

# Familial melanoma

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[Abstract](#)

[Key words](#)

[Definition / Diagnosis criteria](#)

[Differential diagnosis](#)

[Etiology](#)

[Clinical description](#)

[Diagnostic methods](#)

[Incidence](#)

[Associated cancers](#)

[Genetic counselling](#)

[Management](#)

[References](#)

## Abstract

*Malignant melanoma is a neoplasm of melanocytes, arising de novo or from a pre-existing benign nevus. Familial melanoma is described as a family in which either two first-degree relatives are diagnosed with melanoma, or families with three melanoma patients (irrespective of degree of relationship). The co-existence of melanoma and atypical nevi within families has been named familial atypical multiple mole-melanoma (FAMMM). Melanoma is hereditary in approximately 8-12% of cases. Studies of families with a high incidence of melanoma culminated in the identification of two susceptibility genes –CDKN2A and CDK4- the products of which are known to be components of tumour-suppression pathways. CDKN2A has an unusual and complex genomic organization: encodes two distinct tumour-suppressor proteins in alternative reading frames, INK4A (also known as p16) and ARF (also known as p14). The incidence of CDKN2A mutations among melanoma-prone families ranges from 25-40%. The mutation in CDK4 gene was identified in 2 melanoma families. Other cancers, besides melanoma, are observed: pancreatic carcinoma, other gastrointestinal cancers and breast cancer. In several families the co-occurrence of eye and skin melanoma is reported.*

*When a family has been diagnosed with familial melanoma, melanoma patients and their first-degree relatives should have yearly skin examinations from the age of 10.*

## Key words

Malignant neoplasm, familial atypical multiple mole-melanoma, hereditary cancer, CDKN2A gene, CDK4 gene, INK4A proteine, ARF proteine, p16, p14, MC1R receptor

## Definition / Diagnosis criteria

Malignant melanoma is a malignant neoplasm of melanocytes, arising *de novo* or from a pre-existing benign nevus, which occurs most often in the skin but also may involve other sites. The definition of hereditary melanoma is now described as a family in which either two first-degree relatives are diagnosed with melanoma, or families with three melanoma patients (irrespective of degree of relationship). The co-existence of melanoma and [atypical nevi](#) within families has been described and the syndrome

has therefore been named familial atypical multiple mole-melanoma (FAMMM) (Lynch *et al.*, 1978).

## Differential diagnosis

Macroscopic clinical diagnosis of malignant melanoma involves an error rate of about 10-20%, which means that in any individual case may not be simple to decide whether the diagnosis is malignant melanoma or some other condition (Braun-Falco *et al.* 2000). There are numerous skin lesions that lead one to consider

the possibility of malignant melanoma because of their shape, colour, and consistency. The most frequent misdiagnoses concern melanocytic nevus, pigmented seborrheic keratoses, pigmented basal cell carcinoma, pigmented dermatofibroma, and pigmented histiocytoma.

### Etiology

Melanoma is hereditary in approximately 8-12% of cases (Fountain *et al*, 1990).

Linkage-analysis studies of families with a high incidence of melanoma have contributed to the localization of a melanoma susceptibility gene to chromosome 9p21 (Cannon-Albright *et al*, 1992). Deletion studies in tumor-derived cell lines resulted in the cloning from 9p21 of the *MTS1* gene, which is now generally known as *CDKN2A* (cyclin-dependent kinase inhibitor) (Kamb *et al*, 1994; Nobori *et al*, 1994). Human cell division is regulated primarily at the G1-to-S or the G2-to-M boundaries. The sequential activation of cyclin-dependent kinases (CDKs) and their subsequent phosphorylation of critical substrates promote orderly progression through the cell cycle. The complexes formed by CDK4 and the D-type cyclins are involved in the control of cell proliferation during the G1 phase. CDK4 is inhibited by p16, also known as cyclin-dependent kinase inhibitor-2 (*CDKN2A*). *CDKN2A* acts as a true tumour suppressor gene and has a crucial role in cell cycle regulation and senescence. This locus has an unusual and complex genomic organization, as *CDKN2A* actually encodes two distinct tumour-suppressor proteins in alternative reading frames, *INK4A* (also known as p16) and *ARF* (also known as p14, or p19 in mice) (Quelle *et al*, 1995). The two alternative proteins products, p16 and p14, have a crucial role in cell death and apoptosis: 1) the Rb pathway for p16; 2) p53 pathway for p14 *ARF* (Alternative Reading Frame). The p16 protein is a cyclin-dependent kinase inhibitor (by binding to CDK4). If it is not inhibited, the CDK4 complex, in turn, phosphorylates the retinoblastoma protein, allowing a cell to progress through the G1 phase of the cell cycle. Thus, p16 acts as a tumor suppressor protein, and mutations in *CDKN2A* can result in unregulated cell growth and neoplastic progression.

