Inverse Relationship between Vitiligo-Related Genes and Skin Cancer Risk

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TO THE EDITOR

Vitiligo, the most common cutaneous depigmentation disorder, affects up to 2% of the population and is characterized by immune-mediated destruction of melanocytes, causing depigmentation of the skin, hair, and oral mucosa (Kruger and Schallreuter, 2012). Affected skin lacks melanin, which plays a critical role in protecting against UV-mediated mutagenesis (Jin et al., 2012). Because UV exposure is a well-established risk factor for skin cancers, vitiligo was initially presumed to confer increased risk for both melanoma and nonmelanoma skin cancer (NMSC) (Rodrigues, 2017). Surprisingly, a number of studies have instead found that vitiligo is associated with a lower risk of melanoma and NMSC, via unknown mechanisms (Paradisi et al., 2014; Rodrigues, 2017). To date, genome-wide association studies have identified 58 genetic loci associated with vitiligo (Birlea et al., 2010; Jin et al., 2010, 2012, 2016; Quan et al., 2010). We investigated the role of these vitiligo-associated genetic loci in risk of melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC), using genome-wide association study data on 6,628 melanoma cases, 12,945 BCC cases, 6,579 SCC cases, and more than 274,000 controls of European ancestry.

We performed the analysis in three studies. Melanoma analysis (study 1) was based on a two-stage meta-analysis. 23andMe (Mountain View, CA) provided free access to aggregated genetic and phenotypic information for study 1 (Supplementary Figure S1a online). Study 2 participants were from a hospital-based case-control study of melanoma recruited at the MD Anderson Cancer Center (Ransohoff et al., 2017; Supplementary Figure S2 online). The nonmelanoma skin cancer study (study 3), including both BCC and SCC, was limited to 23andMe research participants (Chahal et al., 2016a, 2016b; Supplementary Figure S1b, S1c online). 23andMe research participants provided written informed consent, in accordance with the company's human subjects protocol (reviewed and approved by Ethical and Independent Review Services, an Association for the Accreditation of Human Research Protection Programs (AAHRPP)—accredited Institutional Review Board). Study protocols for study 2 were approved by the Institutional Review Board at MD Anderson, and written informed consent was obtained from all participants. Further information on methodology is presented in Supplementary Material online.

A combined analysis of melanoma study 1 and study 2, totaling 6,628 melanoma cases and 287,591 controls (Supplementary Table S1 online), identified four vitiligo-susceptibility loci reaching a Bonferroni-adjusted *P*-value threshold ($P < 8.6 \times 10^{-4}$ for 58 single-nucleotide polymorphisms), with three loci also reaching genome-wide significance ($P < 5 \times 10^{-8}$): *RALY-EIF252-ASIP-AHCY-ITCH*, *IRF4*, *TYR*, and *MC1R* (Table 1, Supplementary Table S2 online).

All 58 loci were investigated for BCC (12,945 cases and 274,252 controls) (Chahal et al., 2016b) and SCC (6,579 cases and 280,558 controls) (Chahal et al., 2016a) (Supplementary Table S1). Sixteen loci for BCC and seven loci for SCC reached the Bonferroni-adjusted *P*-value threshold (Supplementary Table S3 online). Interestingly, all four melanoma-associated loci were also significantly associated with the risk of BCC and SCC. Three additional SCC-associated loci were also found to be significantly related to the risk of BCC.

Within those loci with *P*-value $\leq$ 0.05, 100% (11 of 11), 80.0% (25 of 27), and 100% (19 of 19) indicated an inverse correlation between risk of vitiligo and risk of melanoma, BCC, and SCC, respectively (Figure 1, Supplementary Tables S2 and S3). Furthermore, among the loci that reached a Bonferroni-adjusted *P*-value threshold, we observed very consistent inverse relationships between vitiligo and risk of melanoma, BCC, and SCC (100%, 93.75%, 100% consistency). To identify possible causal genes, we interrogated publicly available Genotype-Tissue Expression Project (GTEx) expression quantitative trait loci (eQTL) v7 data sets for three tissues (Supplementary Table S4 online). Of the 58 loci, 20 were identified as eQTLs for whole blood. It was intriguing to find inverse associations for *rs12203592* and *IRF4* gene expression levels within whole blood and sun-exposed skin tissue. Further information on methods and imputation quality can be found in Supplementary Material and Supplementary Table S5 online.

