Association of Known Melanoma Risk Factors with Primary Melanoma of the Scalp and Neck

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ABSTRACT

Background: Scalp and neck (SN) melanoma confers a worse prognosis than melanoma of other sites but little is known about its determinants. We aimed to identify associations between SN melanoma and known risk genes, phenotypic traits, and sun exposure patterns.

Methods: Participants were cases from the Western Australian Melanoma Health Study ($n = 1,200$) and the Genes, Environment, and Melanoma Study ($n = 3,280$). Associations between risk factors and SN melanoma, compared with truncal and arm/leg melanoma, were investigated using binomial logistic regression. Facial melanoma was also compared with the trunk and extremities, to evaluate whether associations were subregion specific, or reflective of the whole head/neck region.

Results: Compared with other sites, increased odds of SN and facial melanoma were observed in older individuals [SN: OR = 1.28, 95% confidence interval (CI) = 0.92–1.80, $P_{trend} = 0.016$; Face: OR = 4.57, 95% CI = 3.34–6.35, $P_{trend} < 0.001$] and those carrying *IRF4*-rs12203592*T (SN: OR = 1.35, 95% CI = 1.12–1.63, $P_{trend} = 0.002$; Face: OR = 1.29, 95% CI = 1.10–1.50, $P_{trend} = 0.001$). Decreased odds were observed for females (SN: OR = 0.49, 95% CI = 0.37–0.64, $P < 0.001$; Face: OR = 0.66, 95% CI = 0.53–0.82, $P < 0.001$) and the presence of nevi (SN: OR = 0.66, 95% CI = 0.49–0.89, $P = 0.006$; Face: OR = 0.65, 95% CI = 0.52–0.83, $P < 0.001$).

Conclusions: Differences observed between SN melanoma and other sites were also observed for facial melanoma. Factors previously associated with the broader head and neck region, notably older age, may be driven by the facial subregion. A novel finding was the association of *IRF4*-rs12203592 with both SN and facial melanoma.

Impact: Understanding the epidemiology of site-specific melanoma will enable tailored strategies for risk factor reduction and site-specific screening campaigns.

Introduction

Cutaneous malignant melanoma is a major public health issue, particularly in light-skinned populations. It is a complex cancer thought to arise from multiple genetic and environmental factors and their interactions, and it also exhibits a site-specific pattern of development (1, 2). Most current research has focused on the head and neck, upper limbs, lower limbs, and the trunk as broad anatomic sites of interest. The head and neck region is of particular interest, as while it accounts for 9.0% of the body's total surface area, melanoma tumors in the region account for 12.0%–26.0% of total melanoma incidence (3, 4). They also have a poorer prognosis compared with melanomas arising on other sites of the body, with reported 5-year survival rates of 78.9% compared with 93.1% (4, 5). Further prognostic differences have been observed within the head and neck region. Studies have consistently shown a worse prognosis for scalp and neck (SN) melanomas compared with melanoma of other sites (including other head and neck sites), with lower 5- and 10-year survival rates and a higher incidence of melanoma-specific mortality (4, 6–9). Several histopathologic factors, such as tumor thickness and the presence of ulceration, have been associated with poorer prognosis in SN melanoma but these do not account for all of the variation seen in survival rates and prognosis between melanoma in this region and other anatomic sites (10, 11).

SN melanoma is therefore an important subset of melanoma and further investigation is required to better understand the underlying biology and determinants of melanoma at this site. Identifying risk factors associated with SN melanoma will also inform strategies for tailoring risk prevention in those at greater risk of this subset of melanoma. To date, most research into the individual and environmental determinants of anatomic site of melanoma development has focused on the broader anatomic regions. The limited research into

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risk factors specifically associated with SN melanoma has shown that it occurs more frequently in males than females, and in comparison with melanoma of all other sites, often occurs at an older age (4, 6). There is also little known regarding genetic polymorphisms associated with site-specific melanoma development, including whether there is a genetic predisposition specifically to SN melanoma.

