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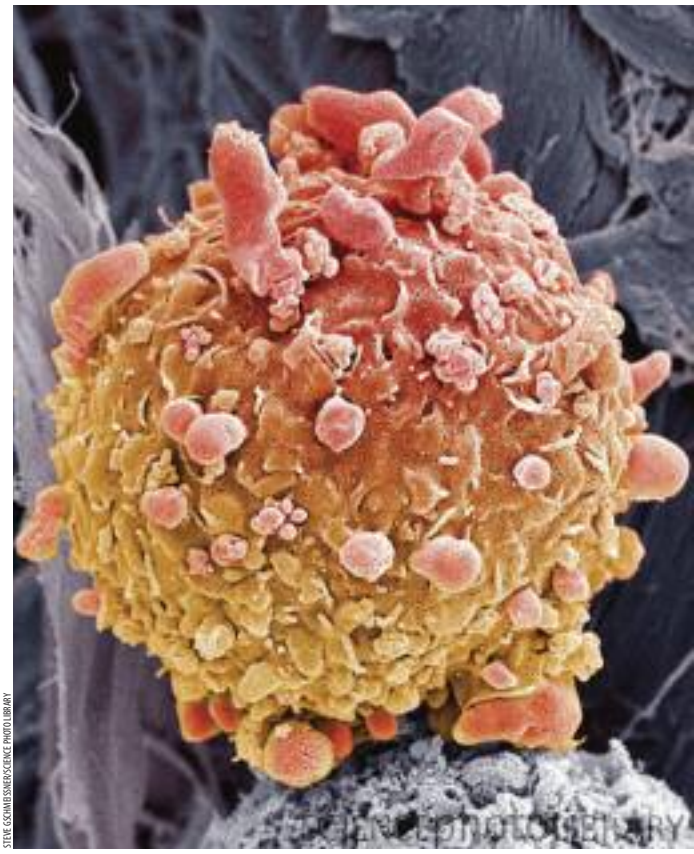
The genetics of skin cancer

Like all cancers, melanoma can cluster in some families, with 10% of melanoma cases reporting a family history. The hunt for melanoma genes started in the early nineties, when it was observed that many melanomas lost similar chromosomal regions. This article describes progress in our understanding of the genetics of melanoma.

Germline mutations in rare high-penetrance genes

Early cytogenetic studies documenting regions of chromosomal loss in melanomas, in conjunction with linkage analyses based on melanoma families led to the discovery, in 1994, of a major tumour suppressor gene, p16 (also known as CDKN2A) on chromosome 9p21.[1] In melanoma families, p16 is mutated in the germline, so it is transmitted down generations, by comparison with most other cancers where this gene is only altered in the tumour. The p16 is a crucial cell cycle gene that controls senescence in all cells. The Melanoma Genetics Consortium, established in 1996, has recruited melanoma families from all over the world, and it is now estimated that around 40% of melanoma families have p16 germline mutations.[2] The prevalence of p16 mutations in sporadic melanoma is very low – around 1–2.5%.[3] The increased melanoma risk in relation to p16 mutations is observed in most Caucasian populations in Europe, the USA and Australia, but appear to be more common in Europe compared with Australia.[4] The prevalence of p16 mutations in families depends on the number of melanomas within the family.[5] Individuals with multiple primary melanomas are also more likely to have p16 mutations, with up to 15% being positive.[3]

There are more than 60 different types of p16 mutations reported in the world.[2] However, most melanomas are not attributed to germline p16 mutations, especially in the non-familial setting, and many other common, low penetrance melanoma genes remain to be discovered. Testing for p16 mutations is not clinically indicated in melanoma patients with a positive family history, as the chance of detecting a mutation is small, especially in families with only two melanomas. The mutation status does not change the management of the patient as the decision to follow up is made on the basis of the family history and the presence of multiple atypical naevi.[5] Furthermore, this test only screens the coding region of p16, so is not completely sensitive. Melanoma can also be found in family cancer syndromes, with a susceptibility to pancreatic tumours, osteosarcoma, brain tumours, breast cancers and many other cancers. Therefore, melanoma is likely to share susceptibility genes with other tumours.[6]



