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Does *MC1R* genotype convey information about melanoma risk beyond risk phenotypes?

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Abstract

Purpose—To describe associations of *MC1R* variants and melanoma in a US population and to investigate whether genetic risk is modified by pigmentation characteristics and sun exposure measures.

Methods—Melanoma patients (n=960) and controls (n=396) self-reported phenotypic characteristics and sun exposures via structured questionnaire and underwent a skin examination. Logistic regression was used to estimate associations of high [R] and low [r] risk *MC1R* variants and melanoma, overall and within phenotypic and sun exposure strata. A meta-analysis of results from published studies was undertaken.

Results—Carriage of two [r] or any [R] variant was associated with increased risk of melanoma (odds ratio (OR) = 1.7; 95% CI, 1.0-2.8; OR=2.2; 95% CI 1.5-3.0, respectively). However, risk was stronger in or limited to individuals with protective phenotypes and limited sun exposure such as those who tanned well after repeated sun exposure (OR=2.4; 95% CI 1.6-3.6), had dark hair (OR=2.4; 95% CI 1.5-3.6), or had dark eyes (OR=3.2, 95% CI 1.8-5.9). We noted this same pattern of increased melanoma risk among persons who did not freckle, tanned after exposure to first strong summer sun, reported little or average recreational or occupational sun exposure, or reported no sun burning events. Meta-analysis of published literature supported these findings.

Conclusions—These data indicate that *MC1R* genotypes provide information about melanoma risk in those individuals who would not be identified as high risk based on their phenotypes or exposures alone.

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Keywords

melanoma; melanocortin-1 receptor; pigmentation phenotype; genetic variation

Introduction

The melanocortin-1 receptor gene (*MC1R* [MIM *155555]) encodes the melanocyte stimulating hormone receptor, a membrane-bound protein central to pathways that signal the production of melanins. Inherited variation in *MC1R* is a robust genetic marker for increased risk of melanoma. However, the translational impact of *MC1R* genotype depends upon whether this genetic "exposure" can provide information about melanoma risk beyond that already known for phenotypic risk markers such as red hair, fair complexion, high nevus counts, and presence of dysplastic nevi.[1, 2] The frequency of *MC1R* variants in the general population suggests that a considerable proportion of melanoma risk may be attributable to these genetic variants.[3]

Several studies have noted that the association of *MC1R* genotype with risk was stronger in or limited to persons with "protective" cutaneous phenotypes, i.e. persons with darker hair and darker skin color.[4-6] Although the impact of *MC1R* variants on melanoma risk within strata of phenotypic measures was not directly addressed in a recent meta-analysis of eleven published studies, heterogeneity of effect of the p.D294H variant was observed when comparing studies set in northern European countries (odds ratio (OR)=1.3; 95% confidence interval (CI) 0.76-2.1) to those in southern European countries (OR=2.8; 95% CI 0.16-4.7), presumably related to deeper pigmentation of southern European populations.[7]

To assess the association of *MC1R* genotype and melanoma risk, we present results from a case-control study of melanoma set in the Mid-Atlantic region of the United States that strongly suggest that the effect of certain *MC1R* variants is confined to persons without traditional risk factors for melanoma. We also undertook a meta-analysis of data available from the published literature to validate our finding that the risk associated with inherited *MC1R* variants is greater among persons with "low risk" phenotypes such as dark hair and dark skin. Our data indicate that *MC1R* genotyping should be considered in prediction models assessing melanoma risk.

Methods

Study participants were recruited into a case-control of melanoma susceptibility from the University of Pennsylvania Health System Pigmented Lesion Clinic (PLC) between September 1997 and December 2006. Prior work from the PLC has shown its patient population to be reasonably representative of the general population with early stage melanoma.[8] Information about the study methodology previously has been published.[9, 10] Briefly, melanoma subjects had a first invasive cutaneous melanoma diagnosed within the past year. We asked each enrolled case for the name of a contact without melanoma and who was not a blood relative to serve as a potential control. Because only a modest proportion (36%) of melanoma cases were willing to disclose information about potential controls, additional controls were obtained from patients with clinically dysplastic nevi who did not have melanoma and who were referred to the PLC. The majority (85.1%) of controls were spouses or partners of PLC patients, the remaining were friends (11.9%), or persons related by law (3.0%). The University of Pennsylvania Institutional Review Board approved this study; and informed consent was obtained from all participants. Information on cutaneous phenotypes and sun exposure history was obtained from a self-administered questionnaire. Each participant underwent a skin examination by a trained research nurse who recorded

nevus counts, eye color, and degree of freckling. DNA was collected using a sterile buccal swab. *MC1R* genotypes were determined as previously described.[10, 11] We used previously suggested nomenclature and definitions to group *MC1R* variants as higher-risk [R] variants (D84E, R151C, R160W, and D294H) or lower-risk [r] variants (all other variants excluding synonymous changes).[12]

Meta-analysis

We undertook a literature search for publications that presented results of *MC1R* associations with melanoma stratified by at least one phenotype (e.g., hair color, skin type) or sun exposure (e.g., sun burns). We searched MEDLINE through January Week 3, 2009 for publications that were referenced under the MeSH subject heading of "Melanoma" and either the MeSH subject heading of "Receptor, Melanocortin, Type 1" or the keyword "MC1R." After limiting the search findings to human studies, 105 articles were returned including four non-English publications that were review articles. Overall, 18 reported results of associations between *MC1R* variants and risk of first sporadic melanoma by comparison of a melanoma group to a referent group. After cross-referencing these publications with those cited in a recent meta-analysis,[7] one publication was added that was referenced under 'Skin Neoplasms" rather than "Melanoma".

We excluded one study in which the majority of the case group (73%) was targeted for study enrollment based on increased likelihood of underlying genetic susceptibility. Of the remaining 18 publications, we excluded studies 1) for which data on *MC1R*~melanoma associations were available in a second article; 2) that did not include information on phenotypic or sun exposure measures; 3) that enrolled fewer than 50 melanoma cases and 50 controls; and 4) for which information on stratum-specific associations could not be abstracted. We also excluded results from one genome-wide association study because of fundamental differences in this study methodology compared to more traditional case-control approaches. After applying these inclusion/exclusion criteria, data were available from seven publications.[4-6, 13-16]

We abstracted stratum-specific associations in the form of adjusted odds ratio (aOR) and 95% confidence interval (CI) in three publications.[4, 6, 13] Data in the form of number of cases and controls with and without *MC1R* variants were abstracted from the remaining four publications.[5, 14-16] We noted whether stratum-specific melanoma associations were based on *MC1R* genotype categories corresponding to carriage of i) only [r] variants, ii) [R] variants (regardless of carriage of [r] variants), or iii) either [r] or [R] variants when the determination of (i) or (ii) was not possible. In the two studies that reported stratum-specific melanoma associations with *MC1R* [r] variants,[4, 13] it was not possible to distinguish between carriage of only one [r] variant or two [r] variants.