Therefore, the purpose of this study was to use data from two large population-based melanoma studies to determine whether the associations between demographic factors, known melanoma susceptibility traits, environmental exposures, and genetic polymorphisms differed between SN melanoma and other anatomic sites. Facial melanoma was considered separately to enable us to discern whether any observed associations were specific to SN melanoma, or more reflective of an association with melanoma of the broader head and neck region.

Materials and Methods

Study design and sample

Two independent population-based collections of primary melanoma cases were used: the Western Australian Melanoma Health Study (WAMHS) and the Genes, Environment, and Melanoma (GEM) study. Analyses to investigate the association between known melanoma risk factors and anatomic site were conducted as pooled analyses, using both the WAMHS and GEM cases.

Both study populations have previously been described in detail (12, 13). Briefly, the WAMHS consists of 1,643 consenting participants, who were diagnosed with primary, invasive melanoma between the ages of 18 and 80 years. All participants were recruited from the Western Australian Cancer registry between 2006 and 2009. There were 1,215 individuals with both questionnaire and genetic data available and after excluding those with missing anatomic site data ($n = 4$) and missing or non-European ancestry ($n = 11$), there were 1,200 WAMHS individuals available for analyses.

The GEM study is an international, multicenter study, consisting of 3,579 melanoma cases, who were recruited as either single primary melanoma cases (first invasive, primary melanoma) or multiple primary melanoma cases (second- or higher-order primary melanoma, either invasive or *in situ*). Participants were recruited from 2000 to 2003 from eight population-based cancer registries and one hospital center in four countries: Australia, Canada, Italy, and the United States. Our analyses included only the primary melanoma that was used for recruitment into the study for both single and multiple primary cases. Cases without the relevant genetic SNP data ($n = 16$), unspecified head and neck site data ($n = 11$), non-European ancestry ($n = 12$), and *in situ* melanoma ($n = 274$) were excluded (not mutually exclusive). This resulted in 3,280 GEM cases and a total of 4,480 melanoma cases from both studies that were available for the pooled analyses.

Ethics approval

Ethical approval was obtained from each study site's institutional review board for all data collection and subsequent analyses, and written informed consent was obtained from all participants.

Assessment of anatomic site

Anatomic site was defined by International Classification of Disease for Oncology 3rd Edition (ICD O-3) topography codes for the skin (C440–C449; ref. 14). The dependent variables for analysis were categorical variables of SN melanoma versus melanoma of the trunk and extremities, and facial melanoma versus melanoma of the trunk and extremities. SN melanoma was classified by ICD O-3 code C444 and facial melanomas were classified by ICD O-3 codes C440, C441, C442, and C443, which included melanoma of the lip, eyelid, ear, and other parts of the face. Histopathology data were obtained from pathology reports for WAMHS participants and by pathologist review for GEM participants.

Demographic, phenotypic, and sun exposure data

All demographic, phenotypic trait, and sun exposure variables were derived from the harmonization of the WAMHS and GEM questionnaire data. Comparable self-reported data had previously been collected by both studies, using questionnaires that were administered by telephone interview. Synonymous definitions were created for each risk factor and identical inclusion and exclusion criteria were applied to all variables.

Demographic variables were sex and age at diagnosis. Phenotypic variables were the presence of nevi (based on pictures of four bodies showing different degrees of nevi coverage), freckles in childhood (based on six pictures showing degree of facial freckling), hair color, eye color, and skin color. Propensity to burn and ability to tan were based on reported skin response to one hour of sun exposure at the beginning of summer and repeated exposure during summer, respectively. Categories were condensed into binary burn and tan indices for ease of analysis due to sample distribution, as were categories for freckling and nevi.

Environmental variables focused on sun exposure during the critical childhood and adolescence periods (15). For both time periods, the number of painful and blistering sunburns were used as proxy measures of intermittent exposure, and average weekday and weekend exposure between 9:00 am and 5:00 pm during the warmer months were used as measures of cumulative exposure. Whether patients had ever used a sunbed in their lifetime was also included.

Genetic data

We included known melanoma susceptibility SNPs that had previously been identified from the literature and genotyped prior to commencement of this study. There were 22 SNPs common to both the GEM and WAMHS data that were extracted for this study. The minor allele frequency was determined for each SNP and compared with the 1000 Genomes-CEU minor allele frequency (ref. 16; Supplementary Table S1).

