Different Pigmentation Risk Loci for High-Risk Monosomy 3 and Low-Risk Disomy 3 Uveal Melanomas

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Abstract

Background: Uveal melanoma (UM), a rare malignant tumor of the eye, is predominantly observed in populations of European ancestry. UMs carrying a monosomy 3 (M3) frequently relapse mainly in the liver, whereas UMs with disomy 3 (D3) are associated with more favorable outcome. Here, we explored the UM genetic predisposition factors in a large genome-wide association study (GWAS) of 1142 European UM patients and 882 healthy controls.

Methods: We combined 2 independent datasets (Global Screening Array) with the dataset described in a previously published GWAS in UM (Omni5 array), which were imputed separately and subsequently merged. Patients were stratified according to their chromosome 3 status, and identified UM risk loci were tested for differential association with M3 or D3 subgroups. All statistical tests were 2-sided.

Results: We recapitulated the previously identified risk locus on chromosome 5 on CLPTM1L (rs421284: odds ratio [OR] = 1.58, 95% confidence interval [CI] = 1.35 to 1.86; P = 1.98 × 10^-9) and identified 2 additional risk loci involved in eye pigmentation: IRRF4 locus on chromosome 6 (rs12203592: OR = 1.76, 95% CI = 1.44 to 2.16; P = 3.55 × 10^-5) and HERC2 locus on chromosome 15 (rs12913832: OR = 0.57, 95% CI = 0.48 to 0.67; P = 1.88 × 10^-11). The IRRF4 rs12203592 single-nucleotide polymorphism was found to be exclusively associated with risk for the D3 UM subtype (ORD3 = 2.73, 95% CI = 1.87 to 3.97; P = 1.78 × 10^-7), and the HERC2 rs12913832 single-nucleotide polymorphism was exclusively associated with risk for the M3 UM subtype (ORD3 = 2.43, 95% CI = 1.79 to 3.29; P = 1.13 × 10^-9). However, the CLPTM1L risk locus was equally statistically significant in both subgroups.

Conclusions: This work identified 2 additional UM risk loci known for their role in pigmentation. Importantly, we demonstrate that UM tumor biology and metastatic potential are influenced by patients’ genetic backgrounds.
Asian Pacific Islander ancestry (9,10). Fair skin and blue–gray eyes are also risk factors for UM (11). With the hypothesis that higher frequency of risk alleles exists in populations of European ancestry to explain UM epidemiology, we performed the first genome-wide association study (GWAS) in UM and identified rs421284 as the leading single-nucleotide polymorphism (SNP) on the CLPTM1L/TERT risk locus on chromosome 5p15.33. Moreover, a trend for association between variants in CLPTM1L/TERT (SNP) on the risk locus on chromosome 5p15.33. Moreover, a trend for association between variants in OCA2 and IRF4 was observed (12). Recently, another UM GWAS identified 11 loci with a P value of association less than 10⁻⁵, but none reached statistical significance (13).

The CLPTM1L risk allele identified by our first UM GWAS had a higher frequency in individuals of African American ancestry compared with Europeans and thus could not explain the peculiar prevalence of UM in individuals of European ancestry (12). To identify additional UM risk loci in the European population, we increased the power of our GWAS by performing genome-wide genetic imputation and by accruing 1142 UM patients and 882 controls, a threefold increase of our first study, allowing subgroup analysis depending on chromosome 3 status.

Methods

Study Populations

This study was approved by the ethical committee and internal review board at the Institut Curie. Blood samples were obtained from 946 UM patients who consented to participate in the study and from 496 control individuals of French origin from the KIDRISK consortium (US NCI U01CA155309; G. Scelo). Genotypes obtained on the Infinium Global Screening Array 24 v1.0 were called using default parameters in GenomeStudio (Illumina).

