

Genetic variants associated with skin photosensitivity in a southern European population from Spain

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4 population from Spain
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CONFLICT OF INTERESTS

The authors have no conflict of interest to declare.

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ABSTRACT

Background/Purpose: Recent GWAS studies, mostly performed in populations of North European origin, have identified the genetic loci associated with pigmentation, sun sensitivity, freckling, and skin cancer susceptibility. Here we aimed at addressing the genetic determinants of sunlight sensitivity in Spain, a southern European population.

Methods: Nine SNPs located in 8 pigmentation-related genes (*IRF4*, *TYR*, *ASP*, *HERC2*, *OCA2*, *BNC2*, *SLC24A4* and *SLC45A2*) were genotyped in 456 Spaniards. Additionally, the complete sequence of the *MC1R* gene was obtained, testing each non-synonymous mutation supported by the classification as R or r alleles. A standardised questionnaire was used to collect demographic characteristics, pigmentation and sun sensitivity traits, as well as sun exposure habits.

Results: *MC1R* R alleles and *IRF4* rs12203592 were significantly associated with sunlight sensitivity at the Bonferroni-corrected level (P -value $< 4.54 \times 10^{-3}$). Genetic variants in *SLC45A2* (rs16891982) and *HERC2* (rs12913832) were also found to be significantly associated with skin photosensitivity in our Spanish sample. Interaction analysis using the MDR method revealed epistatic effects when these four variants were considered together.

Conclusion: *MC1R*, *IRF4*, *HERC2* and *SLC45A2* play a significant role in skin sensitivity to sunlight in the Spanish population. Moreover, interaction among these four loci seems to modulate the ability of the skin to respond to UV radiation.

Keywords: Photosensitivity, Pigmentation, Polymorphisms, UV Light

INTRODUCTION

In recent years, there have been important advances in the elucidation of the genetic determinants of human skin colour, skin sensitivity to sunlight and tanning ability (1–8). Both cutaneous pigmentation and the skin's response to sunshine are extremely relevant to individual susceptibility to developing skin cancers (9–11).

Although skin sensitivity to ultraviolet (UV) radiation and the ability to tan are genetically determined, exposure to ambient sunlight is necessary for UV light to reveal its harmful effects on human skin (12). People with high sensitivity to sunlight have a tendency to develop sunburns and frequently lack the ability to acquire a tan following exposure to UV light. These individuals with diminished sun response tend to display cutaneous hyperpigmented spots such as nevi or ephelides more commonly than people who are able to tan easily (13,14).

Skin sensitivity to sunlight, together with light skin (and light hair and eye colour) and incapacity to tan are all risk phenotypes conferring susceptibility to develop skin cancers – including basal cell carcinoma, squamous cell carcinoma and the more dangerous melanoma. In fact, several genes involved in skin pigmentation – such as *MC1R*, *IRF4*, *SLC45A2*, and so on – are known to behave as low-penetrance genes for melanoma and other skin cancers (15).

Most of the studies aimed at addressing the genetic determinants of skin photosensitivity and/or tanning ability have been performed in populations of North European origin, both in northern Europe and in North America (3–5,16–19). However, there is a shortage of studies carried out in darker-skinned populations such as southern

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3 Europe or the Mediterranean (20–25). These more southerly populations present lower
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5 percentages of highly sun-sensitive individuals and higher percentages of individuals
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7 that are capable of tanning with ease. Accordingly, allele frequencies of the variants
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9 responsible for pigmentation in southern Europe may differ from those further north
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11 (26). Due to higher UV radiation in South Europe, mainly during the summer months,
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13 evolution has probably influenced the distribution of allele frequencies of several
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15 human pigmentation genes in a different way to North Europe. For example, the F374
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17 allele in *SLC45A2*, responsible for darker skin, is significantly more frequent in Spain
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19 than in more northerly European populations (27,28).
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25 In this study, we set out to elucidate the genetic determinants of sun photosensitivity in
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27 Spain, a population of Mediterranean origin, by means of testing variation in the genes
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29 previously associated with sun sensitivity. We have performed SNP genotyping in 8
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31 pigmentation-related genes (*HERC2*, *SLC45A2*, *SLC24A4*, *TYR*, *ASIP*, *OCA2*, *BNC2*
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33 and *IRF4*) as well as complete gene sequencing of the *MC1R* gene in 456 individuals of
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35 Spanish origin. The correlation of the genetic variants with skin photosensitivity, and
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37 the interaction among all the associated genes, are analysed.
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43 **MATERIALS AND METHODS**

