

Table SI. Characteristics associated to CDKN2A⁺ familial melanoma vs. sporadic melanoma

	Familial melanoma CDKN2A ⁺ vs. sporadic melanoma		
	Univariate		
	OR	95% CI	p-value
Sex			
Man	Ref.	Ref.	0.059
Woman	3.0	1.0–9.3	
Age at diagnosis			
≤ 50 years	3.5	1.2–10.2	0.020
> 50 years	Ref.	Ref.	
Eye colour			
Dark (brown/black)	Ref.	Ref.	0.099
Fair (blue/green)	0.4	0.1–1.2	
Hair colour			
Black/brown	Ref.	Ref.	0.655
Blonde	1.6	0.5–5.0	
Red	1.9	0.2–15.3	
Phototype			
I–II	1.1	0.4–3.0	0.880
III–V	Ref.	Ref.	
Lifetime severe sunburns			
≤ 5	Ref.	Ref.	0.996
> 5	1.0	0.3–3.5	
Outdoor worker			
No	Ref.	Ref.	0.989
Yes	1.0	0.3–3.1	
Freckling in childhood			
No	Ref.	Ref.	0.496
Yes	1.5	0.5–4.7	
Solar lentigines			
No	Ref.	Ref.	0.116
Yes	0.4	0.1–1.3	
Solar lentigines at melanoma site			
No	Ref.	Ref.	0.190
Yes	0.5	0.2–1.4	
Actinic keratosis			
No	Ref.	Ref.	0.819
Yes	0.8	0.2–3.6	
Second non-cutaneous neoplasia			
No	Ref.	Ref.	0.393
Yes	1.7	0.5–6.2	
Personal history of basal cell carcinoma			
No	Ref.	Ref.	0.072
Yes	3.2	0.9–11.5	
Personal history of squamous cell carcinoma			
No	N.C.	N.C.	N.C.
Yes	N.C.	N.C.	N.C.
Common melanocytic naevi			
< 20	Ref.	Ref.	0.007
≥ 20	4.1	1.5–11.4	
Atypical melanocytic naevus			
No	Ref.	Ref.	0.001
Yes	6.2	2.2–17.6	
Multiple primary melanomas			
No	Ref.	Ref.	<0.001
Yes	18.2	6.5–50.6	
Family history of pancreatic cancer			
No	Ref.	Ref.	0.443
Yes	2.2	0.3–17.3	
Family history of cancer			
No	Ref.	Ref.	0.977
Yes	1.0	0.4–2.7	
Site of first primary melanoma			
Head/neck	Ref.	Ref.	0.368
Upper extremity (hand excluded)	1.5	0.2–10.7	
Trunk	2.9	0.6–13.1	
Lower extremity (foot excluded)	0.5	0.1–5.9	
Acral (hand/foot)	1.3	0.1–14.2	
Stage at diagnosis			
<i>In situ</i>	Ref.	Ref.	0.740
Localized disease (stage I/II)	3.0	0.4–22.8	
Locoregional (stage III)	2.0	0.2–22.5	
Distant metastases (stage IV)	N.C.	N.C.	
Histological type			
Lentigo maligno melanoma	Ref.	Ref.	0.638
Superficial spreading melanoma	2.5	0.3–19.4	
Nodular melanoma	0.6	0.0–9.7	
Acral lentiginous melanoma	2.4	0.2–39.7	
Other/non-specified	N.C.	N.C.	
Solar elastosis			
No	N.C.	N.C.	N.C.
Yes	N.C.	N.C.	N.C.
R variants in MC1R			
No	Ref.	Ref.	0.932
Yes	1.0	0.3–3.0	

Ref.: reference category; N.C.: not calculable.

