MC1R genotype may modify the effect of sun exposure on melanoma risk in the GEM study

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Abstract

We investigated whether MC1R genotype modifies the effect of sun exposure on melanoma risk in 1,018 cases with multiple melanomas (MPM) and 1,875 controls with one melanoma (SPM). There was some suggestion that MC1R genotype modified the effect of beach and water activities on MPM risk: ORs were 1.94 (95% CI 1.40–2.70) for any activities for no R variants and 1.39 (95% CI 1.05–1.84) with R variants (R151C, R160W, D294H, D84E) (*p* for interaction 0.08). MC1R modification of sun exposure effects appeared most evident for MPM of the head and neck: for early life ambient UV the OR was 4.23 (95% CI 1.76–10.20) with no R and 1.04 (95% CI 0.40–2.68) with R (*p* for interaction=0.01; *p* for three-way interaction=0.01). Phenotype modified the effect of sun exposure and MPM in a similar manner. We conclude that MC1R and pigmentary phenotype may modify the effects of sun exposure on melanoma risk on more continuously sun-exposed skin. Possible explanations include that risk may saturate with higher sun sensitivity for melanomas on continuously sun-exposed sites but continue to increase as sun exposure increases with lower sun sensitivity, or that sun sensitive people adapt their behaviour by increasing sun protection when exposed.

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Keywords

melanoma; MC1R polymorphism; sun exposure; pigmentary phenotype

Introduction

People who have had one melanoma have an increased risk of a second. The Genes, Environment and Melanoma (GEM) study population includes cases who had a second or higher order melanoma and controls who had a first primary incident melanoma. We have found that risk of a subsequent or multiple primary melanoma (MPM) increased with increasing ambient UV irradiance at places of residence and with lifetime recreational exposure, particularly in beach and waterside activities. The results for ambient UV were very consistent with evidence from studies of individual risk of any primary melanoma in relation to place of birth and age at migration from or to areas of high ambient UV irradiance [1,2]. The increased risk for recreational sun exposure was likewise consistent with the findings of Gandini et al's meta-analysis [3].

Melanoma is mainly a disease of light-skinned populations. The chief pigmentary traits associated with melanoma risk are fair skin, blonde or red hair, blue eyes, a skin that sunburns easily, tans poorly and freckles. These are highly correlated traits, however, and are known to be partially determined by the melanocortin 1 receptor, MC1R [4,5], some variants of which result in a defect in activation of melanin production [6]. Almost all GEM participants (90%) had MC1R genotypes measured: cases were more likely than controls to carry multiple and higher-risk MC1R variants [7].

In this paper we examine whether variants in MC1R and pigmentary phenotypes modify the relationship between sun exposure and risk of subsequent melanoma in GEM and, if so, what the patterns in exposure-response relationships by genotype were.

Methods

GEM included as participants all incident cases of melanoma notified to 8 population-based cancer registries in Australia (2 registries), Canada (2), Italy (1) and the USA (3) in a defined accrual period; participants from a Michigan center were excluded from this report because of incomplete data on sun exposure and related covariates. Detailed methods have been described elsewhere [7–9]. Briefly, controls were diagnosed with a first invasive primary melanoma in 2000 and cases with a second or higher order invasive or in situ melanoma in 2000–2003. Inclusion of in situ cases was designed to avoid exclusion of subjects who would have been diagnosed with an invasive subsequent primary if the lesion had not been detected in the in situ stage. All participants provided written informed consent and approval for the study protocol was obtained from Institutional Review Boards at the GEM Coordinating Center, the Memorial Sloan–Kettering Cancer Center, New York, and each contributing center.

All participants completed a self-administered calendar and questionnaire before a one hour telephone interview, and gave a buccal DNA sample [10]. Lifetime residential histories were recorded in the calendar and used for assigning levels of ambient UV exposure. The questionnaire asked for skin, hair and eye color in standard categories. The interview included questions on ethnicity, ancestry, propensity to burn on first sun exposure in summer, tanning ability on repeated sun exposure and sun exposure in decade years from 10 years of age.

