Mendelian Randomization Analysis reveals Inverse Genetic Risks between Skin Cancers and Vitiligo

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Several observational studies have demonstrated a consistent pattern of decreased melanoma risk among patients with vitiligo. More recently, this finding has been supported by a suggested genetic relationship between the two entities, with certain variants significantly associated with an increased risk of melanoma, basal cell carcinoma, and squamous cell carcinoma but a decreased risk of vitiligo. We compared 48 associated variants from a recently published GWAS and identified three variants—located in the *TYR*, *MC1R-DEF8*, and *RALY-EIF2S2-ASIP-AHCY-ITCH* loci— that correlated with an increased risk for melanoma, basal cell carcinoma, and squamous cell carcinoma and a decreased risk for vitiligo. We then used results of skin cancers and vitiligo GWAS to compare the shared genetic properties between these two traits through an unbiased Mendelian randomization analysis. Our results suggest that the inverse genetic relationship between common skin cancers and vitiligo is broader than previously reported owing to the influence of shared genome-wide significant associations.

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INTRODUCTION

Over the past decade, there has been increasing interest among researchers regarding the possible relationship between skin cancer and vitiligo. Vitiligo is an acquired disorder of depigmentation caused by immune-mediated destruction of melanocytes and can be observed in up to 2% of the population (Krüger and Schallreuter, 2012). Previous reports have suggested enhanced tumor immunosurveillance in vitiligo patients through the increased expression of IFN-γ and programmed death ligand−1 in regulatory T cells (Speeckaert and van Geel, 2017; Yang et al., 2015).

The role of UVR in the carcinogenesis of melanoma and the lack of photoprotective melanin in vitiliginous skin originally led researchers to believe that vitiligo conferred an increased risk of keratinocytic skin cancer (Rodrigues, 2017). However, multiple observational cohort studies have suggested that patients with vitiligo coincidentally show a decreased risk of developing melanoma, with OR estimates ranging from 0.24 (Paradisi et al., 2014) to 0.32 (Teulings et al., 2013). Similar inverse associations for keratinocytic skin cancer development have been reported (OR = 0.19) (Paradisi et al., 2014). Furthermore, clinical evidence of antimelanocytic immunity has been observed in both vitiligo and cutaneous melanoma, with reports showing improved survival in patients with melanoma with vitiligo and improved response to therapy in patients with melanoma who acquire vitiligo concurrently with treatment (Alonso-Castro et al., 2013; Hua et al., 2016; Mochel et al., 2016; Naveh et al., 2013). Finally, GWASs have identified inverse relationships between SNPs associated with vitiligo risk and the risk of skin cancers, including skin cutaneous melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC) (Jin et al., 2016; Wu et al., 2018).

In this study, we investigated the hypothesis that risk-conferring SNPs for vitiligo causally increased or decreased skin cancer (melanoma and keratinocytic) risk. We analyzed GWAS summary statistics from a large pool of samples from the UK Biobank (UKBB) (Imputed v3, file manifest release 20180731) and identified SNPs in three culprit loci: *TYR*, *MC1R-DEF8*, and *RALY-EIF2S2-ASIP-AHCY-ITCH*. We further identified the presence of a causal inverse relationship between these traits through unbiased Mendelian randomization (MR) analysis, which highlighted the presence of important shared biological properties outside of previously reported loci. Our results provide additional evidence to support a genetic link between vitiligo and skin cancer, which may further elucidate the role of immunosurveillance in skin cancer.

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Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; MR, Mendelian randomization; SCC, squamous cell carcinoma; UKBB, UK Biobank

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RESULTS

We utilized a list of 48 confirmed vitiligo-associated variants and investigated their association with skin cancers in the UKBB (Jin et al., 2016). Three SNPs—in the *TYR*, *MC1R-DEF8*, and *RALY-EIF2S2-ASIP-AHCY-ITCH* loci—reached both genome-wide statistical significance and Bonferroni-corrected significance ($0.05/58 = 8.6 \times 10^{-4}$) for melanoma risk ($P < 8.6 \times 10^{-4}$) from the two-stage meta-analysis (Wu et al., 2018). None of the 48 vitiligo-risk SNPs were significantly associated with SCC in UKBB analyses.

All three of the SNPs mentioned earlier had a causal effect on melanoma with β of 1.67×10^{-3} ($P = 2.28 \times 10^{-4}$) for *TYR*, 2.31×10^{-3} ($P = 2.27 \times 10^{-4}$) for *MC1R-DEF8*, and 2.46×10^{-3} ($P = 3.49 \times 10^{-4}$) for *RALY-EIF2S2-ASIP-AHCY-ITCH* (Table 1). The same was true for BCC and SCC risk with β of 0.120 ($P = 2.4 \times 10^{-24}$) and 0.114 ($P = 1.5 \times 10^{-4}$) for *TYR*, 0.138 ($P = 3.1 \times 10^{-32}$) and 0.197 ($P = 3.5 \times 10^{-11}$) for *MC1R-DEF8*, and 0.216 ($P = 8.5 \times 10^{-37}$) and 0.265 ($P = 5.3 \times 10^{-10}$) for *RALY-EIF2S2-ASIP-AHCY-ITCH*, respectively. The remaining 45 vitiligo risk SNPs did not reach genome-wide significance in either cohort. *TYR*, *MC1R*, and *RALY-EIF2S2-ASIP-AHCY-ITCH* SNPs were all protective against vitiligo, with ORs of 0.67 (95% confidence interval [CI] = 0.63–0.71), 0.71 (95% CI = 0.67–0.75), and 0.61 (95% CI = 0.55–0.68), respectively (Jin et al., 2016). The minor allele frequencies of the vitiligo-associated SNPs were 0.306, 0.311, and 0.108, respectively. Variant rs1126809 is a *TYR* missense variant c.1205G>A, p.R402Q, whereas variant rs4268748 and variant rs6059655 can be found in the non-coding (intronic) regions of *MC1R-DEF8* and *RALY-EIF2S2-ASIP-AHCY-ITCH* (Table 1).

