Table 1. Descriptive characteristics of study population

	Children/adolescent cases (N=233)	Adult cases (N=932)	p-value [a]	Adult controls (N=932)	p-value [a]
Sex (N, %)			**0.03**		**0.0003**
Males	95 (41)	456 (49)		500 (54)	
Females	138 (59)	475 (51)		426 (46)	
Breslow thickness (mm; median, IQR)	0.93 (0.50-2.10)	1.00 (0.50-2.40)	0.16	-	-
Common melanocytic nevi (count; median, IQR)	30 (15-64)	25 (10-45)	**0.0007**	21 (5-30)	**<0.0001**
Any atypical melanocytic nevi (N, %)	49 (43)	165 (30)	**0.01**	46 (9)	**<0.0001**
Melanoma body site (N, %)			**0.037**		**-**
Head/neck	27 (12)	127 (16)		-	
Trunk	91 (41)	313 (39)		-	
Upper limbs	11 (5)	90 (11)		-	
Lower limbs	75 (34)	236 (29)		-	
NOC[b]	18 (8)	42 (5)		-	
Histolopathogical subtype (N, %)			**<0.0001**		**-**
LMM	0 (0)	50 (7)		-	
NM	33 (17)	127 (18)		-	
SSM	124 (63)	493 (69)		-	
ALM	7 (3)	39 (5)		-	
Spitzoid	13 (7)	2 (0)		-	
Others[c]	21 (11)	8 (1)		-	
Hair color (N, %)			0.73		**0.0003**
Red	14 (7)	55 (6)		24 (3)	
Blonde	60 (28)	216 (24)		129 (18)	
Brown	139 (65)	609 (68)		535 (76)	
NOC[b]	0 (0)	15 (2)		21 (3)	
Eye color (N, %)			**0.01**		**<0.0001**
Blue	65 (36)	420 (50)		330 (47)	
Brown	77 (42)	314 (37)		364 (51)	
Black	2 (1)	2 (0)		5 (1)	
Green, gray, hazel	5 (3)	0 (0)		0 (0)	
NOC[b]	32 (18)	109 (13)		10 (1)	
Skin type (N, %)			0.67		**0.015**
I	16 (8)	59 (7)		26 (4)	
II	68 (33)	320 (36)		191 (28)	
III	94 (44)	400 (45)		378 (55)	
IV	32 (15)	59 (13)		87 (13)	
Any solar lentigines (N, %)	15 (15)	321 (75)	**<0.0001**	203 (68)	**<0.0001**

ALM: Acral lentiginous melanoma. IQR: interquartile range; LMM: Lentigo maligna melanoma; NM: Nodular melanoma; SSM: Superficial spreading melanoma

Note: significant p-values are in bold

[a] Logistic regression model, adjusted by matching stratum variable;

[b] NOC, not otherwise classifiable. This group includes patients with doubtful or mixed information, thus, not classifiable.

[c] Among children/adolescents: N=4 nevoid, N=3 epithelioid, N=1 desmoplastic, N=13 others not specified; among adults: N=5 epithelioid, N=1 nevoid, N=1 desmoplastic, N=1 others not specified

Table 2. Association between *MC1R* variants and childhood/adolescent melanoma in the whole group of studied cases (N=233) and in the subgroup of cases with a confirmed melanoma diagnosis after centralized slide review (N=64). For each group of children/adolescents, study/geographical frequency matched adult cases and unaffected controls were used as comparison groups.

