



Characteristics of Familial Melanoma in Valencia, Spain, Based on the Presence of *CDKN2A* Mutations and *MC1R* Variants

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Melanoma results from a complex interplay between environmental factors and individual genetic susceptibility. Familial melanoma is attributable to predisposition genes with variable penetrance. The aim of this study was to identify differences between familial melanoma and sporadic cases in our population, based on the presence of *CDKN2A* mutations and *MC1R* variants. Comparing 107 patients with familial melanoma from 87 families (17% *CDKN2A* mutated) with 1,390 cases of sporadic melanomas, the former were younger and exhibited an increased prevalence of atypical naevi and squamous cell carcinoma (SCC). *CDKN2A* mutation carriers presented more atypical naevi, multiple melanomas, and basal cell carcinoma, while non-carriers were more likely to have light-coloured hair, atypical naevi, and SCC. *MC1R* variants decreased the age at diagnosis in all groups and were associated with an increased prevalence of SCC, especially in patients with familial melanoma without *CDKN2A* mutations. These characteristics may help to establish prevention measures targeting patients with familial melanoma in the Mediterranean area.

Key words: cutaneous malignant melanoma; genetic susceptibility; risk factors; *CDKN2A*; *MC1R*.

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Melanoma is an increasingly common and potentially deadly cancer that develops through interactions between environmental factors, mainly ultraviolet (UV) radiation, and genetically determined phenotypic characteristics (1–8). Numerous low-to-moderate penetrance genes found in a relatively high proportion of the general population contribute to the genetic risk of developing melanoma, and sporadic melanoma in particular. These genes are involved in skin pigmentation (*MC1R*, *ASIP*, *OCA2*, *Tyrp1*, *TYR*, *SCL45A2* and *MITF*), number of naevi (9p21, 22q13 and 6p25-p23) (9, 10), immune response (*IFNWI* and *IL6R*), DNA repair (*XRCC3*) and vitamin D metabolism (*GC* and *VDR*) (11–13). Numerous high-penetrance gene mutations (*CDKN2A*, *CDK4*,

MITF, *BAP1*, *TERT* promoter and *POT1* mutations) are also mainly associated with cases of multiple or familial melanoma (5, 14–17).

Given that familial melanoma is associated with an increased genetic load compared with sporadic melanoma, one can assume that environmental factors play a smaller role in its aetiology and pathogenesis. The aetiopathogenic pathways involved in both conditions can be modified by low-penetrance genes, resulting in different gene expression patterns associated with particular clinical and pathological phenotypes.

The main aim of this study was to characterize familial melanoma according to the presence or absence of both *CDKN2A* mutations and *MC1R* variants. A secondary aim was to investigate differences among familial melanoma, subgroups of familial melanoma, and sporadic melanoma.

PATIENTS AND METHODS

A retrospective, cross-sectional, descriptive, analytical, epidemiological, case-case study was performed of melanoma cases from the cutaneous melanoma database at the Instituto Valenciano de Oncología, which is the reference centre for the genetic assessment of familial melanoma in the Community of Valencia, Spain. The study was approved by the ethics committee of the institute. Data analysed were obtained from 1 January 2000 to 23 November 2014.

The database contains information on patients who received definitive treatment at the centre, and patients with melanoma referred for genetic testing due to a family history of melanoma.

The present study excluded patients with extracutaneous melanomas, melanomas of unknown primary origin, and those with a family history of melanoma who had not undergone genetic testing.

Patients were initially classified into 2 groups: sporadic melanoma and familial melanoma. Familial melanoma was defined as a case in which at least 2 first- or second-degree relatives had a diagnosis of melanoma. This group was further divided into 2 groups according to the presence or absence of a germline *CDKN2A* mutation. The following variables were compared between groups: (i) demographic variables: age (≤ 50 vs. > 50 years) and sex (male vs. female). (ii) Skin phenotype: skin phototype (I–II vs. III–V), freckles in childhood (yes vs. no), solar lentigines (yes vs. no), actinic keratosis (yes vs. no), number of common melanocytic naevi (< 20 , 20–50 vs. 50–100, > 100), and presence of ≥ 1 clinically atypical melanocytic naevus (yes vs. no). (iii) Environmental exposure: personal history of severe sunburn (no, 1–5 episodes vs. 6–10, > 10) and job involving sun exposure (yes vs. no). (iv) Personal and family history (first- or second-degree

