A Germline Variant in the Interferon Regulatory Factor 4 Gene as a Novel Skin Cancer Risk Locus

Jiali Han1,2, Abrar A. Qureshi1,2, Hongmei Nan2, Jiangwen Zhang6, Yiqing Song3, Qun Guo2, and David J. Hunter2,4,5

Abstract

Genome-wide association studies on pigmentation phenotypes provide a pool of candidate genetic markers for skin cancer risk. The SNPs identified from a genome-wide association study of natural hair color were assessed for associations with the risk of three types of skin cancer simultaneously in a nested case-control study within the Nurses’ Health Study [218 melanoma, 285 squamous cell carcinoma (SCC), and 300 basal cell carcinoma (BCC) cases, and 870 common controls]. Along with two known pigmentation loci, MCIR and OCA2, the IRF4 rs12203592 T allele was associated with an increased risk of each type of skin cancer (P value, 6.6 × 10−4 for melanoma, 7.0 × 10−7 for SCC, and 0.04 for BCC). This association was further replicated in additional samples (190 melanoma, 232 SCC, and 634 common controls). The P value in the replication set was 0.03 for melanoma and 4.2 × 10−3 for SCC. The risk of BCC was replicated in an independent set of 213 cases and 718 controls (P value, 0.02). The combined results showed that the association with SCC reached the genome-wide significance level [odds ratio (OR) for additive model = 1.61, 95%CI, 1.36–1.91, P = 3.2 × 10−3]. The OR was 1.49 for melanoma (95%CI, 1.23–1.80; P = 4.5 × 10−5), and 1.32 for BCC (95%CI, 1.11–1.57; P = 1.6 × 10−3). Given that the T allele was shown previously to be associated with increased expression of IRF4 locus, further studies are warranted to elucidate the role of the IRF4 gene in human pigmentation and skin cancer development. Cancer Res 71(5); 1533–9. ©2011 AACR.

Introduction

Skin cancer is the most common form of cancer in the United States. There are 3 major types of skin cancer, of which melanoma is the most fatal form. The most common type of nonmelanoma skin cancer is basal cell carcinoma (BCC), followed by squamous cell carcinoma (SCC). Genome-wide association studies (GWAS) on melanoma and BCC have identified several risk loci (1–6). Because of the different etiology and cell types giving rise to melanoma and SCC/BCC, the risk loci for each type of skin cancer may be different except for the common underlying pathways or mechanisms. For example, less constitutive cutaneous pigmentation is a well-known risk factor common for the 3 types of skin cancers. Pigmentation genes, such as MCIR, TYR, and ASIP, were identified as risk loci for both melanoma and BCC (1–3), whereas some keratin-related loci, such as KRT5, KLF14, and loci at 1p36 and 1q42, were identified as risk loci for BCC only (5, 6). GWAS for SCC has not been published thus far. Given that the GWAS on melanoma and BCC have successfully identified pigmentation genes as risk loci, GWAS on pigmentation phenotypes offer an opportunity to identify novel loci for human pigmentation and at the same time provide a pool of candidate genetic markers for skin cancer risk. We have previously conducted a GWAS of natural hair color in 2,287 U.S. women of European ancestry using data on 528,173 single nucleotide polymorphisms (SNPs) genotyped as part of the Cancer Genetic Markers of Susceptibility breast cancer GWAS (7). In this report, we evaluated those SNPs highly associated with hair color in relation to the risk of 3 types of skin cancer simultaneously in U.S. Caucasians.

Materials and Methods

Study design overview

We first evaluated those highly significant SNPs from our previous GWAS on hair color in relation to the risks of 3 types of skin cancer simultaneously in a discovery set, a nested case-control study within the Nurses’ Health Study (NHS) (218 melanoma, 285 SCC, and 300 BCC cases, and 870 common controls). We further replicated the association between the SNP rs12203592 in the IRF4 gene and skin cancer risk in additional samples within the NHS and the Health
Professionals Follow-Up Study (HPFS). The replication set 1 consisted of 190 melanoma cases, 252 SCC cases, and 634 common controls. The replication set 2 consisted of 213 BCC cases and 718 controls with genotyped rs12203592 SNP data. The study was restricted to Caucasians and the study protocol was approved by the Committee on Use of Human Subjects of the Brigham and Women’s Hospital, Boston, MA.

