Genetic predisposition to ocular melanoma

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CLINICAL STUDY

Abstract

Uveal melanoma is the most common primary intraocular malignancy, with an annual incidence of 6 per million. The environmental factors known to increase the risk of cutaneous melanoma appear to be less important in ocular melanoma and it is conceivable that host factors have a greater impact. The coexistence of ocular and cutaneous melanoma in some patients suggests a predisposition to both types and implicates mutations in the *CDKN2A* gene in a proportion of these cases. An association between ocular melanoma and breast and/or ovarian cancer has also been reported and recent studies of breast cancer families strongly implicate *BRCA2* as a predisposition gene. Other more common genes predisposing to ocular melanoma may be of low penetrance. An example of a gene in this class is *MC1R*, which affects host response to ultraviolet radiation. Identification of genes conferring an increased risk of ocular melanoma should provide insights into the pathogenesis of this tumour. Furthermore, it offers an opportunity to identify individuals at a high risk who may benefit from targeted surveillance. At present the identification of such individuals is restricted to the small number belonging to *BRCA2* families and those with the atypical mole syndrome.

Key words *BRCA2*, *CDKN2*, Genetics, Ocular melanoma

Uveal melanomas are the most common primary intraocular malignant tumour (incidence 6 per million per year; lifetime risk 1 in 2500).[1–3] They differ substantially in their incidence and biological behaviour from cutaneous melanoma.[1–6] In contrast to cutaneous melanoma, the peak incidence of uveal melanoma occurs between 50 and 70 years of age and metastases are common (related to histology and site). Half the patients developing uveal melanomas die of their disease within 15 years after treatment.[4]

Environmental, host and genetic factors involved in the pathogenesis of uveal melanoma have not been clearly defined.[6–8] The role of sunlight as an environmental risk factor for uveal melanoma is controversial,[9–17] although the tendency to develop uveal melanoma is greater in whites compared with blacks.[5,6] There has been no evidence for an increase in eye cancer incidence or mortality over the last 20 years in any part of the world, even in countries such as Australia which have seen a rapid increase in cutaneous melanoma cases.[9,10] Furthermore, there is little variation in the incidence of uveal melanoma within or between countries.[12] It is therefore probable that host factors play a greater role in the development of ocular melanoma than in cutaneous melanoma.

Epidemiological evidence for a genetic predisposition to uveal melanoma

Silcock[18] was the first to question whether there could be a hereditary basis for uveal melanoma when he reported a mother and daughter with the disease in 1892. Since then there have been over 50 further reports of ocular melanomas occurring within families.[19,20] Some uveal melanomas are associated with neurofibromatosis[21] or Gorlin's syndrome;[22] however, the vast majority of familial cases reported are non-syndromic. Although the familial occurrence of uveal melanoma is rare there is strong statistical evidence that it is not coincidental. In a systematic survey of a series of patients with primary uveal melanoma, Singh *et al*.[23] identified 17 kindreds with a first-degree relative affected with primary uveal melanoma. The expected number of affected first-degree relatives was 0.81 (RR = 20.99; 95% CI, 12.2–33.6). The majority of the familial cases reported are one- or two-generation families and have only one affected member in addition to the proband. However, a few contain three or more cases of ocular melanoma and are compatible with the inheritance of an autosomal dominant gene with incomplete penetrance.

Individuals with a cancer predisposition tend to develop the disease at an earlier age, have bilateral involvement of paired organs and are at an increased risk of developing multiple primary cancers at different sites. The mean ages at diagnosis in familial and sporadic uveal melanomas reported by Canning and Hungerford[19] were 42 and 56 years respectively. Several cases of bilateral melanoma of the uvea have been reported, including one with a documented family history of uveal melanoma.[24–27]

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A number of inherited susceptibility genes tend to cause cancer at several sites. Any excess of cancer in relatives at sites other than the eye may therefore reflect in part the pleiotropic effects of an inherited predisposition. There are a number of anecdotal reports of uveal melanoma in association with other cancers.[28–30] One of the most spectacular of these is a family first reported by Silcock,[18] which has been the subject of a recent follow-up study.[28] Three of eight individuals who developed uveal melanoma also developed breast cancer (bilateral breast cancer in one case). Similarly striking is a case of bilateral uveal melanoma in association with primary bilateral ovarian carcinoma reported by Mullaney *et al*.[29] A relationship between ocular melanoma and other cancers is supported by some,[20,32,34] but not all,[31,33] systematic studies. In an analysis of 27 uveal melanoma families, Sing *et al*.[20] found the risk of a second primary was increased 4-fold. The most common malignancies observed in family members were breast, prostate and cutaneous melanoma. In a follow-up study of 32 251 women with ovarian cancer the risk of ocular melanoma was increased 4-fold.[32] An increased risk of melanoma of the skin or eye has also been reported in a follow-up study of 18 010 breast cancer patients.[34]