To investigate the causal effect of the three-variant vitiligo signature on skin cancer, we performed two-sample MR (Figure 1a). Vitiligo variants were subjected to linkage disequilibrium–based pruning and harmonization with skin cancer summary statistics. Using the standard inverse variance–weighted method, we observed significant inverse relationship between effects of this three-variant signature in vitiligo and melanoma (effect size = −0.511; $P = 2.41 \times 10^{-5}$), BCC (effect size = −0.377; $P = 1.08 \times 10^{-10}$), and SCC (effect size = −0.452; $P = 7.84 \times 10^{-5}$), suggesting a strong contribution of these variants to the anticancer effect of vitiligo.

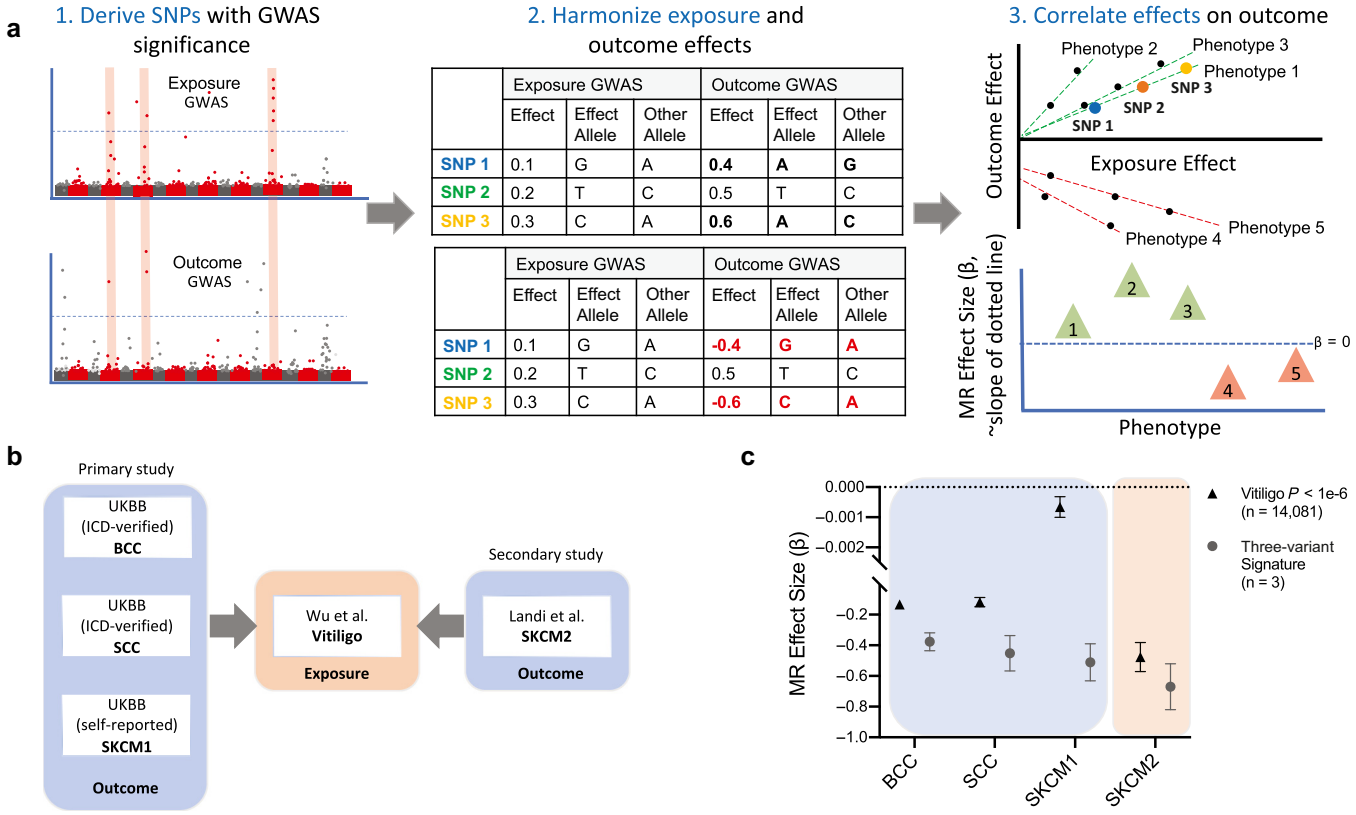
We further sought to verify whether the causal effect examined from the three-variant signature was a unique interaction driving the inverse phenotype correlations. We selected all variants with $P < 1 \times 10^{-6}$ in vitiligo GWAS summary statistics as exposure data for secondary MR analysis (Figure 1b). The final set of outcome variants kept for MR analysis included 14,081 variants, including the previously analyzed three-variant signature.