relative) of cancer: multiple melanoma (yes vs. no), second non-cutaneous malignancy (yes vs. no), basal cell carcinoma (BCC) (yes vs. no), squamous cell carcinoma (SCC) (yes vs. no), and pancreatic cancer (yes vs. no). (v) Clinical and histological characterization of melanoma: lentiginos in the area of melanoma (yes vs. no), location (head/neck, upper extremities, trunk, lower extremities, or acral site [hands and feet]), stage (*in situ*, localized, locoregional, or distant metastasis), histological subtype (lentigo maligna melanoma, superficial spreading melanoma (SSM), nodular melanoma, acral lentiginous melanoma, or other/unclassified), and solar elastosis in healthy perilesional skin (yes vs. no). (vi) Genotype: presence vs. absence of *CDKN2A* mutations for patients with family melanoma and *MC1R* variants for all patients. In the second case, we only considered some of the common variants associated with red hair colour (R variants), namely, p.D84E, p.D294H, p.R151C, p.R142H and p.R160W.

The 3 groups (sporadic melanoma and familial melanoma with and without *CDKN2A* mutations) were compared using contingency tables with analysis of distribution of variables and between-group differences using the Pearson χ^2 test. Associations between variables in the between-group comparisons were quantified by univariate and multivariate logistic regression analyses. For the

multivariate analysis, missing values were handled by multiple imputation with 5 iterations and calculation of combined estimates and standard errors using Rubin's rules. A *p*-value <0.05 was considered statistically significant.

Statistical analysis was performed using SPSS, version 20.0 (IBM SPSS Statistics, Illinois, USA).

RESULTS

Of the 2,092 cases of melanoma in the database, 1,497 met the inclusion criteria. In total, 731 of the patients were men (48.8%) and 766 were women (51.2%). The median age at diagnosis of the first melanoma for the whole population was 56 years (interquartile range 43–69 years).

For the subgroup analyses, there were 1,390 patients (92.8%) in the sporadic melanoma group and 107 patients (7.1%) from 87 families in the familial melanoma group (Table I). In total, 15 of the families (17.2%) had

Table I. Characteristics of the studied population

	Familial (n = 107)			p-value*
	Sporadic (n = 1,390) n (%)	CDKN2A+ (n = 16) n (%)	CDKN2A- (n = 91) n (%)	
Sex				
Man	693 (49.9)	4 (25)	34 (37.4)	0.011
Woman	697 (50.1)	12 (75)	57 (62.6)	
Age				
≤ 50 years	534 (38.4)	11 (68.8)	54 (59.3)	<0.001
> 50 years	856 (61.6)	5 (31.2)	37 (40.7)	
Eye colour (missing: 80)				
Dark (brown/black)	818 (60.0)	13 (81.2)	52 (57.8)	0.203
Fair (blue/green)	545 (40.0)	3 (18.8)	38 (42.2)	
Hair colour (missing: 84)				
Black/brown	1,062 (78.1)	11 (68.8)	59 (65.6)	0.032
Blonde	247 (18.2)	4 (25.0)	23 (25.6)	
Red	50 (3.7)	1 (6.2)	8 (8.9)	
Phototype (missing: 29)				
I	42 (3.1)	0 (0)	7 (7.8)	0.264
II	444 (32.6)	6 (37.5)	27 (30.0)	
III	502 (36.9)	7 (43.8)	39 (41.1)	
IV	347 (25.5)	3 (18.8)	19 (21.1)	
V	27 (2.0)	0 (0)	0 (0)	
Lifetime severe sunburns (missing: 41)				
No	656 (48.6)	7 (43.8)	31 (34.4)	0.243
1–5	440 (32.6)	6 (37.5)	39 (43.3)	
6–10	116 (8.6)	2 (12.5)	8 (8.9)	
> 10	138 (10.2)	1 (6.2)	12 (13.3)	
Outdoor worker (missing: 74)				
No	970 (73.5)	11 (73.3)	74 (84.1)	0.089
Yes	350 (26.5)	4 (26.7)	14 (15.9)	
Ephelides in childhood (missing: 328)				
No	732 (67.7)	7 (58.3)	42 (56.0)	0.096
Yes	350 (32.3)	5 (41.7)	33 (44.0)	
Solar lentiginos (missing: 84)				
No	154 (11.8)	4 (25.0)	14 (15.9)	0.148
Yes	1,155 (88.2)	12 (75.0)	74 (84.1)	
Solar lentiginos at melanoma site (missing: 77)				
No	650 (49.3)	10 (66.7)	45 (52.3)	0.358
Yes	669 (50.7)	5 (33.3)	41 (47.7)	
Actinic keratosis (missing: 129)				
No	1,078 (85.2)	14 (87.5)	80 (93.0)	0.128
Yes	188 (14.8)	2 (12.5)	6 (7.0)	
Personal history of non-cutaneous neoplasia (missing: 1)				
No	1,226 (88.3)	13 (81.2)	78 (85.7)	0.539
Yes	163 (11.7)	3 (18.8)	13 (14.3)	
Personal history of BCC (missing: 3)				
No	1,295 (93.3)	13 (81.2)	86 (95.6)	0.108
Yes	93 (6.7)	3 (18.8)	4 (4.4)	
Personal history of SCC (missing: 3)				
No	1,366 (98.4)	16 (100)	84 (93.3)	0.002
Yes	22 (1.6)	0 (0)	6 (6.7)	