DNA samples from WAMHS participants were extracted from peripheral blood samples and genotyped on an Illumina OmniXpressExome-v1 chip, using standard quality control procedures. DNA samples from GEM participants were collected from buccal brushes and SNPs were genotyped on the MassArray iPLEX platform (Agena Bioscience, formerly Sequenom, Inc.), using quality control measures reported previously (17).

Statistical analyses

Distributions of key participant characteristics in the pooled sample were summarized using means, SDs, frequencies, and proportions. Logistic regression models were used to estimate ORs and 95% confidence intervals (CI) for SN melanoma and facial melanoma, compared separately with other sites of melanoma. Models were adjusted for age at diagnosis, sex, study center (each of the nine GEM collection sites plus WAMHS as the 10th site), and whether it was a first- or higher-order melanoma.

Candidate gene analyses used an additive genetic model and the same logistic regression model approach to estimate the per-allele (based on the minor allele) ORs and CIs for each SNP. Models were

also adjusted for study features. The Monte Carlo test (18) was used to adjust for multiple testing and take into account linkage disequilibrium between the 22 SNPs, with an estimated significance threshold of $P < 0.003$ determined. To check the appropriateness of pooling the data from the GEM and WAMHS studies, we conducted random-effects meta-analyses and tests of heterogeneity using the R package "metafor" (19) for all variables with a statistically significant result. All analyses were undertaken using the software program R v.3.3.3 (20).

Results

Study sample characteristics

The demographic and phenotypic characteristics of the final study sample are presented in **Table 1**. The sample comprised 293 cases of SN melanoma (6.5%), 460 cases of facial melanoma (10.3%), and 3,727 cases of melanoma at other anatomic sites [trunk: $n = 1{,}883$ (42.0%), extremities: $n = 1{,}844$ (41.2%)]. There were more males (56.2%) than females (43.8%), and the average age of diagnosis was 58.2 years (SD = 15.1 years).

Demographic, phenotypic, and environmental risk factors

The associations of each variable with SN melanoma and facial melanoma, compared with other anatomic sites, are presented in **Table 1** (demographic and phenotypic traits) and **Table 2** (sun exposure). The strongest association observed was for sex, with female sex conferring a significantly decreased odds of developing both SN melanoma (OR = 0.49, 95% CI = 0.37–0.64) and facial melanoma (OR = 0.66, 95% CI = 0.53–0.82), compared with other sites. Age at diagnosis was also associated with both regions of the head and neck compared with other sites, although the pattern of association differed between the two sites. The odds of developing facial melanoma increased consistently with increasing age, with an OR of almost five observed in individuals more than 70 years of age (OR = 4.57, 95% CI = 3.34–6.35). On the other hand, a reduced odds of SN melanoma was observed for persons in the age group 50 to 59 years as compared with other ages.

The presence of nevi was associated with a reduced risk of melanoma at both anatomic sites (Face: OR = 0.65, 95% CI = 0.52–0.83; SN melanoma: OR = 0.66, 95% CI = 0.49–0.89). A significant association was observed between facial melanoma and hair color but not with SN melanoma. Lighter (OR = 0.79, 95% CI = 0.64–0.98) and red hair (OR = 0.65, 95% CI = 0.42–0.97) conferred a decreased odds of developing facial melanoma, compared with dark hair. A greater number of painful (OR = 0.73, 95% CI = 0.58–0.92) and blistering sunburns (OR = 0.72, 95% CI = 0.56–0.92) in childhood were also each associated with decreased odds of facial melanoma. No significant associations were observed for any other pigmentary traits or environmental exposures.

Candidate gene associations

Prior to adjustment for multiple testing, the minor alleles of two SNPs were significantly associated with facial melanoma, and one with SN melanoma (**Table 3**). The minor T allele of rs12203592 in the interferon regulatory factor-4 (*IRF4*) gene was associated with an increased odds of melanoma at both sites (Face: OR = 1.29, 95% CI = 1.10–1.50; SN melanoma: OR = 1.35, 95% CI = 1.12–1.63) and the T allele of rs11263498 in the cyclin D1 (*CCND1*) gene was associated with a decreased odds of facial melanoma (OR = 0.81, 95% CI = 0.70–0.94). Following adjustment for multiple testing, only rs12203592 (*IRF4*) passed the Monte Carlo significance threshold ($P < 0.003$) and remained significantly associated with both anatomic sites.