We observed opposite effects when comparing each skin cancer with vitiligo: melanoma (effect size = -6.78×10^{-4}, $P = 0.054$), BCC (effect size = −0.134, $P = 9.52 \times 10^{-11}$), and SCC (effect size = −0.118, $P = 9.43 \times 10^{-5}$) (Figure 1c). Because the effect size between vitiligo and melanoma was below the multiple hypothesis threshold, we next performed a replication analysis using an independent melanoma GWAS meta-analysis of 36,760 cases of melanoma (67% newly genotyped) and 375,188 controls (Landi et al., 2020). Again, we found evidence for an MR association with

Table 1. Summary of Known Vitiligo Risk SNPs that Reached Genome-Wide Significance in UKBB Skin Cancer Cohorts

rsid	Locus	Region	Min/ Maj	Consequence	MAF	Malignant Melanoma (SKCM)		BCC		SCC		Vitiligo
						UKBB	Wu et al., 2018	UKBB	Wu et al., 2018	UKBB	Wu et al., 2018	Jin et al., (2016)
rs1126809	TYR	11q14.3	G/A	Missense variant	0.306	OR (95% CI) = 1.24 (1.17, 1.31)[1] β (95% CI) = 1.67×10^{-3} (1.44×10^{-3}, 1.90×10^{-3})[2]	OR (95% CI) = 1.17 (1.12, 1.22)[2,3]	OR (95% CI) = 1.13 (1.11, 1.14)[4] β (95% CI) = 0.120 (0.108, 0.132)[2]	OR (95% CI) = 1.14 (1.11, 1.18)[2,3]	OR (95% CI) = 1.12 (1.09, 1.15)[3] β (95% CI) = 0.114 (0.084, 0.144)	OR (95% CI) = 1.17 (1.15, 1.19)[2,3]	OR (95% CI) = 0.67 (0.63, 0.71)[2,3]
rs4268748	MC1R-DEF8	16q24.3	T/C	Noncoding	0.311	OR (95% CI) = 1.35 (1.27, 1.44)[1] β (95% CI) = 2.31×10^{-3} (2.08×10^{-3}, 2.53×10^{-3})[2]	OR (95% CI) = 1.31 (1.18, 1.46)[3]	OR (95% CI) = 1.15 (1.13, 1.17)[4] β (95% CI) = 0.138 (0.126, 0.150)[2]	OR (95% CI) = 1.21 (1.17, 1.24)[2,3]	OR (95% CI) = 1.22 (1.18, 1.25)[3] β (95% CI) = 0.197 (0.167, 0.227)[2]	OR (95% CI) = 1.22 (1.20, 1.24)[2,3]	OR (95% CI) = 0.71 (0.67, 0.75)[2,3]
rs6059655	RALY-EIF2S2-ASIP-AHCY-ITCH	20q11.22	G/A	Noncoding	0.108	OR (95% CI) = 1.33 (1.23, 1.43)[1] β (95% CI) = 2.46×10^{-3} (2.11×10^{-3}, 2.81×10^{-3})[2]	OR (95% CI) = 1.38 (1.29, 1.47)[2,3]	OR (95% CI) = 1.24 (1.22, 1.26)[4] β (95% CI) = 0.216 (0.199, 0.233)[2]	OR (95% CI) = 1.27 (1.21, 1.32)[2,3]	OR (95% CI) = 1.30 (1.25, 1.36)[3] β (95% CI) = 0.265 (0.222, 0.308)[2]	OR (95% CI) = 1.28 (1.24, 1.32)[2,3]	OR (95% CI) = 0.61 (0.55, 0.68)[2,3]

Abbreviations: CI, confidence interval; MAF, minor allele frequency; Maj, major allele; Min, minor allele; rsid, reference SNP cluster identification; SKCM, skin cutaneous melanoma; UKBB, UK Biobank.
[1]OR converted from beta estimated using linear regression.
[2]Associations reached genome-wide significance ($P < 5 \times 10\text{-}8$).
[3]OR reproduced from respective publications.
[4]OR converted from beta estimate using logistic regression.