Genotyping, Imputation, and Merge

Genotypes from the previously published GWAS (dataset1) (12) and for the 2 new sets (dataset2 and dataset3) were filtered (Supplementary Methods, available online) and independently imputed on the Michigan Imputation Server using Eagle for the phasing and Haplotype Reference Consortium r1.1 as the reference dataset. Imputed datasets were merged together, and another quality control was performed (Supplementary Table 1, available online). An exact number of patients and controls (Supplementary Table 2, available online) and for the 2 new sets (dataset2 and dataset3) were filtered (Supplementary Methods, available online) and independently imputed on the Michigan Imputation Server using Eagle for the phasing and Haplotype Reference Consortium r1.1 as the reference dataset. Imputed datasets were merged together, and another quality control was performed (Supplementary Table 1, available online). Data from individuals of European ancestry were stringently selected from principal component analyses (PCA) using plink2 in which the first 2 principal components were used. Outliers were then excluded from those selected samples using SmartPCA with 10 iterative PCAs (Supplementary Figures 1-3, available online). The final dataset for the UM GWAS analysis consisted of 7 488 175 SNPs in 1142 patients and 882 controls (Figure 1).

The GWAS Manhattan plot showed 3 distinct loci reaching genome-wide significance (fifth logistic regression P < 5.00 × 10⁻⁸) (chr5, CLPTM1L/TERT locus; chr6, IRF4 locus; and chr15, HERC2/OCA2 locus) (Figure 2; Supplementary Table 3, available online). Within the HERC2/OCA2 locus, 8 SNPs in high linkage disequilibrium reached statistical significance. The most statistically significant SNPs at this locus were rs1129038 and rs12913832 (OR = 0.56, 95% CI = 0.48 to 0.66; P = 5.97 × 10⁻¹²); and OR = 0.57, 95% CI = 0.48 to 0.67; P = 1.88 × 10⁻¹³, respectively), located in HERC2. A single SNP located in IRF4 was found to be well above the genome-wide significance: rs12203592 (OR = 1.76, 95% CI = 1.44 to 2.16; P = 3.55 × 10⁻⁸). Finally, the association study recapitulated the previously identified 5p15.33 risk locus (TERT/CLPTM1L) (12), with several SNPs in high linkage disequilibrium (r² > 0.9) reaching statistical significance (Supplementary Table 3, available online). The most statistically significant SNP was rs370348 (OR = 1.59, 95% CI = 1.35 to 1.86; P = 1.48 × 10⁻⁸), the leading risk SNP in our first GWAS, rs421284 (12), also showed high statistical significance (OR = 1.58, 95% CI = 1.35 to 1.86; P = 1.98 × 10⁻⁸) and was further analyzed in this study. A few other loci showed suggestive evidence for an association with UM but did not reach genome-wide significance (P < 5.00 × 10⁻⁸) (Supplementary Table 3, available online and Figure 2).

Conditional analyses enable the detection of secondary independent association signals within a genomic locus by conditioning on the primary associated SNP at the locus. At the CLPTM1L, IRF4, and HERC2 loci, no other statistically significant SNP was found to be independently associated with UM when conditioning on rs421284, rs12203592, or rs12913832, respectively. Moreover, these 3 conditional analyses did not reveal any statistically significant regions other than CLPTM1L, IRF4, and HERC2 (Supplementary Figure 4, available online).
UM Risk Loci and Pigmentation

To evaluate the impact of risk SNPs on gene regulation, eQTL analyses were performed for the statistically significant loci using expression data from tumors of an in-house series of 73 UMs (14). We previously identified an association between \( \text{CLPTM1L} \) expression and rs421284 with higher expression of \( \text{CLPTM1L} \) in individuals carrying the risk allele (C) (12). Interestingly, the other 2 major risk loci identified in this association study, \( \text{IRF4} \) and \( \text{HERC2} \), are known to be strongly implicated in the regulation of the pigmentation pathways determining eye and skin colors (15-17), prompting us to further investigate the expression of pigmentation genes in UM.