	All studied children/adolescent cases					Children/adolescent cases with centralized confirmed melanoma diagnosis				
	N=233 children/adolescent cases (%)	N=932 adult cases (%)	p-value[a]	N=932 adult controls (%)	p-value[a]	N=64 children/adolescents cases (%)	N=256 adult cases (%)	p-value[a]	N=256 adult controls (%)	p-value[a]
Any *MC1R* variants	173 (75)	662 (71)	0.33	550 (59)	**<0.0001**	46 (72)	193 (75)	0.56	145 (57)	**0.03**
Any R variants	86 (37)	350 (38)	0.86	238 (26)	**0.0006**	24 (37)	102 (40)	0.73	58 (23)	**0.016**
Any r variants	115 (49)	420 (45)	0.24	370 (40)	**0.008**	29 (45)	115 (45)	0.95	102 (40)	0.43
Score			0.85		**<0.0001**			0.38		**0.003**
0	60 (26)	270 (29)		382 (41)		18 (28)	63 (25)		111 (43)	
1	71 (31)	260 (28)		261 (28)		16 (25)	70 (27)		77 (30)	
2	64 (27)	227 (24)		201 (22)		20 (31)	72 (28)		47 (19)	
3	28 (12)	106 (11)		57 (6)		7 (11)	24 (9)		15 (6)	
≥4	10 (4)	69 (8)		31 (3)		3 (5)	27 (11)		6 (2)	
Any V60L variants	77 (33)	270 (29)	0.22	251 (27)	0.06	24 (37)	82 (32)	0.40	70 (27)	0.11
Any D84E variants	3 (1)	14 (2)	0.81	7 (1)	0.43	1 (2)	3 (1)	0.80	1 (0)	0.32
Any V92M variants	30 (13)	115 (12)	0.82	115 (12)	0.83	9 (14)	25 (10)	0.32	29 (11)	0.55
Any R142H variants	7 (3)	34 (4)	0.63	22 (2)	0.57	0 (0)	12 (5)	0.98	11 (4)	0.98
Any R151C variants	30 (13)	142 (15)	0.36	91 (10)	0.17	11 (17)	45 (18)	0.94	23 (9)	0.06
Any I155T variants	4 (2)	18 (2)	0.83	15 (2)	0.91	1 (2)	5 (2)	0.84	2 (1)	0.57
Any R160W variants	21 (9)	93 (10)	0.66	63 (7)	0.23	7 (11)	29 (11)	0.92	15 (6)	0.16
Any R163Q variants	13 (6)	59 (3)	0.67	34 (4)	0.18	0 (0)	17 (7)	0.97	7 (3)	0.98
Any D294H variants	19 (8)	54 (6)	0.18	37 (4)	**0.009**	4 (6)	17 (7)	0.91	8 (3)	0.25

Note: significant p-values are in bold

[a] Logistic regression model, adjusted by matching stratum variable;

MC1R, melanocortin-1 receptor.

R variants include D84E, R142H, R151C, I155T, R160W, D294H and other rare variants classified as R according to the algorithm proposed by Davies et al (2012).[34]

r variants include V60L, V92M, R163Q and other rare variants classified as r according to the algorithm proposed by Davies et al (2012).[34]

Table 3. Subgroup analysis by age at diagnosis

	Children/adolescent cases ≤18 years (N=148)		Children/adolescent cases ≤14 years (N=52)	
	N children-adolescent/ N adult cases	OR [a] (95% CI)	N children-adolescent/ N adult cases	OR [a] (95% CI)
Any variants	148/592	1.45 (0.89; 2.34)	52/208	1.86 (0.69; 5.03)
Any R variants	73/330	0.99 (0.52; 1.89)	27/115	1.63 (0.42; 6.36)
Any r variants	98/374	**1.80 (1.06; 3.07)**	35/142	2.27 (0.76; 6.83)
Any V60L variants	88/357	1.59 (0.91; 2.76)	31/136	2.27 (0.76; 6.80)
Any D84E variants	43/192	0.97 (0.13; 6.99)	15/73	Not calculated
Any V92M variants	61/253	1.62 (0.79; 3.33)	18/93	0.95 (0.11; 7.97)
Any R142H variants	45/201	1.32 (0.34; 5.13)	13/80	Not calculated
Any R151C variants	56/277	0.82 (0.38; 1.80)	18/97	0.61 (0.10; 3.88)
Any I155T variants	43/192	1.13 (0.17; 7.64)	15/71	Not calculated
Any R160W variants	55/234	1.08 (0.45; 2.58)	21/87	3.57 (0.62; 20.52)
Any R163Q variants	51/219	1.61 (0.61; 4.22)	16/84	0.68 (0.03; 14.81)
Any D294H variants	52/272	1.47 (0.58; 3.70)	14/86	Not calculated

MC1R, melanocortin-1 receptor; CI, Confidence Intervals; OR, Odds Ratio. R variants include the D84E, R142H, R151C, I155T, R160W, D294H and other rare variants classified as R according to the algorithm proposed by Davies et al (2012); r variants include the V60L, V92M, R163Q and other rare variants classified as r according to the algorithm proposed by Davies et al (2012).[34]

Significant p-values are in bold.

[a] ORs adjusted by, sex, matching stratum variable, melanoma body site and histological subtype, and skin type. Hair color was not included because of more than 30% of missing data for these groups of patients. For each OR, the comparison group included 4:1 frequency matched adult cases by study/geographical area. The reference category for OR were *MC1R* wild-type (WT) subjects. Number of children and adults reported here are the total number of subjects included in each analysis, independently by *MC1R* status. Note that for the analysis on each variant vs WT, subjects carrying only other *MC1R* variants were excluded.