	Exposure GWAS			Outcome GWAS		
	Effect	Effect Allele	Other Allele	Effect	Effect Allele	Other Allele
SNP 1	0.1	G	A	**0.4**	**A**	**G**
SNP 2	0.2	T	C	0.5	T	C
SNP 3	0.3	C	A	**0.6**	**A**	**C**

	Exposure GWAS			Outcome GWAS		
	Effect	Effect Allele	Other Allele	Effect	Effect Allele	Other Allele
SNP 1	0.1	G	A	**-0.4**	**G**	**A**
SNP 2	0.2	T	C	0.5	T	C
SNP 3	0.3	C	A	**-0.6**	**C**	**A**

Figure 1. Data preparation and analysis workflow for two-sample Mendelian randomization. (**a**) Publicly available GWAS summary statistics are extracted from exposure and outcome instruments. Effect sizes for the exposure and outcome of interest are associated and consequently harmonized to ensure that the same reference alleles are compared. Finally, MR is performed to generate an effect size (β) for each comparison. (**b**) Instrumental variables were linear regression based and derived from the UKBB and an independent GWAS meta-analysis for skin cancer and vitiligo, respectively (BCC, SCC, or SKCM1). Data to perform the secondary study were derived from a second meta-analysis study (Landi et al., 2020) for melanoma (SKCM2). (**c**) MR study results indicate that the opposite effects of vitiligo variants with $P < 1 \times 10^{-6}$ on cancer risks (black triangles) are smaller than the effect of three-variant signature from Table 1 (gray circles) for melanoma, BCC, and SCC. BCC, basal cell carcinoma; ICD, International Classification of Diseases; MR, Mendelian randomization; SKCM, skin cutaneous melanoma; SCC, squamous cell carcinoma; UKBB, UK Biobank.

opposite effect for the three-variant signature (−0.670, $P = 7.70 \times 10^{-6}$) and 54 significant loci reaching genome-wide significance (−0.477, $P = 4.68 \times 10^{-7}$). As we demonstrate in our replication analysis, cohorts with a more robust phenotyping approach yield a significant signal in MR.

Such strengthening of the three-variant signature effect suggests that the protective effect is largely attributed to decreased inherited risk of skin cancers rather than the autoimmune component of the vitiligo. Although the conflicting role of vitiligo in skin cancer remains to be explored, the sensitivity analysis presented in this study demonstrates consistently opposite associations between vitiligo and skin cancer.

Expression quantitative trait loci for the three-variant signature is shown in Figure 2. In rs6059655, *ASIP* was shown to have significantly decreased levels of expression with the risk phenotype. ASIP functions as an antagonist to MC1R through α-melanocyte-stimulating hormone to modulate melanin pigmentation (Robbins et al., 1993; Yan et al., 2022), though an inverse expression quantitative trait loci association with *MC1R* was found to be nonsignificant. On the basis of 2008 case-control study, a haplotype near *ASIP* was found to confer an increased risk of cutaneous melanoma (OR = 1.27, 95% CI = 1.02−1.57) without adjustment for pigmentation characteristics, whereas *MC1R* did not (Gudbjartsson et al., 2008). Single tissue expression quantitative trait loci association of the three-variant signature further showed a high association of rs4268748 to *CDK10* expression in both sun-exposed (normalized enrichment score = −0.22, $P = 1.4 \times 10^{-17}$) and nonexposed (normalized enrichment score = −0.25, $P = 1.2 \times 10^{-19}$) skin—an association previously suggested by a 2020 summary-based MR study (Bonilla et al., 2021). *MC1R* and *CDK10* were found to harbor unique methylation sites (including cg04378830, cg09569215, and cg10062109 on 16q24.3), which correspond to high-risk skin cancer phenotypes (Bonilla et al., 2021; Cai et al., 2021). These findings suggest a broad yet undefined mechanism for tumor predisposition within the three-variant signature and the need to prioritize such genes in future mechanistic studies.

DISCUSSION

Despite recent research efforts, the relationship between vitiligo and skin cancer remains to be poorly understood. A presumed connection between decreased epidermal melanin and a resultant increase in UVR has prompted some dermatologists to empirically advise against the use of phototherapy and urge additional protection from sun exposure in patients with vitiligo (Hexsel et al., 2009; Schallreuter et al., 2002; Teulings et al., 2013). Meanwhile, the reports from