Ambient solar UV irradiance for each participant was estimated as the annual average erythemally weighted UV at their place of residence at birth and in each decade of age. These values were model-based and supplied to GEM by the US National Center for Atmospheric Research (Dr Julia M Lee Taylor). To calculate the lifetime average annual UV irradiance for each participant, the value for UV irradiance at birth (age 0) was assigned to each year from birth to age 4, that at age 10 to each year from age 5 to age 14, and so on, using irradiance in the last decade year up to the exact age at diagnosis and dividing the total by age. Early life ambient UV was calculated as the average of UV irradiance at birth and age 10.

Recreational sun exposure in beach and water activities from age 15 was obtained from direct questions about participation between 9am and 5pm on at least 10 days in any year since leaving school, the years started and stopped, the frequency, usual outdoor hours per day and the seasons; a lifetime sum of hours was calculated. Although vacations in a sunnier climate and sunburns were included initially in the present analyses because of their known associations with MPM [9], we excluded them from this report because they appeared to add little information beyond the contribution of beach and water activities and ambient UV.

DNA was isolated from buccal cells and MC1R sequenced for 2,202 controls and 1,099 cases in the GEM study (90% of participants), in whom 85 unique variants were identified [7]; 88% of participants in the centers included in this report had MC1R genotyped. The current analyses follow Kanetsky et al's [7] grouping in which people with two copies of the consensus wild type (con/con) were the reference category and there were two additional categories, one formed by grouping people with any red-hair associated (R) variant (R151C, R160W, D294H, D84E) in an 'any R' category (con/R, r/R, R/R) and those having only other variants into an 'r' category (con/r; r/r). For most analyses we examined MC1R variants in 2 categories as no R (con/con, con/r; r/r) and any R variants (con/R, r/R, R/R). Carriage of synonymous variants did not affect group assignment. When we examined the association of each MC1R variant with red hair, ORs were 3.0 or higher for each of 7 variants: the 4 R variants R151C, R160W, D294H, D84E had p values <0.01 and Y152X, 86insA, and 537insC had p values <0.09 and had been previously identified as significantly associated with melanoma risk [11] or likely to produce a non-functional transmembrane receptor [12]. The latter 3 variants were included in the R genotype in sensitivity analyses.

We included only participants who reported exclusively European ancestry because of the known phenotypic differences of other ethnic groups and their small numbers in GEM. Included in these analyses are 1,018 cases and 1,875 controls (2,893 GEM participants) who had MC1R variants genotyped, of whom 75 participants developed their first primary in the control accession period and their second primary in the case accession period. Since epidemiologic theory clearly indicates that these participants should be included as both cases and controls in the analysis [13], they were included as both [10].

Statistical analyses

Conventional methods for case-control studies were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for occurrence of an MPM in unconditional logistic regression models in SAS software version 9.1 (SAS Institute, Cary NC, 1989). Individuals with missing data for a variable were excluded from the relevant analysis. Two-sided p values were calculated. Study center was included as a covariate in all regression models in this analysis and all were adjusted for a priori confounders: age (continuous; age at first melanoma diagnosis for controls, age at most recent for cases), sex, European ancestry in 6 categories, and an age*sex interaction term [9]. A GEM-wide pigment score was calculated using a multivariate confounder score [14,15] to summarize the contribution of ability to tan, propensity to burn, skin, eye and hair color and childhood freckling. Beta-values for each of

these factors were estimated using a single unconditional logistic regression model, with case-control status as the outcome. A summation score for each participant was then calculated using these beta-values. Skin color made the largest contribution to fit of the model. An individual's pigment score was included in analyses as a continuous variable, a higher score indicating a more sun sensitive phenotype. Site of the melanoma was examined in 2 categories: melanoma on the head and neck (more sun exposed), trunk and limbs (less sun exposed).

A multiple variable logistic regression model was used to identify each sun exposure variable that was independently associated with MPM risk: it included MC1R and sun exposure variables with p≤0.05 for their associations with MPM, and age, sex, age * sex, center, ancestry and pigment score as covariates. To test for statistical interaction between MC1R genotype and phenotype or sun exposure, MC1R genotype was treated as a binary variable (no R variant, any R variant) and all pigmentary and sun exposure variables were dichotomized. The effects of two-way interactions on MPM risk were evaluated on a multiplicative scale for MC1R and sun exposure, phenotype and sun exposure, and MC1R and phenotype. ORs were calculated with reference to the joint low exposure category for main effect terms for each of the variables (eg, genotype and exposure) and the cross product interaction term. The likelihood ratio test was used to assess departure from lack of interaction, comparing a model with main effects to a model with main effects and the interaction term. To generate p values for differences in two way interactions by site of the melanoma, we compared a model with the main effects, all 2 way product terms and all relevant covariates to a corresponding model with the three way product term, eg, MC1R by sun exposure by body site.