\( \text{IRF4} \) expression was found to be strongly associated with rs12203592 alleles, with a decreased expression in tumors carrying the risk TT genotype (linear regression \( P = 2.00 \times 10^{-6} \); Supplementary Figure 5, A, available online). Looking at eQTLs in the Genotype-Tissue Expression database, rs12203592 is linked to \( \text{IRF4} \) expression in most tissues, but the directionality of the association varies. As in UM, sun-exposed skin had a lower \( \text{IRF4} \) expression linked to the T allele, whereas a lower expression of \( \text{IRF4} \) is associated with the C allele in all other tissues, suggesting a tissue-specific regulation for this gene (Supplementary Figure 5, A, available online). At the \( \text{HERC2} \) locus, no correlation was found between rs12913832 alleles and expression of this gene in UM (Supplementary Figure 6, A, available online), in contrast to whole blood, where there is a statistically significant decrease in \( \text{HERC2} \) expression associated with the G allele (Supplementary Figure 6, B, available online). However, expression of \( \text{OCA2} \), a nearby gene known to be regulated by \( \text{HERC2} \) in melanocytes (17), was found with a highly statistically significant association with rs12913832 genotypes \( (P = 9.08 \times 10^{-4}) \) in UM, with decreased expression for tumors carrying the risk G allele (Supplementary Figure 6, C, available online).

Our finding of 2 major pigmentation loci is in accordance with the high prevalence of light eye color in UM patients of European ancestry (11). We investigated whether the risk of developing UM conferred by the risk alleles of \( \text{HERC2} \) and \( \text{IRF4} \) was fully linked to their determining role in eye pigmentation. We thus predicted the eye color of all UM and control individuals included in this study, using the algorithm developed in the IrisPlex System, based on the genotype combination of 6 SNPs (\( \text{HERC2} \) rs12913832, \( \text{OCA2} \) rs1800407, \( \text{SLC45A2} \) rs16891982, \( \text{TYR} \) rs1393350, \( \text{IRF4} \) rs12203592, and \( \text{LOC105370627} \) intron variant) (18). We predicted the eye color of UM patients and controls to be brown (41.6% of patients vs 60.1% of controls, respectively), green (1.7% vs 1.1%), or blue (56.7% vs 38.9%), allowing us to confirm the statistically significant association of blue eye color (vs other eye colors) with UM risk \( (OR = 2.07, 95\% \ CI = 1.72 \) to 2.49; 2-sided Fisher test \( P = 1.21 \times 10^{-15} \) (Figure 3, A and B), confirming the recent study by Jager and colleagues (19). Strikingly, when we added eye color
Pigmentation Risk Loci and UM Epidemiology

The higher prevalence of UM among individuals of European ancestry strongly supports the existence of inherited risk alleles for the disease. The TERT/CLPTM1L risk locus does not account for this population bias, as the risk haplotype is more frequent in African American populations than those of European ancestry (rs421284: VAF = 0.597 vs 0.429, respectively) (Supplementary Table 5, available online; Genome Aggregation Database v2.1). However, the risk haplotypes of both IRF4 and HERC2 are found at statistically significantly higher frequencies in populations of non-Finnish European ancestry (NFE) than in those of African or African American and East Asian origins (populations defined by Genome Aggregation Database) (IRF4 rs12203592: VAF = 0.144, 0.034, and 0.000, respectively; HERC2 rs12913832: VAF = 0.803, 0.125, and 0.001, respectively; 2-sided Fisher test P < 1.00 × 10^-20 for all statistical comparisons of NFE vs East Asian and NFE vs African and African American). Therefore, the higher frequency of the risk alleles of these 2 pigmentation loci may at least partly explain the higher prevalence of UM in European populations.