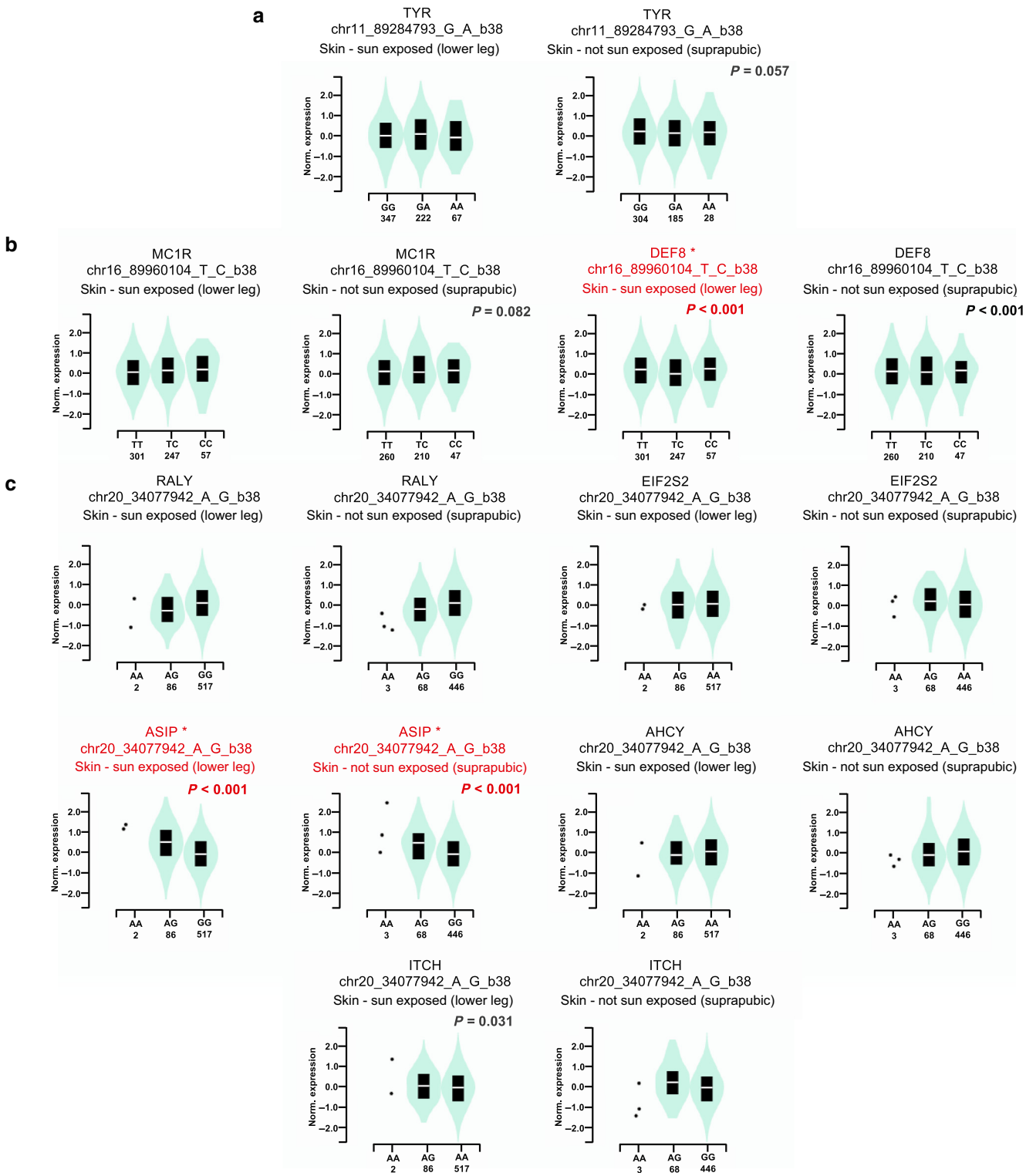


Figure 2. eQTL for gene loci contained within the three-variant signature. (**a**) *TYR* in rs1126809 demonstrates no significant association for all risk genotypes. (**b**) *DEF8* in rs4268748 was significantly differentially expressed among ordered genotypes for sun-exposed skin. (**c**) Expression was *ASIP* in rs6059655 was significantly decreased in risk genotypes (GG) for both sun-exposed and nonexposed skin. Red highlights denote eQTL loci with $P < 0.10$, whereas asterisks (*) denote $P < 0.001$. eQTL, expression quantitative trait loci.

observational studies of an inverse risk between vitiligo and skin cancer suggest that these patients may in fact be more inherently protected than their nonvitiliginous counterparts (Paradisi et al., 2014; Teulings et al., 2013). In these reports, the increased immune response associated with vitiligo has been suspected to fortify resilience against skin cancer pathogenesis.

The results of the present analysis of a large sample size in the UKBB cohort confirm the findings of similar studies in other populations (Bishop et al., 2009; Gudbjartsson et al.,

2008; Wu et al., 2018) and corroborate a genetic basis to the proposed inverse risk between vitiligo and skin cancer by identifying three candidate loci—*TYR*, *MC1R-DEF8*, and *RALY-EIF2S2-ASIP-AHCY-ITCH*. All the three loci significantly correlated with decreased risks of vitiligo and increased risks of melanoma, BCC, and SCC. The *TYR* gene encodes for tyrosinase in melanocytes and is involved in catalyzing melanin formation (Seruggia et al., 2021). *MC1R* is a G protein–coupled receptor that upregulates melanin production through cAMP signaling (Wolf Horrell et al., 2016). A haplotype near *ASIP*, which affects pigmentation phenotype similar to *MC1R*, was found to be significantly associated with both skin cutaneous melanoma and BCC (Gudbjartsson et al., 2008). Unlike the findings in similar studies, none of the vitiligo-risk SNPs correlated with SCC.

In contrast to traditional epidemiological approaches, MR enables the quantification of causal effects for a modifiable exposure to disease. The method is analogous to traditional randomized control trials, in which genetic variants are employed that do not naturally suffer from confounders or reverse causation. Two-sample MR is an extension to the traditional one-sample approach in which the association of genetic variants with exposure and with outcome are derived from nonoverlapping samples—this is particularly useful given the large sample size requirement. Our investigation of the effects of vitiligo-associated variants on three major forms of skin cancer—melanoma, BCC, and SCC—indicates strong evidence for association when using samples derived from the UKBB and an independent GWAS meta-analysis. Initial analysis of the vitiligo–melanoma relationship did not reach statistical significance, likely owing to ascertainment noise in the UKBB data. Upon usage of a summary statistic from well-powered case-control GWAS for melanoma, the relationship between the two phenotypes was found to be significant (Bonferroni-corrected threshold, $P < 0.05/3 = 0.017$).

