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Familial melanoma syndrome - phenotypic characterization and comparison with sporadic melanoma and healthy individuals – A Brazilian study

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Abstract

Background: Multiple members affected (at the same branch) and/or multiple primary melanomas (2 or more) may characterize Familial Melanoma Syndrome (FMS).

Objectives: To characterize the phenotypic characteristics of three groups of patients, FMS, Sporadic Melanoma (SM) and healthy individuals (HI). And evaluate if there is a predominant phenotype on those with FMS or significant differences between the 3 groups assessed.

Methods: We included 59 individuals with FMS, 54 with sporadic melanoma and 74 healthy individuals. Characteristics evaluated: eye color and pigmentation on the iris, hair color, skin type (Fitzpatrick classification), freckles, atypical and total nevi count, history of sunburn, atypical mole syndrome (AMS).

Results: Concerning the germline mutation status on the *CDKN2A* gene, association was not observed at the analyzed features. Familial Melanoma Syndrome patients had mostly dark eyes and hair, high-density freckles, less than 50 moles and phototype I or II. Phenotypic characteristics known to be related to higher melanoma risk were also prevalent on this group of patients, when compared with the two other groups – Sporadic melanoma and Healthy Individual: freckles in the lower arm ($p=0.026$) and in the trunk ($p<0.001$), great number of nevi ($p<0.001$), AMS ($p<0.001$), skin type I and II ($p<0.001$) and iris pigmentation ($p=0.008$). History of sunburn was more frequently seen in SM patients ($p=0.050$). Melanoma patients with AMS, phototype I or II and without history of sunburn have 98% of estimated probability to FMS.

Abbreviations: FMS: Familial melanoma syndrome; MPM: Multiple primary melanomas; SM: Sporadic melanoma; HI: Healthy individuals; CDKN2A: Cyclin dependent kinase inhibitor type 2A; AMS: Atypical mole syndrome; FM: Familial melanoma; CNS: Central nervous systems; CDK4: Cyclin dependent kinase 4; CM: Cutaneous melanoma.

Introduction

The Familial Melanoma Syndrome (FMS) can be characterized by families with multiple members affected with melanoma at the same branch of the family and patients with multiple primary melanomas (2 or more) [1,2]. Other cancers could be associated with the syndrome, such as pancreatic cancer and central nervous system (CNS) tumors. It is estimated that up to 10% of melanoma cases are in a familiar context [3].

Although many genes associated to familial melanoma have been described and can be tested nowadays, such as *CDK4, BAP1, TERT, TERF2IP, CXC, ACD or POT1* [4] they represent less than 3% of all familial cases [4], the most studied and relevant is *CDKN2A*. Mutations on this gene has, so far, been found to confer a higher risk for developing melanoma and occurs in about 20 to 40% of familial melanoma cases [5-7]. Clinical risk factors associated to melanoma development are both environmental (mainly sun exposure) and phenotypical [8-10] being the phenotype the result from the expression of individual's genes and the interaction of these genes with environmental factors [11,12]. In association with personal and/or family history, phenotype plays an important role in melanoma development.

Aims

Although FMS has been broadly studied regarding genotype and phenotype, as well; data about Brazilian population are scarce. Furthermore, as CM could be the result of an interaction between genetic, environmental and behavior factors and, the risk for the development of the disease differs according to the geographic region, the study of specific populations becomes relevant [7,13].

The purpose was to characterize the phenotype features of FM patients and analyze it regarding the *CDKN2A* mutation status, and also to compare phenotypic characteristics of this group with the same features assessed for sporadic melanoma patients and healthy individuals, trying to identify a predominant phenotype in the population clinically diagnosed with the FMS.

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Patients and methods

Three groups were assessed on Skin Cancer Department at A.C. Camargo Cancer Center - São Paulo (Brazil). Group A- melanoma patients with FMS (from GenoMEL- Brazil study), group B- sporadic melanoma patients (SM), and group C- healthy individuals without family history of melanoma, pancreatic cancer or CNS tumor.

Inclusion criteria

FMS: multiple primary melanomas and/or 1 CM and at least one familiar (1st or 2nd degree) with CM or pancreatic cancer or CNS tumor.

SM: only one melanoma by the time of informed consent signature, no family history of any cancer related to the syndrome.