44 **Study subjects and data collection**

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46 A total of 456 cancer-free volunteers (272 controls and 184 cases) were included in this
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48 case-control study. Individuals with low sensitivity to sunlight, who never or rarely burn
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50 and always tan after sun exposure (Fitzpatrick skin phototypes III-IV-V), were included
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52 in the control group. Conversely, individuals presenting high sensitivity to sunlight,
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54 who always or often burn and never or seldom tan after sun exposure (phototypes I-II),
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3 were defined as cases. All individuals were Europeans of Spanish origin. Written
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5 informed consent was provided by all participants, and the study was approved by the
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7 Ethics Committee of the Jaume I University of Castellon (Castellon, Spain).
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11 A standardised questionnaire was used to collect information on sex, age, place of birth,
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13 place of residence during childhood, pigmentation traits (skin, hair and eye colour),
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15 freckling degree, history of childhood sunburns, skin sensitivity to sunlight (tanning
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17 ability *versus* tendency to burn), Fitzpatrick's skin type classification, and sun exposure
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19 habits. To avoid misclassification, all questionnaires were completed by a professional
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21 dermatologist.
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24 25 26 **DNA isolation, SNP selection and genotyping assays**

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28 Genomic DNA was isolated from saliva samples using QIAamp DNA Mini Kit
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30 (Qiagen, Hilden, Germany), according to the manufacturer's protocol.
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35 We selected genes previously associated with skin sensitivity to sunlight and tanning
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37 ability (4,5,16,18,19). Nine SNPs located in 8 pigmentation-related genes were finally
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39 genotyped: rs4911442 (located in the *ASIP* gene), rs2153271 (*BNC2* gene), rs12913832
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41 (*HERC2* gene), rs1800407 (*OCA2* gene), rs12896399 (*SLC24A4* gene), rs16891982
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43 (*SLC45A2* gene), rs1393350 and rs1042602 (*TYR* gene), and rs12203592 (*IRF4* gene).
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48 Genotyping assays were performed by using KASP Genotyping Chemistry (LGC,
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50 Hoddesdon, United Kingdom) or TaqMan technology (Applied Biosystems, Foster
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52 City, USA). PCR conditions varied depending on the requirements of each probe,
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54 always according to the manufacturer's recommendations. For quality control, we
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2 included a negative control and a trio of samples with known genotype (major allele
3 homozygous, heterozygous and minor allele homozygous) in each 96-well plate.
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7 Unsuccessful genotyping rate was lower than 5% in all SNPs analysed.
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11 The *MC1R* gene was studied by direct genetic sequencing with the Sanger method, as
12 previously described (29). A sample with known *MC1R* genotype per 96-well plate was
13 added for quality control. Sixteen samples (3.49%) were discarded because of
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18 unsuccessful *MC1R* sequencing.
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20 21 22 **Statistical analysis**

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24 Statistical analyses were performed using the R software (<http://www.R-project.org>).
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26 All analyses were two-sided, and a significance level of 0.05 was considered for
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28 rejection of the null-hypothesis. Correction for multiple hypothesis testing was carried
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30 out using the Bonferroni method ($P\text{-value} < 4.54 \times 10^{-3} = 0.05/11$). Unknown and
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32 missing values were excluded at each specific analysis.
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37 Descriptive statistics (means, standard deviations, sample size, percentages) were used
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39 to report demographic characteristics, sun sensitivity traits, and sun exposure habits of
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41 participants (Table 1). For categorical variables, Fisher's exact test was used to evaluate
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43 differences between cases and controls. Mann-Whitney *U* test was used to account for
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45 differences in age between cases and controls, since age was not normally distributed
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47 according to the Shapiro-Wilk test.
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3 For genetic association analyses, non-synonymous *MC1R* mutations were classified as
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5 previously described (25). Individuals were then classified according to the number of R
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7 and/or r alleles carrying. The individual effect of each *MC1R* variant was evaluated.
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11 Association between all variants studied and sunlight sensitivity was assessed according
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13 to the additive model of inheritance via logistic regression adjusted by sex, estimating
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15 odds ratios (ORs) per variant carried, their corresponding 95% confidence intervals
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17 (CIs) and associated *P*-values. All genetic analyses were performed estimating the effect
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19 of the minor allele in the Spanish population.
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24 Fisher's exact test was used to study combinations of protective and risk genotypes in
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26 different genes for skin photosensitivity. Interactions among sunlight sensitivity-
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28 associated genes were tested using the multifactor dimensionality reduction (MDR)
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30 method (MDR software v.1.2) (30). The MDR method tests all potential locus-locus
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32 combinations to create a model that sorts cases and controls with the lowest possible
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34 classification error. That procedure is repeated 10 times in order to obtain both the
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36 cross-validation (CV) consistency, the number of times that a particular model is chosen
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38 as the best one; and the balanced accuracy (BA), the proportion of occurrences correctly
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40 classified using the model.
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RESULTS

