases) at different sites of origin, especially with MM diagnosed under the age of 55: breast cancer surveillance is suggested (yearly physical examination, ultrasonography and finally mammography starting from the age of 25).

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