The genetic secrets of Uveal Melanoma

Uveal melanoma (UM) is the most common primary cancer occurring in the eyes of adults, with 1/100,000 new cases per year in the Western world. Most patients are between 60 and 65 years old. Although it is a relatively rare type of cancer, UM is highly aggressive, and up to 50% of patients eventually develop metastases, usually to the liver. The median survival time of patients with liver metastases is only 4 to 15 months, since there is currently no effective treatment available for metastases.

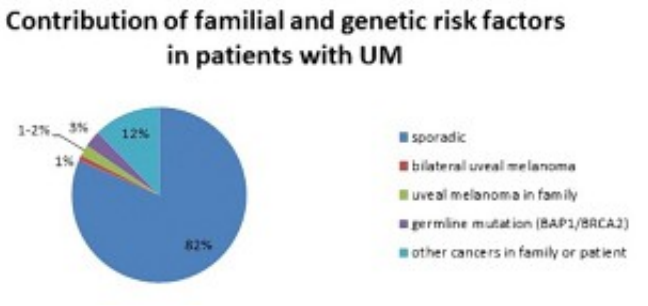

Fig. 1. Contribution of familial and genetic risk factors in patients with UM.

The majority of UM cases occurs in white individuals and accordingly a fair skin color, inability to tan, light iris color and blond hair have been found to be significant risk factors. These observations, in combination with the facts that UM in both eyes is more common than predicted by chance alone, 1-4% of patients have family members with UM, suggest that there is an underlying genetic susceptibility in patients for developing UM (Fig. 1). Supporting this notion, other cancers, such as skin melanoma, liver, pancreas, prostate, stomach and kidney cancer have been shown to occur more frequently in UM patients than expected based on the frequency of the cancer in the general population.
This emphasizes the importance of a thorough understanding of the genetic biology of UM, in order to implement adequate screening guidelines and to identify high risk patients in an early stage.

However, although a genetic influence seems to be important, the exact genetic factors playing a role in the development of UM have not yet been elucidated. The only gene clearly associated with UM is the *BAP1* gene on chromosome 3, which has also been shown to be mutated in skin and kidney tumors. Germline mutations in this gene have been reported in 1-2% of UM patients and 10-15% of UM families. Patients with germline mutations in *BAP1* are also at a higher risk for developing skin melanoma, kidney cancer, and mesothelioma.

Another gene that is possibly correlated with UM is the *CDKN2A* gene, which is known to play a role and skin melanoma. One family with UM and skin melanoma has been described with a

CDKN2A mutation suggesting a role for *CDKN2A* in UM besides skin melanoma. However, disputing this is a large study that screened 385 patients with UM for germline mutations in among others *CDKN2A,* and found only one pathogenic mutation in *CDKN2A.*

The genes important in the regulation of skin, hair and eye color have also been the subject of genetic studies in UM patients. However, the genetic background of these physical characteristics is complex and involves more than one gene. Nevertheless, two genes that are frequently mutated in UM, the *GNAQ* and *GNA11* genes, are known to affect the darkness of both hair and skin color. On a tumor level, besides *BAP1*, there are several other genetic aberrations shown to be correlated with UM. This include chromosomal aberrations such as loss of one copy of chromosome 3, gain of the long arm of chromosome 8, which are both related to a bad prognosis, while the gain of the short arm of chromosome 6 is correlated with a favorable outcome. Recently, mutations in the genes *SF3B1* and *EIF1AX* have been associated with a good prognosis as well.

In conclusion, some UM patients seem to have a genetic susceptibility for UM and possibly for other cancers as well. While there is a lot of progress made in understanding the genetics of UM, the secrets are not revealed. A thorough understanding of the genetic background of UM on a germline and on a tumor level is relevant for comprehending the pathogenesis of this disease and will provide opportunities for the establishment of appropriate screening guidelines to improve survival.

Publication

The genetic basis of uveal melanoma.
Nielsen M, Dogrusöz M, Bleeker JC, Kroes WG, van Asperen CA, Marinkovic M, Luyten GP, Jager MJ.
J Fr Ophtalmol. 2015 Jun