	Familial (n = 107)			p-value*
	Sporadic (n = 1,390) n (%)	CDKN2A+ (n = 16) n (%)	CDKN2A- (n = 91) n (%)	
Common melanocytic naevi (missing: 165)				
<20	895 (71.1)	6 (37.5)	47 (53.4)	<0.001
20–50	189 (15.0)	4 (25.0)	26 (26)	
50–100	117 (9.3)	5 (31.2)	9 (10.2)	
>100	58 (4.6)	1 (6.2)	6 (6.8)	
Atypical naevus (missing: 61)				
No	1,077 (80.6)	6 (40.0)	50 (59.5)	<0.001
Yes	260 (19.4)	9 (60.0)	34 (40.5)	
Multiple melanoma				
No	1,333 (95.9)	9 (56.2)	82 (90.1)	<0.001
Yes	57 (4.1)	7 (43.8)	9 (9.9)	
Family history of pancreatic cancer (missing: 13)				
No	1,338 (97.1)	15 (93.8)	87 (95.6)	0.544
Yes	40 (2.9)	1 (6.2)	4 (4.4)	
Family history of cancer (missing: 11)				
No	780 (56.6)	9 (56.2)	52 (57.1)	0.994
Yes	598 (43.4)	7 (43.8)	39 (42.9)	
Melanoma site				
Head/neck	292 (21.0)	2 (12.5)	6 (6.6)	0.001
Upper extremities (excl. hands)	196 (14.1)	2 (12.5)	12 (13.2)	
Trunk	513 (36.9)	10 (62.5)	54 (59.3)	
Lower extremities (excl. feet)	275 (19.8)	1 (6.2)	15 (16.5)	
Acral	114 (8.2)	1 (6.2)	4 (4.4)	
Stage (missing: 16)				
<i>In situ</i>	215 (15.6)	1 (6.2)	22 (25.3)	0.249
Localized (I/II)	941 (68.3)	13 (81.2)	54 (62.1)	
Locoregional disease (III)	212 (15.4)	2 (12.5)	11 (12.6)	
Distant metastases (IV)	10 (0.7)	0 (0)	0 (0)	
Histological type				
LMM	159 (11.4)	1 (6.2)	6 (6.6)	0.026
SSM	822 (59.1)	13 (81.2)	70 (76.9)	
NM	265 (19.1)	1 (6.2)	7 (7.7)	
ALM	65 (4.7)	1 (6.2)	2 (2.2)	
Other/NOS	79 (5.7)	0 (0)	6 (6.6)	
Solar elastosis (missing: 690)				
No	650 (85.1)	7 (100)	34 (94.4)	0.162
Yes	114 (14.9)	0 (0)	2 (5.6)	
R variants in MC1R (missing: 249)				
No	832 (72.3)	11 (73.3)	61 (73.5)	0.972
Yes	318 (27.7)	4 (26.7)	22 (26.5)	

**p*-value by χ^2 of Pearson test for trend comparing the 3 groups (sporadic, familial/CDKN2A+, familial/CDKN2A-). BCC: basal cell carcinoma; SCC: squamous cell carcinoma; LMM: lentigo maligna melanoma; SSM: superficial spreading melanoma; NM: nodular melanoma; ALM: acral lentiginous melanoma.

a *CDKN2A* mutation. *CDKN2A* mutation was more frequent in families with more than 2 melanoma patients than with only 2 (38.5% vs. 13.5%; $p=0.025$) and was present in only 1 of 20 families in which the affected individuals had a second-degree of family relationship (Table II). Median age at diagnosis for sporadic, familial *CDKN2A*⁻ and familial *CDKN2A*⁺ cases was 57, 46, and 36.5 years, respectively.