Results

The majority of GEM participants in these analyses (2431 of 2893, 84%) carried at least one MC1R variant. Consistent with a previous report from GEM [7], carriage of any R variant (R151C, R160W, D294H, D84E) relative to none (con/con or r in the absence of R) had ORs of 1.45 (95% CI 1.22–1.72), 1.43 (95% CI 1.20–1.71) for just one R variant and 1.53 (95% CI 1.14–2.07) for two or more; adjusted for age, sex, center, ancestry, age*sex (Table 1). With reference to the con/con genotype, the ORs were 1.02 (95% CI 0.78–1.34) for any r variant in the absence of R (con/r or r/r) and 1.47 (95% CI 1.14–1.89) for any R (p for trend <0.001) (not tabulated).

ORs for MPM by phenotype were lowest for poor tanning ability, tendency to burn and any childhood facial freckling, intermediate for red hair, relative to other colors, and highest for fair skin and for the most sun sensitive pigment score, Q4; all *p* values were <0.05 (Table 1). Relative to black hair, the OR for red hair was 2.05 (95% CI 1.26–3.34), that for blond or fair 1.58 (95% CI 1.02–2.45), for light brown hair 1.46 (95% CI 0.95–2.25) and that for dark brown 1.14 (0.74–1.78) (*p* for trend=0.001). Eye color had no apparent effect on MPM risk. All models for phenotype were adjusted for age, sex, center, ancestry, and age*sex interaction.

The strongest associations of sun exposure with MPM were for any beach and waterside activities and > median average annual lifetime ambient UV (Table 1). In a multivariable model, any beach and waterside activities (OR=1.58; 95% CI 1.25–1.99) and having any R genotype (OR=1.34; 95% CI 1.11–1.62) were both statistically significantly associated with MPM (p <0.05) with pigment score, age, sex, center, ancestry and age*sex interaction included as covariates. The p values were >0.05 for addition individually to this model of the variables for ambient lifetime and early life UV. The ORs changed very little when the R

genotype included the 3 variants Y152X, 86insA, and 537insC in addition to R151C, R160W, D294H, D84E.

There was some evidence that MC1R genotype modified the effects of beach and water activities (Table 2). The OR for MPM was higher for any activities in the absence of R variants (OR=1.94) than in their presence (OR=1.39) (*p* for interaction 0.08) (Table 2). Adding the 3 variants Y152X, 86insA and 537insC to the 4 variants R151C, R160W, D294H, D84E changed the ORs only slightly. There was little evidence of any similar modification of the effects of lifetime or early life ambient UV (Table 2).

We further examined modification of the association of sun exposure with MPM by MC1R genotype in two body site categories. The ORs for ambient early life UV were higher in those with no R (OR=4.23) than in those with any R (OR=1.04) for melanomas on the head and neck (*p*=0.01 for 2 way interaction) and significantly different by body site (*p*=0.01 for 3 way interaction), with no evidence of a similar interaction for MPM at other body sites. Lifetime ambient UV had a similar pattern of ORs but all *p* values for interaction were high. The higher OR of MPM with beach and water activities in those with no R variants was mostly for MPM on body sites other than the head and neck but not significantly different by body site (*p*=0.89 for 3 way interaction) (Table 3).

Risk for MPM of the head and neck increased strongly with increasing lifetime ambient UV across 4 exposure categories, the OR for Q4 was 5.30 (95% CI 1.44–19.58; p for trend 0.01); for early life UV it was 4.19 (95% CI 1.83–9.63; p for trend <0.001). For other body sites, ORs for ambient UV rose only to 1.75 and showed no apparent trend. The increase in ORs for MPM on the head and neck with increasing lifetime ambient UV was evident only in the absence of MC1R R variants. In people with no R variants the ORs for Q4 were 14.61 for lifetime ambient UV, 7.8 for early life ambient UV and 2.75 for beach and water activities, compared with ORs <2.0 when R variants were present (see Figure 1). There was little evidence of these divergent patterns of increasing MPM risk with increasing ambient UV for melanomas of other body sites. For beach and water activities, MPM risk did not increase consistently beyond the second exposure quarter (OR ~2) and there was little evidence that the pattern of increase differed by body site or by MC1R genotype (Figure 1).