The presence of *CDKN2A* germline mutations in individuals with familial melanoma provided definitive evidence that *INK4A* was important for melanoma suppression in humans. Data obtained from human tumors have implicated loss of *INK4A*, and with it pRB function, as the most significant mutational event at this locus in melanomagenesis (Chin *et al*, 1998). The incidence of *CDKN2A* mutations among

melanoma-prone families ranges from 25-40%, whereas only 0.2-2% of sporadic-melanoma patients (Aitken *et al*, 1999; Tsao *et al*, 2000). The p16 gene appears to be a rare, highly penetrant gene, which is transmitted in most families in an autosomal dominant fashion. p16 mutations have also been linked to multiple melanoma primaries, with or without a family history of the disease. However, the prevalence of p16 mutations, even in these highly susceptible individuals, was low (Hashemi *et al*, 2000).

The International Melanoma Genetics Consortium, in which research groups from all over the world participate, has recently investigated the penetrance of melanoma in *CDKN2A* mutation carriers and this has been estimated to be 67% by the age of 80 years. This same study also showed the penetrance figures in hereditary melanoma to be different depending on geographic location (58% in Europe compared with 91% in Australia and 76% in the USA). These differences between geographic locations were proportionate to the differences seen in sporadic melanoma, with the penetrance in Australia, USA and Sweden being 3.74 times higher than in Western Europe (Bishop *et al*, 2002). This geographical variation in *INK4A* penetrance parallels the baseline population incidences of melanoma for these regions, which is influenced to a large degree by the amount of UV-light exposure.

Another melanoma susceptibility gene is the gene which codes for CDK4, the protein to which p16 binds, on chromosome 12q13. The arg24-to-cys mutation in *CDK4* gene was identified as a germline mutation in 2 melanoma families that did not carry germline p16 (*INK4A*) mutations (Zuo *et al*, 1996). This mutation was detected in 11/11 melanoma patients, 2/17 unaffected, and 0/5 spouses. This mutation has a specific effect on the domain of CDK4 that binds p16 (*INK4A*) but has no effect on its ability to bind cyclin D and form a functional kinase. They concluded that the germline arg24-to-cys mutation in *CDK4* generates a dominant oncogene that is resistant to normal physiologic inhibition by p16 (*INK4A*). They noted that the only previous example of a dominant oncogene transmitted in the human germline was the *RET* gene that gives rise to [medullary thyroid carcinoma](#), [Multiple Endocrine Neoplasia](#) type 2A and type 2B.

### *MC1R* and melanoma

More recently, a pigmentation-associated predisposition to cancer has been indicated by the melanoma association of melanocortin-1 receptor (*MC1R*) polymorphic variants with the

red hair, fair skin, sun sensitivity and freckling phenotype, the so-called RHC "red hair colour" phenotype (Chin, 2003). The human MC1R is a seven-transmembrane G-protein-coupled receptor that is expressed on epidermal melanocytes. The MC1R ligand is melanocyte-stimulating hormone (MSH) and together these molecules comprise key determinants of the pigmentary process. An Australian study of 15 familial melanoma revealed that the presence of a single MC1R variant significantly increased the penetrance of CDKN2A mutation from 50% to 84%, and this increase was accompanied by a decrease in the mean age of onset from 58 years to 37 years (Box et al, 2001). In a separate study of Dutch melanoma families, an increase in CDKN2A mutation penetrance from 18% to 35% or 55% was also found in those with one or two MC1R variant alleles respectively (van der Velden *et al*, 2001). Both of these studies showed that the effect of MC1R on penetrance of the CDKN2A locus is primarily contributed by the common Red Hair Colour variants. The molecular basis of this gene-gene interaction on melanoma risk will no doubt be the focus of future genetic studies.

