

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Age and sex of the study population

Variable		ALL (n=1791)	CASES (n=991)	CONTROLS (n=800)
Sex	female	905 (50,5)	473 (47,7)	533 (50,6)
	male	886 (49,5)	518 (52,3)	520 (49,4)
Age at recruitment (years)	Mean (\pm SD)	59,2 (\pm 15,6)	60,7 (\pm 14,7)	57,3 (\pm 16,4)

eTable 2. Histological subtypes of melanoma

Subtype	CASES ^a (n=978)
SSM	482 (49,3)
NMM	160 (16,4)
Unclassified	141 (14,4)
LMM	86 (8,8)
Others ^b	42 (4,3)
ALM	39 (4,0)
Occult	28 (2,9)

^a Information was available for 978 cases.

^b Includes desmoplastic, spindle cell and nevoid melanoma.

eTable 3. Site of tumor occurrence

Site of the primary tumor	CASES ^a (n=990)
Trunk	475 (48)
Lower Extremity	234 (23,6)
Upper Extremity	107 (10,8)
Head&Neck	100 (10,1)
Other Location ^b	46 (4,6)
Occult	28 (2,8)

^a Information was available for 990 cases.

^b Includes acral and mucosal melanoma.

eTable 4. Pigmentation phenotype of the study population

Variable ^a		CASES (n=991)	CONTROLS (n=800)
Skin Phototype	I/II	703(73,8)	476(61,5)
	III	138(14,5)	142(18,3)
	IV/V	111(11,7)	156(20,2)
Tanning ability	low	103(10,4)	58(7,3)
	intermediate	759(76,7)	604(75,6)
	high	127(12,8)	137(17,1)
Burning tendency	high	210(21,2)	91(11,4)
	intermediate	547(55,3)	424(53,1)
	low	232(23,5)	284(35,5)
Haircolor	red	82 (8,3)	43 (5,4)
	blond	240 (24,2)	141 (17,6)
	light brown	223 (22,5)	224 (28)
	brown/black	445 (44,9)	392 (49)
Eyecolor	grey-green	136 (13,7)	70 (8,8)
	blue (incl. grey-blue)	499 (50,4)	361 (45,1)
	green	47 (4,7)	41 (5,1)
	brown	309 (31,2)	328 (41)
Freckles in childhood	yes	335(35,9)	219(28,7)
	no	598(64,1)	545(71,3)

^a Variables do not sum up to the total number of *MC1R*-sequenced participants because of missing data.

eTable 5. Association between *MC1R* variants and pigmentation phenotype

Variable^a					AOR^b					
Skin Phototype	I/II	III	IV/V*		I/II		III			
	n (%)	n (%)	n (%)		OR (95% CI)	P Value	OR (95% CI)	P Value		
R/R	74 (6,3)	7 (2,5)	7 (2,6)		4,07 (1,8-9,22)	0,001	1,11 (0,37-3,29)	0,86		
R/r	171 (14,5)	19 (6,8)	16 (6)		3,99 (2,26-7,06)	<0,001	1,33 (0,64-2,77)	0,44		
R/0	220 (18,7)	51 (18,2)	41 (15,4)		2,16 (1,43-3,26)	<0,001	1,44 (0,87-2,39)	0,15		
r/r	114 (9,7)	19 (6,8)	11 (4,1)		4,42 (2,27-8,63)	<0,001	2,09 (0,94-4,66)	0,07		
r/0	344 (29,2)	92 (32,9)	85 (31,8)		1,7 (1,22-2,38)	0,002	1,3 (0,86-1,96)	0,22		
0/0	256 (21,7)	92 (32,9)	107 (40,1)		Ref		Ref			
Tanning ability	low	intermediate	high*		low		intermediate			
	n (%)	n (%)	n (%)		OR	P Value	OR	P Value		
R/R	26 (16,1)	61 (4,5)	6 (2,3)		24,64 (8,6-70,59)	<0,001	2,18 (0,91-5,23)	0,08		
R/r	38 (23,6)	161 (11,8)	11 (4,2)		17,74 (7,39-42,61)	<0,001	3,04 (1,57-5,88)	0,001		
R/0	32 (19,9)	237 (17,4)	53 (20,1)		3,3 (1,62-6,71)	0,001	0,97 (0,66-1,43)	0,9		
r/r	17 (10,6)	120 (8,8)	14 (5,3)		6,71 (2,72-16,53)	<0,001	1,88 (1,03-3,45)	0,04		
r/0	33 (20,5)	406 (29,8)	97 (36,7)		1,83 (0,93-3,61)	0,08	0,91 (0,66-1,26)	0,58		
0/0	15 (9,3)	378 (27,7)	83 (31,4)		Ref		Ref			
Burning tendency	high	intermediate	low*		high		intermediate			
	n (%)	n (%)	n (%)		OR (95% CI)	P Value	OR (95% CI)	P Value		
R/R	36	43 (4,4)	14		10,55	<0,	2,38 (1,26-	0,00		