Vitiligo is an autoimmune disease characterized by loss of skin pigmentation and affects approximately 0.5% to 2% of the population worldwide (Rodrigues, 2017). It has been associated with other autoimmune diseases such as rheumatoid arthritis and adult-onset type I diabetes (Alkhateeb et al., 2003). Interestingly, although individuals with vitiligo were initially presumed to be more susceptible to UV mutagenesis and skin cancer because of their lack of melanoma, previous studies have instead highlighted an inverse relationship between vitiligo and both melanoma and NMSC (Jin et al., 2016). A large retrospective study of 10,040 patients

Abbreviations: BCC, basal cell carcinoma; NMSC, nonmelanoma skin cancer; SCC, squamous cell carcinoma

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Table 1. Loci reaching statistical significance after Bonferroni correction for melanoma risk

SNP	Region	Gene	Min/Maj	MAF[1]	23andMe (study 1)			MD Anderson (study 2)			Meta-Analysis[2]			Previous reported (Jin et al., 2016)[4]	
					OR	95% CI[3]	*P*	OR	95% CI[3]	*P*	OR	95% CI[3]	*P*	OR	*P*
rs6059655	20q11.22	RALY-EIF252-ASIP-AHCY-ITCH	A/G	0.07	1.37	(1.28−1.46)	1.69×10^{-18}	1.44	(1.2−1.74)	1.02×10^{-4}	1.38	(1.29−1.47)	5.04×10^{-23}	0.61	1.04×10^{-19}
rs12203592	6p25.3	IRF4	T/C	0.17	1.21	(1.15−1.27)	1.47×10^{-12}	1.16	(1.01−1.33)	3.71×10^{-2}	1.20	(1.14−1.26)	8.29×10^{-14}	0.79	2.95×10^{-10}
rs1126809	11q14.3	TYR	A/G	0.28	1.16	(1.11−1.21)	4.62×10^{-11}	1.23	(1.09−1.39)	6.32×10^{-4}	1.17	(1.12−1.22)	1.26×10^{-13}	0.67	1.16×10^{-43}
rs4268748[5]	16q24.3	MC1R	C/T	0.27	1.26	(1.2−1.31)	1.25×10^{-23}	1.40	(1.25-1−.58)	1.29×10^{-8}	1.31	(1.18−1.46)	6.23×10^{-7}	0.71	2.88×10^{-33}

SNPs that met Bonferroni-adjusted significance ($P < 8.6 \times 10^{-4}$) in the overall meta-analysis are listed. In addition, we report genetic locus, nearest genes, major allele, minor allele, MAF in study 1 controls, average imputation r^2 (a measure of imputation quality) for study 1, and OR with *P*-value for each stage, calculated with respect to the minor allele. Study 1 included 4,842 melanoma cases and 286,565 controls from 23andMe. Study 2 included 1,804 melanoma cases and 1,026 controls from the MD Anderson Cancer Center. The combined fixed-effect meta-analysis totaling 6,628 melanoma cases and 287,591 controls. Statistics for effect heterogeneity (P_{het} and I^2) are included in Supplementary Table S2. All subjects lived in the USA and were of European ancestry.

Abbreviations: CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism.

[1]MAF = minor allele frequency in study 1 controls.

[2]Meta-analysis = Combined 23andMe + MD Anderson.

[3]CI = 95% confidence interval.

[4]OR with *P*-value for risk of vitiligo in a previous report by Jin et al. (2016), associated with the minor allele.

[5]Meta-analysis odds ratios calculated with the random-effects method.

with vitiligo reported a lower risk of melanoma and NMSC in such patients. However, this association remains controversial, as another study reported a higher risk of skin cancer among patients with vitiligo who underwent phototherapy (Paradisi et al., 2014). In addition, most studies did not describe how vitiligo might influence the risk of melanoma and NMSC.

We observed a consistent inverse relationship between risk of vitiligo and skin cancers in the *RALY-EIF252-ASIP-AHCY-ITCH, IRF4, TYR,* and *MC1R* genes. A haplotype near *ASIP* has been associated with skin sensitivity to sun, red, and blonde hair, and was shown to confer a significant risk of melanoma and BCC (Gudbjartsson et al., 2008). IRF4 protein activates melanin synthesis by tyrosinase, an enzyme found in melanocytes. The genetic variant *rs12203592* T allele impairs transcription factor binding and results in decreased protein expression of IRF4 and tyrosinase (Asgari et al., 2017). The *TYR* gene encodes tyrosinase, catalyzing melanin biosynthesis rate-limiting steps (Jin et al., 2010). The melanocortin 1 receptor is a G protein-coupled receptor protein important for melanocyte proliferation and function regulation (Garcia-Borron et al., 2014). In all these well-established pigmentation genes, inherited variants have been identified as the most promising loci for melanoma and NMSC (Chahal et al., 2016a; Ransohoff et al., 2017). Moreover, it is interesting to find that immune-related single-nucleotide polymorphisms located in the *HLA-DRB1/DQA1, CTLA4,* and *PTPN22* genes, which encode important immunoregulative proteins, showed consistent inverse relationships between vitiligo and skin cancers, especially BCC. Overall, the inverse relationship might indicate that different or opposed biological pathways mediate vitiligo and skin cancer (Jin et al., 2010), or vitiligo might lead to enhanced immune activity against malignant melanoma and NMSC (Jin et al., 2016).