Like MC1R genotype (Table 3), phenotype also appeared to modify the effects of sun exposure on risk of MPM of the head and neck (Table 4). This effect was most evident for beach and water activities: the OR was 3.74 in those with a pigment score less than or equal to the median and 0.87 in those with a greater than median score (p=0.04 for 3 way interaction) (Table 4). The OR estimates in Table 4 changed little when MC1R genotype (no R, any R) was added to the model. The ORs in 4 quarters of beach and water activities for MPM of the head and neck rose with increasing exposure to Q3 in the less sun sensitive; ORs for the more sun sensitive were low (see Figure 1).

There was no consistent pattern of modification of effects of phenotype by MC1R genotype: p for interaction >0.20 for each of skin color, hair color, freckling, ability to tan and pigment score (results not shown). It may be noteworthy, though, that the positive association of red hair with MPM was restricted to those with any R variants: OR=1.35 (95% CI 1.00–1.83) for red hair with reference to other hair colors in those with any R variants compared with OR=0.60 (95% CI 0.18–1.98) in those with no R variants (p for interaction=0.21). Similarly, when the associations of all hair colors with MPM were examined with reference to black hair, the ORs in those with any R were all appreciably greater than unity: ORs of 1.75 (95% CI 0.80–3.83) for dark brown hair, 1.66 (95% CI 0.78–3.57) for light brown, 1.97 (95% CI 0.91–4.25) for blonde or fair, 2.37 (95% CI 1.08–5.21) for red hair.The highest OR in those with no R was 1.32 (95% CI 0.78–2.23) for light brown hair (p for interaction 0.86).

Discussion

We observed a moderately consistent pattern of increasing risk of melanoma with increasing sun exposure in people who had no MCIR R variants and thus had lower sun sensitivity. This pattern was confined to early life ambient UV and melanomas on the head and neck. Phenotype appeared to modify the effects of sun exposure on melanoma risk in a manner similar to MC1R genotype, but for beach and water activities only. There was no consistent evidence of genotype-phenotype interaction apart from some suggestion that a positive association of red hair with melanoma might be restricted to people with R variants.

Our findings are consistent with a report on sun exposure modification of MC1R effects in which risk of melanoma for R variants was increased threefold for lower sun exposure but not all for higher exposure [16]. Other studies found no evidence of modification of MC1R effects by sun exposure [17–19] or did not report on sun exposure separately [20–22]. No study apart from our own has directly examined MC1R genotype modification of sun exposure effects.

In the few studies exploring how phenotype modifies the effects of sun exposure, melanoma risk with high sun exposure was greater with more sun sensitive (summary ORs 2.4 to 4.0) than less sun sensitive phenotypes (summary ORs 1.1 to 1.5) [23]. In our data, an increase in melanoma risk with higher sun exposure was generally more evident in the less sun sensitive phenotype, especially on the more continuously sun-exposed sites of the head and neck (Table 4), the opposite of the pattern in the earlier studies [23]. Our findings, however, are supported by more recent studies reporting a greater relative risk of melanoma with cumulative time outdoors in those who usually develop a deep tan than in those who do not [24], a stronger association between sunbed use and melanoma in people with dark than light or red hair [25], and that severe sunburn was associated with an increased risk of melanoma for a sun-resistant but not a sun-sensitive phenotype (Cust et al unpublished data).

That the effect of pigmentary phenotype appeared independent of MC1R genotype suggests that other genes that determine pigmentary or sun sensitivity phenotype also modify sun exposure effects on melanoma risk. Other gene variants consistently associated with pigmentary phenotype [26,27] and with melanoma [28–31] may have such a role. There are, however, no reports in which the effects of the interactions of other gene variants with sun exposure on melanoma risk have been studied.

