

Supplementary Table 1 (online only). Associations of *MC1R* genotypes with self-reported phenotypic characteristics for controls combined^a

Phenotypic characteristic	Comparison	<i>MC1R</i> categories ^b					
		No variant (wildtype only; 0 r and 0 R alleles)		Any r in absence of R (≥ 1 r and 0 R alleles)		Any R (1 or more R alleles)	
		No. with vs without high-risk phenotype	OR (referent)	No. with vs without high-risk phenotype	OR (95% CI) ^c	No. with vs without high-risk phenotype	OR (95% CI) ^c
Hair colour	red hair <i>cf.</i> blonde/brown/black	1 / 209	1.0	3 / 274	2.3 (0.2-22.0)	67 / 372	34.3 (4.7-250.3)
Skin colour	very fair/fair skin <i>cf.</i> olive or dark	155 / 55	1.0	224 / 52	1.5 (1.0-2.4)	407 / 31	3.9 (2.4-6.4)
Ability to tan ^d	never/sometimes <i>cf.</i> usually/always	58 / 152	1.0	97 / 179	1.4 (1.0-2.1)	269 / 169	3.9 (2.7-5.6)
Freckling in childhood ^e	few/some/many <i>cf.</i> none/very few	51 / 159	1.0	89 / 186	1.5 (1.0-2.2)	268 / 170	4.7 (3.2-6.9)
Solar lentigines ^f	60-100 <i>cf.</i> 0-40	27 / 82	1.0	58 / 91	1.8 (1.0-3.2)	114 / 103	2.9 (1.7-5.0)

^a Controls include unrelated controls (population controls and spouse/friend controls) and sibling controls. Cases are not included in this table.

^b The *MC1R* categories are mutually exclusive. Silent changes (i.e. changes that are synonymous or occur in non-coding regions) are counted as consensus alleles.

^c Unconditional logistic regression, adjusted for age, sex, city of recruitment, European ancestry and control type.

^d Usual skin response to sun exposure: Never or sometimes tans, usually or always burns *cf.* Usually or always tans, never or sometimes burns.

^e Based on a 6-level picture scale of the face.

^f Objective measure based on a 6-level picture scale (0,20,40,60,80,100) of the top of the back and shoulders, with 0 representing no solar lentigines and 100 representing 'very many'. Data for this variable were only available for those who had a clinical skin examination.

Supplementary Table 2 (online only). Mutually-adjusted per R allele and per r allele associations with melanoma, by demographic factors, phenotype, sun exposure and melanoma characteristics