Healthy individual: no personal or familiar history of cancer (melanoma, non-melanoma skin cancer, pancreatic cancer and CNS tumor).

Phenotypic features

Eye and hair color, phototype (Fitzpatrick), freckles density (from 0 to 100, in 10 gradations according to density and proportion of each site covered – arms and shoulders – 0=no freckling; 20/40=low; 60/80/100=high), history of sunburn, iris pigmentation, total number of nevi, presence of clinically atypical nevi (diameter ≥ 5 mm, when a papular component was present, the mole must have also a macular component; and at least two of the three: color variegated, contour uneven or border not well defined) and presence of AMS - according to Newton classification [14-17].

Genetic studies

Genetic sequencing was performed only in FMS group. Patients had DNA samples extracted from leukocytes. *CDKN2A* and *CDK4* exons were amplified using 50 ng of genomic DNA. Sequencing reactions were performed using Big Dye v.3.1 cycle sequencing kit on an ABI Prism 3500 genetic analyzer (Applied Biosystems). Details of genetic data were described in de Ávila, A.L.R. 2014 [18].

Statistic analyses

The baseline patient characteristics are expressed as absolute and relative frequencies for qualitative variables; and mean, median, standard deviation for quantitative variables. The chi-square or Fisher's tests were applied to evaluate the association between the phenotype characteristics and the study groups. For comparison of means among groups (HI, SM and FMS), the normality of distribution and homogeneity of variance of all continuous variables were assessed to determine the use of parametric or nonparametric tests. Additionally, in order to understand whether factors such as history of sunburn, phototype, AMS phenotype, eye and hair colour, freckles, iris pigmentation and nevi count affect patient's group the multinomial logistic regression model was fitted to data set. We fixed the significance level at 0.05. The software R, version 3.2.1 (www.r-project.org.br) was used for the analysis.

Ethical principles for medical research involving human subjects has been respected and followed according to the Declaration of Helsinki. The Ethics Committee of A C Camargo Cancer Center approved the study. Signed informed consent were obtained from all patients, and those with personal or family history of cancer presented pathology report by specialist, death certificate or physician letter to confirm the cancer.

Results

To evaluate if there is a predominant phenotype on those with FMS or significant differences between the 3 groups assessed, we included 59 patients on FMS group, 54 on Sporadic Melanoma and 74 healthy individuals.

Main features of familial melanoma syndrome group

On FMS group most of the patients had high-density freckles (61%), phototype I or II (83%), dark eyes and dark hair (53%) and history of sunburn (66%), while 58% of the individuals had less than 50 nevi. Mutation on *CDKN2A* was observed on 8 patients.

Phenotypic characteristics related to *CDKN2A* mutation status on FMS group are described on Table 1. All patients carrying the mutation had phototype I or II; 75% had less than 50 common nevi, absence of AMS phenotype, brown eyes and dark hair. However, no statistical significance was observed associating the phenotypic characteristics and the mutational status for the analyzed features. Of 59 patients, 8 (13.6%) carried the mutation. Clinical and molecular data from probands carrying mutations are described on Table 2.

Familial melanoma, sporadic melanoma and healthy individual

Phenotypic characteristics of Familial Melanoma Syndrome, Sporadic Melanoma and Healthy Individual are described on Table 3. Comparing the 3 groups, many features that increase the risk for developing melanoma [19,20] were statistically significant and predominant on FMS group, such as: high density freckles in the lower arm and in the back ($p=0.026$ and $p<0.001$, respectively), common nevi count ($p<0.001$), iris pigmentation ($p=0.008$), phototype I and II ($p<0.001$), presence of atypical nevi ($p=0.006$) and atypical mole syndrome ($p<0.001$). However, a positive sunburn history has been seen on 83% of patients with SM, followed by FMS individuals and HI, with 66% and 65%, respectively. Iris pigmentation was observed more frequently on FMS group (34%) curiously followed by Healthy Individual group (18%) and SM group (11%), $p=0.008$.

With the purpose of evaluating possible risk factors on individual characterization for FMS, multinomial regression model was adjusted.