Evidence of association with skin sensitivity to sunlight for the genetic variants studied was assessed (Table 2). All associations observed were significant after Bonferroni correction. R variants of the *MC1R* gene were the most strongly associated with sunlight sensitivity (P -value = 2.00×10^{-6}), being the OR estimated per variant carried of 2.55. The rs16891982 polymorphism in *SLC45A2* presented the second strongest association with sunlight sensitivity (P -value = 6.79×10^{-5}), observing a protective effect of the G minor allele regarding tolerance to sunlight (OR = 0.57). Significant associations were also observed for *HERC2* rs12913832 (P -value = 9.35×10^{-5}) and *IRF4* rs12203592 (P -value = 4.75×10^{-4}). For these two polymorphisms, carrying a copy of the minor allele significantly increased the risk of being highly sensitive to sunlight (OR = 1.62 for rs12913832, and OR = 1.98 for rs12203592). No associations were found for the remaining genetic variants.

Moreover, interaction effects between *SLC45A2* rs16891982 and the other genetic variants influencing sunlight sensitivity were assessed. A significantly increased percentage of *HERC2* rs12913832*C carriers (P -value = 9.97×10^{-3}), *IRF4* rs12203592*T carriers (P -value = 3.62×10^{-3}) or *MC1R* R carriers (P -value = 1.31×10^{-3}) were detected in highly photosensitive individuals harbouring at least one copy of the rare protective allele in *SLC45A2* rs16891982 (Figure 1). According to the MDR method, sunlight sensitivity was best explained assuming interaction between polymorphisms in all four sun sensitivity-associated genes (BA = 0.679, CV consistency = 10/10, P -value < 0.0001). Significant redundant interaction was observed between *MC1R* R variants, *IRF4* rs12203592 and *SLC45A2* rs16891982 (indicated by black lines in Figure 2).

DISCUSSION

In the current study, nine pigmentation-related genes were examined in 456 individuals from Spain, with the intention of analysing their putative implication in skin sensitivity to sunlight – a phenotypic trait with substantial clinical importance for both melanoma and non-melanoma skin cancer.

As shown in previous studies performed in populations of North European ancestry (4,5,16,31), our results confirm an association between sunlight sensitivity and genetic variants in the *MC1R*, *SLC45A2*, *HERC2* and *IRF4* genes in a Mediterranean population.

The *MC1R* gene has been previously described as one of the major contributors to the diversity of human pigmentation (32). The melanocortin-1 receptor is a G protein-coupled receptor expressed on the melanocyte's membrane surface that is involved in the regulation of melanocyte proliferation and function (33). Stimulation of MC1R by melanocortins following sunlight exposure leads to the activation of photoprotective eumelanin biosynthesis, being essential to the tanning response and offering greater protection against skin cancer (34,35). Among all non-synonymous *MC1R* variants described (33), R variants have been the most frequently associated with fair skin, red hair, freckling and poor tanning ability (36,37) – all phenotypes increasing the risk of developing skin cancer. As expected, in this study individuals carrying R variants in *MC1R* present a significantly higher risk of sunburn after sunlight exposure, confirming the impact of *MC1R* gene polymorphism on tanning ability and the risk of sunburn shown in previous population-based studies (38,39). However, our findings show an