If our findings were confirmed in future studies, it would suggest that MC1R or other sun sensitivity genotypes and pigmentary phenotype are modifiers of the effects of sun exposure on risk of melanoma, especially on more continuously sun-exposed skin. Further, it could suggest that the relative increase in sun exposure within the observed ranges on risk of melanoma is greater with lower than higher sun sensitivity. One potential explanation may be a 'saturation' effect in which genotype or phenotype modifies the risk associated with high doses of UV exposure. Under this model, more sun-sensitive people may reach a limit beyond which sun exposure does not increase their risk further while those less sensitive show a continuing rise in relative risk across the observed range of exposures. That effect modification was observable on the head and neck may suggest the effect was limited to one of the possible causal pathways to melanoma under the divergent pathway hypothesis, a pathway in which high levels of more continuous cumulative sun exposure drive the proliferation of epidermal melanocytes to cancer [32].

Differences in sun protection behaviour between more sensitive and less sensitive people are another possible explanation. People with sun-sensitive phenotypes adapt their behavior to make greater use of sun protection when exposed [33], an adaptive behaviour that might

flatten the increase in melanoma risk with increasing sun exposure. It may occur before or after, and possibly as a consequence of, a first diagnosis of sun-related neoplasia or pre-neoplasia [23].

We also observed that the associations of red and other fairer hair colors with melanoma may be confined to people with MC1R variants. This observation was unexpected. Adding the red hair phenotype to its main genetic determinants should have had little additional effect on melanoma risk. It was consistent, however, with addition of risk of melanoma by the R151C MC1R variant (which is strongly correlated with red hair) in red haired women [20].

It is important to consider that some observed associations or interactions may have arisen by chance, given the number of gene-environment combinations that we explored and that the p values for interaction were not very low. On the other hand, that findings in other studies [24,25] [Cust et al unpublished data] were in the same direction as ours argues against it being due simply to chance. The GEM study relied on self-reported pigmentary phenotype and sun exposure history which could produce both non-differential and differential misclassification and lead to bias. Differential recall bias, however, would be minimised for the measurements of ambient UV irradiance at places of residence used in our analyses, since they offer a largely objective measure of potential for sun exposure at each decade of age. In addition, differential recall depending on a complex mix of case or control status, sun sensitivity and melanoma site would be required to produce the patterns we observed. Finally, studies on the reproducibility of standard sun exposure questions suggest reasonable reliability of participant responses [34,35] and agreement with histologic assessment of solar skin damage [36]. Other strengths in GEM were population-based ascertainment of participants, that participation was unlikely to be related to MC1R genotype since observed genotype frequencies were in the range of previous studies (see Kanetsky [7]), and that relative risk estimates in GEM for skin type, skin color, eye color and recreational sun exposure were consistent with a meta analysis [3,9,37,38].

Ours is the first substantial examination of MC1R genotype and pigmentary phenotype modification of the effect of sun exposure on risk of melanoma. Our findings offer suggestive evidence that the effect of sun exposure on melanoma risk for the more continuously exposed head and neck sites may be modified by MC1R genotype and by pigmentary phenotype. Risk of melanoma rose the most with increasing sun exposure in people without R variants in MC1R or with less sun sensitive phenotypes. These findings should be replicated in studies that are large enough to demonstrate them with much greater certainty, if present, before a model of the interaction of sun exposure and genotype or phenotype based on them can be suggested with any confidence. Pooled analyses involving multiple studies with relevant data would be informative.