Statistical analysis

The PLC Study

For all models, independent variables including phenotypes, exposures and *MC1R* genotypes were entered as class indicator variables and aOR and CI were estimated as an indirect measure of risk for each level compared to the referent level. Independent variables with more than two levels were considered as ordinal variables, and trend across categories was assessed by the chi-square test for trend. To evaluate whether phenotypic characteristics or sun exposure measures modified associations of *MC1R* variants and melanoma status, we determined aORs and 95% CIs within strata. Age of melanoma diagnosis within strata was compared using the non-parametric Kruskal-Wallis test. To maximize sample sizes within strata of eye color and freckling, we substituted self-reported values for their clinically

assessed counterparts for those participants who did not complete a skin examination (n=170; 12.5%).

Meta-analysis

Meta-analyses were run using the Comprehensive Meta Analysis software v2.2.046 (Biostat, Inc., Englewood, NJ). We report pooled OR (pOR) estimates derived from random effects models and assessed heterogeneity of study results by the Q statistic. Within strata, a pOR was determined separately for three *MC1R* genotype categories, each compared to carriage of no *MC1R* variants: i) only [r] variants, ii) [R] variants regardless of carriage of [r] variants, and iii) either [R] or [r] variant. The primary pOR of interest represents likely carriage of at least one [R] variant and was derived by combining pORs determined for the [R] variant (ii) and either [r] or [R] variant (iii) groups, where appropriate. Absence of publication bias in studies of *MC1R* variants and melanoma previously has been reported.[7]

Results

The PLC Study

The PLC study sample consisted of 960 melanoma cases and 396 controls, all of whom reported being white of non-Hispanic origin. On average, cases were slightly older (49.8±14.5 years) than controls (47.7±13.4 years; p=0.014) and more likely to be male (49% and 45%, respectively; p=0.16).

Table 1 presents adjusted odds ratios for melanoma and cutaneous phenotype and sun exposure measures collected by questionnaire or clinical examination. We found statistically significant associations with all known risk factors. We did not find an association of occupational sun exposure with melanoma. A family history of melanoma among first degree relatives was reported by 13% of melanoma cases and 9% of controls, and was associated with a 50% increased risk of melanoma (aOR=1.5, 95% CI 1.0-2.2).

Genomic DNA was obtained from 952 (99.2%) cases and 330 (98.5%) controls. *MC1R* genotypes were obtained from 779 (81.2%) cases and 325 (82.1%) controls. We detected 44 unique *MC1R* variants (Table 2). We found a statistically significant trend (p<0.001) of increasing melanoma risk comparing carriage of multiple and higher-risk variants to carriage of the *MC1R* consensus sequence alone (Table 3). After adjustment for age, sex, and hair color, carriage of two *MC1R* [r] variants was associated with a 70% increased risk of melanoma (aOR=1.7; 95% CI 1.0-2.8), while carriage of at least one high risk *MC1R* [R] variant was associated with a near 2-fold risk of melanoma (aOR=1.9; 95% CI 1.3-2.8). Carriage of only one low risk *MC1R* [r] variant was not associated with melanoma. We found similar results when separately adjusting for other phenotypic characteristics, including eye color, freckling, and skin reaction to first strong summer sun or repeated sun exposure (data not tabulated).

Results from analyses of *MC1R* stratified by phenotypic and sun exposure measures are shown in Table 4. Compared to persons who inherited no *MC1R* variants, carriage of any [R] variants increased melanoma nearly 2½-fold (OR=2.4; 95% CI 1.6-3.6) among those who tanned moderately or deeply after long and repeated sun exposure, while among those who tanned only lightly or not at all, no association with *MC1R* [R] variants was noted (OR=1.0; 95% CI 0.44-2.4; and OR=0.60; 95% CI 0.06-5.9, respectively). Similarly, carriage of any *MC1R* [R] variant was also associated with increased risk among participants with dark hair (OR=2.4; 95% CI 1.5-3.6), while no increased risk was evident among those with blond (OR=1.1; 95% CI 0.44-2.5) or red (OR=0.81; 95% CI 0.16-4.1) hair. Without exception for all other phenotypes and sun exposure measures, the strongest effect of *MC1R* [R] variants on melanoma risk was seen in those “protected” individuals. We also noted a

similar pattern of increased risk associated with carriage of two *MC1R* [r] variants among those with the more protective phenotypic and sun exposure measures. To explore whether skin type accounted for our observed associations, we adjusted for skin reaction to long and repeated sun exposure and skin reaction in response to the first strong summer sun in analyses of hair color, eye color, and freckling as well as those of sun exposure measures. Although we noted some change in stratum-specific associations (Table 4), none impacted the interpretation of the results.

For counts of total, dysplastic, and large nevi, we did not find the same pattern of association between *MC1R* variants and melanoma risk (Table 4). In contrast, risk of melanoma associated with *MC1R* [R] variants among persons with few total moles (OR=1.3, 95% CI 0.68-2.6 for ≤8) or no dysplastic nevi (OR=1.5, 95% CI 0.98-2.4) were similar to or less than those among persons with increased numbers of total nevi (OR=9.0, 95% CI 1.7-47 for ≥54; OR=1.5, 95% CI 0.62-3.5 for 21-53) or dysplastic nevi (OR=9.6, 95% CI 0.89-103 for ≥4; OR=1.2, 95% CI 0.21-6.7 for 2-3).

We also explored whether age at melanoma diagnosis was associated with *MC1R* genotype. For most comparisons, median age of diagnosis was not statistically significantly different across genotype categories within strata of phenotypic variables (data not tabulated). In those strata where differences were noted, there was no consistent pattern of diagnosis age across genotypic categories. However, we found a difference in the median age of diagnosis by *MC1R* status among persons without a family history of melanoma in first degree relatives (p=0.01), with melanoma cases who carried at least one [R] variant tending to have earlier median age at diagnosis (46 years, interquartile range 36-55) than those in other *MC1R* genotype categories. No difference in age at diagnosis by genotype status was noted among those with a family history of melanoma (p=0.48).