Based on this regression model, the statistically significant variables that settled an estimated probability were AMS phenotype, phototype and history of sunburn (Table 4). This allowed us to determine that the patient with melanoma diagnosis, AMS, photype I or II and no history of sunburn presented 98% of estimated probability for FMS. For those with AMS, photype I or II and with history of sunburn this probability was 92.7%. On the other hand, when they had no AMS, photype III or IV and history of sunburn the probability was only 4.4% (Table 5).

Familial melanoma versus sporadic melanoma

Data comparing familial melanoma (group A) and sporadic melanoma (group B) are shown on Table 6. We observed that patients have resembling characteristics, except for pigmentation on the iris, affecting 34% and 11% of individuals with FMS and SM, respectively ($p=0.003$) and AMS phenotype, presented on 39% of the FMS and 4% of the SM group ($p < 0.001$).

FMS group had a younger mean age at diagnosis (46 years vs 51 years p=0,034), with 61% of patients younger than 50 years compared with 41% of SM group.

Table 1. Phenotypic characteristics related to the CDKN2A mutation status on FMS group (n=59) [1]The red hair patient was excluded from this analyses

Variables		Mutation			
		No	Yes	Total n	P value
		n	n		
Phototype	I / II	41 (80,4%)	8 (100%)	49 (83%)	0.32
	III / IV	10 (19.6%)	0 (0%)	10 (17%)	
AMS	No	30 (58.8%)	6 (75%)	36 (61%)	0.26
	Yes	21 (41.2%)	2 (25%)	23 (39%)	
Eye color	Blue	9 (17.5%)	2 (25%)	11 (19%)	0.88
	Green	15 (29.5%)	2 (25%)	17 (29%)	
	Brown/black	27 (53%)	4 (50%)	31(52%)	
Hair color[1]	Red	1 (2%)	0 (0%)	1 (2%)	0.35
	Blond	25 (49%)	2 (25%)	27 (46%)	
	Brown	25 (49%)	6 (75%)	31 (52%)	
nevi count	0 - 50	28 (55%)	6 (75%)	34 (58%)	0.33
	≥50	23 (45%)	2 (25%)	25 (42%)	
Iris pigmantation	No	35 (90%)	4 (50%)	39 (66%)	0.73
	Yes	16 (80%)	4 (50%)	20 (34%)	
sunburn	No	14 (70%)	6 (75%)	20 (34%)	0.06
	Yes	37 (95%)	2 (25%)	39 (66%)	

[1]The red hair patient was excluded from this analyses
FMS: familial melanoma syndrome

Table 2. Clinical and molecular characterization of individuals carrying CDKN2A mutations, from FMS group

Individual	Age(a)	Melanomas		Clinical Criteria	*CDKN2A*	Mutation Description		Gene Region
(ID)		proband[b]	family[c]	(FM/MPM)[d]	(*p14/p16*)	c.DNA	Aminoacid	
5	49	2	2	FM + MPM	*p16*	c.301G>T	p.G101W	Exon 2
6	48	2	2	FM + MPM	*p16*	c.142C>A	p.P48T	Exon 2
17	23	2	1	FM + MPM	*p16*	c.-34G>T	n/a	Promoter
18	53	4	1	FM + MPM	*p16*	c.-34G>T	n/a	Promoter
33	33	4	0	MPM	*p16*	c.142C>A	p.P48T	Exon 2
36	59	1	1	FM	*p16*	c.-34G>T	n/a	Promoter
44	39	1	3	FM	*p16*	c.142C>A	p.P48T	Exon 2
46	36	1	2	FM	*p16*	c.IVS-105G>A	n/a	Intron 2

[a]first melanoma, age of onset
[b]number of melanoma cases
[c]number of relatives affected
[d]FM: familial melanoma; MPM - multiple primary melanoma

Discussion

Many studies about FMS have already been conducted around the world, especially in Europe and Australia. However, most of them were about germline mutations and polymorphism on *CDKN2A* gene, MC1R polymorphism and risk factors for CM development [21-25]. Few of them have focused on phenotype characterization within melanoma-prone families. On Table 7, we gather some studies that described phenotypic features in melanoma patients, sporadic and/ or familial. There is no previous study comparing FMS versus SM including control group, regarding all the characteristics we have studied.

Thus, in this study we tried to find out if there is a specific phenotype for FMS population in Brazil and whether it differs or not from the other groups (SM and HI).

We were able to see that many features that confer higher risk for melanoma development were prevalent on FMS patients.