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R/R	12 (5,8)	42 (4,9)	6 (6,8)	33 (5,2)	1,20 (0,57- 2,52)	0,62 9	0,55 (1,5- 0,71)	0,70 6	1,13 (0,42- 3,0)	0,80 8
R/r	24 (11,7)	110 (12,8)	12 (13,6)	64 (10,0)	1,15 (0,65- 2,06)	0,62 7	0,82 (1,71- 0,38)	0,37 7	1,19 (0,55- 2,55)	0,65 5
R/0	44 (21,4)	150 (17,4)	15 (17,0)	114 (17,9)	1,28 (0,79- 2,07)	0,31 2	0,67 (1,26- 0,61)	0,60 7	0,94 (0,47- 1,88)	0,86 4
r/r	18 (8,7)	76 (8,8)	6 (6,8)	51 (8,0)	1,20 (0,64- 2,26)	0,56 9	0,71 (1,6- 0,76)	0,76 3	0,81 (0,31- 2,09)	0,66 1
r/0	61 (29,6)	252 (29,3)	23 (26,1)	202 (31,7)	1,06 (0,68- 1,63)	0,80 9	0,70 (1,20- 0,51)	0,51 0	0,76 (0,41- 1,38)	0,36 5
0/0	47 (22,8)	230 (26,7)	26 (29,5)	173 (27,2)	Ref		Ref		Ref	
Freckles in childhood	yes	no*			yes					
	n (%)	n (%)			OR (95% CI)	P Val ue				
R/R	75 (13,5)	15 (1,3)			32,4 (17,38- 60,3)	<0, 001				
R/r	121 (21,8)	84 (7,3)			9,1 (6,11- 13,4)	<0, 001				
R/0	109 (19,7)	190 (16,6)			3,7 (2,58- 5,3)	<0, 001				
r/r	56 (10,1)	86 (7,5)			4,2 (2,71- 6,5)	<0, 001				
r/0	129 (23,3)	373 (32,6)			2,1 (1,53- 3)	<0, 001				
0/0	64 (11,6)	395 (34,6)			Ref					

Abbreviations: AOR= adjusted Odds Ratio; CI=Confidence Interval; Ref=Reference group

R= 86_87insA, 142H, R151C, R160W, D294H

r= D84E, V60L, V92M, I155T, R163Q

^a Variables do not sum up to the total number of *MC1R*-sequenced participants because of missing data.