Meta-analysis of *MC1R* variants and melanoma by level of cutaneous phenotype

Summary information on the seven studies[4, 5, 13-16] included in the meta-analysis is available from the corresponding author upon request. We calculated pORs for measures for which data were available from at least three publications, including our present results. Forest plots for associations of *MC1R* genotypes and melanoma by for phenotype and sun exposure are given in Figure 1a-l. Results from these analyses indicated that pORs for associations of *MC1R* [R] variants were stronger among individuals with dark hair (pOR=2.5, 95% CI 2.0-3.1) than those with light hair (pOR=1.4, 95% CI, 0.97-2.1), with dark eyes (pOR=2.8, 95% CI 1.7-4.5) than those with light eyes (pOR=1.8, 95% CI 1.3-2.6), with dark skin (pOR=2.1, 95% CI 1.2-3.9) than those with light skin (pOR=1.4, 95% CI 0.81-2.5). Further, associations were as strong among individuals with skin type III/IV (pOR=2.3, 95% CI 1.5-3.5) than those with type I/II skin (pOR=2.2, 95% CI 0.90-5.1) and among those reporting low recreational sun exposure (pOR=2.2, 95% CI 1.5-3.2) than those with high recreational sun exposure (pOR=2.0, 95% CI 1.2-3.3).

In contrast, the pOR for associations of *MC1R* [R] variants and melanoma were smaller among individuals with low nevus counts (pOR=1.6, 1.0-2.5) and no dysplastic nevi (pOR=1.4, 95% CI 0.90-2.1) than those with high nevus counts (pOR=2.3, 95% CI 1.1-4.6) or any dysplastic nevi (pOR=3.1, 95% CI 0.62-16).

Discussion

Since first shown to be associated with human pigmentation characteristics, numerous investigators have demonstrated that natural variation in *MC1R* is associated with increase risk of melanoma. Palmer et al. first reported that the melanoma risk conferred by *MC1R* genotypes was strongest among persons with darker skin tones even after adjustment for hair

color and suggested that risk associated with *MC1R* may be modified by pigmentation characteristics.[5] This effect measure modification was later noted in a second study set in Australian and one set in Italy.[4, 6] Here, we confirmed that *MC1R* variants are associated with increased melanoma risk in a U.S. population and extended previous findings to show that genetic risk is greater not only in those with darker hair or skin, but is largely limited to those characterized by phenotypes and sun exposure levels considered protective against melanoma development. The results of our meta-analyses further demonstrate increased risk of melanoma among person with dark hair, dark eyes, dark skin color, skin type III or IV, and low levels of recreational sun exposure. Thus, results from the PLC study together with results from these meta-analyses strongly suggest that *MC1R* genotype provides information about melanoma risk beyond that of oculocutaneous phenotype and sun exposure. We conclude that the combination of *MC1R* genotype and phenotype or sun exposure data may be vital to melanoma risk prediction in persons with otherwise "protective" phenotypes. Without knowledge of *MC1R* genotypes, these individuals would otherwise be considered at low melanoma risk.

We considered several potential sources of bias in the PLC study. First, we compared melanoma cases who referred a control for study recruitment (n=339, 35%) to those who did not provide a referred control (n=621, 65%) and found no difference for most associations of pigmentation or sun exposure phenotypes; further, *MC1R* genotype categories did not differ between these cases. Second, we compared characteristics of the 339 controls referred by melanoma cases to the 57 controls referred by patients with a clinically dysplastic nevus, all of whom were seen in the same ascertainment clinic. We did not observe a difference in *MC1R* genotypes between these groups. As expected, controls referred by clinically dysplastic nevus patients were younger (mean age=42.3) than controls referred by melanoma cases (mean age=48.7; p=0.0007); they were also more likely to have a dysplastic nevus (χ^2=5.80, df=1, p=0.016) and more extensive freckling (χ^2=8.42, df=1, p=0.038). This suggests that patients diagnosed with dysplastic nevi were more likely to refer a control based on perceived increased risk of melanoma and the need to undergo a free full-body skin examination as part of this research. This selection pressure would tend to create a control group that overall was more similar to melanoma cases and a potential bias toward the null hypothesis. Despite these potential biases, all traditional risk factors were statistically significantly associated with melanoma status in our study; and strengths of associations were consistent with previously published work.[1, 2]

We defined high risk *MC1R* [R] variants as p.D84E, p.R151C, p.R160W, p.D294H based on prior work,[12] but other classification schemes are possible. Secondary analysis considering the p.R142H, p.I155T, g.86_87insA, g.411delC, and g.537_538insC as [R] variants did not meaningfully alter interpretation of results. Our finding that carriage of two *MC1R* [r] variants increases risk of melanoma by 70% (95% CI 1.0-2.7) is consistent with recent results demonstrating a per allele risk of 1.2 (95% CI 1.1-1.3) associated with carriage of the p.V60L, p.V92M, p.I155I, or p.R163Q variant[17] and with functional analysis demonstrating that the activity of the p.V60L and p.R163Q variant receptor is compromised compared to native *MC1R* function.[18]

We acknowledge that for several of the meta-analyses, the total number of studies contributing information was small and power to detect heterogeneity of effect was modest. Interestingly, while many meta-analyses did demonstrate significant heterogeneity, it is notable that we did not find heterogeneity in the pooled estimate for any meta-analysis of *MC1R* [R] variants within the "protective" phenotypic or sun exposure strata. This suggests that the MC1R-phenotype relationship with melanoma risk is robust across various studies and further supports the credibility of this finding.

There is potential for a substantial public health impact of using *MC1R* genetic information in conjunction with phenotype and/or exposure data. Raimondi et al. reported a combined etiologic fraction (EF) for the p.D84E, p.R151C, p.R160W, and p.D294H variants of 15.0%.[7] Under the assumption of a causal relationship between *MC1R* and melanoma, this EF would mean that nearly 15% of melanomas are attributable to the genetic effects of these four *MC1R* variants. This figure, however, likely underestimates the EF among those persons with protective phenotype and sun exposure measures because associations with [R] variants are stronger in these groups.