These associations suggest a possible genetic relationship between vitiligo and skin cancers. In our analysis of each of the three types of skin cancers, we did not exclude those with a history of the other skin cancer types. However, given the large sample size, those with such a history represented a small

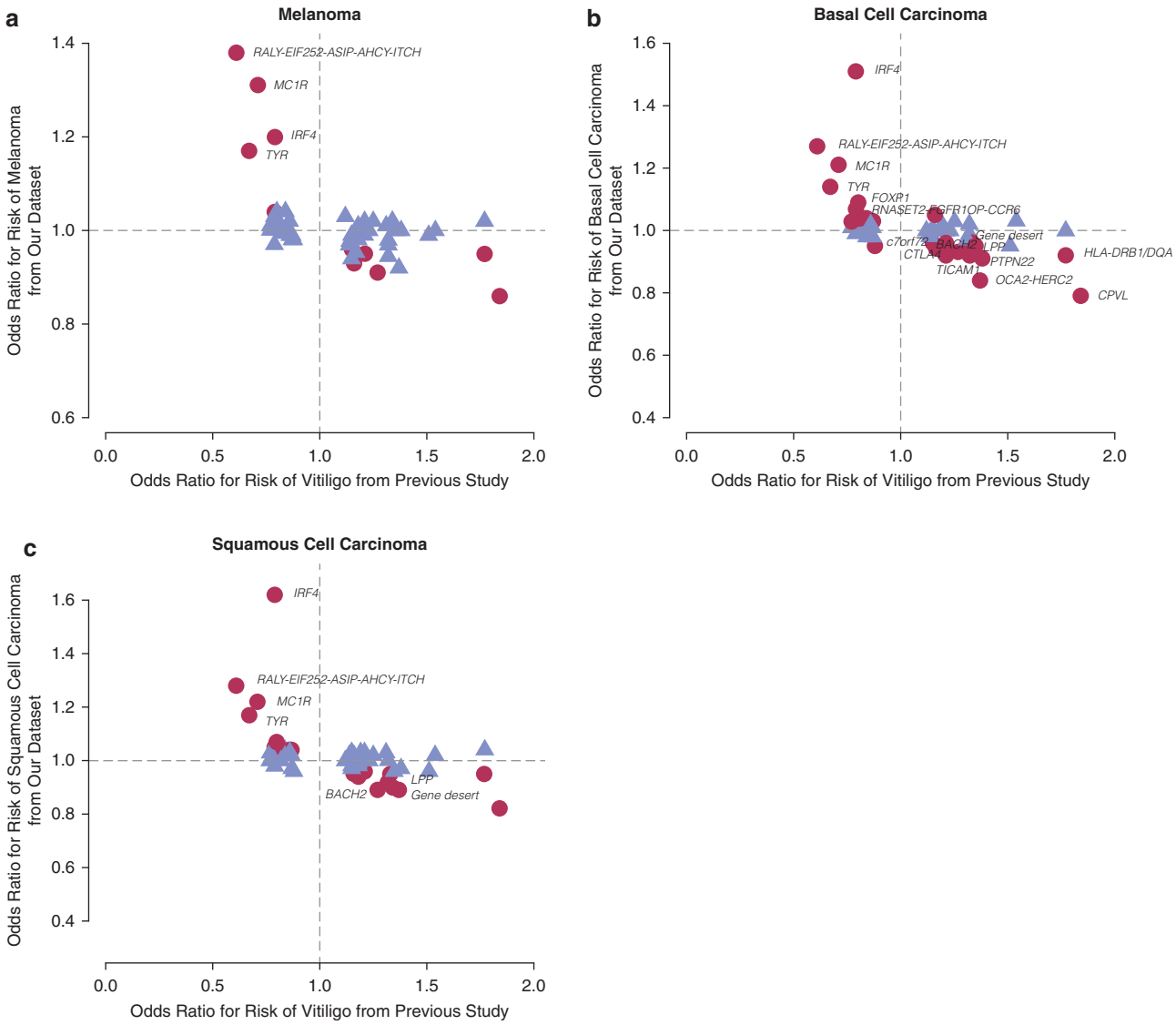

Figure 1. Effect sizes estimated in skin cancer versus vitiligo, for the 58 SNPs from a previously reported vitiligo GWAS (Jin et al., 2016). Both *x*- and *y*-axes display odds ratio values associated with the minor allele. SNPs with $P < 8.6 \times 10^{-4}$ (significant after Bonferroni correction) are labeled with the gene name corresponding to that locus. Effect size estimated in vitiligo was reported by a previous GWAS study (Jin et al., 2016). (**a**) Effect sizes estimated in melanoma versus vitiligo. SNPs with $P < 0.5$ in the meta-analysis are shown in red; the other SNPs are shown in blue. For effect sizes estimated in the melanoma meta-analysis, SNPs with heterogeneity statistics $I^2 \geq 60\%$ were calculated with a random-effects method. (**b**) Effect sizes estimated in basal cell carcinoma versus vitiligo. SNPs with $P < 0.05$ are shown in red; other SNPs are shown in blue. (**c**) Effect sizes estimated in squamous cell carcinoma versus vitiligo. SNPs with $P < 0.05$ are shown in red; other SNPs are shown in blue. GWAS, genome-wide association study; SNP, single-nucleotide polymorphism.

percentage of cases and controls, probably resulting in a limited bias in genetic risk estimates for each specific type of skin cancers. Further studies are warranted to understand the underlying mechanisms.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2018.03.1511.

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