For FMS group, our results regarding the presence of dark hair and eyes (53% for both) are in accordance to previous studies [22,24,26]. About tan ability, an Italian and a Spanish study showed predominance of phototypes III and IV [24,26]. On the other hand, Yang XR *et al.* [27] found 85.6% of familial melanoma patients with pale/fair skin type, also observed in our study.

Our results agree with previous studies, which reported familial melanoma associated to younger age at diagnosis, increased nevi number and high density of freckles [26-28].

In the bivariate analyses, comparing the 3 groups, both the presence of atypical nevi and the AMS phenotype were prevalent on FMS group,

Table 3. The three groups analysed according to phenotipic features: Familial melanoma, Sporadic Melanoma and Healthy Individual

Variables	Categories	FMS (n=59)	SM (n=54)	HI (n=74)	P value
Eye color	Blue	11 (19%)	06 (11%)	13 (18%)	0.236
	Green	17 (29%)	13 (24%)	11 (15%)	
	Brown/black	31 (53%)	35 (65%)	50 (68%)	
Hair color[1]	Blond	27 (47%)	20 (38%)	21 (29%)	0.109
	Brown/black	31 (53%)	32 (62%)	52 (71%)	
Freckles in the lower arm	0-40	48 (81%)	47 (87%)	71 (96%)	**0.026**
	60-100	11 (19%)	07 (13%)	03 (04%)	
Freckles in the back	0-40	23 (39%)	26 (48%)	57 (77%)	**<0.001**
	60-100	36 (61%)	28 (52%)	17 (23%)	
Common nevi count	0 - 50	34 (58%)	37 (69%)	66 (89%)	**<0.001**
	≥50	25 (42%)	17 (31%)	08 (11%)	
Iris pigmentation	No	39 (66%)	48 (89%)	61 (82%)	
	Yes	20 (34%)	06 (11%)	13 (18%)	**0.008**
Phototype	I/II	49 (83%)	39 (72%)	31 (42%)	**<0.001**
	III/IV	10 (17%)	15 (28%)	43 (58%)	
Atypical Nevi	No	37 (63%)	39 (72%)	64 (86%)	**0.006**
	Yes	22 (37%)	15 (28%)	10 (14%)	
AMS	No	36 (61%)	52 (96%)	73 (99%)	**<0.001**
	Yes	23 (39%)	2 (4%)	1 (1%)	
Sunburn	No	20 (34%)	09 (17%)	26 (35%)	**0.05**
	Yes	39 (66%)	45 (83%)	48 (65%)	

[1]The red hair patient was excluded from this analyses
AMS: atypical mole syndrome

Table 4. Familial Melanoma Syndrome versus Sporadic melanoma: phenotypic characteristics

Variables	categories	FMS (n=59)	SM (n=54)	p
Eye color	Blue	11 (19%)	6 (11%)	
	Green	17 (29%)	13 (24%)	0.53
	Brown/black	31 (53%)	35 (65%)	
Hair color	Blond	27 (46%)	20 (37%)	0.39
	Brown/black	31 (52%)	32 (59%)	
Freckles in the lower arm	0 - 40	48 (81%)	47 (87%)	0.34
	60 - 100	11 (19%)	7 (13%)	
Freckles in the back	0 - 40	23 (39%)	26 (48%)	0.6
	60 - 100	36 (61%)	28 (52%)	
Common nevi count	0 - 50	34 (58%)	37 (69%)	0.12
	≥ 50	25 (42%)	17 (31%)	
Iris pigmentation	No	39 (66%)	48 (89%)	**0.003**
	Yes	20 (34%)	6 (11%)	
Phototype	I and II	49 (83%)	39 (72%)	0.11
	III and IV	10 (17%)	15 (28%)	
Sunburn	No	20 (34%)	9 (17%)	**0.03**

	Yes	39 (66%)	45 (83%)	
AMS	No	36 (61%)	52 (96%)	**< 0.001**
	Yes	23 (39%)	2 (4%)	
Atypical Nevi	No	37 (63%)	39 (72%)	0.281
	Yes	22 (37%)	15 (28%)	