Using data from the present study and focusing on only the four *MC1R* [R] variants for simplicity, the estimated EFs {[(OR-1) / OR] × proportion of cases carrying *MC1R* [R] variants} ranged from 33% among dark haired individuals to 42% among dark eyed individuals. We applied these EFs to population estimates of the proportion of melanoma occurring in individuals within each protective phenotype as reported by the Genes, Environment, and Melanoma study. This study enrolled over 2400 cases with first primary melanoma from across nine international ascertainment centers.[19] These results suggest that between 8 to 33% of all melanomas could be detected early in their natural history and potentially cured by screening for *MC1R* [R] variants among persons with protective phenotypes. Although two risk estimation models for melanoma have been published,[20, 21] neither had *MC1R* genotypes available for analysis. Echoing prior commentary by Whiteman and Green,[22] we believe that this study establishes the carriage of *MC1R* [R] variants as a risk factor to be considered when developing and testing new multivariable risk models. Its addition may improve a model's clinically utility by increasing calibration, improving risk categorization and enhancing classification accuracy.[23] Knowing *MC1R* status can empower clinicians to emphasize skin self-examination and sun-protection behavior for those patients who otherwise believe that they are at lower risk for melanoma based on their phenotypic characteristics alone.

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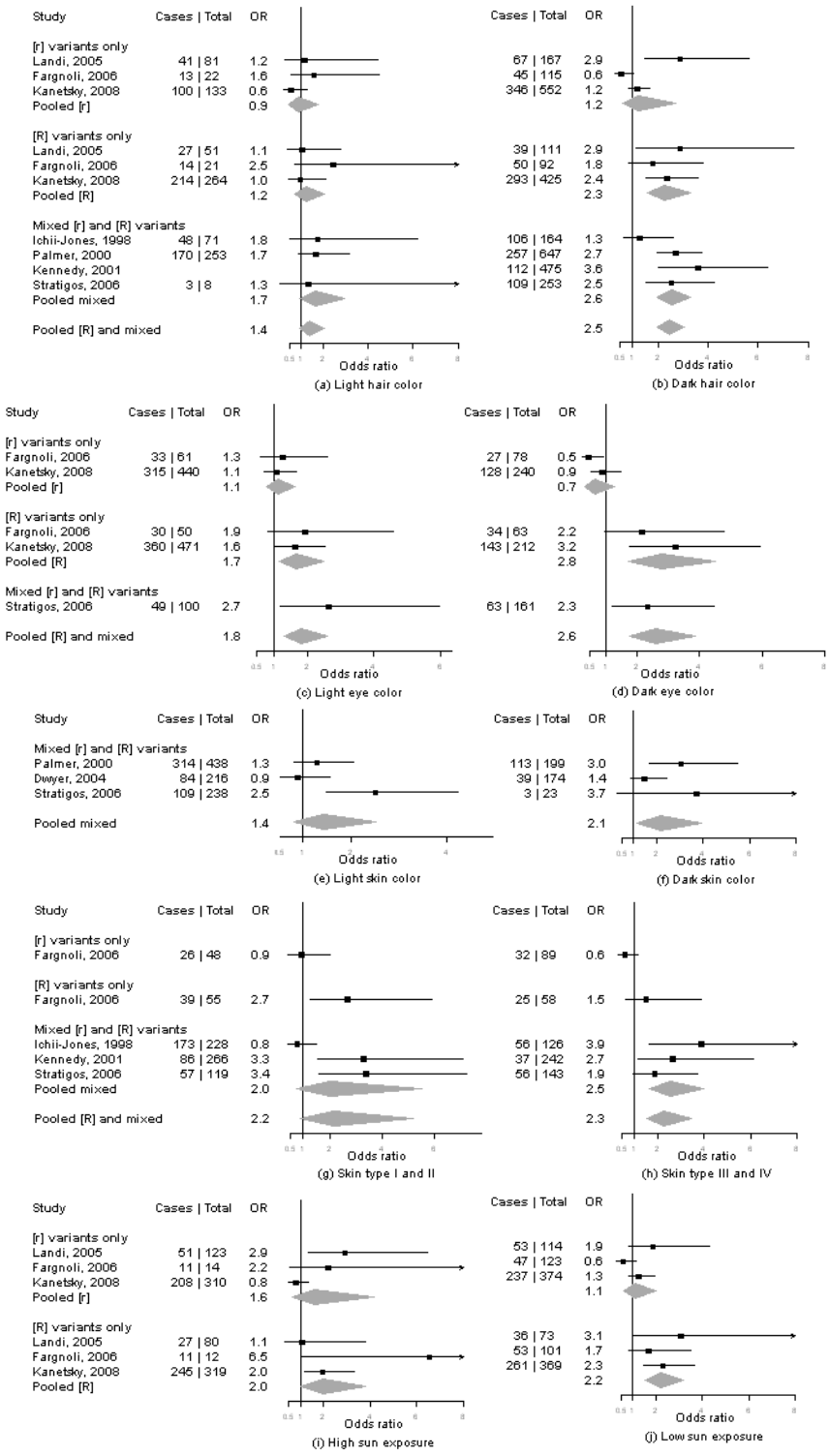

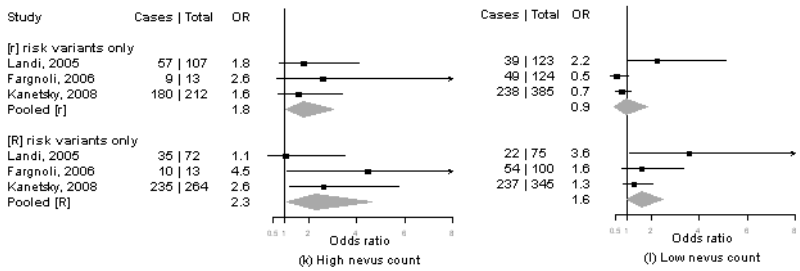

Figure 1. Meta-analysis of associations of *MC1R* genotype and melanoma stratified by hair color (a, b), eye color (c,d), skin color (e, f), skin type (g, h), sun exposure (i, j), and nevus count (k, l)

Study-specific odds ratios (OR, squares) and 95% confidence intervals (CI, horizontal lines) and pooled odds ratios and 95% CI (diamonds) for carriage of *MC1R* variants are shown; for all comparisons, the referent group is individuals who do not carry any *MC1R* variant. Number of cases and total number of individuals within each stratum are indicated.