Acknowledgments

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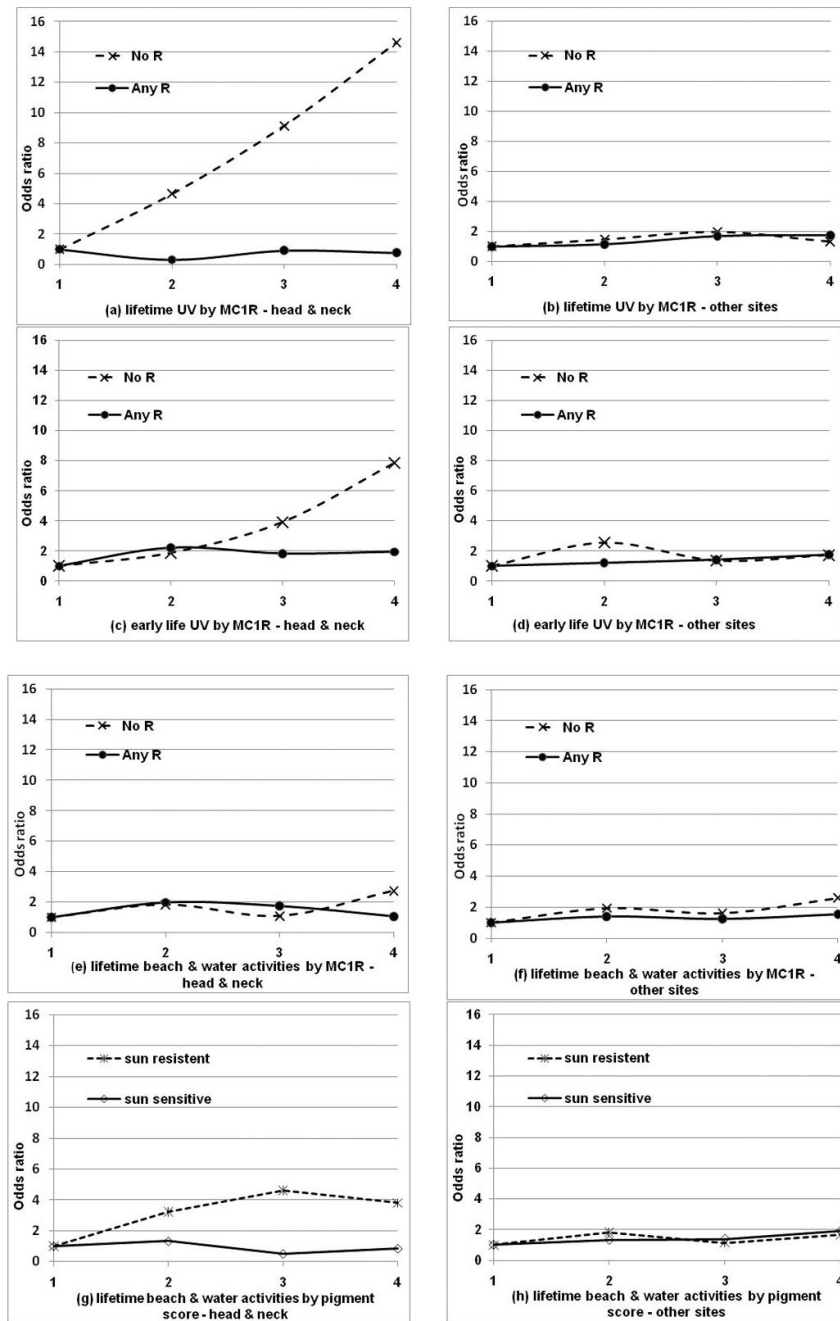
Figure 1.
Risk of MPM on head and neck and other body sites: ORs for quartiles of average annual lifetime ambient UV (a,b) and average early life UV (c,d), and ORs for beach and water activities (none, tertiles of hours of average annual lifetime activities) (e,f) by MC1R genotype (no R, any R) in analyses adjusted for age, sex, age * sex, center, ancestry, pigment score; and ORs for beach and water activities (none, tertiles of hours of average annual lifetime activities) by pigmentary phenotype (sun resistant, sun sensitive) (g,h) in analyses adjusted for age, sex, age * sex, center, ancestry.

Table 1

Association between genotype, phenotype and sun exposure variables and risk of MPM in 2,893 GEM participants (1875 SPM, 1018 MPM)

Variable	Comparison	OR (95% CI)[a]	p value
MC1R genotype	Any R vs no R	1.45 (1.22–1.72)	<0.001
	No R	1.0 (reference)	
	1R vs no R	1.43 (1.20–1.71)	
	2 or more R vs no R	1.53 (1.14–2.07)	<0.001[b]
Phenotype			
Tanning ability	Poor v good	1.22 (1.03–1.46)	0.02
Propensity to burn	Burn readily v resistant	1.18 (1.00–1.41)	0.05
Skin colour	Fair v dark	1.95 (1.45–2.62)	<0.001
Hair colour	Red v other	1.48 (1.12–1.96)	0.006
Eye color	Light v dark	1.03 (0.87–1.23)	0.74
Facial freckling	Any v none	1.32 (1.11–1.58)	0.002
Red hair or freckling	Neither	1.0 (reference)	
	Freckling only v neither	1.30 (1.09–1.57)	
	Red hair v neither	1.72 (1.28–2.33)	<0.001[b]
Pigment score	1st quartile (low risk)	1.0 (reference)	
	2nd quartile	1.30 (1.01–1.66)	
	3rd quartile	1.47 (1.15–1.87)	
	4th quartile (high risk)	1.65 (1.29–2.10)	<0.001[b]
Sun exposure[c]			
Beach and water activities from age 15	Any	1.55 (1.26–1.92)	<0.001
Average annual lifetime ambient UV	>median (849–1,500 kj/m^2)	1.60 (1.08–2.37)	0.02
Early life ambient UV	>median (814–1,723 kj/m^2)	1.34 (1.00–1.80)	0.05