Meta-analyses

Tests of heterogeneity showed that the results for both SN and facial melanoma were generally very consistent between the GEM and WAMHS samples ($P > 0.3$ for all variables), and the forest plots show that the CIs for the results are highly overlapping between the GEM and WAMHS samples (Supplementary Figs. S1 and S2). Together, these data indicate that because heterogeneity between the GEM and WAMHS results is low, a pooled data analysis was appropriate. Furthermore, the direction of association in each of the separate GEM and WAMHS samples was the same as in the pooled analyses for each significant demographic, pigmentary, and sun exposure variable (Supplementary Figs. S1 and S2). The association between the *IRF4* SNP and SN melanoma in the smaller WAMHS sample suggested a reduced risk when rs12203592*T was present instead, although this association was close to the null (OR = 0.92, 95% CI = 0.64–1.29). All other associations with *IRF4* were observed in the same direction.

Discussion

We identified several significant differences in risk factors between SN and facial melanoma, and melanoma of other anatomic sites. The decreased odds of both face and SN melanoma among females was the strongest association observed for both sites, and was consistent with previously observed patterns of sex-specific incidence across anatomic sites (21–23). A striking result was the substantial increase in the odds of developing facial melanoma, compared with other sites, with each decade after the age of 50 years. Although it has been widely reported that older individuals are more likely to develop head and neck melanoma in general (21, 24), it has not been shown previously that this association may be driven predominantly by the facial subregion.

The inverse association we observed between lighter hair color and facial melanoma was also novel. A previous meta-analysis found melanoma of sun-exposed regions, including the arms and the entire head and neck region, to be associated with hair color (25). Our results suggest that this association may be primarily driven by the facial subregion. Similarly, the likelihood of both SN melanoma and facial melanoma was reduced in the presence of nevi, compared with other sites, in line with previous study findings (25–28). We also observed a reduced odds of facial melanoma in individuals with a history of childhood sunburn, which is indicative of intermittent sun exposure.

While previous studies have investigated genetic associations with the broader regions of the trunk and head/neck (5, 29, 30), we investigated for the first time whether there is a genetic predisposition specifically to SN melanoma and if it is biologically distinct from facial melanoma. We observed a significant increase in the odds of both SN melanoma and facial melanoma with each additional copy of the minor T allele of *IRF4* SNP rs12203592, a functional variant known to influence expression of the gene (31). These results are in line with a recent hospital-based study that observed a positive association between rs12203592*T and the development of all head and neck melanomas (30), and suggest that melanoma risk SNPs may play a role in the site-specific development of melanoma.

The same T allele of the *IRF4* SNP has also previously been associated with various pigmentation traits, including associations with fewer nevi in adulthood and darker hair (32–35). The direction of association we observed between these phenotypic traits and anatomic site suggested the association could be driven by the rs12203592 C>T polymorphism. To assess the independence of our observed associations, we included rs12203592 in the phenotypic trait models but found no notable differences in results (Supplementary Table S2). Similarly, when the rs12203592 model was adjusted for each relevant

Table 1. Demographic and pigmentary characteristics and their association with melanoma of the scalp/neck and face, compared with melanoma of other sites, in the combined WAMHS and GEM Study sample ($n = 4,480$).