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Table 1

Associations of self-reported and clinically assessed cutaneous phenotypic and sun exposure measures and melanoma status: PLC Study

	Control (n=396) n[a] (%)	Case (n=960) n[a] (%)	OR (95% CI)	aOR[b] (95% CI)	P_{trend}
Hair color					
Dark	309 (78.0)	623 (64.9)	1.0	1.0	
Blond	66 (16.7)	216 (22.5)	1.6 (1.2-2.2)	1.7 (1.2-2.3)	
Red	21 (5.3)	121 (12.6)	2.9 (1.8-4.6)	3.0 (1.9-4.9)	p<0.001
Eye color					
Brown	148 (37.4)	255 (26.6)	1.0	1.0	
Green or hazel	106 (26.8)	307 (32.0)	1.7 (1.2-2.3)	1.7 (1.3-2.3)	
Blue or grey	142 (35.9)	397 (41.4)	1.6 (1.2-2.1)	1.6 (1.2-2.1)	p=0.0012
Skin reaction to first strong summer sun					
No burn	33 (8.4)	44 (4.6)	1.0	1.0	
Mild burn then tan	208 (52.7)	393 (41.3)	1.4 (0.88-2.3)	1.5 (0.90-2.4)	
Burn without blister	119 (30.1)	381 (40.1)	2.4 (1.5-3.9)	2.6 (1.5-4.2)	
Burn and blister	35 (8.9)	133 (14.0)	2.9 (1.6-5.1)	3.0 (1.7-5.5)	p<0.001
Skin reaction to long and repeated exposure to sun					
Medium or dark tan	296 (75.5)	583 (61.7)	1.0	1.0	
Light tan	84 (21.4)	297 (31.4)	1.8 (1.4-2.4)	1.9 (1.4-2.5)	
No tan	12 (3.1)	65 (6.9)	2.8 (1.5-5.2)	2.9 (1.5-5.4)	p<0.001
Freckling					
None	163 (41.3)	198 (20.7)	1.0	1.0	
Some	141 (35.7)	357 (37.4)	2.1 (1.6-2.8)	2.1 (1.6-2.8)	
A lot	91 (23.0)	401 (42.0)	3.6 (2.7-4.9)	3.8 (2.8-5.2)	p<0.001
Recreational sun exposure					
A little	10 (2.5)	32 (3.3)	1.5 (0.74, 3.2)	1.5 (0.71, 3.1)	
Average	230 (58.1)	480 (50.2)	1.0	1.0	
A lot	156 (39.4)	445 (46.5)	1.4 (1.1, 1.7)	1.4 (1.1, 1.8)	p=0.028[c]
Occupational sun exposure					

	Control (n=396) n[a] (%)	Case (n=960) n[a] (%)	OR (95% CI)	aOR[b] (95% CI)	P_{trend}
A little	248 (62.6)	606 (63.3)	1.0	1.0	
Average	104 (26.3)	237 (24.8)	0.93 (0.71, 1.2)	0.88 (0.67, 1.2)	
A lot	44 (11.1)	114 (11.9)	1.1 (0.73, 1.5)	1.0 (0.70, 1.5)	p=0.83
Number of sunburns (before age 18)					
0	80 (22.3)	138 (16.1)	1.0	1.0	
1-3	145 (40.4)	317 (37.0)	1.3 (0.90-1.8)	1.3 (0.95-1.9)	
4-10	100 (27.9)	263 (30.7)	1.5 (1.1-2.2)	1.6 (1.1-2.4)	
11 or more	34 (9.5)	139 (16.2)	2.4 (1.5-3.8)	2.5 (1.6-4.0)	p<0.001
Number of sunburns (after age 18)					
0	96 (25.2)	199 (22.3)	1.0	1.0	
1-3	193 (50.7)	434 (48.6)	1.1 (0.81-1.5)	1.1 (0.83-1.5)	
4-10	76 (20.0)	198 (22.2)	1.3 (0.88-1.8)	1.3 (0.91-1.9)	
11 or more	16 (4.2)	63 (7.1)	1.9 (1.0-3.5)	1.9 (1.0-3.5)	p=0.023
Clinically assessed cutaneous phenotypes					
Eye color					
Brown	117 (39.4)	240 (27.2)	1.0	1.0	
Green or hazel	70 (23.6)	235 (26.6)	1.6 (1.2-2.3)	1.6 (1.2-2.3)	
Blue or grey	110 (37.0)	407 (46.2)	1.8 (1.3-2.4)	1.8 (1.3-2.4)	p<0.001
Freckling					
None	45 (15.1)	45 (5.1)	1.0	1.0	
Mild	84 (28.2)	164 (18.5)	2.0 (1.2-3.2)	2.0 (1.2-3.2)	
Moderate	57 (19.1)	229 (25.9)	4.0 (2.4-6.7)	4.1 (2.4-6.8)	
Heavy	112 (37.6)	448 (50.6)	4.0 (2.5-6.4)	4.1 (2.5-6.6)	p<0.001
Total nevus count					
0-8	134 (44.6)	196 (22.1)	1.0	1.0	
9-20	86 (28.7)	184 (20.8)	1.5 (1.0-2.1)	1.7 (1.2-2.4)	
21-53	60 (20.0)	231 (26.1)	2.6 (1.8-3.8)	3.2 (2.2-4.7)	
54 or more	20 (6.7)	275 (31.0)	9.4 (5.7-15)	13 (7.7-22)	p<0.001
Number of dysplastic nevi					

	Control (n=396) n[a] (%)	Case (n=960) n[a] (%)	OR (95% CI)	aOR[b] (95% CI)	P_{trend}
0	249 (84.4)	472 (53.5)	1.0	1.0	
1	20 (6.8)	134 (15.2)	3.5 (2.2-5.8)	3.7 (2.3-6.1)	
2	14 (4.8)	108 (12.2)	4.1 (2.3-7.3)	4.4 (2.5-7.9)	
3 or more	12 (4.1)	169 (19.1)	7.4 (4.1-14)	8.6 (4.7-16)	p<0.01
Number of large (≥8mm) nevi					
0	251 (83.7)	570 (64.3)	1.0	1.0	
1	32 (10.7)	160 (18.0)	2.2 (1.5-3.3)	2.3 (1.5-3.5)	
2	8 (2.7)	58 (6.6)	3.2 (1.5-6.8)	3.8 (1.7-8.2)	
3 or more	9 (3.0)	98 (11.1)	4.8 (2.4-9.6)	7.2 (3.3-16)	p<0.001

[a] Totals may vary due to missing data.

