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Melanoma susceptibility variants on chromosome 20q11.22 are associated with pigmentary traits and the risk of non-melanoma skin cancer

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MADAM, A recent genome-wide association study (GWAS) identified a cutaneous melanoma risk locus at 20q11.22 (rs910873 and rs1885120), which is adjacent to a pigmentation gene, *ASIP* encoding a 132-amino acid protein¹. At the same locus, two previous GWASs identified that a haplotype near *ASIP* (hereafter called *ASIP* AH) carrying rs4911414 variant allele[T] and rs1015362 major allele[G] was associated with pigmentary phenotypes (red hair color, skin sensitivity to sun, and freckling) as well as with increased risks of melanoma and basal cell carcinoma (BCC)^{2,3}. Also, a single nucleotide polymorphism (SNP) in the 3' untranslated region of the *ASIP* gene (rs6058017, g.8818 A>G) has been previously reported to be associated with darker pigmentation^{4,5}. These three SNPs (rs4911414, rs1015362, and rs6058017) were previously examined for the associations with pigmentary phenotypes (hair color, skin color, and tanning ability) and skin cancer risks in our skin cancer study⁶. We found that the haplotype *ASIP* AH was significantly associated with fair skin color as well as the risks of melanoma and squamous cell carcinoma (SCC)⁶. None of these three SNPs ($r^2 < 0.1$ in controls), but the *ASIP* AH ($r^2 = 0.7$ in controls), were in strong LD with the newly identified two SNPs (rs910873 and rs1885120).

In this study, we performed a skin cancer case-control study of Caucasians nested within the Nurses' Health Study (NHS) to evaluate whether these two melanoma susceptibility variants (rs910873 and rs1885120) identified by the GWAS are associated with pigmentary phenotypes (hair color, skin color, and tanning ability) and the risks of nonmelanoma skin cancers (SCC and BCC) along with melanoma risk. Furthermore, by entering the haplotype *ASIP* AH and three SNPs (rs910873, rs1885120, and rs6058017) near or within the *ASIP* gene into the multivariate models, we compare the strength of their association with pigmentary phenotypes and skin cancer risk. The nested case-control study consisted of 218 incident melanoma cases, 285 incident SCC cases, 300 incident BCC cases, and 870 age-matched controls. A detailed description of the characteristics of cases and controls in the skin cancer nested case-control study was published previously⁷.

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We genotyped the two melanoma susceptibility SNPs on chromosome 20 (rs910873 and rs1885120) by the 5' nuclease assay (TaqMan®) in 384-well format, using the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). The distributions of genotypes for the two SNPs (rs910873 and rs1885120) were in Hardy-Weinberg equilibrium among controls. Because the two SNPs are in high LD ($r^2 > 0.9$ in controls), we anticipated that these two SNPs would show similar effects on pigmentary phenotypes and skin cancer risk.

We evaluated the associations between the two SNPs and pigmentary phenotypes among controls using linear regression models (Table 1). The *p*-values for rs910873 (rs1885120) were 0.02 (0.06) for hair color (black to blonde); 0.02 (0.02) for skin color; and 0.04 (0.02) for tanning ability, respectively. In the multivariate analyses mutually adjusting for the SNPs and haplotype near or within the *ASIP* gene including rs910873 (or rs1885120), *ASIP* AH, and rs6058017, the association of rs910873 (or rs1885120) with the pigmentary phenotypes was eliminated, while the association between the *ASIP* AH and fair skin color remained significant (Supplementary Table 1).

We evaluated the main effect of both polymorphisms across the three types of skin cancer using unconditional logistic regression (Table 2). Overall, the results indicated similar effects of both SNPs (rs910873 and rs1885120) on skin cancer risks. In the analyses controlling for the age, we observed that the rs910873 was significantly associated with increased risks of melanoma and SCC in both additive and dominant models (additive Odds Ratio (OR) for melanoma, 1.67; 95% Confidence Interval (CI), 1.19–2.34; additive OR for SCC, 1.51; 95% CI, 1.09–2.10). For BCC risk, the significant association of rs1885120 was not found in the additive model but in the dominant model. The dominant OR (95% CI) was 1.48 (1.02–2.16). These associations were modestly attenuated after additionally adjusting for pigmentary phenotypes (hair color, skin color, and tanning ability) (Table 2). In the multivariate analysis adjusting for the SNPs within or near *ASIP* gene including rs910873 (or rs1885120), *ASIP* AH, and rs6058017, only *ASIP* AH remained significant for the risks of melanoma and SCC (Supplementary Table 2).