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3 absence of a significant effect of the r variants on sunlight sensitivity. These results are
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5 consistent with those reported by Latreille *et al.* (38), which found that r variants were
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7 significantly associated with freckling (usually a signal of high sensitivity to sunlight)
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9 but not with sunburn event frequency nor suntan intensity.
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15 The *SLC45A2* gene, which encodes a membrane-associated transporter protein involved
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17 in arranging melanogenic enzymes during melanosome maturation, has been previously
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19 defined as a human pigmentation-related and melanoma-susceptibility gene. Genetic
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21 variants of the *SLC45A2* gene, located in both the promoter region and the coding
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23 region, have been significantly associated with dark pigmentation and with protection
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25 against melanoma in southern European populations (40–42). In this study, we focused
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27 on the rs16891982 polymorphism in *SLC45A2*, which results in a non-synonymous
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29 change (F374L). The percentage of the ancestral F374 allele among European
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31 individuals is only 6.2%, conferring a protective effect against melanoma and other skin
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33 cancers in populations of European ancestry, while more than 96% of Africans harbour
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35 this protective allele (www.ensembl.org). In our Spanish dataset, the percentage of the
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37 ancestral allele was 9.0% in individuals with high sunlight sensitivity, while a
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39 considerable increase was observed in individuals with higher tanning ability and lower
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41 susceptibility to sunburns (16.2%). This clearly indicates that the *SLC45A2*
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43 rs16891982*C minor European allele is evidently associated with a protective
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45 phenotype against skin cancer.
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52 The *HERC2* locus is also associated with human pigmentation variation, through the
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54 modification of the expression of *OCA2*, a pigmentation gene contiguous to *HERC2*.
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56 Variation in rs12913832 has been identified as a genetic determinant for human blue-
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3 brown eye colour as well as hair colour (31,43). In our study, the derived C allele is
4 significantly associated with high sensitivity to sunlight, as in previous studies in
5 populations of northern European origin (5).
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11 *IRF4* has also been associated with pigmentation characteristics in several studies
12 (4,44). This interferon regulatory factor cooperates with MITF to activate the expression
13 of tyrosinase in melanocytes, a function that seems to be impaired in carriers of the
14 rs12203592*T derived minor allele (45). From the results of our study, we can confirm
15 that this gene is important in the skin sensitivity to sunlight in the Spanish population,
16 since it is highly associated with this phenotype. The derived T allele has previously
17 been associated with tanning ability (5), and melanoma susceptibility (21).
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30 Since human pigmentation has been demonstrated to be a highly polygenic trait
31 (1,2,15), and epistasis has been suggested to play an important role in the determination
32 of human pigmentation traits (46–48), we decided to perform a gene-gene interaction
33 analysis in order to obtain clues on the possible epistatic effects influencing skin
34 photosensitivity.
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43 Regarding sensitivity to sunlight, and noticing that the frequency of the *SLC45A2*
44 ancestral protective allele in Spain (18.2%, www.ensembl.org) is considerably higher
45 than in other European populations (including Italian Tuscans at 3.3%), we decided to
46 extend our analyses to assess the interaction between protective (carriers of at least one
47 ancestral *SLC45A2* rs16891982*C allele) and risk genotypes in other sun sensitivity-
48 associated genes. The MDR interaction analysis found that sunlight sensitivity is better
49 explained by taking into account the effect of *MC1R*, *IRF4*, *SLC45A2* and *HERC2*. As
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3 seen in Figure 1 and Table 3, risk alleles in *MC1R*, *IRF4* and *HERC2* are able to
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5 mitigate the protective effect of carrying at least one *SLC45A2* rs16891982*C allele.
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10 It is important to keep in mind that there is still considerable ambiguity in the definition
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12 of the term ‘skin sensitivity to sunlight’ or ‘skin photosensitivity’, being difficult to
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14 perform a comprehensive comparison with previous published studies. Data
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16 standardisation should be addressed in future investigations by employing consistent
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18 definitions in order to allow for meta-analysis studies. **Another possible caveat is that**
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20 **this study may indeed be ignoring the effect of other unknown genetic variants on skin**
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22 **photosensitivity, since we only focused on pigmentation-related genes previously**
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24 **associated – though through several potent GWAS – with skin sensitivity to sunlight**
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26 **and tanning ability.**
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33 In short, this study shows that the *MC1R* gene is the major contributor to skin
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35 photosensitivity in the Spanish population, specifically by way of its R variants.
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37 Besides, genetic variants in *SLC45A2*, *HERC2* and *IRF4* are also significantly
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39 associated with sunlight sensitivity in individuals of Spanish origin, independently of
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41 sex. However, large-scale replication collecting phenotypic traits related to
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43 photosensitivity in different southern European populations is necessary to confirm our
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45 findings.
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Table 1. Mean ages and distribution of sex, pigmentation and sun sensitivity traits, and sun exposure habits among Spanish cases and controls