[b] OR adjusted for age and sex; OR for clinically assessed cutaneous phenotypes further adjusted for examiner.

[c] P-value for χ^2 analysis testing heterogeneity among categories is reported.

Table 2

***MC1R* variants, allele and genotype frequencies in individuals with (cases) and without (controls) melanoma: PLC Study**

Nucleotide change	Amino acid change	Control (n=325)		Case (n=779)	
		n	%	n	%
Allele Frequency[a]					
Nonsynonymous					
g.178T>G	p.V60L	95	14.6	226	14.5
g.252C>A	p.D84E	6	0.9	14	0.9
g.274G>A	p.V92M	62	9.5	144	9.2
g.425G>A	p.R142H	9	1.4	11	0.7
g.451C>T	p.R151C	35	5.4	156	10.0
g.464T>C	p.I155T	8	1.2	16	1.0
g.478C>T	p.R160W	44	6.8	151	9.7
g.488G>A	p.R163Q	23	3.5	60	3.9
g.880G>C	p.D294H	10	1.5	58	3.7
Rare[b,f]		8	1.4	29	1.9
Insertion/deletion[c,f]		0	0	14	0.9
Synonymous					
g.942A>G	p.T314T	71	10.9	175	11.2
Rare[d,f]		6	0.9	17	1.1
Genotype Frequency[e]					
Any variant (excluding synonymous)					

Nucleotide change	Amino acid change	Control (n=325)		Case (n=779)	
		n	%	n	%
0		96	29.5	174	22.3
1		157	48.3	336	43.1
2		72	22.2	264	33.9
3		0	0.0	5	0.64
Any [R] variant					
0		239	73.5	446	57.3
1		77	23.7	287	36.8
2		9	2.8	46	5.9
Any [r] variant					
0		148	45.5	373	47.9
1		148	45.5	315	40.4
2		29	8.9	88	11.3
3		0	0.0	3	0.39

[a] Allele frequency is determined from the total number of chromosomes genotyped.

[b] A group indicating carriage of any of 24 nsSNP.

[c] A group indicating carriage of g.86_87insA, g.411delC, or g.537_538insC.

[d] A group indicating carriage of any of nine sSNP.

[e] Genotype frequency is determined from the total number of individuals genotyped.

[f] A detailed listing of variants is available upon request.

Table 3

Associations of *MC1R* genotype categories and melanoma status: PLC Study

***MC1R* genotype**	**Control**	**Case**			
	n (%)	**n (%)**	**OR (95% CI)**	**aOR[a] (95% CI)**	**aOR[b] (95% CI)**
consensus[a] / consensus	96 (29.5)	174 (22.3)	1.0	1.0	1.0
[r] / consensus	114 (35.1)	183 (23.5)	0.89 (0.63, 1.2)	0.88 (0.62, 1.2)	0.89 (0.63, 1.3)
[r] / [r]	29 (8.9)	89 (11.4)	1.7 (1.0, 2.8)	1.7 (1.0, 2.7)	1.7 (1.0, 2.8)
[R] / con	43 (13.2)	153 (19.6)	2.0 (1.3, 3.0)	2.0 (1.3, 3.0)	1.8 (1.2, 2.8)
[R] / [r]	34 (10.5)	134 (17.2)	2.2 (1.4, 3.4)	2.2 (1.4, 3.5)	1.9 (1.2, 3.1)
[R] / [R]	9 (2.8)	46 (5.9)	2.8 (1.3, 6.0)	2.9 (1.3, 6.0)	1.9 (0.84, 4.4)
				$P_{trend}<0.001$	$P_{trend}<0.001$
Any [R]	86 (26.5)	333 (42.8)	2.1 (1.5, 3.0)	2.2 (1.5, 3.0)	1.9 (1.3, 2.8)

[a] Adjusted for age and sex.

[b] Adjusted for age, sex, and hair color.

[c] Consensus indicates no observed *MC1R* variants.

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Table 4

Associations of MC1R genotype and melanoma stratified by cutaneous phenotype, nevus phenotype, and sun exposure measures

Phenotype or Exposure Category	MC1R genotype	Controls[a]	Cases[a]	OR[b] (95% CI)	OR[c] (95% CI)
Cutaneous Phenotype					
Hair Color					
Red	[r] / consensus	3 | 5	5 | 18	0.25 (0.03 - 2.1)	0.28 (0.02, 3.7)
	[r] / [r]	0 | 2	7 | 20	n.e.[d]	n.e.[d]
	Any [R]	14 | 16	71 | 84	0.81 (0.16 - 4.1)	0.86 (0.14, 5.4)
Blond	[r] / consensus	16 | 25	30 | 64	0.50 (0.19 - 1.3)	0.47 (0.18, 1.2)
	[r] / [r]	3 | 12	11 | 44	1.0 (0.23 - 4.4)	0.98 (0.22, 4.4)
	Any [R]	25 | 34	96 | 130	1.1 (0.44 - 2.5)	0.99 (0.41, 2.4)
Dark	[r] / consensus	95 | 180	148 | 275	1.0 (0.70 - 1.5)	0.98 (0.66, 1.4)
	[r] / [r]	26 | 111	71 | 198	1.8 (1.0 - 3.0)	1.6 (0.95, 2.9)
	Any [R]	47 | 132	166 | 293	2.4 (1.5 - 3.6)	2.2 (1.4, 3.3)
Eye Color					
Blue/grey	[r] / consensus	39 | 67	75 | 139	0.86 (0.48 - 1.6)	0.86 (0.47, 1.6)
	[r] / [r]	9 | 37	44 | 108	2.2 (0.94 - 5.1)	2.6 (1.1, 6.3)
	Any [R]	39 | 67	158 | 222	1.8 (1.0 - 3.1)	1.8 (1.0, 3.2)
Green/hazel	[r] / consensus	21 | 42	56 | 109	1.0 (0.51 - 2.1)	1.0 (0.48, 2.1)
	[r] / [r]	7 | 28	23 | 76	1.3 (0.48 - 3.4)	1.2 (0.42, 3.3)
	Any [R]	23 | 44	85 | 138	1.5 (0.73 - 2.9)	1.3 (0.64, 2.7)
Darker	[r] / consensus	53 | 99	51 | 106	0.77 (0.44 - 1.3)	0.72 (0.41, 1.3)
	[r] / [r]	13 | 59	22 | 77	1.4 (0.63 - 3.1)	1.2 (0.51, 2.7)
	Any [R]	23 | 69	88 | 143	3.2 (1.8 - 5.9)	2.6 (1.4, 4.9)
Skin reaction to first strong summer sun					
Burn and blister	[r] / consensus	13 | 17	19 | 35	0.35 (0.09 - 1.3)	
	[r] / [r]	3 | 7	13 | 29	1.1 (0.20 - 5.8)	
	Any [R]	10 | 14	56 | 72	1.4 (0.37 - 5.0)	
Burn without blister	[r] / consensus	29 | 49	70 | 138	0.72 (0.37 - 1.4)	