The genetics defects in the other families are unknown.

### Clinical description

Melanoma is a type of skin cancer that can often be recognized by its appearance. A changing mole is an important warning sign that a melanoma could be developing.

Based on clinical and histological criteria, four major types of malignant melanoma can be differentiated. The most frequent type of melanoma is *the superficial spreading melanoma*. It is a small lesion with irregular border and brown, red, white, blue, blue-black spots on trunk or limbs. *The nodular melanoma* is shiny, firm, dome-shaped brown, black, or pink bumps anywhere on skin. *The acral lentiginous melanoma* is irregular brown to black flat lesions on palms, soles, tips of fingers or toes, or mucous membranes; it can also be a brown or black streak under a finger or toenail. *The lentigo maligna melanoma* is a large brownish irregular spot with darker speckles on skin overexposed to sun, particularly the face or arms.

To diagnosis melanoma, the ABCDE rule for the pigmented skin lesion should be used: Asymmetric configuration, irregular Border, speckled Colour, Diameter of more than 5 mm, and Evolution (Friedman *et al*. 1985). A mole that increases in size, changes shape or colour is suspicious to be a melanoma. The diagnosis is confirmed by doing a biopsy of the entire lesion. The possible occurrence of [atypical nevi](#) - *ie*. benign melanocytic lesions- showing some

or all the ABCD criteria, is the main pitfall in melanoma diagnosis. In some cases, even the recent techniques for non-invasive diagnosis of melanoma (dermoscopy) are unable to reliably separate [atypical nevus](#) from early melanoma. Indeed, a number of benign nevi are referred to surgery in order to avoid leaving a melanoma unexcised. Currently, no clinical or histological difference between sporadic and familial melanoma is documented. Regarding microstaging, since familial melanoma occurs in kindred already affected by this tumor, the level of awareness as to early diagnosis (*ie*. habits for skin self-examination) is higher than in general population. This may lead to earlier detection. A lower frequency of second primary melanoma (about 5% of melanoma patients) is found.

### Diagnostic methods

The diagnosis of a malignant melanoma is based on clinical examination and epiluminescence microscopy. This is simple in most cases, but may be very difficult in some one. In any case, it is very much dependent on the physician's experience. Incisional biopsy is contraindicated because even if the result is negative, a risk of lymphatic or blood metastasis may exist. Thus, diagnosis should be histologically confirmed in each case. Consequently, the method of choice is excisional biopsy with histological exam. The microscopic examination is essential for the diagnosis of melanoma.

The tumor thickness is measured in mm according to Breslow technique, which a better prognostic factor rather than using anatomical structures (level of invasion) according to Clark. The risk of progression increases with the lesion's thickness, being low for lesions thinner than 1 mm. Ten-years survival of patients with invasive melanoma lower than 1,00 mm in thickness is about 90%. Conversely, survival is not more than 30-40% for those with thick lesions (4 mm or more)

The subsequent treatment is based on the thickness of the cancer, the location, and the presence or absence of melanoma elsewhere in the body.

### Incidence

The incidence of cutaneous melanoma in Caucasians has been growing at a rate of 3%-7% per year since the early 1960s. It has doubled in the last 20 years, and is increasing faster than any other cancer (Armstrong *et al*, 1996). In 1990, incidence of cutaneous melanoma in Italian population was approximately 7.6 cases per 100,000 per year (World standard population rate of 3.6 for men and 4.1 for women) (Balzi *et al*. 1997).