^b AOR =adjusted for age, sex and Case-Control status

*=Reference Category

eTable 6. Association of actinic skin damage and melanoma risk

Variable		ALL ^a	CASES	CONTROLS	univariate		AOR ^b	
		(n=1791)	(n=991)	(n=800)	OR (95% CI)	P Value	OR (95% CI)	P Value
		n (%)	n (%)	n (%)				
Freckling Face	++,++ +	642 (36,1)	369 (37,3)	273 (34,6)	1,52 (1,16-2)	0,003	1,18 (0,86-1,61)	0,03
	+	835 (46,9)	479 (48,4)	356 (45,1)	1,52 (1,16-1,97)	0,002	1,29 (0,97-1,71)	0,08
	0	302 (17)	142 (14,3)	160 (20,3)	Ref		Ref	
Wrinkling Face	++,++ +	801 (44,8)	471 (47,6)	330 (41,5)	2,10 (1,61-2,74)	<0,001	1,79 (1,23-2,59)	0,002
	+	671 (37,6)	392 (39,6)	279 (35,1)	2,07 (1,58-2,72)	<0,001	1,87 (1,37-2,55)	0,000
	0	314 (17,6)	127 (12,8)	187 (23,5)	Ref		Ref	
Solar lentiginos Face	++,++ +	367 (20,7)	211 (21,3)	156 (19,8)	1,94 (1,49-2,54)	<0,001	1,81 (1,31-2,52)	<0,001
	+	863 (48,6)	554 (56)	309 (39,3)	2,58 (2,07-3,21)	<0,001	2,49 (1,94-3,19)	<0,001
	0	546 (30,7)	224 (22,6)	322 (40,9)	Ref		Ref	
Freckling Back	++,++ +	742 (41,9)	482 (48,8)	260 (33,1)	3,18 (2,41-4,19)	<0,001	3,02 (2,19-4,15)	<0,001
	+	726 (41)	393 (39,8)	333 (42,4)	2,02 (1,54-2,66)	<0,001	1,97 (1,47-2,64)	<0,001
	0	304 (17,2)	112 (11,3)	192 (24,5)	Ref		Ref	
Wrinkling Neck	++,++ +	594 (33,6)	399 (40,5)	195 (24,9)	3,29 (2,55-4,25)	<0,001	3,83 (2,74-5,35)	<0,001
	+	724 (40,9)	413 (41,9)	311 (39,7)	2,13 (1,68-2,71)	<0,001	2,33 (1,78-3,05)	<0,001
	0	451 (25,5)	173 (17,6)	278 (35,5)	Ref		Ref	
Solar lentiginos Back	++,++ +	606 (34,3)	404 (41)	202 (25,8)	3,48 (2,67-4,53)	<0,001	3,62 (2,64-4,95)	<0,001
	+	764 (43,2)	436 (44,3)	328 (41,9)	2,31 (1,8-2,96)	<0,001	2,40 (1,82-3,17)	<0,001
	0	397 (22,5)	145 (14,7)	252 (32,2)	Ref		Ref	
Freckling Hand	++,++ +	217 (12,2)	145 (14,7)	72 (9,2)	2,14 (1,57-2,93)	<0,001	1,90 (1,35-2,59)	<0,001
	+	709 (40)	432 (43,7)	277 (36,2)	1,66 (1,35-2,03)	<0,001	1,53 (1,22-1,93)	<0,001
	0	848 (47,8)	411 (41,6)	437 (55,6)	Ref		Ref	

Solar lentigin es Hand	++,++ +	483 (27,3)	315 (31,9)	168 (21,4)	2,34 (1,82-3)	<0,00 1	2,64 (1,88- 3,71)	<0,00 1
	+	716 (40,4)	418 (42,3)	298 (38)	1,75 (1,4- 2,18)	<0,00 1	1,87 (1,43- 2,45)	<0,00 1
	0	573 (32,3)	255 (25,8)	318 (40,6)	Ref		Ref	

Abbreviations: OR= Odds Ratio; AOR= adjusted Odds Ratio; CI=Confidence Interval; Ref=Reference group

^a The single variants do not sum up to the total number of cases and controls because of missing data

^b=adjusted for age at recruitment and sex

eTable 7. MC1R and melanoma risk (adjusted for age at recruitment, sex, sunburns 0-20 years and facial actinic skin damage)