Antimelanocyte autoimmunity in melanoma has garnered an increasing amount of attention owing to several reports of patients developing vitiligo both before and after immune therapy treatment. Melanoma-associated vitiligo occurs at a variably reported but considerably higher rate than that of the general population and has long been associated with favorable outcomes in melanoma (Boasberg et al., 2006; Bystryn et al., 1987; Hua et al., 2016; Nordlund et al., 1983; Quaglino et al., 2010). There have been similar reports of an association with other autoimmune disorders, such as hypothyroidism and hyperthyroidism and antiphospholipid antibody syndrome (Becker et al., 1994; Gogas et al., 2006) and of a similar phenomenon in uveal melanoma (Rishi et al., 2013). There are even cases of repigmentation in the vitiliginous skin of patients with melanoma that has begun to progress or relapse (Nakamura et al., 2017a; Nardin et al., 2019). These observations have become even more pertinent with the introduction of immune checkpoint inhibitors in the management of late-stage disease. Because the use of these immune-mediated therapies has become more prevalent, so also have reports of vitiligo as both a possible adverse event and a harbinger of a favorable therapeutic response (Freeman-Keller et al., 2016; Hua et al., 2016; Nakamura et al., 2017b; Teulings et al., 2015). Associations in this study also show consistency with candidate-gene association signals previously reported for vitiligo. In particular, the *TYR* R402Q variant is a major vitiligo autoimmune antigen that reduces the availability of TYR for antigen presentation by HLA*02:01 (Jin et al., 2012, 2010). Compared with 402Q, this variant shows increased expression levels and immune presentation efficacy by HLA*02:01 and thus is more likely to contribute toward immune susceptibility in vitiligo (Jin et al., 2010).

Given this potential genetic association between vitiligo and skin cancer, future mechanistic studies are needed to fully explore skin cancer immunosusceptibility in the context of pigmentation phenotype. This is particularly relevant for melanoma in light of the relatively high tumor mutational burden caused by UVR, which has been identified as a marker of improved survival and improved sensitivity to immune checkpoint therapy (Chalmers et al., 2017; Chan et al., 2015; Gupta et al., 2015; Klebanov et al., 2019). Finally, an increased understanding of the role of immunosurveillance will allow us to further develop immune-mediated therapies and predict which tumors are more likely to benefit from such therapies.

MATERIALS AND METHODS

As the source of vitiligo-associated SNPs, we manually curated data on 48 SNPs reported as significantly associated with vitiligo in a published meta-analysis of three GWASs with 4,680 vitiligo cases and 39,586 controls of European ancestry (Jin et al., 2016). ORs (with 95% CIs) were found in the study using logistic regression and are presented in Table 1. We also obtained data on SNPs associated with melanoma, BCC, and SCC from the results of a high-throughput GWAS analysis (Neale Lab, 2017) of the UKBB study population using linear regression models. Correlation coefficients (β) were used to estimate ORs using natural logarithm conversion. Study participants in the UKBB had previously been filtered using standard GWAS sample and SNP quality check parameters and narrowed to individuals of White British genetic ancestry. We then identified 14,081 overlapping SNPs representing the following phenotypes: International Classification of Diseases, Ninth Revision/International Classification of Diseases, Tenth Revision–verified BCC (16,847 cases, 340,302 controls); International Classification of Diseases, Ninth Revision/International Classification of Diseases, Tenth Revision SCC (2,274 cases, 340,302 controls); and self-reported malignant melanoma (2,898 cases, 358,243 controls) (Liyanage et al., 2019; Neale Lab, 2017). Data preparation for MR was carried out using a standard protocol from the R-package TwoSampleMR (Hemani et al., 2018, 2017). Clumping was performed using a window of 10Kb with default parameters. Exposure and outcome data were then harmonized to matching effect alleles, and palindromic SNPs were excluded. The inverse variance–weighted method was selected for this study, which is a common estimator employed by two-sample MR that assumes all genetic variants to be instrumental variables (Burgess et al., 2020).

Data availability statement

Publicly available datasets related to this article can be requested from https://www.ukbiobank.ac.uk/, an open-source repository hosted by the UK Biobank Resource. Additional data used for the analyses described in this manuscript were obtained from the GTEx Portal and database of Genotypes and Phenotypes accession number phs000424.v8.p2 on January 5, 2022.

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CONFLICT OF INTEREST
MJD is a founder of Maze Therapeutics. The other authors have no conflicts of interest to declare.

ETHICS DECLARATION
This study was based on publicly available data and did not actively enroll patients; therefore, a consenting process was not applicable. However, the original cohort assembly utilized for the UK Biobank obtained written, informed consent according to requirements outlined by the Declaration of Helsinki.