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■ Coloured scanning electron micrograph of a skin cancer cell

Common low-penetrance genes

Collaborative studies pooling thousands of melanoma samples have recently identified common low penetrance genes that predict melanoma risk.[7–10] These genes are mostly involved in pigmentation, but two new genes have also been discovered, which confer a risk of melanoma by predisposing to large numbers of naevi.[9] These discoveries are important, as these gene variants are much more common and, therefore, may be more useful for screening. However, the risk of melanoma associated with these genes is smaller than the risks associated with p16, with relative risks compared with the general population in the order of 1.5. Many more genes are likely to be involved, and the search continues.

Somatic mutations

Loss of the 9p21 locus where the tumour suppressor gene p16 lies can also be found in a large proportion of sporadic melanomas, and this increases

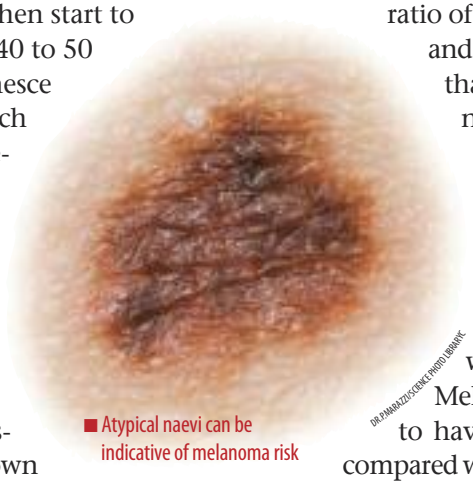
with the progression of the disease. The frequency of mutations in p16 in these tumours is not high, so other mechanisms of p16 inactivation, such as methylation, may explain this, or it may be that other tumour suppressor genes remain to be discovered in the same region.[11] The BRAF oncogene is also commonly mutated, affecting over 70% of melanomas.[12] Mutated BRAF melanomas are more likely to be tumours present on intermittently exposed body sites in association with multiple naevi, but with little sun damage. Mutations in p53 are also found in melanoma, but these are more common in lentigo maligna or melanoma on sun-exposed sites in older patients with sun damage and very few naevi.[13] Other somatic mutations in genes such as c-kit have been linked to melanoma of the mucosa or the palms and soles.[14]

The genetics of risk factors for melanoma

Naevi

An excess number of naevi is the most powerful predictor of risk for melanoma with odds ratios for more than 100 naevi, or more than two atypical naevi, in the order of five–ten, which is far greater than any relative risks associated with sun exposure[15,16] The atypical mole syndrome phenotype, characterised by multiple common and atypical naevi, is found in 15% of sporadic melanoma cases and 2% of controls, and is an important risk factor in all caucasian populations irrespective of levels of sun exposure.[16,17]

Naevi are benign melanocytic tumours, which start to appear in childhood, increase in number steadily in early adulthood, then start to decrease gradually from age 40 to 50 onwards. Therefore, naevi senesce with age, and the speed at which this occurs varies greatly between individuals.[18] Why naevi decrease in number with age is unknown, but it appears that in subjects with a high number of common and atypical naevi this decrease with age occurs later, reflecting a delayed senescence. A recent study has shown that excess numbers of naevi are associated with longer telomeres in white blood cells, so persistent naevi may be a marker of delayed aging.[18] Twin studies in the UK and Australia have shown that 60% of the variation in naevus number is explained by genes, and that the contribution of additive genetic effects increases with age.[19–21] Recent collaborations between Australia and the UK, using genome-wide association studies based on more than 4,000 healthy individuals, have led to the discovery of new gene variants that predict naevus numbers, and these were replicated in very large melanoma case-control studies. This is the first time that common low penetrance genes for melanoma acting via naevus number have been discovered.[9]