		Anatomic site distributions						Association compared with other anatomic sites of melanoma[a,b]					
		Scalp and neck ($n = 293$)		Face ($n = 460$)		Other anatomic sites ($n = 3,727$)		Scalp and neck melanoma			Facial melanoma		
Characteristic		***N***	**(%)**	***N***	**(%)**	***N***	**(%)**	**OR**	**95% CI**	**P_{trend}**	**OR**	**95% CI**	**P_{trend}**
Sex	Male	212	(72.4)	316	(68.7)	1,992	(53.4)	1.00	(reference)		1.00	(reference)	
	Female	81	(27.6)	144	(31.3)	1,735	(46.6)	0.49	0.37–0.64	**<0.001**	0.66	0.53–0.82	**<0.001**
Age (years)	<50	74	(25.3)	56	(12.2)	1,138	(30.5)	1.00	(reference)		1.00	(reference)	
	50–59	40	(13.7)	80	(17.4)	879	(23.6)	0.60	0.40–0.89		1.77	1.24–2.55	
	60–69	81	(27.6)	106	(23.0)	833	(22.4)	1.18	0.84–1.67		2.49	1.77–3.55	
	≥70	98	(33.4)	218	(47.4)	877	(23.5)	1.28	0.92–1.80	**0.016**	4.57	3.34–6.35	**<0.001**
Nevi[c]	None	70	(23.9)	134	(29.1)	674	(18.1)	1.00	(reference)		1.00	(reference)	
	Few/some/many	206	(70.3)	312	(67.8)	2,901	(77.8)	0.66	0.49–0.89	**0.006**	0.65	0.52–0.83	**<0.001**
	Missing	*17*	*(5.8)*	*14*	*(3.0)*	*152*	*(4.1)*						
Freckling[d]	None/very few/few	238	(81.2)	381	(82.8)	3,025	(81.2)	1.00	(reference)		1.00	(reference)	
	Some/many/very many	42	(14.3)	67	(14.6)	580	(15.6)	1.05	0.73–1.47	0.783	1.18	0.88–1.57	0.254
	Missing	*13*	*(4.4)*	*12*	*(2.6)*	*122*	*(3.3)*						
Hair color index	Dark	85	(29.0)	168	(36.5)	1,105	(29.6)	1.00	(reference)		1.00	(reference)	
	Light	171	(58.4)	253	(55.0)	2,214	(59.4)	1.03	0.79–1.36		0.79	0.64–0.98	
	Red	33	(11.3)	30	(6.5)	365	(9.8)	1.30	0.84–1.97	0.338	0.65	0.42–0.97	**0.010**
	Missing	*4*	*(1.4)*	*9*	*(2.0)*	*43*	*(1.2)*						
Eye color index	Dark	50	(17.1)	68	(14.8)	663	(17.8)	1.00	(reference)		1.00	(reference)	
	Light	241	(82.3)	388	(84.3)	3,038	(81.5)	1.00	0.73–1.39	0.999	1.19	0.91–1.59	0.211
	Missing	*2*	*(0.7)*	*4*	*(0.9)*	*26*	*(0.7)*						
Skin color	Brown/olive	25	(8.5)	42	(9.1)	406	(10.9)	1.00	(reference)		1.00	(reference)	
	Fair/very fair	265	(90.4)	417	(90.7)	3,306	(88.7)	1.29	0.85–2.02	0.250	1.22	0.87–1.74	0.263
	Missing	*3*	*(1.0)*	*1*	*(0.2)*	*15*	*(0.4)*						
Burn index	No burn/mild burn	151	(51.5)	236	(51.3)	1,833	(49.2)	1.00	(reference)		1.00	(reference)	
	Burn & peel/burn & blister	136	(46.4)	210	(45.7)	1,837	(49.3)	0.94	0.73–1.20	0.616	0.99	0.80–1.22	0.906
	Missing	*6*	*(2.0)*	*14*	*(3.0)*	*57*	*(1.5)*						
Tan index	Moderate tan/deep tan	159	(54.3)	263	(57.2)	2,111	(56.6)	1.00	(reference)		1.00	(reference)	
	Mild tan/no tan	127	(43.3)	189	(41.1)	1,557	(41.8)	1.20	0.93–1.53	0.161	1.04	0.84–1.28	0.728
	Missing	*7*	*(2.4)*	*8*	*(1.7)*	*59*	*(1.6)*						
Histogloic subtype[e]	Non-lentigo maligna	234	(79.9)	261	(56.7)	3,547	(95.2)	1.00	(reference)		1.00	(reference)	
	Lentigo maligna	59	(20.1)	199	(43.3)	180	(4.8)	4.67	3.28–6.58	**<0.001**	12.74	9.84–16.54	**<0.001**

[a]Logistic regression was used to estimate ORs, 95% CIs, and trend *P*-values for scalp/neck and facial melanoma, compared with other sites. Bold type indicates $P < 0.05$.
[b]Baseline adjustment for study features: sex, age at diagnosis (continuous), study center, and whether first- or higher-order melanoma.
[c]Categories based on pictures of four bodies showing different degrees of nevi coverage.
[d]Categories based on six pictures showing degree of facial freckling.
[e]Including superficial spreading melanoma, nodular melanoma, and spindle cell melanoma.

