Editorial



# A genetic link between blue eyes and black cancer

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*Comment on:* Ferguson R, Vogelsang M, Ucisik-Akkaya E, *et al.* Genetic markers of pigmentation are novel risk loci for uveal melanoma. Sci Rep 2016;6:31191.

Received: 06 June 2017; Accepted: 19 June 2017; Published: 20 June 2017.

doi: 10.21037/jphe.2017.06.02

**View this article at:** http://dx.doi.org/10.21037/jphe.2017.06.02

Uveal melanoma is a malignant tumor that originates from melanocytic cells in the iris, ciliary body and chorioid of the eye in 4%, 6%, and 90% of patients, respectively (1). At 5.1 cases per million per year, the incidence of this tumor is low (1). However, there are marked differences worldwide (2) and the variation of incidence appears to be associated with differences of host factors related to melanocyte functioning (3). Specifically, iris color, skin color, and ability to tan are associated with risk of uveal melanoma (3). These host factors are heritable traits and the distribution of these traits is variable between different ethnicities of the human (4).

With respect to variation of skin color it is plausible that differences between ethnicities are at least in part the result of evolutionary adaptation with the aim to balance the beneficial and detrimental effects of sunlight exposure and this can explain the covariance of geographical localization and skin color between human populations (4). A relevant detrimental effect of sunlight is increased risk of certain cancers of the skin including cutaneous melanoma. Mechanistically this can be explained by mutagenic action of the UV part of the sunlight spectrum (5). In the case of uveal melanoma, however, it is debatable if a relevant UV exposure of potential target cells exists because most of the UV part of the spectrum is absorbed by the different structures of the eye before reaching the chorioid (6). In fact, results epidemiological studies provide no unequivocal support for an association between sunlight exposure and the incidence of uveal melanoma (6).

Few factors other than pigmentation related host traits are known to be correlated to the risk of uveal melanoma and some of these correlations are difficult to explain mechanistically (7). For arc welding, which is an occupational risk factor, mechanisms linking cause and effect might be construed (7). For other risk factors that have been uncovered by epidemiological studies, e.g., occupational cooking, the mechanisms suggested to underlie the purported cause and effect relationships are at best esoteric (8). Only few patients develop uveal melanoma because of rare, functionally inactivating gene mutations that cause a heritable cancer predisposition with high penetrance (familial cancer) (9). Prior to the study by Ferguson *et al.* (10), no variant allele with moderate to high allele frequency in a population, i.e., a genetic polymorphism, has been associated with risk to uveal melanoma.

In recent years, technical advances in parallel genotyping of polymorphic variants have enabled genome wide analyses (genome-wide association study, GWAS) and these have resulted in the discovery of numerous genetic differences that are associated with various human traits [one way to get access these data is described here (11)]. In the case of rare traits, such as uveal melanoma, the numbers of cases and controls required to detect risk factors of moderate effect size are difficult to obtain. Therefore, Ferguson *et al.* did not use a genome wide approach, i.e., a GWAS, but analyzed a small set comprising 28 genetic variants.

The selection of these genetic variants was motivated by the assumption that uveal melanoma shares heritable risk factors with another melanocytic malignancy, cutaneous melanoma. This assumption is plausible because some host factors associated with risk, most prominent iris color and skin color, are shared between uveal melanoma and cutaneous melanoma and, at the same time, are heritable

 

traits (5). Moreover, some of the very rare families with aggregation of uveal melanoma also show an aggregation of cases with cutaneous melanoma (12). However, it must be pointed out that uveal melanoma and cutaneous melanoma show distinct landscapes of somatic genetic alterations (13) and this is in line with their disparate clinical behavior.

Compared to melanoma of the uvea, cutaneous melanoma is frequent and this has facilitated population-based genome-wide association studies. Several published GWASs have identified association between variation at genetic loci and risk of cutaneous melanoma (14). Many of these loci are located within or next to genes that have also been associated with pigmentation phenotypes that are known host factors. Some other loci point to the influence of heritable variation in DNA maintenance pathways (14). In addition, there are loci for which the mechanisms underlying the observed association are still unresolved (14).

Ferguson *et al.* determined the genotypes of 28 single nucleotide polymorphisms linked to pigmentation traits and/or cutaneous melanoma in a population of 272 patients with uveal melanoma and 760 controls of European ancestry. Their main finding was that the risk of uveal melanoma was associated with genetic variation at 3 correlated SNPs ($r^2$ >0.5) localized in the HERC2/OCA2 gene region. In several independent studies, genetic variation in this region was identified to have the strongest influence on iris color, as well as having associations with skin and hair color in European derived populations (4,14). Specifically, of the three SNPs highlighted by Ferguson *et al.*, blue-brown eye color in Europeans can be explained almost in full by the genotype of rs12913832 (15). Considering that rs12913832 is part of a haplotype spanning 166 kB on chromosome 15 (16) is important to point out that the single nucleotide change (NM_004667.5:c.13272 + 874T > C) that defines rs12913832 alters the recognition site for a helicase-like transcription factor and is postulated to lead to decreased expression of OCA2 protein in melanocytes (15,17) Consequently it is plausible that the phenotypic consequences depend at least in part on the rs12913832 genotype rather than on the action of numerous other variants that are in linkage disequilibrium to the C allele of rs12913832.

The study by Ferguson *et al.* confirms the link between the inherited genetics of pigmentation and uveal melanoma risk that previously was established on the phenotype level only. In fact, as (I) in European derived populations most of the variation of iris color is determined by rs12913832 and (II) phenotypic variation of iris color is associated with uveal melanoma risk it follows, if (I) and (II) are true, that rs12913832 is associated with uveal melanoma risk. It is also reassuring that the effect sizes of iris color and rs12913832 genotype are comparable [OR 1.78 and 1.75, respectively (3,10)]. It must be pointed out that absolute risk of individuals homozygous for the rs12913832-C-allele is still low. The effect of this allele on risk is a far cry from the impact of variants that cause familial uveal melanoma and are associated with high penetrance (i.e., absolute risk).

With only 272 patients the study has limited power. It is plausible that the remaining subset of variants in the selection by Ferguson *et al.* may have risk effects of smaller size. Therefore, the author's suggestion of a larger studies, preferably as part of national or international consortia is well justified. In aggregation, genotype data may help to delineate individual risk profiles and this may aid in improving patient management. Moreover, the results of these studies may also help to answer the fundamental question of why the two melanocytic malignancies, cutaneous and uveal melanoma, display vastly disparate sets of somatic genetic alterations.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the editorial office, *Journal of Public Health and Emergency*. The article did not undergo external peer review.

*Conflicts of Interest:* The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jphe.2017.06.02). The author has no conflicts of interest to declare.

*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/jphe.2017.06.02
**Cite this article as:** Lohmann D. A genetic link between blue eyes and black cancer. J Public Health Emerg 2017;1:63.