■ Atypical naevi can be indicative of melanoma risk

The atypical mole syndrome is found in 2–6% of the normal population and is predictive of an increased risk of melanoma. This phenotype can also be found in individuals belonging to kindreds with rare cancer syndromes in the family, such as neurofibromatosis, retinoblastoma and Li-Fraumeni syndrome, but is also found in families with an excess of cancers, such as breast cancer, cancer of the pancreas, brain tumours and osteosarcoma. This suggests that multiple atypical naevi may be a marker of cancer susceptibility in general, and not just of melanoma.[6,22] Therefore, it is important to take a family history of all cancers in patients with the atypical mole syndrome, as this may change the follow-up strategy. It is not possible to follow all atypical mole syndrome patients, but a personal or family history of melanoma, or an excess of cancers in the family, is associated with an increased risk of melanoma, and these patients should be followed up as well as educated about self-examination.

An excess number of naevi is the most powerful predictor of risk for melanoma

Genetics of skin pigmentation

Having fair skin, fair hair and blue eyes makes an individual more prone to melanoma, with an odds ratio of 2.[23] However, research in skin and hair pigmentation has revealed that the link with melanoma may not be explained by pigmentation alone. Fair skin types are more likely to have several variants in the MC1R melanocortin 1 receptor (MC1R) gene, but variants are very common and do not always predict skin colour. Melanoma patients are more likely to have one or two MC1R variants compared with controls; these increase the risk of melanoma up to threefold, depending on the number of variants.[24] Patients with more MC1R variants also appear to have their melanoma at a younger age, compared with those with the wild type gene. The presence of both MC1R variants and p16 mutations increases the risk of melanoma even further.[24] MC1R variants are more likely to be found in melanoma with somatic BRAF mutations, which would imply there are interactions between

pigmentation genes and the BRAF pathway.[25] Recent genome-wide analyses looking for common single-nucleotide polymorphism variants associated with melanoma have mainly found associations with pigmentation genes such as MC1R, ASIP, TYR, TYRP1 and Agouti, among others.[7,8,10]

Research into melanocyte stem cells and new targets for melanoma treatment

Progress has been made in the research on melanocyte stem cell biology. These cells are present in the hair bulge (part of the developing hair follicle), but, more recently, have also been found in the dermis. Undifferentiated melanocytes are one of the most pluripotent cells, as they can also differentiate into adipocytes, chondrocytes, osteoblasts or endothelial cells, depending on the micro-environment during embryogenesis, which, via different signals, directs the cells to different lineage.[26] Genes such as MITF, SOX9 and SOX1O, among many, are important for melanocyte differentiation, and MITF has recently been associated with melanoma susceptibility.[27,28] It is well known that melanoma can behave very differently in terms of its potential to grow quickly and/or metastasize, and research into these pluri-potent cells, and the micro-environment that decides their fate, may lead to important discoveries with potential therapeutic targets.[29,30] Multiple pathways are activated in melanoma differentiation, involving the CDKN2A, CDK4, AKT3, p53, c-kit, GAB2, NRAS, BRAF and PTEN pathways, as well as many others.[31] New therapeutic targets based on these pathways are currently being tested in melanoma. Various types of melanomas are being targeted differently, with melanoma of the palms and soles with cKIT mutations being treated with cKIT inhibitor, and other types of melanomas being targeted with new specific BRAF mutant V600E inhibitors.[31] Therefore, it is likely that looking at genetic changes in the tumour may, in the future, be an important step towards delivering the best targeted therapy for this type of tumour ■

Key points

- Up to 40% of melanoma families with two or more melanomas may carry a p16/CDKN2A mutation.
- Melanoma in the familial setting is more likely to present at a younger age, be associated with a large number of naevi and be a superficial spreading melanoma type.
- Testing for p16 mutations in melanoma families does not change the follow-up strategy, so is not recommended outside the research setting.
- Melanoma can be caused by rare, high-risk and high-penetrance genes such as p16/CDKN2A, but the prevalence of these mutations is rare outside the familial setting.
- Common low penetrance genes conferring a risk of melanoma have now been identified and mainly involve pigmentation genes.
- New common low-penetrance genes associated with high naevus counts have recently been identified and these genes are also melanoma genes.

Declaration of interest.
None declared.

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