Table 2. Sun exposure characteristics and their associations with melanoma of the scalp/neck and face, compared with melanoma of other sites, in the combined WAMHS and GEM Study sample ($n = 4,480$).

		Anatomic site distributions						Association compared with other anatomic sites of melanoma[a,b]					
		Scalp and neck ($n = 293$)		Face ($n = 460$)		Other anatomic sites ($n = 3,727$)		Scalp and neck melanoma			Facial melanoma		
Characteristic		***N***	**(%)**	***n***	**(%)**	***n***	**(%)**	**OR**	**95% CI**	**P_{trend}**	**OR**	**95% CI**	**P_{trend}**
Painful sunburns – childhood	0	105	(35.8)	193	(42.0)	1,362	(36.5)	1.00	(reference)		1.00	(reference)	
	≥1	94	(32.1)	158	(34.3)	1,491	(40.0)	0.79	0.60–1.06	0.116	0.73	0.58–0.92	**0.007**
	Missing	*47*	*(16.0)*	*61*	*(13.3)*	*411*	*(11.0)*						
Blistering sunburns - childhood	0	158	(53.9)	278	(60.4)	2,053	(55.1)	1.00	(reference)		1.00	(reference)	
	≥1	66	(22.5)	104	(22.6)	994	(26.7)	0.80	0.59–1.06	0.125	0.72	0.56–0.92	**0.008**
	Missing	*46*	*(15.7)*	*56*	*(12.2)*	*476*	*(12.8)*						
Painful sunburns - adolescence	0	136	(46.4)	250	(54.3)	1,820	(48.8)	1.00	(reference)		1.00	(reference)	
	≥1	100	(34.1)	143	(31.1)	1,284	(34.5)	1.05	0.79–1.40	0.723	0.90	0.71–1.14	0.362
	Missing	*22*	*(7.5)*	*29*	*(6.3)*	*217*	*(5.8)*						
Blistering sunburns - adolescence	0	195	(66.6)	329	(71.5)	2,512	(67.4)	1.00	(reference)		1.00	(reference)	
	≥1	62	(21.2)	78	(17.0)	734	(19.7)	0.99	0.72–1.35	0.964	0.85	0.64–1.12	0.227
	Missing	*25*	*(8.5)*	*38*	*(8.3)*	*325*	*(8.7)*						
Weekday sun exposure (hours) - childhood[c]	Mean (SD)		2.4 (1.2)		2.4 (1.3)		2.3 (1.2)	1.01	0.90–1.13	0.852	1.04	0.95–1.13	0.384
	Missing		*2*		*4*		*29*						
Weekend sun exposure (hours) - childhood[c]	Mean (SD)		5.3 (1.9)		5.2 (2.0)		5.0 (1.2)	1.02	0.96–1.09	0.475	1.02	0.96–1.07	0.548
	Missing		*3*		*4*		*31*						
Weekday sun exposure (hours) - adolescence[c]	Mean (SD)		2.3 (2.4)		2.4 (2.5)		2.2 (1.2)	0.95	0.90–1.00	0.072	0.99	0.94–1.03	0.567
	Missing		*4*		*3*		*42*						
Weekend sun exposure (hours) - adolescence[c]	Mean (SD)		4.5 (2.2)		4.3 (2.2)		4.2 (1.2)	0.99	0.94–1.06	0.852	0.97	0.93–1.02	0.303
	Missing		*4*		*3*		*45*						
Sunbed use (more than once)	No	113	(38.6)	160	(34.8)	1,592	(42.7)	1.00	(reference)		1.00	(reference)	
	Yes	178	(60.8)	300	(65.2)	2,122	(56.9)	1.15	0.82–1.63	0.414	1.05	0.80–1.41	0.717
	Missing	*2*	*(0.7)*	*0*	*(0)*	*13*	*(0.3)*						

[a]Logistic regression was used to estimate ORs, 95% CIs, and trend *P*-values for scalp/neck and facial melanoma, compared with other sites. Bold type indicates $P < 0.05$.
[b]Baseline adjustment for study features: sex, age at diagnosis (continuous), study center, and whether first- or higher-order melanoma.
[c]Self-reported average sun exposure between 9:00 am and 5:00 pm during the warmer months.