Table SII. Characteristics associated to familial melanoma *CDKN2A*⁺ vs. sporadic melanoma

	Familial melanoma <i>CDKN2A</i> ⁺ vs. sporadic melanoma		
	Univariate		
	OR	95% CI	p-value
Sex			
Man	Ref.	Ref.	0.022
Woman	1.7	1.1–2.6	
Age at diagnosis			
≤ 50 years	2.3	1.5–3.6	<0.001
> 50 years	Ref.	Ref.	
Eye colour			
Dark (brown/black)	Ref.	Ref.	0.675
Fair (blue/green)	1.1	0.7–1.7	
Hair colour			
Black/brown	Ref.	Ref.	0.009
Blonde	1.7	1.0–2.8	
Red	2.9	1.3–6.4	
Phototype			
I–II	1.1	0.7–1.7	0.688
III–V	Ref.	Ref.	
Lifetime severe sunburns			
≤ 5	Ref.	Ref.	0.426
> 5	1.2	0.7–2.1	
Outdoor worker			
No	1.9	1.1–3.4	0.030
Yes	Ref.	Ref.	
Freckling in childhood			
No	Ref.	Ref.	0.040
Yes	1.6	1.0–2.6	
Solar lentigines			
No	Ref.	Ref.	0.249
Yes	0.7	0.4–1.3	
Solar lentigines at melanoma site			
No	Ref.	Ref.	0.584
Yes	0.9	0.6–1.4	
Actinic keratosis			
No	Ref.	Ref.	0.050
Yes	0.4	0.2–1.0	
Second non-cutaneous neoplasia			
No	Ref.	Ref.	0.467
Yes	1.3	0.7–2.3	
Personal history of BCC			
No	Ref.	Ref.	0.406
Yes	0.7	0.2–1.8	
Personal history of SCC			
No	Ref.	Ref.	0.002
Yes	4.4	1.8–11.2	
Common melanocytic naevi			
< 20	Ref.	Ref.	0.001
≥ 20	2.2	1.4–3.3	
Atypical melanocytic naevus			
No	Ref.	Ref.	<0.001
Yes	2.8	1.8–4.5	
Multiple primary melanomas			
No	Ref.	Ref.	0.012
Yes	2.6	1.2–5.4	
Family history of pancreatic cancer			
No	Ref.	Ref.	0.422
Yes	1.5	0.5–4.4	
Family history of cancer			
No	Ref.	Ref.	0.920
Yes	1.0	0.6–1.5	
Site of first primary melanoma			
Head/neck	Ref.	Ref.	0.001
Upper extremity (hand excluded)	3.0	1.1–8.1	
Trunk	5.1	2.2–12.1	
Lower extremity (foot excluded)	2.7	1.0–6.9	
Acral (hand/foot)	1.7	0.5–6.2	
Stage at diagnosis			
<i>In situ</i>	Ref.	Ref.	0.143
Localized disease (stage I/II)	0.6	0.3–0.9	
Locoregional (stage III)	0.5	0.2–1.1	
Distant metastases (stage IV)	N.C.	N.C.	
Histological type			
Lentigo maligno melanoma	Ref.	Ref.	0.014
Superficial spreading melanoma	2.3	1.0–5.3	
Nodular melanoma	0.7	0.2–2.1	
Acral lentiginous melanoma	0.8	0.2–4.2	
Other/non-specified	2.0	0.6–6.4	
Solar elastosis			
No	Ref.	Ref.	0.137
Yes	0.3	0.1–1.4	
R variants in MC1R			
No	Ref.	Ref.	0.821
Yes	0.9	0.6–1.6	

Ref.: reference category; N.C.: not calculable; BCC: basal cell carcinoma; SCC: squamous cell carcinoma.

Table SIII. Characteristics associated to *CDKN2A*⁺ vs. *CDKN2A*⁻ familial melanomas