Association Study for the Two Major UM Subtypes

Loss of chromosome 3 is the strongest factor associated with poor metastatic outcome in UM and correlates with increased mortality (2,3). The genomic status was available for 384 UM patients, allowing us to test for differential association of UM risk loci according to chromosome 3 status. Association studies...
Figure 3. Eye pigmentation and uveal melanoma risk. A) Proportion of blue, green, and brown eye colors among uveal melanoma (UM) patients (dark shade) and controls (light shade), as predicted by the IrisPlex System (18). B) Proportion of blue eyes vs other eye colors in UM patients and controls. The number of individuals is indicated. C) Effect of eye color as a GWAS covariate on the odds ratio for the 3 main SNPs of statistically significant UM risk loci (CLPTM1L, IRF4, and HERC2). The error bars indicate the 95% confidence intervals for the odds ratio. Statistical significance was assessed using a 2-sided Fisher test. The + and - indicate the inclusion or exclusion of eye color as a GWAS covariate, respectively. For each SNP and in both covariate conditions, association with UM risk is represented by the odds ratio and 95% confidence interval for the odds ratio (OR). The vertical dotted line is set at odds ratio = 1.00, indicating an absence of association with UM. All statistical tests were 2-sided. CLPTM1L – cleft lip and palate transmembrane protein 1-like; HERC2 – HECT and RLD domain containing E3 ubiquitin protein ligase 2; IRF4 – interferon regulatory factor 4.

Discussion

We extended our initial UM GWAS by including 1142 UM patients and performing genome-wide genotype imputation. This allowed us to recapitulate the previously described CLPTM1L risk locus and to further identify IRF4 and HERC2, 2 pigmentation loci, as UM genetic risk factors. Furthermore, we demonstrated that whereas CLPTM1L is a risk locus in all UM types, IRF4 SNP predisposing specifically to risk in D3 UM, and HERC2 locus to risk in M3 UM.

These data strongly suggest that UM tumor biology is influenced by the genetic background predisposing to UM, with CLPTM1L SNPs predisposing to all UM types, IRF4 SNP predisposing specifically to risk in D3 UM, and HERC2 specifically with M3 UM.

The TERT/CLPTM1L region has frequently been associated in GWAS studies, with higher and lower tumor risk depending on cancer types (20). The function of CLPTM1L is not yet understood, but this protein is thought to contribute to RAS-dependent transformation and tumorigenesis, including in pancreatic tumorigenesis (21-23). On the other hand, TERT (on the same locus) plays a major role in telomere maintenance (24). In a previous study, we revealed a correlation between rs421284...
| IDa SNPb | Symbol | Alternative allele | Total No. (patients/controls) | OR (95% CI) | P  |
|----------|--------|--------------------|------------------------------|-------------|---|
| 5:1325590: T>C | CLPTM1L | rs421284 | C 1126 (244/882) 1.55 (1.18 to 2.03) 0.001 | 1018 (137/881) 2.26 (1.61 to 3.17) 2.64 | 10-6 |
| 6:396321: C>T | IRF4 | rs12203592 | T 1126 (244/882) 1.01 (0.70 to 1.47) 0.95 | 1018 (137/881) 2.73 (1.87 to 3.97) 1.78 | 10-7 |
| 15:28365618: A>G | HERC2 | rs12913832 | G 1126 (244/882) 2.43 (1.79 to 3.29) 1.13 | 1018 (137/881) 1.10 (0.80 to 1.52) 0.56 | 10-8 |

aID refers to chromosome number: chromosomal genomic position: reference allele and alternative allele, based on genome build GRCh37 (hg19). CI = confidence interval; OR = odds ratio.
bSNP = single nucleotide polymorphism, according to the Single Nucleotide Polymorphism Database.

Two-sided P values were calculated by general linear model.

Table 1. Main risk loci in uveal melanoma according to their chromosome 3 status

The present GWAS demonstrates the role of 2 pigmentation genes in the genetic risk of UM, in addition to the CLPTM1L/TERT risk locus. This is consistent with light iris color being a risk factor for UM (OR = 1.75) (11,19,31) similar to our finding (OR = 2.07). Iris pigmentation depends on the production and maturation of melanin as well as on the ratio of the 2 types of melanin: eumelanin (black-brown, densely packed) and pheomelanin (yellow-to-red, loosely packed). Melanin plays a major role in protecting against ultraviolet radiation (UVR) by absorbing free radicals and inhibiting UV-mediated damage (32). Pheomelanin, however, can also induce more oxidative damage on UVR than eumelanin (33), which was proposed to explain the contribution of light iris color in UM (34). However, the steady UM incidence despite increased UVR exposure, the low tumor mutation burden, and absence of UVR mutational signature in UM tumors ruled out this hypothesis (5,35). Interestingly, iris melanoma, a rare form of UM, is associated with high tumor mutation burden and a UVR signature (36), consistent with iris color being a risk factor for iris melanoma (37). However, our GWAS is restricted to choroid melanoma, a tissue that, unlike the iris, is not directly exposed to sunlight. In this respect, IRF4 and potentially HERC2/OCA2 SNPs may play a role outside from iris pigmentation to explain UM risk. However, a limitation of our study is that eye pigmentation is deduced from genotypes, which are also risk SNPs for UM, making it challenging to derive causal statements.