Any R includes R151C, R160W, D294H, D84E; no R includes r in the absence of R, and con/con

[a]Odds ratio (OR) and 95% confidence interval (CI) adjusted for age, sex, age*sex, center, ancestry.

[b]P value for trend

[c]Analyses of sun exposure also included adjustment for pigment score (continuous); early life ambient UV was the average at birth and age 10.

Table 2

Association between MC1R genotype and sun exposure in 2,893 GEM participants

MC1R genotype	Sun exposure	SPM N=1875	MPM N=1018	OR (95% CI)[a] Stratified	p value	OR (95% CI)[a] Joint
Beach and water activities from age 15						
No R	None	248	68	1.0		1.0
	Any	733	380	1.94 (1.40–2.70)	<0.001	1.94 (1.41–2.68)
Any R	None	236	129	1.0		1.83 (1.25–2.66)
	Any	644	438	1.39 (1.05–1.84)	0.02	2.44 (1.77–3.37)
						p for interaction=0.08
Average annual lifetime ambient UV						
No R	369–848 kj/m^2	573	179	1.0		1.0
	849–1,500 kj/m^2	359	249	1.49 (0.85–2.62)	0.17	1.58 (1.02–2.44)
Any R	369–848 kj/m^2	495	212	1.0		1.34 (1.03–1.73)
	849–1,500 kj/m^2	350	336	1.69 (0.97–2.96)	0.07	2.15 (1.39–3.31)
						p for interaction=0.93
Early life ambient UV[b]						
No R	371–853 kj/m^2	563	193	1.0		1.0
	854–1,520 kj/m^2	387	241	1.24 (0.81–1.92)	0.32	1.31 (0.93–1.86)
Any R	371–853 kj/m^2	483	236	1.0		1.33 (1.03–1.71)
	854–1,520 kj/m^2	374	320	1.45 (0.96–2.18)	0.08	1.83 (1.29–2.58)
						p for interaction=0.81

Any R includes R151C, R160W, D294H, D84E; no R includes r in the absence of R, and con/con. Individuals with missing data for a sun exposure variable were excluded from that analysis.

[a] Odds ratio (OR) and 95% confidence interval (CI) adjusted for age, sex, age * sex, center, ancestry, pigment score (continuous).

[b] Early life ambient UV was the average at birth and age 10.

Table 3

Association between sun exposure and MC1R genotype in two categories of body site

MC1R	Sun exposure	Head & neck				Other body sites				
		SPM n	MPM n	OR (95% CI)[a] Stratified	OR (95% CI)[a] Joint	SPM n	MPM n	OR (95% CI)[a] Stratified	OR (95% CI)[a] Joint	p value[b]
	Average annual beach & water activities from age 15									
No R	none	45	22	1.0	1.0	202	45	1.0	1.0	
	any	110	99	1.76 (0.89–3.49)	1.91 (0.99–3.72)	619	281	2.02 (1.37–2.98)	2.05 (1.40–3.00)	
Any R	none	41	30	1.0	1.64 (0.74–3.65)	193	99	1.0	1.97 (1.27–3.05)	
	any	84	97	1.59 (0.82–3.08)	2.41 (1.23–4.71)	551	340	1.39 (1.02–1.91)	2.61 (1.79–3.81)	
					p interaction=0.56				p interaction=0.08	0.89
	Average annual lifetime ambient UV (kj/m²)									
No R	369–848	86	44	1.0	1.0	483	135	1.0	1.0	
	849–1,500	58	74	3.07 (1.09–8.70)	3.38 (1.43–8.00)	301	174	1.20 (0.60–2.40)	1.28 (0.77–2.12)	
Any R	369–848	59	46	1.0	1.82 (0.97–3.41)	425	166	1.0	1.30 (0.97–1.74)	
	849–1,500	58	76	2.03 (0.54–7.68)	3.22 (1.38–7.54)	292	259	1.51 (0.80–2.85)	1.89 (1.14–3.14)	
					p interaction=0.16				p interaction=0.52	0.16
	Early life ambient UV[c] (kj/m²)									
No R	252–813	91	45	1.0	1.0	468	148	1.0	1.0	
	814–1,723	57	74	4.23 (1.76–10.20)	3.66 (1.76–7.63)	330	166	0.82 (0.49–1.37)	0.96 (0.64–1.44)	
Any R	252–813	57	55	1.0	2.26 (1.25–4.09)	415	181	1.0	1.21 (0.92–1.61)	
	814–1,723	62	71	1.04 (0.40–2.68)	3.03 (1.46–6.30)	312	248	1.45 (0.91–2.30)	1.52 (1.02–2.26)	
					p interaction=0.01				p interaction=0.18	0.01