Stratification variable	Case-unrelated-control ^a comparison			Case-sibling-control comparison		
	Cases / controls	per r allele ^b OR ^c (95% CI)	per R allele ^b OR ^c (95% CI)	Cases / controls	per r allele ^b OR ^d (95% CI)	per R allele ^b OR ^d (95% CI)
None	565/409	1.69 (1.33-2.13)	2.23 (1.77-2.80)	328/518	1.25 (0.88-1.79)	2.06 (1.47-2.88)
Sex						
Female	357/241	1.23 (0.92-1.64)	1.99 (1.49-2.66)	145/203	1.17 (0.66-2.06)	1.91 (1.14-3.20)
Male	208/168	3.05 (1.98-4.70)	2.79 (1.88-4.15)	63/78	2.52 (1.05-6.07)	5.68 (2.04-15.78)
<i>p</i> interaction		0.001	1.0		0.5	0.1
Age						
18-29	173/79	2.07 (1.24-3.46)	2.86 (1.72-4.73)	69/80	1.28 (0.59-2.79)	0.97 (0.43-2.18)
30-44	392/330	1.60 (1.22-2.10)	2.16 (1.65-2.81)	218/334	1.35 (0.85-2.14)	2.61 (1.63-4.21)
<i>p</i> interaction		0.7	0.8		0.4	0.03
Family history of melanoma ^e						
No	509/388	1.76 (1.38-2.26)	2.17 (1.71-2.76)			
Yes	56/21	0.68 (0.26-1.74)	2.29 (0.88-5.96)			
<i>p</i> interaction		0.07	0.5			
Pigmentation score ^f						
≤ Median	235/248	1.66 (1.20-2.30)	1.72 (1.17-2.54)	97/202	1.25 (0.61-2.56)	2.61 (1.41-4.86)
>Median	330/161	1.56 (1.10-2.22)	2.13 (1.55-2.93)	151/152	1.17 (0.62-2.23)	2.01 (1.10-3.69)
<i>p</i> interaction		0.6	0.4		1.0	0.5
Hair colour						
Brown/Black	371/338	1.68 (1.29-2.18)	1.85 (1.35-2.52)	194/271	1.54 (0.98-2.44)	2.53 (1.50-4.25)
Red/Blonde/Fair	192/71	1.47 (0.84-2.58)	2.11 (1.33-3.34)	64/78	0.75 (0.25-2.25)	1.72 (0.59-5.03)
<i>p</i> interaction		0.5	0.6		0.3	0.9
Skin colour						
Olive/Brown	55/68	1.84 (0.95-3.57)	2.17 (0.95-4.98)	18/21	0.52 (0.08-3.27)	6.28 (0.38-102.96)
Very fair/Fair	507/340	1.64 (1.27-2.12)	2.20 (1.72-2.82)	268/419	1.30 (0.86-1.95)	1.97 (1.35-2.86)
<i>p</i> interaction		0.8	0.8		0.2	0.4
Eye colour						
Hazel/Brown/Black	307/228	1.86 (1.35-2.58)	2.08 (1.54-2.81)	140/199	1.18 (0.67-2.06)	2.25 (1.29-3.94)
Blue/Grey/Green	256/177	1.56 (1.08-2.24)	2.39 (1.65-3.46)	108/172	1.53 (0.82-2.85)	1.69 (0.97-2.97)
<i>p</i> interaction		0.3	0.4		0.4	0.3
Ability to tan ^g						
Usually/Always	259/238	1.53 (1.12-2.10)	2.03 (1.41-2.92)	103/131	1.65 (0.86-3.13)	2.68 (1.26-5.74)
Sometimes/Never	304/168	2.06 (1.40-3.03)	2.55 (1.81-3.58)	119/175	1.31 (0.69-2.51)	2.45 (1.25-4.80)
<i>p</i> interaction		0.4	0.8		0.5	1.0
Propensity to sunburn ^h						
Mild/No burn	196/196	1.66 (1.16-2.39)	1.93 (1.30-2.87)	72/87	0.83 (0.37-1.86)	1.45 (0.62-3.39)
Severe/Painful burn	368/212	1.62 (1.17-2.23)	2.28 (1.68-3.09)	151/223	1.67 (0.97-2.88)	2.40 (1.38-4.18)
<i>p</i> interaction		0.7	0.5		0.3	0.7
Childhood Freckling ⁱ						
None/Very few	267/240	1.90 (1.37-2.66)	2.41 (1.63-3.55)	117/152	1.37 (0.75-2.49)	2.49 (1.19-5.22)
Few/Some/Many	295/168	1.46 (1.02-2.09)	2.04 (1.47-2.84)	111/160	0.93 (0.48-1.81)	1.40 (0.75-2.62)
<i>p</i> interaction		0.5	0.8		0.6	0.4
Number of nevi ^j						
None/Few	172/234	2.84 (1.87-4.33)	3.20 (2.23-4.59)	78/111	1.40 (0.64-3.06)	2.61 (1.10-6.18)
Some/Many	391/173	1.21 (0.89-1.65)	2.04 (1.45-2.87)	148/192	1.07 (0.62-1.85)	1.60 (0.96-2.66)
<i>p</i> interaction		0.007	0.4		0.8	0.5
Childhood total sun exposure						
≤ Median	286/205	1.23 (0.89-1.71)	1.83 (1.34-2.49)	121/157	1.11 (0.64-1.93)	1.48 (0.84-2.58)
> Median	279/204	2.31 (1.62-3.29)	2.92 (2.05-4.17)	94/127	1.28 (0.64-2.55)	2.64 (1.38-5.05)
<i>p</i> interaction		0.07	0.2		0.8	0.2
Childhood sunburn causing blisters						