**Discovery set**

Detailed descriptions of the 2 cohorts, the NHS and HPFS, and their blood collection protocols were published previously (8). This discovery set is a nested case-control study within the NHS, with a detailed description published previously (9). Briefly, eligible cases were women with incident skin cancer (including SCC and BCC) from the subcohort who had given a blood specimen, with a first diagnosis anytime after the 1989 blood collection up to June 1, 1998; and melanoma cases up to June 1, 2000 with no previously diagnosed skin cancer. One or two controls were matched to each case by year of birth (±1 year). Controls were randomly selected from participants who gave a blood sample and were free of diagnosed skin cancer up to the time when the case was first diagnosed. The nested case-control study consisted of 218 melanoma cases, 285 SCC cases, 300 BCC cases, and 870 common controls.

**Replication set 1**

In the NHS, the replication set was composed of the newly diagnosed incident melanoma and SCC cases during the longer follow-up, that is, eligible cases consisted of women with incident skin cancer from the subcohort who had given a blood specimen, with a first diagnosis anytime after June 1, 2000 for melanoma and June 1, 1998 for SCC, and up to June 1, 2006 with no previously diagnosed skin cancer. One control was matched to each case by year of birth (±1 year). In HPFS, eligible cases consisted of men with melanoma from the subcohort who had given a blood specimen, with a first diagnosis anytime after the 1993 blood collection up to June 1, 2006, with no previously diagnosed skin cancer. One control was matched to each case by year of birth (±1 year). In both NHS and HPFS, we genotyped additional samples who were free of melanoma and SCC as additional controls. In total, the replication set 1 consisted of 190 melanoma cases, 252 SCC cases, and 634 common controls.

**Replication set 2**

Replication set 2 was a postmenopausal invasive breast cancer nested case-control study in the NHS. Only control subjects were included in the analysis. The validity of self-report of BCC is high in this medically sophisticated population (90%) (10). The replication set 2 consisted of 213 subjects who reported a diagnosis of BCC and 718 subjects who were free of any type of skin cancer and with genotyped rs12203592 SNP data.

**Skin cancer risk factors**

Both the NHS and HPFS collected information on skin cancer risk factors using similar wording. We only chose to evaluate 2 such characteristics as potential intermediate phenotypes for pigmentation SNPs and skin cancer risk, which were natural hair color at age 20 and childhood or adolescent tendency to tan and burn. The retrospective assessment of these variables was not likely to substantially bias risk estimates in this study (11).

**Genotyping assays**

We selected the top 31 SNPs from our previous GWAS of hair color for genotyping among controls in the discovery set using the ABI OpenArray assays. Twenty-four were at least nominally significantly ($P$ value < 0.05) associated with hair color among controls, either with the black-to-blond gradient or with red hair color, and then we focused on these 24 SNPs for skin cancer risk assessment in this study. The associations between the other 6 SNPs and hair color from the initial GWAS were not replicated, and 1 SNP (rs6497268 in the OCA2 gene) failed in the assay (8). The SNP rs12203592 was genotyped by using Taqman in the replication set 1. 10% blind duplicates were included in both platforms and genotype concordance was 100%. The SNP rs12203592 was genotyped by the Illumina HumanHap550 in the replication set 2 (7).

**Statistical analysis**

In both the discovery set and replication set 1, we compared each type of skin cancer with the common control series to increase statistical power using unconditional logistic regression. The genotype was coded as the number of minor alleles for each SNP, and the odds ratio (OR) and 95% confidence interval (95%CI) for skin cancer risk were calculated based on the additive model. For melanoma and SCC, we carried out a pooled analysis to combine all the cases and controls from the discovery set and replication set 1. All statistical analyses were 2-sided and carried out using SAS V9.1 (SAS Institute). For BCC, we carried out a meta-analysis using the DerSimonian and Laird (random-effects) model to estimate the summary ORs and 95%CIs from the results of the discovery set and the replication set 2 (12). We adjusted for the 3 largest principal components of genetic variation in the regression model in the replication set 2. These principal components were calculated for all individuals on the basis of ca. 10,000 unlinked markers using the EIGENSTRAT software (13). The top 3 eigenvectors were chosen on the basis of significant ($P < 0.05$) Tracy-Wisdom tests (14). The Cochran’s $\chi^2$-based Q statistic test was used to assess the extent of heterogeneity across 2 data sets. All meta-analyses were conducted using Stata 10.0 (College Station).

**Results**

Basic characteristics of cases and controls in this study (discovery set, replication sets 1 and 2) are presented in Table 1. Skin cancer cases were more likely to have red or blonde hair. The childhood tanning ability of cases was less than that of controls. Melanoma cases tended to have a higher mole count on the left arm than controls.