Status of chromosome 3 and BAP1 delineates 2 UM subtypes, M3 and BAP1-inactivated high-risk tumors and D3 and wild-
type BAP1 low-risk tumors (2-4,8). Strikingly, whereas CLPTM1L region confers similar susceptibility for M3 UM and D3 UM, we show that the risk for M3 UM is associated with the OCA2/HERC2 region and D3 UM with the IRF4 locus. How these processes influence the malignant transformation is unknown but most probably independent of the protective role of melanin against UVR. Furthermore, our data reinforce the idea that UM encompasses at least 2 diseases, with distinct clinicobiological characteristics (6,38-40) and distinct susceptibility loci.

Further studies should investigate the molecular mechanisms behind these UM genetic susceptibility loci to understand the role of pigmentation genes in UM risk. This study provides important insights in the genetics of UM and may lead to improvements in risk prediction and to a better understanding of the biological basis of UM.

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Notes
Role of the funders: The funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

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Author contributions: LM, A-CD, and AH contributed equally to this study. LM, A-CD, AH, and M-HS conceptualized the study and developed its methodology. G C-T, OC, and GS provided resources (GWAS control samples). A-CD, LM, AB, and J-FD, conducted research investigation (experiments). LM, AH, TV, and JN performed data curation and formal analysis. GP, NC, and MM provided resources. A-CD, AH, and LM conducted experiments, performed visualization/data presentation, and wrote and edited the manuscript. GC, MR, JN, and MR reviewed the manuscript. M-HS supervised the study. All authors reviewed and approved the final manuscript.

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Data Availability
Dataset2 and 3 genotyping data used in the analysis have been deposited and are available on the European Genome-Phenome Archive (EGA) (https://ega-archive.org/) under accession number EGAS00001005200. Previously published genotyping of dataset1 patients and controls are found on EGA under Accession number EGAS00001002334 and on the database for Genotypes and Phenotypes (dbGaP) under accession number phs001271.v1.p1., respectively. Previously published expression data (RNA-seq data) of 73 UM tumors are available at EGA under accession no. EGAS00001002932. PCAs were performed using HapMap3 (ftp://ftp.ncbi.nlm.nih.gov/hapmap/genotypes/hapmap3_r3). For expression quantitative trait loci (eQTL) analyses, data was obtained from the Genotype-Tissue Expression (GTex) public database (https://www.gtexportal.org/home/). Allele frequency of SNPs of interest in different populations was obtained from the Genome Aggregation Database (GnomAD v2.1.1, https://gnomad.broadinstitute.org).

Code availability: The following web-based resources were used in the GWAS analysis: PLINK 1.9 and 2.0 (https://www.coggenomics.org/plink1-9/, https://www.coggenomics.org/plink/2.0/), Michigan Imputation Server (https://imputationserver.sph.umich.edu/index.html), GitHub (https://github.com/DReichLab/SiRIC2), and developed its methodology. GC-T, OC, and GS provided resources. A-CD, LM, AB, and J-FD, conducted experiments, and developed its methodology. GC-T, OC, and GS provided resources (GWAS control samples). A-CD, LM, AB, and J-FD, conducted research investigation (experiments). LM, AH, TV, and JN performed data curation and formal analysis. GP, NC, and MM provided resources. A-CD, AH, and LM conducted experiments, performed visualization/data presentation, and wrote and edited the manuscript. GC, MR, JN, and MR reviewed the manuscript. M-HS supervised the study. All authors reviewed and approved the final manuscript.

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