Univariate logistic regression analyses in the between-groups comparisons are detailed in Tables SI–SIII¹.

In multivariate analysis, patients with familial melanoma differed significantly from those with sporadic melanomas in that they more commonly exhibited the following features: age at diagnosis ≤ 50 years, personal history of SCC, increased prevalence of atypical melanocytic naevus (Table III).

Comparing patients with familial melanoma according to the presence or absence of *CDKN2A* mutations, those harbouring a mutation developed melanoma at a significantly younger age and were more likely to have multiple melanomas and a personal history of BCC (Table III).

Compared with patients with sporadic melanoma, patients with familial melanoma and *CDKN2A* mutations were more likely to have atypical naevi, multiple melanomas and personal history of BCC (Table III). Although we were unable to determine the level of statistical association, it is worth noting that none of the patients with familial melanoma and *CDKN2A* mutations had solar elastosis in the skin surrounding the melanoma, whereas 14.5% of patients with sporadic melanoma did (Table I).

Compared with patients with sporadic melanoma, patients with familial melanoma without *CDKN2A* mutations were more likely to be women. These patients were more likely to have light-coloured hair (blonde or red), atypical naevi, a personal history of SCC, and melanomas on the trunk (Table III).

The presence of R variants in *MC1R* in patients with familial melanoma was more frequent in patients with a younger age of onset of melanoma, particularly in the

Table III. Multivariate logistic regression models comparing groups defined by familial/sporadic melanoma type and presence/absence of mutation in *CDKN2A*

	OR	95% CI OR	p-value
<i>Familial vs. sporadic melanoma</i>			
Age at diagnosis			
≤ 50 years	2.4	1.2–5.0	0.015
> 50 years	Ref.	Ref.	
Personal history of SCC			
No	Ref.	Ref.	<0.001
Yes	12.4	3.4–44.6	
Atypical melanocytic naevus			
No	Ref.	Ref.	0.002
Yes	3.0	1.5–6.0	
<i>Familial <i>CDKN2A</i>⁺ vs. sporadic</i>			
Personal history of BCC			
No	Ref.	Ref.	0.040
Yes	4.3	1.1–17.1	
Atypical melanocytic naevus			
No	Ref.	Ref.	0.025
Yes	3.7	1.2–11.3	
Multiple primary melanomas			
No	Ref.	Ref.	<0.001
Yes	9.2	2.8–29.5	
<i>Familial <i>CDKN2A</i>⁻ vs. sporadic</i>			
Sex			
Man	Ref.	Ref.	0.002
Woman	2.3	1.4–3.9	
Hair colour			
Black/brown	Ref.	Ref.	0.017
Blonde	1.9	1.1–3.3	
Red	2.7	1.1–6.8	
Personal history of SCC			
No	Ref.	Ref.	0.001
Yes	6.1	1.9–19.2	
Atypical melanocytic naevus			
No	Ref.	Ref.	0.001
Yes	2.5	1.5–4.1	
<i>Familial <i>CDKN2A</i>⁺ vs. Familial <i>CDKN2A</i>⁻</i>			
Age at diagnosis			
≤ 50 years	6.5	1.5–28.7	0.014
> 50 years	Ref.	Ref.	
Eye colour			
Dark (brown/black)	Ref.	Ref.	0.018
Fair (blue/green)	0.1	0.0–0.7	
Personal history of BCC			
No	Ref.	Ref.	0.004
Yes	17.7	2.5–126.8	
Multiple primary melanomas			
No	Ref.	Ref.	0.001
Yes	15.4	3.2–74.4	

OR: odds ratio; CI: confidence interval; SCC: squamous cell carcinoma; BCC: basal cell carcinoma.

case of *CDKN2A* non-carriers. Patients with sporadic melanoma and R variants exhibited increased rates of a personal history of severe sunburn, solar lentigines, SCC, and multiple melanomas and were also more likely to have atypical naevi, >50 common melanocytic naevi, and typical pigmentary phenotypic characteristics, such as light-coloured hair and freckles in childhood (Table SIV¹).