| | | Skin sensitivity to sunlight | | | | <i>P</i> -value ¹ |
|--------------------------------|------------------|------------------------------|-------|----------------|-------|------------------------------|
| | | Low (N = 272) | | High (N = 184) | | |
| | | Mean | SD | Mean | SD | |
| Age (years) | | 30.06 | 12.33 | 32.74 | 14.75 | 0.401 |
| | | N | % | N | % | <i>P</i> -value ² |
| Sex | Females | 138 | 50.74 | 120 | 65.22 | 2.48E-03 |
| | Males | 134 | 49.26 | 64 | 34.78 | |
| | Unknown | 0 | 0.00 | 0 | 0.00 | |
| Skin colour | Light-brown/Dark | 207 | 76.10 | 6 | 3.26 | 2.62E-52 |
| | Fair/Pale | 65 | 23.90 | 178 | 96.74 | |
| | Unknown | 0 | 0.00 | 0 | 0.00 | |
| Fitzpatrick skin type ‡ | I | 0 | 0.00 | 42 | 22.83 | 1.25E-131 |
| | II | 0 | 0.00 | 142 | 77.17 | |
| | III | 138 | 50.74 | 0 | 0.00 | |
| | IV | 124 | 45.59 | 0 | 0.00 | |
| | V | 10 | 3.68 | 0 | 0.00 | |
| | Unknown | 0 | 0.00 | 0 | 0.00 | |
| Amount of freckles | No freckling | 203 | 74.63 | 63 | 34.24 | 7.66E-18 |
| | Light freckling | 37 | 13.60 | 44 | 23.91 | |
| | Heavy freckling | 32 | 11.76 | 77 | 41.85 | |
| | Unknown | 0 | 0.00 | 0 | 0.00 | |
| Sun exposure | Never | 16 | 5.88 | 23 | 12.50 | 3.04E-03 |
| | Intermittent | 138 | 50.74 | 102 | 55.43 | |
| | Frequent | 118 | 43.38 | 55 | 29.89 | |
| | Unknown | 0 | 0.00 | 4 | 2.17 | |
| Childhood sunburns | No | 136 | 50.00 | 28 | 15.22 | 5.89E-14 |
| | Yes | 132 | 48.53 | 150 | 81.52 | |
| | Unknown | 4 | 1.47 | 6 | 3.26 | |
| Use of sunscreen | Never | 101 | 37.13 | 32 | 17.39 | 1.00E-05 |
| | Occasional | 105 | 38.60 | 72 | 39.13 | |
| | Frequent | 57 | 20.96 | 73 | 39.67 | |
| | Unknown | 9 | 3.31 | 7 | 3.80 | |

N, number of individuals; %, percentage of individuals per group among the total

Significant results are presented in bold

‡ Samples were classified into two groups (skin type I-II, and III-IV-V) for statistical analyses

¹ *P*-value for the Mann–Whitney *U* test.

² *P*-value for the Fisher's exact test.

Table 2. Association of genetic variants with skin sensitivity to sunlight in Spanish population