Phenotype or Exposure Category	MC1R genotype	Controls[a]	Cases[a]	OR[b] (95% CI)	OR[c] (95% CI)
	[r] / [r]	9	29	29	97	0.94 (0.38 - 2.3)	
	Any [R]	37	57	141	209	1.1 (0.60 - 2.1)	
Mild burn then tan	[r] / consensus	60	119	86	165	1.1 (0.66 - 1.7)	
	[r] / [r]	17	59	38	117	1.6 (0.83 - 3.2)	
	Any [R]	37	96	118	197	2.3 (1.4 - 3.8)	
Tan or no change	[r] / consensus	12	25	5	16	0.37 (0.09 - 1.5)	
	[r] / [r]	0	13	6	17	n.e.[d]	
	Any [R]	2	15	16	27	9.1 (1.6 - 50)	
Skin reaction to long and repeated sun exposure							
No tan	[r] / consensus	3	4	9	19	0.31 (0.03 - 3.7)	
	[r] / [r]	1	1	3	13	0.20 (0.01 - 5.3)	
	Any [R]	5	6	31	41	0.60 (0.06 - 5.9)	
Light tan	[r] / consensus	22	31	49	92	0.49 (0.20 - 1.2)	
	[r] / [r]	8	17	30	73	0.79 (0.27 - 2.3)	
	Any [R]	24	33	116	159	1.0 (0.44 - 2.4)	
Medium or dark tan	[r] / consensus	88	174	124	243	0.99 (0.67 - 1.5)	
	[r] / [r]	19	105	53	172	2.0 (1.1 - 3.6)	
	Any [R]	55	141	180	299	2.4 (1.6 - 3.6)	
Freckling							
Heavy	[r] / consensus	28	44	73	143	0.60 (0.30 - 1.2)	0.63 (0.31, 1.3)
	[r] / [r]	10	26	50	120	1.1 (0.47 - 2.7)	1.4 (0.55, 3.3)
	Any [R]	46	62	174	244	0.85 (0.45 - 1.6)	0.81 (0.42, 1.6)
Moderate	[r] / consensus	18	32	55	98	1.0 (0.46 - 2.4)	0.92 (0.40, 2.1)
	[r] / [r]	6	20	19	62	1.0 (0.34 - 3.1)	0.71 (0.22, 2.3)
	Any [R]	20	34	89	132	1.5 (0.68 - 3.3)	1.3 (0.57, 2.9)
Mild	[r] / consensus	33	67	37	82	0.83 (0.44 - 1.6)	0.82 (0.42, 1.6)
	[r] / [r]	9	43	14	59	1.2 (0.45 - 3.0)	1.0 (0.38, 2.7)
	Any [R]	17	51	56	101	2.5 (1.2 - 5.0)	2.2 (1.1, 4.6)
No	[r] / consensus	35	67	18	34	1.0 (0.45 - 2.4)	1.0 (0.44, 2.5)

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Phenotype or Exposure Category	MC1R genotype	Controls[a]	Cases[a]	OR[b] (95% CI)	OR[c] (95% CI)
	[r] / [r]	4	36	6	22	2.9 (0.72 - 12)	2.7 (0.61, 12)
	Any [R]	3	35	12	28	8.2 (2.0 - 33)	8.3 (1.9, 37)
Nevus Phenotype							
Total nevus count							
54+	[r] / consensus	6	12	54	94	1.3 (0.39 - 4.4)	
	[r] / [r]	0	6	24	64	n.e.[d]	
	Any [R]	2	8	112	152	9.0 (1.7 - 47)	
21-53	[r] / consensus	19	30	46	86	0.68 (0.29 - 1.6)	
	[r] / [r]	5	16	28	68	1.6 (0.50 - 5.1)	
	Any [R]	16	27	82	122	1.5 (0.62 - 3.5)	
9-20	[r] / consensus	20	44	27	77	0.64 (0.30 - 1.4)	
	[r] / [r]	8	32	17	67	1.1 (0.40 - 3.0)	
	Any [R]	18	42	50	100	1.4 (0.69 - 3.0)	
0-8	[r] / consensus	43	71	38	74	0.68 (0.34 - 1.3)	
	[r] / [r]	9	37	18	54	1.5 (0.59 - 4.1)	
	Any [R]	32	60	62	98	1.3 (0.68 - 2.6)	
Number of dysplastic nevi							
4+	[r] / consensus	3	3	29	53	1.0 (0.18 - 5.9)	
	[r] / [r]	1	4	21	45	2.6 (0.24 - 28)	
	Any [R]	1	4	68	92	9.6 (0.89 - 103)	
2-3	[r] / consensus	2	4	26	41	1.7 (0.21 - 14)	
	[r] / [r]	2	4	10	25	0.67 (0.08 - 5.7)	
	Any [R]	6	8	47	62	1.2 (0.21 - 6.7)	
1	[r] / consensus	7	11	26	50	0.55 (0.14 - 2.2)	
	[r] / [r]	1	5	17	41	2.5 (0.25 - 25)	
	Any [R]	5	9	48	72	1.6 (0.38 - 6.4)	
0	[r] / consensus	75	135	83	186	0.63 (0.40 - 0.98)	
	[r] / [r]	18	78	39	142	1.3 (0.66 - 2.4)	
	Any [R]	55	115	143	246	1.5 (0.98 - 2.4)	