Predisposition genes

Approximately 10% of cutaneous melanomas arise in individuals with a family history of the disease. About 5% are truly hereditary;[35,36] in these families predisposition to melanoma is transmitted as an autosomal dominant trait with variable penetrance.[37] A number of these cases, linked to chromosome 9p13.22,[38] are caused by mutations in the *p16* gene (*CDKN2A*).[39,40] Individuals with multiple dysplastic naevi (dysplastic naevus syndrome, also known as atypical mole syndrome or AMS, are at increased risk of developing melanoma and are frequently observed in familial melanoma kindreds.[41,42] In families where there is a family history of melanoma and dysplastic naevi, the risk of developing melanoma in susceptible individuals approaches 100%. Not all melanoma-prone families possess dysplastic naevi, so that the concordance of these two syndromes is not absolute.[43,44] Given the common neural crest origin of uveal and skin melanocytes, any inherited syndrome associated with an increased uveal naevus count may be a precursor for some uveal melanomas. Uveal and conjunctival naevi all occur more commonly in patients with the dysplastic naevus syndrome.[45] Bataille *et al*.[46] examined the skin of 207 consecutive patients with ocular melanoma. Five patients had primary melanoma of the skin (relative risk of cutaneous melanoma 12.5). Furthermore, 3 of these 5 cases also had the AMS phenotype. Similarly in a systematic study of 109 uveal melanoma patients reported by van Hees *et al*.[47] 2 patients had cutaneous melanomas and 4 had first-degree relatives affected with melanoma. The linking factor in three of the cases was AMS. The coexistence of ocular and cutaneous melanoma in both of these studies supports a predisposition to both types of melanomas in some family cancer syndromes, particularly AMS. Uveal melanoma risk is also related to the density of common naevi in a similar manner to cutaneous melanoma,[48] and naevi are known to be strongly heritable.[49]

Little is known about the molecular mechanisms involved in the development of uveal melanoma. In addition to the possible involvement of the *CDKN2A* gene on chromosome 9, recent work strongly suggests that mutations in the breast cancer susceptibility locus, *BRCA2* on chromosome 13, may also be involved.[50] Whilst the greatest cancer risks associated with *BRCA2* mutations are breast and ovarian cancer, with lifetime risks of 84% and 27% respectively,[51] 2 of the 14 breast cancer families linked to *BRCA2* reported by Wooster *et al*.[50] had cases of ophthalmic cancer, one of which was confirmed as a uveal melanoma. Data to support *BRCA2* as a uveal melanoma predisposition gene were presented at a recent meeting of the Breast Cancer Linkage Consortium.[52] Sinilikova *et al*.[52] reported that in a series of 62 ocular melanoma patients selected for a history of breast and ovarian cancer or ocular melanoma, 7 harboured rare germline alterations in *BRCA2*. All 3 of the patients with pathogenic mutations (5%) had a history of breast cancer.

Observations from *BRCA2*-linked breast cancer families suggest that the risk of ocular melanoma is increased 20-fold, although the confidence limits are extremely large. On this basis, and assuming a population frequency of *BRCA2* mutations of 1 in 1000, *BRCA2* mutations may account for approximately 2% of ocular melanoma cases. The possible involvement of *BRCA2* in the aetiology of uveal melanomas may underlie the association between this disease and breast and ovarian cancers seen in some patients. *BRCA2*-associated breast cancers have a greater propensity to being higher-grade tumours than sporadic forms of the disease;[53] it is therefore possible that *BRCA2*-associated ocular melanomas may also have a more aggressive tendency.

Although there is compelling circumstantial evidence implicating *CDKN2A* in the aetiology of uveal melanomas, there is currently no direct evidence. No mutations were detected in the studies reported by Wang *et al*.[54] and Tsao *et al*.[55] though these were based on analyses of only 37 and 33 ocular melanoma patients respectively.

Mutations in genes such as *BRCA2* are likely to confer a significant risk of uveal melanoma. In addition to this type of susceptibility gene, it is probable that there will be other predisposition genes for ocular melanoma that will confer more modest risks, but which will be more common. Candidates genes in this class are those that affect the host response to exogenous risk factors. Tissue response to ultraviolet irradiation is an important factor in determining melanoma risk and light skin and irides (blue, grey or green) are associated with an increased risk of uveal melanoma. Both of these traits are heritable.

The genetics of pigmentation are complex. It is known, however, that the relative proportions of phaemomelanin and eumelanin in tissues are regulated by melanocyte stimulating hormone (MSH), which acts via its receptor (MC1R) on melanocytes to increase the synthesis of eumelanin. In mice, mutations at the *MC1R* gene affect the pattern of melanogenesis, resulting in changes in coat colour. In man, *MC1R* sequence variants cause differences in the binding affinity of the MC1R for MSH[56] and are found predominantly in individuals with fair skin and blue eyes.[57] Furthermore, *MC1R* variants have been shown to confer a 4-fold increase in risk of melanoma (95% CI, 1.48–10.35).[58] It is conceivable that as well as being a risk factor for cutaneous melanoma, mutations in the *MC1R* gene could be a risk factor for ocular melanoma.

Conclusions

There is now considerable evidence that, like many cancers, a subset of uveal melanomas are caused by an inherited predisposition. Given that the prognosis associated with ocular melanoma is poor, an attractive proposition to reduce morbidity and mortality is to identify these susceptibility genes. This will allow those at risk to be identified and offered targeted surveillance or other measures. Furthermore, the identification of these genes should provide insights into the pathogenesis of uveal melanoma in general. At present the identification of a high-risk group is restricted to small numbers, comprising individuals from *BRCA2* families and individuals with the AMS.

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