In summary, we replicated the associations of the two melanoma susceptibility SNPs on chromosome 20q11.22 with melanoma risk. In addition, we first provided evidence that these two SNPs are associated with pigmentary phenotypes (hair color, skin color, and tanning ability) as well as with non-melanoma skin cancer risk. We note that these associations are the same signal driven by the haplotype *ASIP* AH. Our results suggested that the *ASIP* AH, compared to the two SNPs (rs910873 and rs1885120) examined in this study, is more strongly associated with both pigmentary phenotypes and skin cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

SCC	squamous cell carcinoma
BCC	basal cell carcinoma

OR odds ratio
CI confidence interval

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Table 1
Associations between two selected SNPs and pigimentary phenotypes among controls

SNP	Hair color (black to blonde)			Skin color			Tanning ability		
	β	SE	p-value	β	SE	p-value	β	SE	p-value
rs910873	0.17	0.07	0.02	0.14	0.06	0.02	0.17	0.08	0.04
rs1885120	0.13	0.07	0.06	0.15	0.06	0.02	0.20	0.08	0.02

The regression parameter beta refers to the mean change in scoring in hair color (black to blonde), skin color, and tanning ability per copy of the SNP minor allele. We regressed an ordinal coding for hair color (1=black; 2=dark brown; 3=light brown; and 4=blonde) or skin color (1=olive; 2=medium; and 3=fair) or tanning ability (1=deep tan; 2=average tan; 3=light tan; and 4=practically none) on an ordinal coding for genotype (0, 1, or 2 copies of SNP minor allele). $\beta > 0$ means that the SNP is associated with lighter hair color, fairer skin color, and less tanning ability.

Table 2

Associations between two selected SNPs and skin cancer risk

	Melanoma			SCC			BCC		
	Controls (%)	Cases (%)	<i>P</i> _{trend}	Cases (%)	<i>P</i> _{trend}	Cases (%)	Cases (%)	<i>P</i> _{trend}	<i>P</i> _{trend}
rs910873									
GG	699 (86.6)	164 (78.1)		217 (79.5)		230 (82.1)			
GA	99 (12.3)	42 (20.0)		54 (19.8)		48 (17.1)			
AA	9 (1.1)	4 (1.9)		2 (0.7)		2 (0.7)			
Age-adjusted OR									
Additive OR		1.67 (1.19–2.34)	0.003	1.51 (1.09–2.10)	0.01	1.29 (0.93–1.80)		0.13	
Dominant OR (GA or AA)		1.81 (1.23–2.67)		1.70 (1.19–2.43)		1.42 (0.98–2.05)			
Multivariate OR^a									
Additive OR		1.52 (1.03–2.24)	0.04	1.17 (0.80–1.71)	0.43	1.22 (0.84–1.78)		0.30	
Dominant OR (GA or AA)		1.72 (1.10–2.67)		1.30 (0.85–1.99)		1.38 (0.91–2.10)			
rs1885120									
GG	712 (87.7)	167 (79.9)		222 (80.7)		227 (82.8)			
GC	92 (11.3)	39 (18.7)		50 (18.2)		45 (16.4)			
CC	8 (1.0)	3 (1.4)		3 (1.1)		2 (0.7)			
Age-adjusted OR									
Additive OR		1.63 (1.15–2.33)	0.007	1.57 (1.13–2.19)	0.007	1.36 (0.96–1.91)		0.08	
Dominant OR (GC or CC)		1.79 (1.20–2.68)		1.73 (1.20–2.50)		1.48 (1.02–2.16)			
Multivariate OR^a									
Additive OR		1.46 (0.97–2.20)	0.07	1.21 (0.82–1.77)	0.34	1.26 (0.85–1.86)		0.25	
Dominant OR (GC or CC)		1.67 (1.06–2.65)		1.27 (0.82–1.96)		1.42 (0.92–2.18)			

The percentages may not sum to 100 due to rounding.

^aUnconditional logistic regression adjusted for age, skin color, natural hair color, and childhood tanning tendency.