We evaluated the associations between the 24 SNPs and the risk for each type of skin cancer, adjusting for age (Supplementary Table 1). Three regions were found to be associated...
with skin cancer risk. SNPs in the \textit{MC1R} region were associated with melanoma, SCC, and to a lesser extent BCC. We previously evaluated the \textit{MC1R} genetic variants in this discovery set in detail (15). After controlling for hair color and the known \textit{MC1R} variants, the associations with other SNPs were attenuated and became nonsignificant (data not shown). This analysis indicates that the signals we detected in this region were mainly driven by the \textit{MC1R}-related genotypes and phenotypes.

In the region of \textit{OCA2} and \textit{HERC2} on chromosome 15, five SNPs were associated with the risk of BCC, but not melanoma or SCC (Supplementary Table 1). In the model that adjusted for hair color and skin color, the SNPs rs7174027, rs11855019, and rs7495174 remained significant with ORs for minor alleles of 0.59 (95\%CI, 0.39–0.89), 0.67 (95\%CI, 0.46–0.97), and 0.58 (95\%CI, 0.36–0.95), respectively. The SNP rs12203592 was also suggested as likely to be in strong linkage disequilibrium (LD) with the causal variant of pigmentation in this region (8, 16), was not associated with the risk of BCC.

The \textit{IRF4} rs12203592 T allele was the only non-MC1R SNP in our discovery set associated with all types of skin cancer: OR of melanoma was 1.54 (95\%CI, 1.20–1.97), SCC 1.78 (95\%CI, 1.42–2.24), and BCC 1.28 (95\%CI, 1.02–1.62). Excluding those with red hair did not change the associations materially. Because this SNP was associated with pigmentary phenotypes, such as hair color and tanning ability (8, 17), we further controlled for pigmentary phenotypes. The associations between this SNP and the skin cancers seemed to be independent from hair color and tanning ability (Table 2).

We further replicated this association in independent data sets in the NHS and HPFS. In the replication set 1, the associations with melanoma and SCC were significant (\textit{P} value, 0.03 for melanoma, and $4.2 \times 10^{-3}$ for SCC), and risk estimates were comparable with the discovery set (Table 2). In the pooled analysis of the discovery set and the replication set 1, we found a genome-wide significant association with SCC (additive OR, T as minor allele $= 1.61; 95\%\text{CI, }1.36–1.91; P = 3.2 \times 10^{-9}$). This SNP (T allele) was also associated with the risk of melanoma (additive OR $= 1.49; 95\%\text{CI, }1.23–1.80; P = 4.5 \times 10^{-7}$) (Table 2).

We examined the association of history of BCC with rs12203592 in the replication set 2 (213 cases and 718 controls). The association between this SNP and history of BCC was replicated (\textit{P} values, 0.02 Table 2). We conducted a meta-analysis to combine the discovery set with the replication set for BCC risk. The \textit{P} value for heterogeneity was not significant. We observed a significant association with BCC, with additive OR (T as minor allele) of 1.32 (95\%CI, 1.11–1.57; $P = 1.6 \times 10^{-3}$) (Table 2).

**Discussion**

Dark pigmentation is an important inherited protective factor against UV-induced skin cancer. The identification of loci related to human pigmentary phenotypes through a GWAS provided a pool of candidate genetic variants for the risk of skin cancer. We evaluated the SNPs that were highly associated with hair color in relation to the risks of 3 types of skin cancer. Human pigmentation phenotypes are determined by pigmentary melanin, which is synthesized in melanocytes and secreted into keratinocytes. Melanin production is a complex process and involves a number of genes.

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**Table 1. Characteristics of discovery and replication sets within the Nurses’ Health Study and Health Professionals Follow-up Study**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Discovery set</th>
<th>Replication set 1</th>
<th>Replication set 2</th>
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<tbody>
<tr>
<td></td>
<td>Controls ((n = 870))</td>
<td>Melanoma ((n = 218))</td>
<td>SCC ((n = 285))</td>
</tr>
<tr>
<td>Age at diagnosis (mean, years)</td>
<td>–</td>
<td>63.4</td>
<td>64.7</td>
</tr>
<tr>
<td>Natural hair color at age 20, red or blonde (%)</td>
<td>13.8</td>
<td>22.3</td>
<td>21.8</td>
</tr>
<tr>
<td>Tanning ability, tan or deep tan (%)</td>
<td>70.5</td>
<td>56.2</td>
<td>62.0</td>
</tr>
<tr>
<td>Mole count on the left arm, (3^{+}) (%)</td>
<td>11.2</td>
<td>22.6</td>
<td>12.5</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

SCC, squamous cell carcinoma. BCC, basal cell carcinoma.

Discovery set, skin cancer (melanoma, SCC, and BCC) nested case-control study within the Nurses’ Health Study (NHS; 1989–2000). Replication set 1, melanoma and SCC nested case-control study within the NHS (2000–2006) and Health Professionals Follow-up Study (HPFS; 1993–2006).