| Gene | SNP #rs | Genotype | Low photosensitivity | High photosensitivity | | |
|----------------|------------|----------|----------------------|-----------------------|------------------|----------------------|
| | | | N (%) | N (%) | OR (95% CI) | P-value ¹ |
| <i>ASIP</i> | rs4911442 | AA | 234 (86.35) | 151 (82.07) | 1.30 (0.82-2.08) | 0.268 |
| | | AG | 34 (12.55) | 31 (16.85) | | |
| | | GG | 3 (1.11) | 2 (1.09) | | |
| <i>BNC2</i> | rs2153271 | TT | 69 (25.37) | 59 (32.07) | 0.86 (0.64-1.14) | 0.292 |
| | | CT | 154 (56.62) | 96 (52.17) | | |
| | | CC | 49 (18.01) | 29 (15.76) | | |
| <i>HERC2</i> | rs12913832 | TT | 101 (37.97) | 46 (25.70) | 1.62 (1.23-2.13) | 4.75E-04* |
| | | CT | 123 (46.24) | 80 (44.69) | | |
| | | CC | 42 (15.79) | 53 (29.61) | | |
| <i>IRF4</i> | rs12203592 | CC | 203 (74.40) | 104 (56.83) | 1.98 (1.40-2.81) | 9.35E-05* |
| | | CT | 64 (23.53) | 67 (36.61) | | |
| | | TT | 5 (1.80) | 12 (6.56) | | |
| <i>OCA2</i> | rs1800407 | CC | 226 (84.01) | 143 (79.89) | 1.26 (0.81-1.97) | 0.302 |
| | | CT | 40 (14.87) | 33 (18.44) | | |
| | | TT | 3 (1.12) | 3 (1.68) | | |
| <i>SLC24A4</i> | rs12896399 | GG | 86 (31.97) | 54 (29.67) | 0.94 (0.73-1.22) | 0.655 |
| | | GT | 120 (44.61) | 76 (41.76) | | |
| | | TT | 63 (23.42) | 52 (28.57) | | |
| <i>SLC45A2</i> | rs16891982 | GG | 200 (73.53) | 160 (87.43) | 0.57 (0.39-0.83) | 6.79E-05* |
| | | CG | 56 (20.59) | 13 (7.10) | | |
| | | CC | 16 (5.88) | 10 (5.46) | | |
| <i>TYR</i> | rs1393350 | GG | 157 (57.72) | 99 (54.10) | 1.11 (0.82-1.51) | 0.485 |
| | | AG | 98 (36.03) | 72 (39.34) | | |
| | | AA | 17 (6.25) | 12 (6.56) | | |
| <i>TYR</i> | rs1042602 | CC | 87 (31.99) | 47 (25.54) | 1.19 (0.91-1.56) | 0.207 |
| | | AC | 134 (49.26) | 99 (53.80) | | |
| | | AA | 51 (18.75) | 38 (20.65) | | |
| <i>MC1R</i> | R alleles | 0/0 | 214 (81.06) | 109 (61.93) | 2.55 (1.73-3.75) | 2.00E-06* |
| | | 0/R | 48 (18.18) | 55 (31.25) | | |
| | | R/R | 2 (0.76) | 12 (6.82) | | |
| <i>MC1R</i> | r alleles | 0/0 | 151 (57.20) | 94 (53.41) | 1.05 (0.77-1.43) | 0.755 |
| | | 0/r | 94 (35.61) | 69 (39.20) | | |
| | | r/r | 19 (7.20) | 13 (7.39) | | |

SNP, single nucleotide polymorphism; MAF, minor allele frequency; OR, odds ratio per allele copy; CI, confidence interval; N, number of individuals; %, percentage of individuals per group among the total

Individuals with low skin sensitivity to sunlight were set as reference group for association analysis. Association analysis were adjusted by sex. Bold indicates statistically significant results. * Indicates significant results at Bonferroni threshold of 4.54E-03

¹ P-values were calculated via logistic regression according to the additive model of inheritance. The minor allele effect was estimated. For *MC1R*, the effect of R and r alleles was estimated.

Table 3. Interactions between variants and their effect in skin photosensitivity

| rs16891982 (<i>SLC45A2</i>) | rs12913832 (<i>HERC2</i>) | Individuals (N) | | | OR (95% CI) | P-value ^a |
|-------------------------------|-----------------------------|----------------------|-----------------------|-------|-------------------|----------------------|
| | | Low photosensitivity | High photosensitivity | Total | | |
| G/G | T/T | 69 | 42 | 111 | 1.00 | reference |
| | C/- | 124 | 116 | 240 | 1.52 (1.13-2.07) | 6.34E-03 |
| C/- | T/T | 31 | 4 | 35 | 0.22 (0.06-0.81) | 0.022 |
| | C/- | 41 | 17 | 58 | 2.50 (1.26-4.96) | 9.97E-03 |
| rs16891982 (<i>SLC45A2</i>) | rs12203592 (<i>IRF4</i>) | N | | | | |
| G/G | C/C | 147 | 94 | 241 | 1.00 | reference |
| | T/- | 53 | 65 | 118 | 1.86 (1.27-2.73) | 1.42E-03 |
| C/- | C/C | 55 | 10 | 65 | 0.41 (0.23-0.74) | 3.09E-03 |
| | T/- | 17 | 13 | 30 | 3.60 (1.52-8.53) | 3.62E-03 |
| rs16891982 (<i>SLC45A2</i>) | R alleles (<i>MC1R</i>) | | | | | |
| G/G | O/O | 158 | 99 | 257 | 1.00 | reference |
| | R/- | 36 | 55 | 91 | 2.32 (1.52-3.55) | 9.70E-05 |
| C/- | O/O | 55 | 9 | 64 | 0.39 (0.22-0.71) | 1.92E-03 |
| | R/- | 14 | 12 | 26 | 5.22 (1.91-14.33) | 1.31E-03 |

OR, odds ratio per allele copy; CI, confidence interval; N, number of individuals

^a P-values were calculated via logistic regression. Significant results are presented in bold.