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Phenotype or Exposure Category	MC1R genotype	Controls[a]	Cases[a]	OR[b] (95% CI)	OR[c] (95% CI)
Number of large nevi					
3+	[r] / consensus	2 | 4	17 | 33	0.76 (0.08 - 6.9)	
	[r] / [r]	2 | 4	13 | 29	0.68 (0.07 - 6.2)	
	Any [R]	2 | 4	38 | 54	2.6 (0.32 - 21)	
2	[r] / consensus	0 | 2	11 | 18	n.e.[d]	
	[r] / [r]	2 | 4	4 | 11	0.36 (0.03 - 4.7)	
	Any [R]	4 | 6	22 | 29	0.99 (0.12 - 8.1)	
1	[r] / consensus	7 | 16	28 | 60	1.2 (0.37 - 3.7)	
	[r] / [r]	0 | 9	20 | 52	n.e.[d]	
	Any [R]	6 | 15	53 | 85	2.7 (0.82 - 8.7)	
0	[r] / consensus	79 | 135	109 | 220	0.68 (0.44 - 1.0)	
	[r] / [r]	18 | 74	50 | 161	1.4 (0.73 - 2.6)	
	Any [R]	56 | 112	193 | 304	1.7 (1.1 - 2.7)	
Sun Exposure					
Recreational sun					
Lots	[r] / consensus	49 | 87	81 | 168	0.70 (0.41 - 1.2)	0.67 (0.39, 1.2)
	[r] / [r]	15 | 53	40 | 127	1.2 (0.57 - 2.3)	1.0 (0.51, 2.2)
	Any [R]	36 | 74	158 | 245	2.0 (1.2 - 3.3)	1.6 (0.94, 2.8)
Little or average	[r] / consensus	65 | 123	101 | 188	1.0 (0.66 - 1.6)	1.0 (0.64, 1.6)
	[r] / [r]	14 | 72	49 | 136	2.3 (1.2 - 4.6)	2.2 (1.1, 4.5)
	Any [R]	50 | 108	174 | 261	2.3 (1.5 - 3.7)	2.1 (1.3, 3.4)
Occupational sun					
Lots	[r] / consensus	10 | 19	17 | 37	0.68 (0.22 - 2.1)	0.61 (0.18, 2.1)
	[r] / [r]	6 | 15	10 | 30	0.67 (0.18 - 2.5)	0.58 (0.14, 2.4)
	Any [R]	12 | 21	43 | 63	1.7 (0.58 - 4.7)	1.2 (0.37, 3.8)
Average	[r] / consensus	28 | 56	47 | 92	1.0 (0.53 - 2.0)	1.0 (0.51, 2.0)
	[r] / [r]	10 | 38	14 | 59	0.84 (0.33 - 2.2)	0.81 (0.29, 2.3)
	Any [R]	21 | 49	87 | 132	2.7 (1.4 - 5.2)	2.2 (1.1, 4.5)
Little	[r] / consensus	76 | 135	118 | 227	0.83 (0.54 - 1.3)	0.78 (0.50, 1.2)

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Phenotype or Exposure Category	MC1R genotype	Controls[a]	Cases[a]	OR[b] (95% CI)	OR[c] (95% CI)
	[r] / [r]	13	72	65	174	2.6 (1.3 - 5.1)	2.3 (1.2, 4.6)
	Any [R]	53	112	202	311	2.1 (1.3 - 3.2)	1.8 (1.2, 2.9)
Number of sunburns (after age 18)							
11+	[r] / consensus	5	7	6	20	0.17 (0.03 - 1.2)	0.11 (0.01, 0.87)
	[r] / [r]	3	5	3	17	0.15 (0.02 - 1.3)	0.11 (0.01, 1.2)
	Any [R]	5	7	28	42	0.81 (0.14 - 4.9)	0.70 (0.11, 4.4)
4-10	[r] / consensus	16	34	33	68	1.0 (0.45 - 2.4)	0.92 (0.39, 2.2)
	[r] / [r]	6	24	21	56	1.7 (0.57 - 4.9)	1.6 (0.50, 5.4)
	Any [R]	23	41	74	109	1.6 (0.78 - 3.4)	1.3 (0.62, 2.9)
1-3	[r] / consensus	52	100	97	176	1.1 (0.69 - 1.9)	1.1 (0.64, 1.8)
	[r] / [r]	13	61	34	113	1.6 (0.76 - 3.3)	1.4 (0.66, 3.0)
	Any [R]	42	90	142	221	2.1 (1.3 - 3.4)	1.8 (1.1, 3.0)
0	[r] / consensus	31	59	35	65	1.0 (0.51 - 2.1)	1.1 (0.54, 2.4)
	[r] / [r]	6	34	24	54	3.6 (1.3 - 10)	3.6 (1.3, 10)
	Any [R]	12	40	69	99	5.3 (2.4 - 12)	4.8 (2.1, 11)
Number of sunburns (before age 18)							
11+	[r] / consensus	10	17	20	43	0.64 (0.20 - 2.0)	0.58 (0.17, 2.0)
	[r] / [r]	3	10	13	36	1.4 (0.31 - 6.5)	2.1 (0.35, 12)
	Any [R]	10	17	58	81	1.9 (0.64 - 5.8)	1.9 (0.59, 6.0)
4-10	[r] / consensus	23	44	54	95	1.2 (0.59 - 2.5)	1.2 (0.56, 2.5)
	[r] / [r]	11	32	14	55	0.65 (0.25 - 1.7)	0.52 (0.19, 1.4)
	Any [R]	29	50	107	148	1.8 (0.94 - 3.6)	1.6 (0.79, 3.2)
1-3	[r] / consensus	41	77	61	114	0.97 (0.54 - 1.7)	1.0 (0.56, 1.8)
	[r] / [r]	8	44	37	90	3.0 (1.2 - 7.2)	2.9 (1.2, 7.1)
	Any [R]	27	63	104	157	2.5 (1.4 - 4.6)	2.4 (1.3, 4.5)
0	[r] / consensus	25	51	27	57	0.92 (0.43 - 2.0)	0.93 (0.42, 2.1)
	[r] / [r]	3	29	16	46	4.5 (1.2 - 17)	4.8 (1.2, 19)
	Any [R]	9	35	38	68	3.6 (1.5 - 9.0)	4.1 (1.5, 11)

[a] Numbers of individuals with *MC1R* variants and total number of individuals (# with | total #).

[b] OR are adjusted for age and sex; the referent group is individuals who do not carry any *MC1R* variant (consensus / consensus) within that stratum.

[c] OR additionally adjusted for skin reaction to long and repeated sun exposure and skin reaction in response to the first strong summer sun; the referent group is individuals who do not carry any *MC1R* variant (consensus / consensus) within that stratum.

[d] OR not estimable due to zero cell count.