Replication set 2, postmenopausal invasive breast cancer-nested case–control study in the NHS. Only control subjects were included in the analysis. The outcome was history of BCC. The rs12203592 was genotyped by the Illumina HumanHap550.
Table 2. Association between the IRF4 rs12203592 and the risk of skin cancers

<table>
<thead>
<tr>
<th></th>
<th>Discovery set</th>
<th>Replication set</th>
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<tr>
<td></td>
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<tr>
<td></td>
<td>Melanoma</td>
<td>Replication set 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Melanoma (Replication set 1)</td>
</tr>
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<td></td>
<td></td>
<td>SCC (Replication set 1)</td>
</tr>
<tr>
<td></td>
<td>BCC</td>
<td></td>
</tr>
<tr>
<td>Cases (%)</td>
<td>126 (58.9)</td>
<td>123 (65.4)</td>
</tr>
<tr>
<td>Controls (%)</td>
<td>565 (68.4)</td>
<td>450 (71.2)</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Adjusted for age, hair color, and tanning response</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCC (Replication set 1)</td>
</tr>
<tr>
<td>Cases (%)</td>
<td>143 (52.4)</td>
<td>156 (62.2)</td>
</tr>
<tr>
<td>Controls (%)</td>
<td>565 (68.4)</td>
<td>450 (71.2)</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Adjusted for age, hair color, and tanning response</td>
<td>1.00</td>
<td>1.00</td>
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(Continued on the following page)
We determined that 2 known pigmentation loci were associated with skin cancer risk. The *MC1R* gene encodes a 317-amino acid seven-pass-transmembrane G protein-coupled receptor. The *MC1R* gene is a well-established locus with several nonsynonymous SNPs associated with human pigmentation and skin cancer risk (15, 18–20). We confirmed this locus in our study.

The *OCA2* gene encodes the integral melanosomal 12 transmembrane-spanning membrane protein P-protein. The *OCA2* gene plays an important role in melanosome biogenesis and controls the eumelanin content in melanocytes (21). We found that 3 SNPs located in the *OCA2* 5′ regulatory region were associated with the risk of BCC, after controlling for hair color and skin color. This suggests that the genotypes may provide additional information on BCC risk beyond their related-pigmentation phenotypes. We did not observe significant results for melanoma or SCC in this study with modest power. We plan to evaluate these associations in larger studies.

Besides these 2 known pigmentation loci, we previously identified the SNP rs12203592 in intron 4 of the *IRF4* gene as strongly associated with hair color and tanning ability (8, 17). The *IRF4* gene product is a member of the interferon regulatory factor family of transcription factors (22), which are involved in the regulation of gene expression in response to interferon and other cytokines. The *IRF4* gene encodes a B-cell proliferation/differentiation protein that has been proposed as a sensitive and specific marker for conventional primary and metastatic melanomas and benign melanocytic nevi (23). In addition to pigmentation, *IRF4* may also have an effect on skin cancer risk via its role in immune response. Through its effects on B-cell lineage and consequently on the cellular immune response, *IRF4* polymorphisms may have a pathophysiologic role via limiting the host immune response against atypical melanocytes and keratinocytes in the skin. SCC in particular has been a scourge in the solid-organ transplant population where individuals on immunosuppressive medications develop aggressive skin SCCs resulting in high morbidity and mortality (24). Although less than SCC, BCC incidence has also been associated with immunosuppression (25). Similarly, tumor infiltrating lymphocytes in cutaneous melanoma have been shown to be a good prognostic feature where lack of an immune response to invasive melanoma is considered a risk factor for melanoma progression (26, 27).

In an Australian population-based melanoma case–control study with 1,738 cases and 4,517 controls, no significant association was found between this SNP and melanoma risk (allelic OR, 1.04; *P* value, 0.32) (28). Because sun exposure is a predominant risk factor for melanoma, the discrepancy between their and our results may be due to different sun exposure patterns and levels. In our study of Caucasians residing in the United States, we found that the T allele