Variable		OR (95% CI)	P Value
MC1R	R/R	1,65 (1,02-2,67)	0,04
	R/r	2,63 (1,82-3,81)	<0,001
	R/0	1,83 (1,36-2,48)	<0,001
	r/r	1,50 (1,01-2,21)	0,04
	r/0	1,26 (0,97-1,64)	0,08
	0/0	Ref	
Age	at recruitment	1,01 (1,0-1,02)	0,2
Sex	female	0,93 (0,76-1,14)	0,51
	male	Ref	
Sunburns (0-20y)	≥ 10	1,97 (1,54-2,52)	<0,001
	1-9	1,15 (0,88-1,49)	0,31
	0	Ref	
Freckling Face	++,+++	0,78 (0,54-1,11)	0,17
	+	0,91 (0,66-1,25)	0,55
	0	Ref	
Wrinkling Face	++,+++	1,18 (0,78-1,79)	0,43
	+	1,37 (0,97-1,94)	0,08
	0	Ref	
Solar Lentigo Face	++,+++	1,80 (1,27-2,55)	0,001
	+	2,33 (1,79-3,04)	<0,001
	0	Ref	

Abbreviations: AOR= adjusted Odds Ratio; CI=Confidence Interval; Ref=Reference group

eTable 8. MC1R and melanoma risk (adjusted for age at recruitment, sex, sunburns 0-20 years and actinic skin damage on the back/neck)

Variable		OR (95 % CI)	P Value
MC1R	R/R	1,25 (0,77-2,04)	0,37
	R/r	2,36 (1,62-3,43)	<0,001
	R/0	1,47 (1,08-1,99)	0,01
	r/r	1,36 (0,92-2,02)	0,13
	r/0	1,13 (0,87-1,47)	0,36
	0/0	Ref	
Age	at recruitment	0,99 (0,98-1)	0,02
Sex	female	1,11 (0,89-1,37)	0,35
	male	Ref	
Sunburns (0-20y)	≥ 10	1,65 (1,28-2,13)	<0,001
	1-9	1,10 (0,84-1,44)	0,48
	0	Ref	
Freckling Back	++,+++	1,27 (0,88-1,85)	0,2
	+	1,21 (0,87-1,67)	0,26
	0	Ref	
Wrinkling Neck	++,+++	2,51 (1,75-3,62)	<0,001
	+	1,73 (1,29-2,31)	<0,001
	0	Ref	
Solar Lentigo Back	++,+++	2,50 (1,76-3,54)	<0,001
	+	1,87 (1,39-2,53)	<0,001
	0	Ref	

Abbreviations: AOR= adjusted Odds Ratio; CI=Confidence Interval; Ref=Reference group

eTable 9. MC1R and melanoma risk (adjusted for age at recruitment, sex, sunburns 0-20 years and actinic skin damage on hands)

Variable		OR (95 % CI)	P Value
MC1R	R/R	1,45 (0,89-2,34)	0,13
	R/r	2,54 (1,76-3,67)	0,000
	R/0	1,75 (1,3-2,36)	0,000
	r/r	1,50 (1,02-2,2)	0,04
	r/0	1,26 (0,97-1,62)	0,08
	0/0	Ref	
Age	at recruitment	1,00 (0,99-1,01)	0,87
Sex	female	0,86 (0,71-1,06)	0,15
	male	Ref	
Sunburns (0-20y)	≥ 10	1,91 (1,49-2,45)	0,000
	1-9	1,12 (0,86-1,45)	0,4
	0	Ref	
Freckling Hand	++,+++	1,19 (0,81-1,75)	0,38
	+	1,09 (0,84-1,41)	0,51
	0	Ref	
Solar Lentigo Hand	++,+++	2,15 (1,47-3,15)	0,000
	+	1,62 (1,21-2,16)	0,001
	0	Ref	

Abbreviations: AOR= adjusted Odds Ratio; CI=Confidence Interval; Ref=Reference group