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AUTHOR CONTRIBUTIONS
Conceptualization: SR, MS, NK, MA, MJD, HT; Data Curation: SR, MS, NK, MA, MJD, HT; Formal Analysis: SR, IM, MS, NK, MA, MJD, HT; Funding Acquisition: HT; Writing - Original Draft Preparation: SR, MS, NK, MA, MJD, HT; Writing - Review and Editing: SR, IM, MS, NK, MA, MJD, HT

REFERENCES
Alonso-Castro L, Ríos-Buceta L, Vano-Galvan S, Moreno C, Soria-Rivas A, Jaén P. Vitiligo in 2 patients receiving vemurafenib for metastatic melanoma. J Am Acad Dermatol 2013;69:e28–9.

Becker JC, Winkler B, Klingert S, Bröcker EB. Antiphospholipid syndrome associated with immunotherapy for patients with melanoma. Cancer 1994;73:1621–4.

Bishop DT, Demenais F, Iles MM, Harland M, Taylor JC, Corda E, et al. Genome-wide association study identifies three loci associated with melanoma risk. Nat Genet 2009;41:920–5.

Boasberg PD, Hoon DSB, Piro LD, Martin MA, Fujimoto A, Kristedja TS, et al. Enhanced survival associated with vitiligo expression during maintenance biotherapy for metastatic melanoma. J Invest Dermatol 2006;126:2658–63.

Bonilla C, Bertoni B, Min JL, Hemani G. Genetics of DNA Methylation Consortium, Elliott HR. Investigating DNA methylation as a potential mediator between pigmentation genes, pigmentary traits and skin cancer. Pigment Cell Melanoma Res 2021;34:892–904.

Burgess S, Foley CN, Allara E, Staley JR, Howson JMM. A robust and efficient method for Mendelian randomization with hundreds of genetic variants. Nat Commun 2020;11:376.

Bystryn JC, Rigel D, Friedman RJ, Kopf A. Prognostic significance of hypopigmentation in malignant melanoma. Arch Dermatol 1987;123:1053–5.

Cai M, Yuan T, Huang H, Gui L, Zhang L, Meng Z, et al. Integrative analysis of omics data reveals regulatory network of CDK10 in vitiligo risk. Front Genet 2021;12:634553.

Chalmers ZR, Connelly CF, Fabrizio D, Gay L, Ali SM, Ennis R, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med 2017;9:34.

Chan TA, Wolchok JD, Snyder A. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2015;373:1984.

Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G, Weber JS. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. Clin Cancer Res 2016;22:886–94.

Gogas H, Ioannovich J, Dafni U, Stavropoulou-Giokas C, Frangia K, Tsoutsos D, et al. Prognostic significance of autoimmunity during treatment of melanoma with interferon. N Engl J Med 2006;354:709–18.

Gudbjartsson DF, Sulem P, Stacey SN, Goldstein AM, Rafnar T, Sigurgeirsson B, et al. ASIP and TYR pigmentation variants associate with cutaneous melanoma and basal cell carcinoma [published correction appears in Nat Genet 2008;40:1029]. Nat Genet 2008;40:886–91.

Gupta S, Artomov M, Goggins W, Daly M, Tsao H. Gender disparity and mutation burden in metastatic melanoma. J Natl Cancer Inst 2015;107:djv221.

Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data [published correction appears in PLoS Genet 2017;13:e1007149] PLoS Genet 2017;13:e1007081.

Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, et al. The MR-Base platform supports systematic causal inference across the human phenome. ELife 2018;7:e34408.

Hexsel CL, Eide MJ, Johnson CC, Krajenta R, Jacobsen G, Hamzavi I, et al. Incidence of nonmelanoma skin cancer in a cohort of patients with vitiligo. J Am Acad Dermatol 2009;60:929–33.

Hua C, Boussemart L, Mateus C, Routier E, Boutros C, Cazenave H, et al. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. JAMA Dermatol 2016;152:45–51.

Jin Y, Andersen G, Yorgov D, Ferrara TM, Ben S, Brownson KM, et al. Genome-wide association studies of autoimmune vitiligo identify 23 new risk loci and highlight key pathways and regulatory variants. Nat Genet 2016;48:1418–24.

Jin Y, Birlea SA, Fain PR, Gowan K, Riccardi SL, Holland PJ, et al. Variant of TYR and autoimmunity susceptibility loci in generalized vitiligo. N Engl J Med 2010;362:1686–97.

Jin Y, Ferrara T, Gowan K, Holcomb C, Rastrou M, Erlich HA, et al. Next-generation DNA re-sequencing identifies common variants of TYR and HLA-A that modulate the risk of generalized vitiligo via antigen presentation. J Invest Dermatol 2012;132:1730–3.

Klebanov N, Artomov M, Goggins WB, Daly E, Daly MJ, Tsao H. Burden of unique and low prevalence somatic mutations correlates with cancer survival. Sci Rep 2019;9:4848.

Krüger C, Schallreuter KU. A review of the worldwide prevalence of vitiligo in children/adolescents and adults. Int J Dermatol 2012;51:1206–12.

Landi MT, Bishop DT, MacGregor S, Machiela MJ, Stratigos AJ, Ghiorzo P, et al. Genome-wide association meta-analyses combining multiple risk phenotypes provides insights into the genetic architecture of cutaneous melanoma susceptibility. Nat Genet 2020;52:494–504.