AMS: Atypical mole syndrome

Table 5. Multinomial regression model- estimation of parameters

Group	Variable	Estimate	Standard error	Odds ratio (O.R.)	95% confidence interval for O.R.		p-value
					Lower	Upper	
HI	Intercept	0.278	0.474				0.557
	AMS (yes)	-1.229	1.258	0.293	0.025	3.443	0.329
	phototype (III-IV)	1.162	0.406	3.195	1.443	7.075	0.004
	Sunburn (yes)	-0.568	0.471	0.567	0.225	1.427	0.228
FMS	Intercept	0.991	0.485				0.041
	AMS (yes)	3.253	0.826	25.865	5.123	130.592	<0.001
	phototype (III-IV)	-1.336	0.572	0.263	0.086	0.807	0.020
	Sunburn (yes)	-1.506	0.528	0.222	0.079	0.624	0.004

*Reference group is level: SM
HI: healthy individual; FMS: familial melanoma syndrome; AMS: atypical mole syndrome; SM: sporadic melanoma

Table 6. Estimated probabily for FMS based on multinomial regression

AMS	Phototype	Sunburn history	Estimated probability		
			HI	SM	FMS
0	I-II	0	0.2634	0.1994	0.5372
0	I-II	1	0.3190	0.4260	0.2550
0	III-IV	0	0.7120	0.1690	0.1190
0	III-IV	1	0.6740	0.2820	**0.0440**
1	I-II	0	0.0054	0.0141	**0.9805**
1	I-II	1	0.0130	0.0600	**0.9270**
1	III-IV	0	0.0601	0.0487	0.8912
1	III-IV	1	0.1210	0.1740	0.7050

HI: Healthy individual; FMS: Familial melanoma syndrome; AMS: Atypical mole syndrome; SM: Sporadic

Table 7. The main phenotypic characteristics analysed in related articles, regarding individuals with cutaneous melanoma

First author, year, country	# of patients	# of groups compared	FMS population	EC	HC	PhT	AN	NC	FR
Bakos L, 2002, Brazil (19)	309	2- SM/ controls	No	X	X	X	X	X	X
Goldstein AM,2007, USA (21)	~42	4- according to home country	Yes	X	X	X	X	X	X
P Ashton-Prolla, 2008, Brazil (29)	30		Yes			X			
F Cuéllar, 2009, Spain (30)	9		Yes	X	X	X			
L Borges, 2009, Uruguai (22)	13		Yes	X	X	X	X		
Yang XR, 2010, USA* (27)	53 families	2- FMS/ controls	Yes	X	X	X		X	X
Pedace L,2011, Italy (24)	100	2- FMS wild-type/ mutated	Yes	X	X	X		X	
MM Peña-Vilabelda, 2014, Spain (31)	1044		Not specifically	X	X	X	X	X	X
M C Fargnoli, 2014, Italy (32)	62		No	X	X	X			
P Aguilera, 2014, Spain (26)	189	2-FMS/ SM	Yes	X	X	X		X	
E Pasquali, 2015, Italy** (9)	17 studies	Acoording to MC1R variant	No		X	X			X

References in brackets ()
*controls were unaffected family members and genetically unrelated spouses
**pooled-analysis
SM: sporadic melanoma; FMS: familial melanoma syndrome; EC: eye color; HC: hair color, PhT: phototype; AN: presence of atypical nevi; NC: nevi count; FR: freckles; MC1R: melanocortin 1 receptor

showing the importance of this phenotype on determining melanoma risk.

However, we were not able to find association between these characteristics and *CDKN2A* mutation, maybe due to the limited number of positive patients [29-32].

Among the most prevalent characteristics found in FMS group, AMS phenotype, phototype I or II and history of sunburn were the ones that allowed us to determined the estimated probability for FM patients, by multinomial regression model. The presence of AMS phenotype and phototype I or II determined the highest probability for FMS. History of sunburn, even though determining high probability when associated with the other two characteristics, whenever present determines a lower probability for FMS compared to its absence. It might suggest that this risk factor plays an important role, not only as a risk marker but also as a keypoint in melanomagenesis.

Conclusion

Our study suggests that when facing a cutaneous melanoma patient with AMS phenotype and phototype I or II, we might investigate properly cancer family history. This work also emphasizes the importance of sunburn as a risk factor for sporadic melanoma.

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Conflict of interest

The authors declare no conflicts of interest.

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