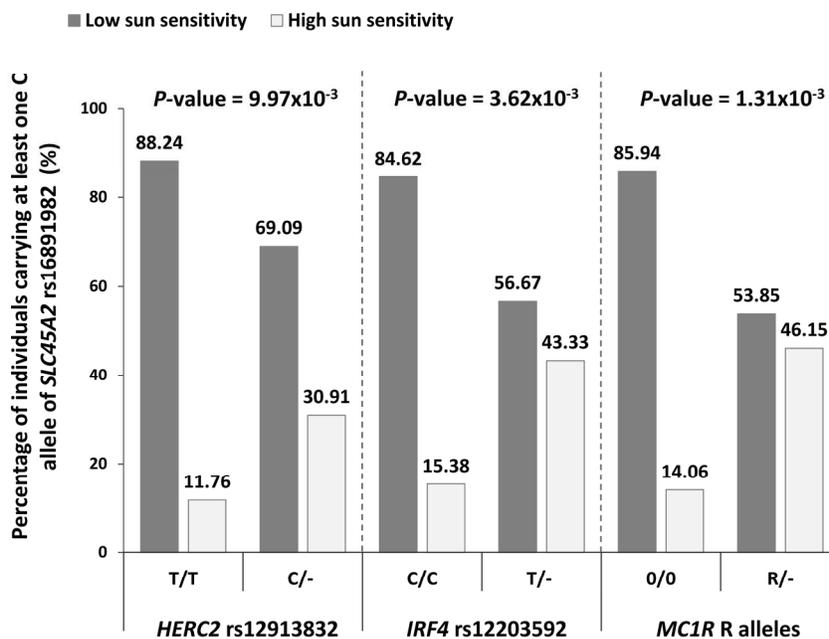
* Indicates significant results at Bonferroni threshold of 4.54E-03

FIGURE LEGENDS

Figure 1. Plot showing the percentage of *SLC45A2* protective rs16891982*C carriers with low and high sensitivity to sunlight according to *HERC2*, *IRF4* and *MC1R* genotype. *P*-value was calculated for the Fisher's exact test.

Figure 2. Dendrograms showing gene-gene interactions that influence skin photosensitivity modelled by using the MDR software. Black lines represent a high degree of redundancy (negative information gain), with a lesser degree represented by grey lines.

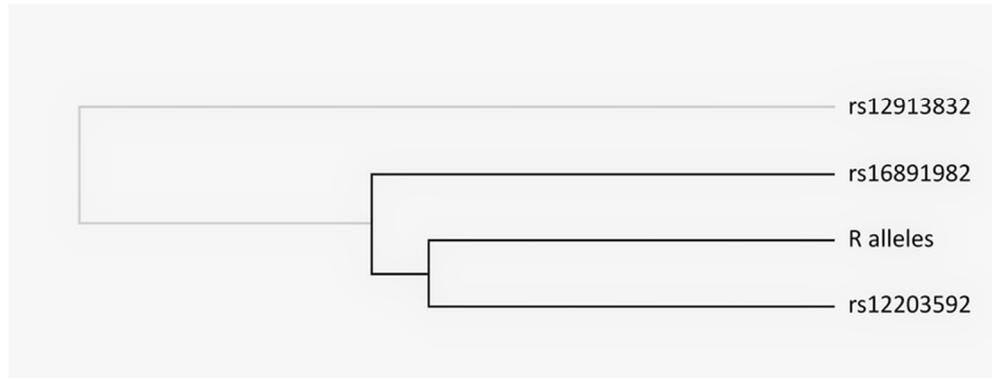
For Review Only



Plot showing the percentage of SLC45A2 protective rs16891982*C carriers with low and high sensitivity to sunlight according to *HERC2*, *IRF4* and *MC1R* genotype. P-value was calculated for the Fisher's exact test.

183x130mm (300 x 300 DPI)

Only



Dendrograms showing gene-gene interactions that influence skin photosensitivity modelled by using the MDR software. Black lines represent a high degree of redundancy (negative information gain), with a lesser degree represented by grey lines.

72x27mm (300 x 300 DPI)

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