	Familial melanoma <i>CDKN2A</i> ⁺ vs. familial melanoma <i>CDKN2A</i> ⁻		
	Univariate		OR
	OR	95% CI	
Sex			
Man	Ref.		
Woman	1.8	0.5–6.0	0.345
Age at diagnosis			
≤ 50 years	3.1	1.1–9.3	
> 50 years	Ref.	Ref.	0.040
Eye colour			
Dark (brown/black)	Ref.		
Fair (blue/green)	0.3	0.1–1.2	0.088
Hair colour			
Black/brown	Ref.		
Blonde	0.9	0.3–3.2	0.936
Red	0.7	0.1–5.9	
Phototype			
I–II	1.0	0.3–3.0	
III–V	Ref.	Ref.	0.983
Lifetime severe sunburns			
≤ 5	1.2	0.3–4.8	
> 5	Ref.	Ref.	0.757
Outdoor worker			
No	0.5	0.2–1.9	
Yes	Ref.	Ref.	0.317
Freckling in childhood			
No	Ref.		
Yes	0.9	0.3–3.1	0.880
Solar lentigines			
No	Ref.		
Yes	0.6	0.2–2.0	0.381
Solar lentigines at melanoma site			
No	Ref.		
Yes	0.6	0.2–1.7	0.308
Actinic keratosis			
No	Ref.		
Yes	1.9	0.4–10.4	0.457
Second non-cutaneous neoplasia			
No	Ref.		
Yes	1.4	0.3–5.5	0.659
Personal history of BCC			
No	Ref.		
Yes	5.0	1.0–24.7	0.051
Personal history of SCC			
No	N.C.	N.C.	N.C.
Yes			
Common melanocytic naevi			
< 20	Ref.		
≥ 20	2.9	0.9–9.3	0.069
Atypical melanocytic naevus			
No	Ref.		
Yes	2.2	0.7–6.8	0.167
Multiple primary melanomas			
No	Ref.		
Yes	7.1	2.1–23.6	0.001
Family history of pancreatic cancer			
No	Ref.		
Yes	1.5	0.2–13.9	0.747
Family history of cancer			
No	Ref.		
Yes	1.0	0.4–3.0	0.947
Site of first primary melanoma			
Head/neck	Ref.		
Upper extremity (hand excluded)	0.5	0.1–4.5	
Trunk	0.6	0.1–3.2	
Lower extremity (foot excluded)	0.2	0.1–2.6	
Acral (hand/foot)	0.8	0.1–11.3	
Stage at diagnosis			
<i>In situ</i>	Ref.		
Localized disease (stage I/II)	5.3	0.7–43.0	
Locoregional (stage III)	4.0	0.3–49.1	
Distant metastases (stage IV)	–	–	
Histological type			
Lentigo maligno melanoma	Ref.		
Superficial spreading melanoma	1.1	0.1–10.0	0.949
Nodular melanoma	0.9	0.0–16.9	
Acral lentiginous melanoma	3.0	0.1–73.6	
Other/non-specified	N.C.	N.C.	
Solar elastosis			
No	N.C.	N.C.	N.C.
Yes			
R variants in <i>MC1R</i>			
No	Ref.		
Yes	1.0	0.3–3.5	0.990

Ref.: reference category; N.C.: not calculable; BCC: basal cell carcinoma; SCC: squamous cell carcinoma; RHC: red hair colour.

Table SIV. Distribution of characteristics by subgroups defined by the presence/absence of R variants in MC1R