DISCUSSION

This analysis of 1,497 patients with cutaneous melanoma, including 107 cases of familial melanoma, suggests that different phenotypic and environmental factors are involved in the aetiopathogenesis of sporadic and familial melanoma. The study also revealed differences between

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Table II. Presence of *CDKN2A* mutations in familial melanoma according to number of affected members, degree of relationship and aggregation pattern

Characteristics	Total <i>n</i> = 87 <i>n</i> (%)	<i>CDKN2A</i> ⁺ <i>n</i> = 15 <i>n</i> (%)	<i>CDKN2A</i> ⁻ <i>n</i> = 72 <i>n</i> (%)	<i>p</i> -value
Family members with melanoma				
2	74 (85.1)	10 (13.5)	63 (86.5)	0.028
≥ 3	13 (14.9)	5 (38.5)	8 (61.5)	
Relation degree				
First	67 (77.0)	14 (20.9)	53 (79.1)	0.175
Second	20 (23.0)	1 (5.0)	19 (95.0)	
Aggregation pattern ^a				
Horizontal	15 (17.2)	1 (6.7)	14 (93.3)	
Vertical	59 (67.8)	10 (16.9)	49 (83.1)	
Horizontal + vertical	13 (14.9)	4 (30.8)	9 (69.2)	0.241

^aHorizontal: only siblings affected; vertical: first- or second-generation relatives affected.

patients with familial melanoma based on the presence of *CDKN2A* mutations. The main difference observed was that patients with familial melanoma, and particularly those with *CDKN2A* mutations, are more predisposed to melanocytic lesions (common and atypical naevi and second melanomas). In all the groups, the presence of *MC1R* R variants was associated with an increased prevalence of environmental risk factors and features associated with UV radiation-induced damage (e.g. SCC).

The prevalence of *CDKN2A* mutations in this study was relatively low (17.2%), but was consistent with that of other Mediterranean countries (18). This finding may be due to the high proportion of families with only 2 affected members and the considerable proportion of families with a horizontal inheritance pattern (siblings), in which the clustering of cases could probably be attributed to shared environmental risk factors and greater individual susceptibility compared with the presence of a *CDKN2A* mutation (14). This idea is supported by the increased prevalence of SCC in patients with familial melanoma without *CDKN2A* mutations (19). Also, this possibility is strengthened by the fact that countries with a high incidence of melanoma, such as Australia and New Zealand, whose populations have very susceptible skin and very high levels of sun exposure, have a low prevalence of *CDKN2A* mutations and a relatively high prevalence of sporadic melanoma cases within families (13, 15). In such countries, some authors have proposed using stricter eligibility criteria for the genetic assessment of familial melanoma in terms of the number of affected family members and the number of multiple melanomas (16, 20).

Early onset is a consistent finding in studies of family melanoma and familial cancer syndromes in general. We observed an increased prevalence of atypical naevi in patients with familial melanoma which, consistent with previous reports, was more pronounced in patients with *CDKN2A* mutations (21). The presence of atypical naevi reflects genetic predisposition to melanocytic proliferations and is also associated with a history of severe sunburn in childhood or adolescence (22).

Patients with familial melanoma exhibited an increased prevalence of multiple melanomas; however, the difference was significant only for those with *CDKN2A* mutations. Although the role of screening bias cannot definitively be ruled out, it is unlikely because all melanoma patients routinely underwent whole skin examination, regardless of their familial/sporadic and *CDKN2A* mutational status, and the median follow-up time did not differ between the study groups. Multiple melanomas are consistently associated with *CDKN2A* mutations in series of patients worldwide supporting its current use as an eligibility factor for genetic testing, even in the absence of a family history (20, 23). In our series, 43.8% of patients with multiple melanomas and family history of melanoma had *CDKN2A* mutations.

A similar tendency was observed for a personal history of BCC, which was significantly increased in patients with mutations. These results are the first to suggest that *CDKN2A* germline mutations may have a role in the pathogenesis of BCC. This could be due to the increased number of melanocytic naevi in *CDKN2A*⁺ patients, a well known risk factor associated with development of BCC (24). Also, it has been shown that an intronic variant in 9p21 near to *CDKN2A* confers susceptibility to BCC, although its impact in *CDKN2A* functionality has not been demonstrated so far (25).

