Melanoma in children and adolescents: analysis of susceptibility genes in 123 Italian patients

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S. Raimondi[1], C. Pellegrini[2], L. di Nardo[2], P. Ghiorzo[3], L. Pastorino[3], C. Menin[4], M.A. Manganoni[5], G. Palmieri[6], G. Guida[7], P. Quaglino[8], I. Stanganelli[9], G. Tosti[1], M.C. Fargnoli[2], M. Rodolfo[10] for IMI

[1]IEO, Milan, Italy; [2]University of L'Aquila,Italy; [3]University of Genoa and Ospedale Policlinico San Martino, Genoa, Italy; [4]IOV-IRCCS, Padua, Italy; [5]Spedali Civili di Brescia, Italy; [6]Istituto di Chimica Biomolecolare, CNR, Sassari, Italy; [7]University of Bari "A. Moro", Italy; [8]University of Torino, Italy; [9] IRCCS-IRST Scientific Institute of Romagna for the Study and Treatment of Cancer, Meldola and University of Parma, Italy; [10]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.

Objective

Melanoma is rare in children and adolescents. A polygenic mechanism of inheritance involving high- and medium-penetrance genes has been suggested for melanoma susceptibility in adults, but genetic information is scarce for pediatric patients. Herein we report the results of genetic testing for melanoma risk occurring in children and adolescents (≤20 years) in an Italian population.

Methods and Materials

A total of 123 patients from 9 medical centers were studied by sequence analysis for the following melanoma predisposing genes, CDKN2A, CDK4, MITF, POT, and MC1R. The rate of gene alterations was compared between sporadic and familial/multiple cases and between children and adolescents and the association with individual and clinical characteristics was evaluated.
Specifically, we compared sporadic with familial and/or multiple primary melanomas, and adolescents with children by using the nonparametric Wilcoxon two-independent sample test for continuous variables, and the Chi Square test for categorical variables. Similarly, Chi Square test was used to compare genetic characteristics. The association between the number of common naevi and genetic characteristics of the patients was evaluated by the Wilcoxon two-independent sample test.

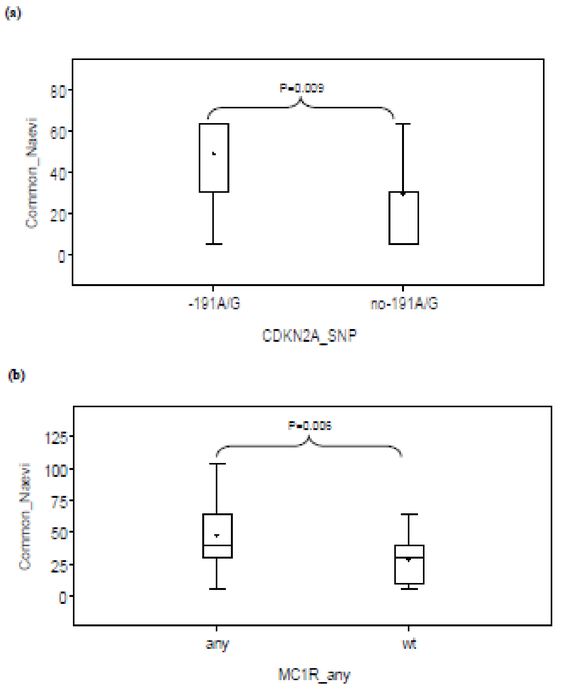
Results

CDKN2A pathogenic variants (PV) were detected in 9% of cases, with a higher frequency in familial and multiple melanoma cases, MITF E318K variant was detected in 3 patients, while CDK4 and POT1 PVs were not identified in the studied population. Most of the studied cases displayed MC1R variants (70%). Sporadic melanoma cases and familial/multiple primary melanoma patients displayed significant differences in the frequency rate of CDKN2A PV and MC1R R160W variant (**Tab. 1**); in addition, they differed for hair color, number of nevi, body site of primary melanoma and age at diagnosis. In detail, sporadic cases were younger, infrequently red haired, displayed a lower number of nevi and head/neck melanoma than familial/multiple melanoma cases. CDKN2A common polymorphisms were found associated with nevi (**Fig1A)** and red hair. MC1R variants were associated to primary melanoma body site, Breslow thickness, higher number of nevi (**Fig1B and 1C**) in addition to fair skin type and red hair color, thus confirming a role for MC1R variants in melanoma susceptibility in young patients. In children (≤ 12 years) primary melanoma differed from that of the older study population for histotype, being more frequently spitzoid, for higher Breslow thickness and for the more frequent occurrence on the head/neck and upper limbs as compared to trunk and lower limbs. CDKN2A gene PVs were less frequent and MC1R variants V92M and D84E more common in children than in the adolescent group (**Tab.2**).

Tab. 1 – Genetic characteristics of the study population according to sporadic, familial and multiple melanoma

	All cases (N=123) N(%)	Sporadic single primary cases (N=91) N(%)	Familial cases (N=24) N (%)	Multiple melanoma cases (N=14) N (%)	p-value
CDKN2A mutations[§]	11 (9%)	2 (2%)	7 (29%)	7 (50%)	**<0.0001**
CDKN2A SNPs (any)	67 (66%)	50 (69%)	15 (65%)	7 (58%)	0.30
CDKN2A SNP coding region[x]	6 (5%)	4 (4%)	2 (8%)	2 (14%)	0.65
CDKN2A SNP -191A/G	33 (40%)	22 (39%)	10 (48%)	3 (30%)	0.80
CDKN2A SNP 3'[+]	55 (45%)	43 (48%)	10 (42%)	6 (43%)	0.32
MC1R (any)	83 (68%)	64 (70%)	15 (65%)	8 (57%)	0.35
R160W	7 (6%)	2 (2%)	3 (13%)	3 (21%)	**0.01**
MITF	3 (3%)	2 (2%)	1 (5%)	0 (0%)	1.00

Fig. 1 – Box plot representing common nevi number according to (a) CDKN2A SNP -191A/G, (b) MC1R (any variant) and (c) MC1R Red Hair Color (R) variants.



Conclusion

Our results confirm the involvement of the major melanoma associated genes in melanoma occurring in children and adolescents. In addition, they suggest the implication of unknown susceptibility genes especially in the children population.

Tab. 2 – Genetic characteristics of the study population according to age at melanoma diagnosis

	All cases (N=123) N(%)	Cases>12 years (N=105) N(%)	Cases ≤12 years (N=18) N (%)	p-value°
CDKN2A mutations	11 (9%)	10 (10%)	1 (6%)	1.00
CDKN2A SNPs (any)	67 (66%)	60 (70%)	7 (47%)	0.08
MC1R (any)	83 (68%)	73 (70%)	10 (56%)	0.22
R* variants	36 (30%)	32 (31%)	4 (22%)	0.46
R* variants	55 (45%)	47 (45%)	8 (44%)	0.95
V60L	45 (37%)	39 (38%)	6 (33%)	0.74
R151C	15 (12%)	13 (13%)	2 (11%)	1.00
V92M	10 (8%)	6 (6%)	4 (22%)	**0.04**
R160W	7 (6%)	7 (7%)	0 (0%)	0.59
D294H	6 (5%)	6 (6%)	0 (0%)	0.59
R142H	6 (5%)	5 (5%)	1 (6%)	1.00
R163Q	3 (2%)	3 (3%)	0 (0%)	1.00
D84E	1 (1%)	0 (0%)	1 (6%)	0.15
MITF	3 (3%)	2 (2%)	1 (6%)	0.38

*R=Red Hair Color; r=non Red Hair Color