Any R includes R151C, R160W, D294H, D84E; no R includes r in the absence of R, and con/con. Individuals with missing data for a sun exposure variable or body site were excluded from that analysis.

[a] Odds ratio (OR) and 95% confidence interval (CI) adjusted for age, sex, age * sex, center, ancestry, pigment score (continuous).

[b] P value for 3 way interaction of MC1R by sun exposure by body site

[c] Early life ambient UV was the average at birth and age 10.

Table 4

Association between sun exposure and phenotype in two categories of body site

Pigment score	Sun exposure	Head & neck				Other body sites				
		SPM n	MPM n	OR (95% CI)[a] Stratified	OR (95% CI)[a] Joint	SPM n	MPM n	OR (95% CI)[a] Stratified	OR (95% CI)[a] Joint	p value[b]
	Average annual beach & water activities from age 15									
Low or dark	none	48	17	1.0	1.0	202	55	1.0	1.0	
	any	104	94	3.74 (1.77–7.89)	3.26 (1.60–6.63)	652	278	1.53 (1.07–2.20)	1.56 (1.09–2.23)	
high or fair	none	38	35	1.0	3.50 (1.56–7.86)	193	89	1.0	1.49 (0.98–2.27)	
	any	90	102	0.87 (0.46–1.64)	3.13 (1.54–6.33)	518	343	1.51 (1.09–2.09)	2.19 (1.53–3.12)	
					p interaction=0.006				p interaction=0.79	0.04
	Average annual lifetime ambient UV (kj/m²)									
Low or dark	369–848	78	44	1.0	1.0	506	134	1.0	1.0	
	849–1,500	67	64	3.23 (0.99–10.54)	2.50 (1.02–6.11)	314	186	1.51 (0.82–2.78)	1.33 (0.81–2.19)	
high or fair	369–848	67	46	1.0	1.26 (0.68–2.34)	402	167	1.0	1.41 (1.06–1.88)	
	849–1,500	49	86	2.35 (0.81–6.83)	3.59 (1.46–8.85)	279	247	1.05 (0.52–2.14)	1.87 (1.13–3.08)	
					p interaction=0.76				p interaction=0.98	0.49
	Early life ambient UV[c] (kj/m²)									
Low or dark	252–813	80	48	1.0	1.0	495	143	1.0	1.0	
	814–1,723	68	62	2.65 (1.09–6.48)	2.40 (1.15–5.00)	338	182	1.26 (0.78–2.06)	1.13 (0.76–1.68)	
high or fair	252–813	68	52	1.0	1.40 (0.78–2.52)	388	186	1.0	1.48 (1.12–1.95)	
	814–1,723	51	83	1.90 (0.75–4.77)	3.16 (1.49–6.70)	304	232	0.88 (0.55–1.42)	1.51 (1.02–2.23)	
					p interaction=0.88				p interaction=0.61	0.64

Any R includes R151C, R160W, D294H, D84E; no R includes r in the absence of R, and con/con. Analyses included only individuals with phenotype data; individuals with missing data for a sun exposure variable were excluded from the relevant analysis. Pigment score was the predicted probability from a logistic regression model of phenotypic characteristics and was included in analyses as a continuous variable; a higher score indicated a more sun sensitive phenotype.

[a] Odds ratio (OR) and 95% confidence interval (CI) adjusted for age, sex, age*sex, center, ancestry.

[b] P value for 3 way interaction of pigment score by sun exposure by body site

[c] Early life ambient UV was the average at birth and age 10.