As suggested above, the increased prevalence of SCC in *CDKN2A*⁻ familial patients is most probably due to the combination of family-shared environmental effects and an increased prevalence of fair-skin phenotype. An effect of screening is unlikely for the same reasons described above for multiple melanomas.

Other authors have reported an increased prevalence of other neoplasms, mainly tobacco-related cancers, particularly pancreatic cancer, in patients with familial melanoma carriers of a *CDKN2A* mutation (26). In our series, a personal history of pancreatic cancer was more common in patients with familial melanoma and again particularly in those with a *CDKN2A* mutation, but the association was not significant for any of the comparisons.

Analysing each of the groups according to the presence or absence of *MC1R* R variants, we observed that the variants were associated not only with known phenotypic characteristics but also with earlier onset of melanoma, SSM and factors that are influenced by UV radiation-induced damage, such as solar lentigines and personal history of SCC.

This study has some limitations, most of which are related to the retrospective nature of the study, which must be taken into account when interpreting our data. For example, recall bias is an inevitable limitation when the veracity of data depends on patients' recollection of past events (e.g. number and severity of sunburns). Furthermore, the validity of some of our findings is limited by the small number of patients with *CDKN2A* mutation.

One strength of this study is that the variables were recorded and collected prospectively and systematically by a single observer with experience in the treatment of melanoma.

In conclusion, the presence of *CDKN2A* mutations in this series of melanoma patients is similar to that expected in a Mediterranean population. Prevalence varied according to the number of family members affected and the degree of relatedness. However, considering the criteria for the genetic assessment of familial melanoma in regions with a low prevalence of melanoma, the genetic tests performed were justified.

In general, patients with familial melanoma exhibited a reduced prevalence of environmental risk factors and an increased prevalence of phenotypic risk factors. *CDKN2A* mutations were associated with earlier onset

of melanoma, a naevus phenotype, and the development of second melanomas and BCC. Familial melanoma without *CDKN2A* mutations, which is a pending genetic characterization, was associated with a naevus phenotype and an increased risk of second melanomas and SCC. *MC1R* variants were subsequently associated with an increased prevalence of factors associated with the effects of UV radiation, a significantly earlier age of melanoma onset, and an increased prevalence of SCC, particularly in patients with familial melanoma without *CDKN2A* mutations.

These results provide additional insights into the characteristics of familial melanoma in the Mediterranean area and could be useful for guiding prevention measures targeting this population.