Table 3. Association of selected melanoma risk SNPs with melanoma of the scalp/neck and face, compared with melanoma of other sites, in the combined WAMHS and GEM Study sample ($n = 4{,}480$).

		Association compared with other anatomic sites of melanoma[a,b]					
		Scalp and neck melanoma			Facial melanoma		
Gene/region	SNP	OR	95% CI	P_{trend}	OR	95% CI	P_{trend}
ARNT	rs7412746	1.01	0.85–1.20	0.925	1.01	0.88–1.17	0.853
PARP1	rs3219090	1.10	0.91–1.32	0.322	1.10	0.94–1.28	0.244
NID1	rs3768080	0.98	0.82–1.16	0.785	0.99	0.86–1.14	0.838
TERT;CLPTM1L	rs4975616	0.89	0.75–1.07	0.213	1.04	0.90–1.21	0.595
SLC45A2	rs35391	0.98	0.35–2.17	0.961	1.06	0.47–2.09	0.867
IRF4	rs12203592	1.35	1.12–1.63	**0.002**	1.29	1.10–1.50	**0.001**
IRF4	rs872071	0.92	0.78–1.09	0.348	0.99	0.86–1.14	0.907
TYRP1	rs1408799	0.97	0.80–1.16	0.732	0.95	0.82–1.11	0.531
MTAP	rs7023329	1.00	0.85–1.18	0.980	1.14	0.99–1.31	0.063
MTAP	rs10811629	1.08	0.91–1.28	0.356	1.13	0.98–1.30	0.096
CCND1	rs11263498	0.88	0.74–1.06	0.181	0.81	0.70–0.94	0.007
TYR	rs1042602	0.97	0.81–1.16	0.769	1.06	0.92–1.23	0.409
TYR	rs10765198	1.09	0.91–1.29	0.350	0.95	0.82–1.10	0.511
OCA2	rs1800407	0.93	0.69–1.24	0.629	0.92	0.72–1.17	0.507
HERC2	rs1129038	1.00	0.81–1.23	0.987	0.97	0.81–1.14	0.683
HERC2	rs12913832	1.00	0.81–1.22	0.995	0.97	0.82–1.15	0.711
ASIP	rs17305657	1.24	0.95–1.60	0.099	1.10	0.88–1.37	0.410
ASIP	rs4911414	1.10	0.92–1.31	0.284	0.96	0.83–1.11	0.577
PIGU	rs910873	1.14	0.88–1.45	0.304	0.95	0.76–1.18	0.647
PIGU	rs17305573	1.18	0.91–1.51	0.206	0.89	0.70–1.13	0.351
MX2	rs45430	0.86	0.71–1.03	0.094	0.96	0.83–1.12	0.599
PLA2G6	rs132985	1.16	0.98–1.37	0.093	1.05	0.91–1.21	0.494

[a]Logistic regression was used to estimate the per-allele (based on the minor allele) ORs, 95% CIs, and trend *P*-values for scalp/neck and facial melanoma, compared with other sites. Bold type indicates *P*-values < 0.003 (Monte Carlo adjusted threshold to account for multiple testing).
[b]Baseline adjustment for study features: sex, age at diagnosis (continuous), study center, and whether first- or higher-order melanoma.

phenotypic trait (nevi, freckling, hair color, eye color, and ability to tan), no attenuation of results was observed (Supplementary Table S3). These results suggest that the observed genetic and pigmentary associations are independent from one another

Our observations for nevi and sun exposure are also consistent with the divergent pathway model for melanoma (27). There is growing evidence in the literature for the existence of two distinct pathways to melanoma development. One is driven by high levels of cumulative sun exposure and characterized by melanoma on sun-exposed sites, such as the head and neck, and solar elastoses as a histologic marker. The other is driven by a high propensity for nevus development and characterized by melanoma on less exposed sites and the presence of neval remnants histologically (24, 27, 36, 37). In line with this model, our findings for SNP rs12203592 are also consistent with a recent GEM study that found rs12203592*T was positively associated with melanoma tumors that had solar elastoses present, and inversely associated with tumors that had neval remnants (37).