	Sporadic melanoma (n = 1,150)		Familial melanoma (n = 98)			
	Non-R (n = 832) n (%)	R (n = 318) n (%)	CDKN2A ⁻ (n = 83)		CDKN2A ⁺ (n = 15)	
			Non-R (n = 61)	R (n = 22)	Non-R (n = 11)	R (n = 4)
Sex						
Man	409 (49.2)	157 (49.4)	26 (42.6)	5 (22.7)	3 (27.3)	1 (25.0)
Woman	423 (50.8)	161 (50.6)	35 (57.4)	17 (77.3)	8 (72.7)	3 (75.0)
Age at diagnosis						
≤ 50 years	116 (13.9)	44 (13.8)	11 (18.0)	7 (31.8)	5 (45.5)	2 (50.0)
> 50 years	716 (86.1)	274 (86.2)	50 (82.0)	15 (68.2)	6 (54.5)	2 (50.0)
Eye colour						
Dark (brown/black)	504 (61.1)	192 (60.8)	33 (55.0)	13 (59.1)	9 (75.0)	3 (75.0)
Fair (blue/green)	321 (38.9)	124 (39.2)	27 (45.0)	9 (40.9)	2 (25.0)	1 (25.0)
Hair colour						
Black/brown	678 (82.2)	209 (66.3)	43 (71.7)	10 (45.5)	9 (81.8)	1 (25.0)
Blonde	144 (17.5)	63 (20.0)	16 (26.7)	6 (27.3)	1 (9.1)	3 (75.0)
Red	3 (0.4)	43 (13.7)	1 (1.7)	6 (27.3)	1 (9.1)	0 (0)
Phototype						
I-II	252 (30.7)	154 (49.0)	18 (30.0)	12 (54.5)	2 (18.2)	4 (100)
III-V	570 (69.3)	160 (51.0)	42 (70.0)	10 (45.5)	9 (81.8)	0 (0)
Lifetime severe sunburns						
≤ 5	671 (82.3)	231 (73.8)	51 (85.0)	15 (68.2)	9 (81.8)	3 (75.0)
> 5	144 (17.7)	82 (26.2)	9 (15.0)	7 (31.8)	2 (18.2)	1 (25.0)
Outdoor worker						
No	616 (75.2)	219 (70.6)	51 (83.6)	17 (81.0)	8 (72.7)	3 (75.0)
Yes	203 (24.8)	91 (29.4)	10 (16.4)	4 (19.0)	3 (27.3)	1 (25.0)
Freckling in childhood						
No	518 (74.3)	127 (48.3)	33 (63.5)	8 (42.1)	5 (62.5)	2 (50)
Yes	179 (25.7)	136 (51.7)	19 (36.5)	11 (57.9)	3 (37.5)	2 (50)
Solar lentigines						
No	118 (14.7)	23 (7.4)	8 (13.3)	5 (22.7)	3 (27.3)	0 (0)
Yes	685 (85.3)	289 (92.6)	52 (86.7)	17 (77.3)	8 (72.7)	4 (100)
Solar lentigines at melanoma site						
No	447 (55.1)	119 (38.5)	34 (55.7)	10 (45.5)	6 (60.0)	3 (75.0)
Yes	364 (44.9)	190 (61.5)	27 (44.3)	12 (54.5)	4 (40.0)	1 (25.0)
Actinic keratosis						
No	686 (86.5)	260 (85.0)	59 (98.3)	17 (77.3)	10 (90.9)	3 (75.0)
Yes	107 (13.5)	46 (15.0)	1 (1.7)	5 (22.7)	1 (9.1)	1 (25.0)
Second non-cutaneous neoplasia						
No	738 (88.8)	279 (87.7)	50 (82.0)	20 (90.9)	9 (81.8)	3 (75.0)
Yes	93 (11.2)	39 (12.3)	11 (18.0)	2 (9.1)	2 (18.2)	1 (25.0)
Personal history of basal cell carcinoma						
No	782 (94.0)	293 (92.1)	59 (96.7)	21 (95.5)	9 (81.8)	3 (75.0)
Yes	50 (6.0)	25 (7.9)	2 (3.3)	1 (4.5)	2 (18.2)	1 (25.0)
Personal history of squamous cell carcinoma						
No	824 (99.0)	310 (97.5)	58 (95.1)	19 (86.4)	11 (100)	4 (100)
Yes	8 (1.0)	8 (2.5)	3 (4.9)	3 (13.6)	0 (0)	0 (0)
Common melanocytic naevi						
< 20	707 (88.8)	241 (79.0)	51 (85.0)	18 (81.8)	8 (72.7)	2 (50.0)
≥ 20	89 (11.2)	64 (21.0)	9 (15.0)	4 (18.2)	3 (27.3)	2 (50.0)
Atypical melanocytic naevus						
No	661 (81.0)	235 (75.3)	36 (60.0)	12 (54.5)	4 (36.4)	2 (50.0)
Yes	155 (19.0)	77 (24.7)	24 (40.0)	10 (45.5)	7 (63.6)	2 (50.0)
Multiple primary melanomas						
No	798 (95.9)	301 (94.7)	55 (90.2)	19 (86.4)	6 (54.5)	3 (75.0)
Yes	34 (4.1)	17 (5.3)	6 (9.8)	3 (13.6)	5 (45.5)	1 (25.0)
Family history of pancreatic cancer						
No	802 (96.7)	308 (97.5)	58 (95.1)	21 (95.5)	11 (100)	4 (100)
Yes	27 (3.3)	8 (2.5)	3 (4.9)	1 (4.5)	0 (0)	0 (0)
Family history of cancer						
No	458 (55.2)	177 (56.0)	35 (57.4)	12 (54.5)	5 (45.5)	3 (75.0)
Yes	371 (44.8)	139 (44.0)	26 (42.6)	10 (45.5)	6 (54.5)	1 (25.0)