REFERENCES

- Tucker MA, Goldstein AM. Melanoma etiology: where are we? *Oncogene* 2003; 22: 3042–3052.
- Povey JE, Darakhshan F, Robertson K, Bisset Y, Mekky M, Rees J, et al. DNA repair gene polymorphisms and genetic predisposition to cutaneous melanoma. *Carcinogenesis* 2007; 28: 1087–1093.
- Hill VK, Gartner JJ, Samuels Y, Goldstein AM. The genetics of melanoma: recent advances. *Annu Rev Genomics Hum Genet* 2013; 14: 257–279.
- Kvaskoff M, Pandeya N, Green AC, Perry S, Baxter C, Davis MB, et al. Solar elastosis and cutaneous melanoma: a site-specific analysis. *Int J Cancer* 2015; 136: 2900–2911.
- Bataille V. Melanoma. Shall we move away from the sun and focus more on embryogenesis, body weight and longevity? *Med Hypotheses* 2013; 81: 846–850.
- Bello DM, Ariyan CE, Carvajal RD. Melanoma mutagenesis and aberrant cell signaling. *Cancer Contr* 2013; 20: 261–281.
- Gandini S, Sera F, Cattaruzza MS, Pasquini P, Abeni D, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. *Eur J Cancer* 2005; 41: 28–44.
- Gandini S, Sera F, Cattaruzza MS, Pasquini P, Zanetti R, Masini C, et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. *Euro Eur J Cancer* 2005; 41: 2040–2059.
- Falchi M, Bataille V, Hayward NK, Duffy DL, Bishop JA, Pastinen T, et al. Genome-wide association study identifies variants at 9p21 and 22q13 associated with development of cutaneous nevi. *Nat Genet* 2009; 41: 915–919.
- Newton-Bishop JA, Chang YM, Iles MM, Taylor JC, Bakker B, Chan M, et al. Melanocytic nevi, nevus genes, and melanoma risk in a large case-control study in the United Kingdom. *Cancer Epidemiol Biomarkers Prev* 2010; 19: 2043–2054.
- Sturm RA, Duffy DL, Box NF, Chen W, Smit DJ, Brown DL, et al. The role of melanocortin-1 receptor polymorphism in skin cancer risk phenotypes. *Pigment Cell Res* 2003; 16: 266–272.
- Suzuki I, Im S, Tada A, Scott C, Akcali C, Davis MB, et al. Participation of the melanocortin-1 receptor in the UV control of pigmentation. *J Invest Dermatol Symp Proc* 1999; 4: 29–34.
- Box NF, Duffy DL, Chen W, Stark M, Martin NG, Sturm RA, et al. *MC1R* genotype modifies risk of melanoma in families segregating *CDKN2A* mutations. *Hum J Hum Genet* 2001; 69: 765–773.
- Goldstein AM, Tucker MA. Genetic epidemiology of cutaneous melanoma: a global perspective. *Arch Dermatol* 2001; 137: 1493–1496.
- Bishop DT, Demenais F, Goldstein AM, Bergman W, Bishop JN, Bressac-de Paillerets B, et al. Geographical variation in the penetrance of *CDKN2A* mutations for melanoma. *J Natl Cancer Inst* 2002; 94: 894–903.
- Bishop JN, Harland M, Randerson-Moor J, Bishop DT. Management of familial melanoma. *Lancet Oncol* 2007; 8: 46–54.
- Fargnoli MC, Argenziano G, Zalaudek I, Peris K. High- and low-penetrance cutaneous melanoma susceptibility genes. *Expert Rev Anticancer Ther* 2006; 6: 657–670.
- Pellegrini C, Maturo MG, Martorelli C, Suppa M, Antonini A, Kostaki D, et al. Characterization of melanoma susceptibility genes in high-risk patients from Central Italy. *Melanoma Res* 2017; 27: 258–267.
- Helgadottir H, Hoiom V, Tuominen R, Jonsson G, Mansson-Brahme E, Olsson H, et al. *CDKN2a* mutation-negative melanoma families have increased risk exclusively for skin cancers but not for other malignancies. *Int J Cancer* 2015; 137: 2220–2226.
- Soura E, Eliades PJ, Shannon K, Stratigos AJ, Tsao H. Hereditary melanoma: update on syndromes and management: Genetics of familial atypical multiple mole melanoma syndrome. *J Am Acad Dermatol* 2016; 74: 395–407.
- Punternvoll HE, Yang XR, Vetti HH, Bachmann IM, Avril MF, Benfodda M, et al. Melanoma prone families with *CDK4* germline mutation: phenotypic profile and associations with *MC1R* variants. *J Med Genet* 2013; 50: 264–270.
- Kennedy C, Bajdik CD, Willemze R, De Gruijil FR, Bouwes-Bavinck JN; Leiden Skin Cancer Study. The influence of painful sunburns and lifetime sun exposure on the risk of actinic keratoses, seborrheic warts, melanocytic nevi, atypical nevi, and skin cancer. *J Invest Dermatol* 2003; 120: 1087–1093.
- Puig S, Malvehy J, Badenas C, Ruiz A, Jimenez D, Cuellar F, et al. Role of the *CDKN2A* locus in patients with multiple primary melanomas. *J Clin Oncol* 2005; 23: 3043–3051.
- Khalesi M, Whiteman DC, Tran B, Kimlin MG, Olsen CM, Neale RE. A meta-analysis of pigmentary characteristics, sun sensitivity, freckling and melanocytic nevi and risk of basal cell carcinoma of the skin. *Cancer Epidemiol* 2013; 37: 534–543.
- Stacey SN, Sulem P, Masson G, Gudjonsson SA, Thorleifsson G, Jakobsdottir M, et al. New common variants affecting susceptibility to basal cell carcinoma. *Nat Genet* 2009; 41: 909–914.
- Helgadottir H, Hoiom V, Jonsson G, Tuominen R, Ingvar C, Borg A, et al. High risk of tobacco-related cancers in *CDKN2A* mutation-positive melanoma families. *J Med Genet* 2014; 51: 545–552.