Liyanage UE, Law MH, Han X, An J, Ong JS, Gharahkhani P, et al. Combined analysis of keratinocyte cancers identifies novel genome-wide loci. Hum Mol Genet 2019;28:3148–60.

Mochel MC, Ming ME, Imadojemu S, Gangadhar TC, Schuchter LM, Elenitsas R, et al. Cutaneous autoimmune effects in the setting of therapeutic immune checkpoint inhibition for metastatic melanoma. J Cutan Pathol 2016;43:787–91.

Nakamura Y, Tanaka R, Asami Y, Teramoto Y, Imamura T, Sato S, et al. Correlation between vitiligo occurrence and clinical benefit in advanced melanoma patients treated with nivolumab: a multi-institutional retrospective study. J Dermatol 2017b;44:117–22.

Nakamura Y, Teramoto Y, Asami Y, Matsuya T, Adachi JI, Nishikawa R, et al. Nivolumab therapy for treatment-related vitiligo in a patient with relapsed metastatic melanoma. JAMA Dermatol 2017a;153:942–4.

Nardin C, Pelletier F, Puzenat E, Aubin F. Vitiligo repigmentation with melanoma progression during pembrolizumab treatment. Acta Derm Venereol 2019;99:913–4.

Naveh HP, Rao UNM, Butterfield LH. Melanoma-associated leukoderma—immunology in black and white? Pigment Cell Melanoma Res 2013;26:796–804.

Neale Lab. Details and considerations of the UK biobank GWAS. http://www.nealelab.is/blog/2017/9/11/details-and-considerations-of-the-uk-biobank-gwas;; 2017. (accessed December 6, 2021).

Nordlund JJ, Kirkwood JM, Forget BM, Milton G, Albert DM, Lerner AB. Vitiligo in patients with metastatic melanoma: A good prognostic sign. J Am Acad Dermatol 1983;9:689–96.

Paradisi A, Tabolli S, Didona B, Sobrino L, Russo N, Abeni D. Markedly reduced incidence of melanoma and nonmelanoma skin cancer in a nonconcurrent cohort of 10,040 patients with vitiligo. J Am Acad Dermatol 2014;71:1110–6.

Quaglino P, Marenco F, Osella-Abate S, Cappello N, Ortoncelli M, Salomone B, et al. Vitiligo is an independent favourable prognostic factor in stage III and IV metastatic melanoma patients: results from a single-institution hospital-based observational cohort study. Ann Oncol 2010;21:409–14.

Rishi P, Shields CL, Patrick K, Shields JA. Cutaneous vitiligo following management of uveal melanoma in 6 patients. JAMA Ophthalmol 2013;131:1174–8.

Robbins LS, Nadeau JH, Johnson KR, Kelly MA, Roselli-Rehfuss L, Baack E, et al. Pigmentation phenotypes of variant extension locus alleles result from point mutations that alter MSH receptor function. Cell 1993;72:827–34.

Rodrigues M. Skin cancer risk (nonmelanoma skin cancers/melanoma) in vitiligo patients. Dermatol Clin 2017;35:129–34.

Schallreuter KU, Tobin DJ, Panske A. Decreased photodamage and low incidence of non-melanoma skin cancer in 136 sun-exposed Caucasian patients with vitiligo. Dermatology 2002;204:194–201.

Seruggia D, Josa S, Fernández A, Montoliu L. The structure and function of the mouse tyrosinase locus. Pigment Cell Melanoma Res 2021;34:212–21.

Speeckaert R, van Geel N. Targeting CTLA-4, PD-L1 and IDO to modulate immune responses in vitiligo. Exp Dermatol 2017;26:630–4.

Teulings HE, Limpens J, Jansen SN, Zwinderman AH, Reitsma JB, Spuls PI, et al. Vitiligo-like depigmentation in patients with stage III–IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. J Clin Oncol 2015;33:773–81.

Teulings HE, Overkamp M, Ceylan E, Nieuweboer-Krobotova L, Bos JD, Nijsten T, et al. Decreased risk of melanoma and nonmelanoma skin cancer in patients with vitiligo: a survey among 1307 patients and their partners. Br J Dermatol 2013;168:162–71.

Wolf Horrell EM, Boulanger MC, D'Orazio JA. Melanocortin 1 receptor: structure, function, and regulation. Front Genet 2016;7:95.

Wu W, 23andMe Research Team, Amos CI, Lee JE, Wei Q, Sarin KY, et al. Inverse relationship between vitiligo-related genes and skin cancer risk. J Invest Dermatol 2018;138:2072–5.

Yan X, Terai Y, Widayati KA, Itoigawa A, Purba LHPS, Fahri F, et al. Functional divergence of the pigmentation gene melanocortin-1 receptor (MC1R) in six endemic Macaca species on Sulawesi Island. Sci Rep 2022;12:7593.

Yang L, Wei Y, Sun Y, Shi W, Yang J, Zhu L, et al. Interferon-gamma inhibits melanogenesis and induces apoptosis in melanocytes: A pivotal role of CD8+ cytotoxic T lymphocytes in vitiligo. Acta Derm Venereol 2015;95:664–70.