### Table 2. Association between the *IRF4* rs12203592 and the risk of skin cancers (Cont’d)

<table>
<thead>
<tr>
<th>Combined set</th>
<th>CC</th>
<th>CT</th>
<th>TT</th>
<th>additive model</th>
<th><em>p</em> for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Melanoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for age and gender</td>
<td>1.00</td>
<td>1.31 (1.02–1.69)</td>
<td>2.80 (1.73–4.54)</td>
<td>1.49 (1.23–1.80)</td>
<td>4.5 × 10⁻⁵</td>
</tr>
<tr>
<td>Adjusted for age, gender, hair color, and tanning response</td>
<td>1.00</td>
<td>1.35 (1.02–1.79)</td>
<td>3.08 (1.82–5.21)</td>
<td>1.55 (1.25–1.92)</td>
<td>5.8 × 10⁻⁵</td>
</tr>
<tr>
<td><strong>SCC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>1.00</td>
<td>1.65 (1.33–2.04)</td>
<td>2.49 (1.58–3.92)</td>
<td>1.61 (1.36–1.91)</td>
<td>3.2 × 10⁻⁸</td>
</tr>
<tr>
<td>Adjusted for age, gender, hair color, and tanning response</td>
<td>1.00</td>
<td>1.76 (1.39–2.23)</td>
<td>2.88 (1.75–4.76)</td>
<td>1.73 (1.43–2.10)</td>
<td>2.3 × 10⁻⁸</td>
</tr>
<tr>
<td><strong>BCC (meta-analysis)</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Adjusted for age and gender</td>
<td>1.00</td>
<td>1.09 (0.86–1.37)</td>
<td>2.52 (1.63–3.90)</td>
<td>1.32 (1.11–1.57)</td>
<td>1.6 × 10⁻³</td>
</tr>
<tr>
<td>Adjusted for age, gender, hair color, tanning response, and top 3 principal components of genetic variance</td>
<td>1.00</td>
<td>1.11 (0.86–1.45)</td>
<td>2.40 (1.48–3.88)</td>
<td>1.33 (1.09–1.63)</td>
<td>4.8 × 10⁻³</td>
</tr>
</tbody>
</table>

SCC, squamous cell carcinoma. BCC, basal cell carcinoma.

Discovery set, skin cancer (melanoma, SCC, and BCC) nested case–control study within the Nurses’ Health Study (NHS; 1989–2000). Replication set 1, melanoma and SCC nested case–control study within the NHS (2000–2006) and Health Professionals Follow-Up Study (HPFS; 1993–2006).

Replication set 2, postmenopausal invasive breast cancer-nested case–control study in the NHS. Only control subjects were included in the analysis. The outcome was history of BCC. The rs12203592 was genotyped by the Illumina HumanHap550.
was associated with an increased risk of each type of skin cancer in the discovery set, and these associations were replicated in additional data sets. Combining the discovery set and the replication set, the association with SCC reached the genome-wide significance level.

The SNP rs12203592 is located in intron 4 of the IRF4 gene. The mapping of enhancer and promoter histone marker H3K4Me1 in ENCODE project (29) suggested its intronic enhancer function. Based on the transcription profiling data of 87 HapMap CEU cell lines [NCBI GEO database, accession GSE7792 (30), the expression level of IRF4 locus was 1.3-fold higher for the T-allele carriers compared with that for the CC genotype (\(P\) value < 0.0001). The functional consequences of this SNP were confirmed experimentally (31). The rs12203592 C allele binds more than 2-fold stronger to the transcription factor AP-2\(\alpha\) than the T allele and exerts a repressive effect on the IRF4 transcription activity. The T allele is associated with increased expression of IRF4 gene (\(P < 0.001\)) (31). These data suggest a functional impact of this variant and strengthen the biological plausibility of our results.

In this work, we presented the IRF4 SNP rs12203592 as a risk locus for all 3 types of skin cancer. We think the signal is most likely attributable to the IRF4 locus. First, we imputed genotypes in 2,287 Caucasian samples for all SNPs across the 1 MB flanking region of the IRF4 based on the genotyped SNPs and haplotype information in the Hapmap phase data build 35 (CEU) (32). There is no SNP in strong LD with this IRF4 SNP. Only 2 SNPs have LD of 0.23 and 0.27, and the rest of SNPs have LD less than 0.2. Hence, this SNP represents a unique signal. Second, the association between this SNP and the IRF4 gene expression strongly suggests that the observed SNP association with pigmented phenotypes and skin cancer risk results from affecting IRF4, rather than some other adjacent genes.

Third, the microphthalmia-associated transcription factor (MITF) is a critical master regulator for both melanocyte development and melanoma progression. The IRF4 was shown as a downslope target of the MITF. There was 170-fold increase of IRF4 gene expression up on transformation of the SK-MEL-28 cell line with a MITF-expressing vector (33).

The limitations of this study included the lack of comprehensive evaluation of the IRF4 region, and the modest power in the discovery set to identify additional significant loci. Further studies are warranted to replicate this finding and elucidate the role of the IRF4 gene in human pigmentation and skin cancer development.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Acknowledgments**

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