Approximately 6-18% of cutaneous melanoma patients have at least one first-degree relative with melanoma (Goldstein *et al.* 1995). Previous reports of a family history of melanoma varied depending on the geographical area. The incidence of melanoma is substantially higher among fair-skinner people, and familial aggregation reflects or contributes to the high risk. Also, population differences in age, family size, and environmental factors may affect familial aggregation. In the U.S.A. first-degree relatives with melanoma were present in 4.1% of 116 melanoma cases (Holly *et al.* 1987). In Denmark, among 474 patients, 3.0% had a first-degree relatives (Osterlind *et al.* 1988). In Italy, among 589 patients, 5.1% reported that at least one of their relatives had a melanoma (Calista *et al.* 2000).

### Associated cancers

There are numerous reports of melanoma families in which an exceptional number of other, often rare, cancers are observed (Lynch *et al.* 1981). Most significantly, an unusually high incidence of pancreatic carcinoma, either by itself or in conjunction with other gastrointestinal cancers and breast cancer, has been reported in several studies (Bergman *et al.* 1990; Borg *et al.* 2000). In a large-scale study, 10 melanoma families with a *CDKN2A* mutation were compared to 9 melanoma families without a *CDKN2A* mutation. The median age for melanoma was lower in both groups compared to the general population. The study revealed no significant difference in the prospective risk for melanoma, but it did show a striking difference in the prospective risk for other tumours. The risk of digestive cancers was increased by a factor 3 in the *CDKN2A* positive group because of the high incidence of pancreatic cancer (Goldstein *et al.* 1995).

Besides pancreatic carcinoma, in several families the co-occurrence of eye and skin melanoma is reported. Although *CDKN2A* gene inactivation by methylation plays a role in uveal melanoma (van der Velden *et al.* 2001), lack of germ line mutations in *CDKN2A* and *CDK4* indicate that hereditary eye melanoma seems to be a separate entity with separate casual genetic defect (Soufir *et al.* 2000).

### Genetic counselling

When the causative mutation is detected in a family (which for the majority of melanoma families is not the case), predictive DNA testing can be offered. Pre-symptomatic DNA testing is a predictive test for future risk and allows a family member to find out whether he/she is a carrier of the mutation that runs in the family, irrespective of melanoma development.

On the one hand, predictive testing allows the identification of individuals at highest risk of melanoma. This will ultimately lead to improved prevention and earlier detection. Beside the clinical advantages, the result may offer psychological security. Those who turn out to be non-carriers are relieved of the burden of the high risk factor, and also relieved of the burden of possible transmission to offspring (Duisterhof *et al.* 2001).

On the other hand, predictive DNA testing can be a psychological burden to people. A DNA test result affects not just one person, but has implications for closely related family member as well. First-degree relatives of a carrier have a 50% of risk to carry the same mutation. The offering of pre-symptomatic DNA testing to melanoma-prone families became the subject of debate shortly after the identification of the first melanoma susceptibility gene. The International Melanoma Genetics Consortium (Kefford *et al.* 1999) published all these debates. In familial melanoma, the interpretation of the test result is not well established. This is particularly true for the non-carriers (family members who receive a "good" test result): melanoma incidence is increased even in non-mutation carriers due to other as yet unidentified modifying genes (de Snoo *et al.* 2003). The increased risk for other cancer is suspected but no risk can be estimated as yet. This is particularly relevant regarding pancreatic cancer, which is not consistently, but frequently reported.

In conclusion, the International Melanoma Genetics Consortium does not yet recommend predictive DNA testing for familial melanoma, except in clearly defined research programmes. A good test result for non-mutation carriers would give false security: non-mutation carriers have an increased melanoma risk as well.

### Management

The early detection and treatment of malignant melanoma is of vital significance to the patient. Therefore the prophylaxis is of great practical importance. When a family has been diagnosed with familial melanoma, melanoma patients and their first- and second-degree relatives should have yearly skin examinations from the age of 10 onwards. An important aim of these annual clinical visits, besides the specialist skin screening, is to educate the patient about self-examination of the skin and sun protection (de Snoo *et al.* 2003). It is necessary for the patient always to present for examination if a pigmented growth occurs on the skin or changes of any type occur within pigmented skin conditions.

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