None	366/283	1.50 (1.14-1.99)	2.02 (1.52-2.68)	173/248	1.04 (0.64-1.69)	2.46 (1.52-3.98)
Any	196/126	2.16 (1.39-3.37)	2.71 (1.80-4.09)	57/69	1.76 (0.56-5.55)	5.74 (1.35-24.43)
<i>p</i> interaction		0.4	0.4		0.7	0.6
Childhood ambient UV irradiance ^k						
≤ Median	330/207	1.86 (1.33-2.60)	2.32 (1.66-3.23)	158/248	1.28 (0.79-2.07)	1.99 (1.21-3.27)
> Median	234/202	1.57 (1.12-2.21)	2.18 (1.57-3.02)	163/249	1.20 (0.70-2.05)	2.24 (1.36-3.68)
<i>p</i> interaction		0.5	0.9		0.8	0.6
Sunbed use						
None	432/339	1.81 (1.38-2.38)	2.36 (1.82-3.05)	228/341	1.23 (0.80-1.89)	1.75 (1.18-2.59)
Any	130/68	1.34 (0.81-2.23)	1.73 (1.02-2.93)	27/35	1.43 (0.45-4.47)	3.51 (0.69-17.97)
<i>p</i> interaction		0.4	0.3		0.9	0.5
Body site of melanoma						
Head or neck	74/409	1.51 (0.96-2.38)	2.16 (1.43-3.27)	40/65	1.13 (0.37-3.42)	2.21 (0.62-7.90)
Trunk	190/409	1.54 (1.13-2.09)	1.96 (1.46-2.64)	114/185	1.14 (0.66-1.95)	1.89 (1.02-3.50)
Arms	121/409	1.78 (1.25-2.54)	2.08 (1.47-2.93)	68/104	0.56 (0.18-1.71)	2.45 (1.07-5.61)
Legs	168/409	1.87 (1.34-2.61)	2.93 (2.14-4.01)	100/153	2.31 (1.09-4.88)	2.83 (1.50-5.33)
<i>p</i> interaction		0.5	0.1		0.3	0.8
Breslow thickness						
≤ 0.75 mm	367/409	1.65 (1.28-2.12)	1.97 (1.54-2.53)	222/342	1.17 (0.76-1.82)	2.03 (1.35-3.07)
> 0.75 mm	195/409	1.76 (1.29-2.42)	2.77 (2.06-3.73)	104/173	1.40 (0.76-2.59)	2.02 (1.11-3.68)
<i>p</i> interaction		0.7	0.02		0.6	0.9
Histological subtype ^l						
Superficial spreading	326/409	1.62 (1.24-2.12)	2.31 (1.79-2.98)	13/21	3.65 (0.42-31.37)	2.24 (0.33-15.21)
Nodular	25/409	3.80 (1.86-7.74)	3.69 (1.78-7.68)	108/156	1.22 (0.65-2.30)	1.46 (0.77-2.77)
Other	16/409	0.89 (0.37-2.15)	1.07 (0.46-2.48)	8/15	0.94 (0.02-56.81)	2.25 (0.03-178.12)
Not otherwise specified	198/409	1.73 (1.27-2.35)	2.13 (1.58-2.86)	199/326	1.18 (0.74-1.88)	2.35 (1.53-3.61)
<i>p</i> interaction		0.04	0.1		0.5	0.6

^a Unrelated controls include population controls and spouse/friend controls

^b ORs were calculated as the risk associated with each additional variant allele carried. The models were mutually adjusted in order to estimate their independent effects. R variants include D84E, R142H, R151C, I155T, R160W, D294H. r variants exclude silent changes (i.e. changes that are synonymous or occur in non-coding regions).

^c Unconditional logistic regression, adjusted for age, sex, city of recruitment, and European ancestry.

^d Conditional logistic regression, matched on family and adjusted for age and sex.

^e Confirmed family history of melanoma in 1st degree relatives

^f A continuous variable summarizing the contribution of several correlated, categorical phenotypic variables. A higher score indicates a more sun-sensitive phenotype

^g Usual skin response to sun exposure: Never or sometimes tans, usually or always burns *cf.* Usually or always tans, never or sometimes burns

^h Skin response to exposure to bright sunlight for the first time in summer without protection

ⁱ Based on a 6-level picture scale of the face

^j Number of nevi covering the body based on a 4-level picture scale

^k Erythemally weighted ambient UV irradiance (kJ/m²) derived from residence history and data from satellite observations

^l 'Other' histological subtypes include malignant melanoma, regressing; lentigo maligna melanoma; acral lentiginous melanoma; and desmoplastic melanoma.