Lentigo maligna melanoma is known to occur primarily on the head and neck, especially in older males with sun-damaged skin (3, 38, 39). Therefore, we also performed additional analyses to assess the potential effect of histology on the results. Models for significantly associated variables were adjusted for histology (lentigo maligna melanoma versus other subtypes) but no difference in results was observed for phenotypic traits before and after adjustment for histology (Supplementary Table S4). The estimated ORs were attenuated for age for both face and SN melanoma, and the associations between facial melanoma and sun exposure became only marginally significant when adjusted for histology. These results suggest that the association between anatomic site and both age and sun exposure may be mediated by histologic subtype.

Limitations of the study included the use of self-reported risk factor information that may have been subject to recall bias and the use of two slightly different study questionnaires. Although our rigorous method of data harmonization minimized major discrepancies between the datasets, an inherent limitation of pooled studies is that some variables are not available in both study samples and this therefore constrained some analyses. This included the absence of validated tools for assessing skin color, tumor staging data, detailed sun exposure history, and a subset of known risk SNPs. To address this issue, substitute or proxy variables that were available in both studies were used instead where possible. For example, the use of self-reported skin color as the best available measure, and the use of sunburn as a proxy measure of intermittent sun exposure, as previously suggested in the literature (40). The key strengths of this study were the population-based study design and the use of two large and well-characterized studies with comparable data. This facilitated a robust, pooled study design and made it the largest study to date to investigate the genetic and nongenetic factors associated with SN melanoma.

In summary, our investigation found that known melanoma risk factors may not play a role in distinguishing the profile of SN melanoma. All risk factors associated with SN melanoma, compared with melanoma of other anatomic sites, were also associated with facial melanoma. Additional risk factors were also identified as being associated only with facial melanoma. Our results are novel as we

have demonstrated that some factors known to be associated with head and neck melanoma in general may in fact be driven predominantly by facial melanomas. These findings that subregions of the head and neck area may not share the same risk factors add to the heterogeneous nature of the literature, and provide new avenues for future research. It is possible that factors more biological in nature drive the development of SN melanoma and influence the worse prognosis commonly observed at this site. Further work is now needed to identify new candidate risk factors for SN melanoma and disentangle the biological determinants of this anatomic subregion.

Our results also reinforce the notion of two distinct pathways for the development of melanoma, and further suggest *IRF4* could play a role in determining pathway-specific risk, which is often marked by melanoma of different anatomic sites. A better understanding of the complex etiology of the disease and the development of a site-specific risk profile for individuals who are highly susceptible to melanoma would have significant clinical implications. Early detection is critical for improving melanoma survival and identifying the combination of risk factors associated with melanoma of specific anatomic sites, particularly those that carry a worse prognosis like SN melanoma, may help us to identify melanoma in susceptible individuals at an earlier stage. This knowledge has the potential to be translated into a more accurate risk prediction algorithm for use in clinical settings, enabling site-specific screening campaigns, and encouraging more targeted skin checks to identify melanomas earlier and improve prognosis.

Disclosure of Potential Conflicts of Interest

M. Berwick reports grants from NIH/NCI during the conduct of the study. N.E. Thomas reports grants from NCI of the NIH during the conduct of the study. A.E. Cust reports grants from National Health and Medical Research Council (fellowship) during the conduct of the study and outside the submitted work. S.B. Gruber reports other from Brogent International LLC (cofounder) outside the submitted work. P.A. Kanetsky reports grants from NCI during the conduct of the study. S.V. Ward reports grants from National Health and Medical Research Council (early career fellowship, ID: 1121242) during the conduct of the study. No potential conflicts of interest were disclosed by the other authors.

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