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Association of Incident Amelanotic Melanoma with Phenotypic Characteristics, *MC1R* Status, and Prior Amelanotic Melanoma

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Abstract

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Importance—We previously reported that survival is poorer from histopathologically amelanotic than pigmented melanoma because of more advanced stage at diagnosis. Identifying patients at risk of amelanotic melanoma might enable earlier diagnosis and improved survival; however, the phenotypic characteristics and underlying genetics associated with amelanotic melanoma are unknown.

Objective—To determine whether phenotypic characteristics, carriage of *MC1R* variants, and history of amelanotic melanoma are associated with histopathologically amelanotic melanoma.

Design—The Genes, Environment, and Melanoma (GEM) study is an international study that enrolled patients with incident primary cutaneous melanomas from 1998–2003.

Setting—Cases ascertained from population-based and hospital-based cancer registries.

Participants—The GEM participants included here were 2387 patients with data for phenotypes, *MC1R* genotype, and primary melanomas scored for histopathologic pigmentation. Of these 2387 patients with incident melanomas scored for pigmentation, 527 had prior primary melanomas also scored for pigmentation.

Main Outcome and Measures—Associations of phenotypic characteristics (freckles, nevi, phenotypic index) and *MC1R* status with incident amelanotic melanomas were evaluated using logistic regression models adjusted for age, sex, study center, and primary status (single or multiple primary melanoma); ORs and 95% CIs are reported. Association of histopathologic pigmentation between incident and prior melanomas was analyzed using an exact logistic regression model.

Results—In a multivariable model including phenotypic characteristics, absence of back nevi, presence of many freckles, and a sun-sensitive phenotypic index were independently associated with amelanotic melanoma (each $P < .05$). Carriage of *MC1R* variants was associated with amelanotic melanoma, but lost statistical significance in a model with phenotype. Further, patients with incident primary amelanotic melanomas were more likely to have had a prior primary amelanotic melanoma (OR = 4.62, 95% CI = 1.25–14.13) than those with incident primary pigmented melanomas.

Conclusions and Relevance—Absence of back nevi, presence of many freckles, a sun-sensitive phenotypic index, and prior amelanotic melanoma increase odds for development of amelanotic melanoma. An increased index of suspicion for melanoma in presenting non-pigmented lesions and more careful examination for signs of amelanotic melanoma during periodic skin examination in patients at increased odds of amelanotic melanoma might lead to earlier diagnosis and improved survival.

Introduction

Amelanotic melanoma is defined as melanoma without pigment on inspection[1] or lacking melanin on histopathologic examination.[2] Approximately 2–8% of melanomas are amelanotic.[3] In the international, population-based, Genes, Environment, and Melanoma (GEM) study, we reported that survival is poorer from amelanotic than pigmented melanoma due to more advanced stage at diagnosis.[2] Studies examining patient characteristics associated with amelanotic melanoma have been limited to demographic and genotypic

descriptions.[1,4–7] Amelanotic melanoma was associated with older age in GEM[2] and other studies,[1,4] and predominantly found in Caucasians.[1,4] Associations with sex have been less consistent as previously discussed for GEM.[2] Patients with amelanotic melanoma have been reported to carry *MC1R* variants linked to red hair ('R')[5] and/or *MITF* E318K.[6] A study of 118 melanomas found *MC1R* 'R' variants positively associated with amelanotic cases.[7] Our goal was to compare phenotype, *MC1R* status, and history of amelanotic melanoma between amelanotic and pigmented melanoma patients.

Methods

Population

The GEM study included 3579 patients with incident primary cutaneous melanoma from 1998–2003 at eight sites in Australia, Canada, Italy, and the United States.[8] Institutional review boards at each center reviewed and approved the study. Patients gave written, informed consent. GEM ascertained data for incident (index) and prior melanomas from cancer registries. This report includes 2387 (66.7% of 3579) GEM participants with data for phenotype, *MC1R* genotyping, and melanomas scored for histopathologic pigmentation. Of these 2387 patients with incident melanomas scored for pigmentation, 527 had prior primary melanomas also scored for histopathologic pigmentation. According to GEM protocol, *in situ* melanomas were incident melanomas if patients had prior invasive melanomas.

Self-administered questionnaires and telephone interviews were used to ascertain melanoma risk factors.[8] Back nevi were counted by family using glossy colored guides to aid nevus identification.[8] *MC1R* was sequenced from DNA from buccal swabs.[9] Variants were classified by strength of association with red hair as in Taylor et al. ("R": D84E, R142H, R151C, R160W, and D294H, all nonsense and insertion/deletion; "r": all other variants; "wt": consensus).[10] Histopathologic pigmentation was determined by observation of melanin granules on light microscopy during centralized review of diagnostic slides for both index and prior primary melanomas.[2] We previously reported that histopathologic pigmentation scoring had moderate interobserver agreement (kappa=0.48) and a significant association with clinical, pre-biopsy impression of pigmentation from pathology reports.[2] A scalar phenotypic index was derived by combining hair color, eye color, and ability to tan as previously described.[11] This index was dichotomized to indicate sun-resistant (scores of 0, 1, or 2) and sun-sensitive (scores of 3, 4, or 5) phenotypes.

Statistical Analysis

Among participants with incident single primary melanoma (SPM) or multiple primary melanoma (MPM), we estimated the odds ratios (OR) and 95% confidence intervals (95% CI) for associations of phenotypic characteristics (freckles, nevi, phenotypic index) and *MC1R* status using logistic regression models adjusted for study design features: age, sex, study center, and lesion status (SPM or index MPM). Multivariable models were developed including the three phenotypic characteristics alone or with *MC1R* status to identify factors independently associated with amelanotic melanoma. The same analyses with individual phenotypic characteristics and separated *MC1R* genotypes were also performed. Association of histopathologic pigmentation between incident and prior melanomas for patients with

MPM was analyzed using exact logistic regression. Association with *MITF* E318K mutations was also analyzed using exact logistic regression. Statistical tests were two-sided with $P < .05$ considered significant. Data were analyzed using STATA version 13 (Stata-Corp LP, College Station, TX).

Results

Overall, 178 (7.5% of 2387) incident and 32 (6.1% of 527) prior primary melanomas were amelanotic (Table 1).

Phenotypic Characteristics and *MC1R* Variants

In 2387 participants with incident melanomas (Table 2), absence of back nevi (OR = 1.76, 95% CI = 1.18–2.65; $P = .006$), presence of many freckles (OR = 1.76, 95% CI = 1.17–2.65; $P = .007$), a sun-sensitive phenotypic index (OR = 1.57, 95% CI = 1.14–2.18; $P = .006$), and carriage of *MC1R* variants (OR = 1.70, 95% CI = 1.04–2.78 for r/r, R/r, or R/R genotypes; P for trend = .01) were associated with amelanotic melanoma, adjusting for study design features.

Including the phenotypic characteristics in one multivariable model, absence of back nevi (OR = 1.71, 95% CI = 1.14–2.57; $P = .01$), presence of many freckles (OR = 1.58, 95% CI = 1.04–2.39; $P = .03$), and a sun-sensitive phenotypic index (OR = 1.48, 95% CI = 1.07–2.07; $P = .02$) were significantly associated with amelanotic melanoma.

Adding *MC1R* to the multivariable model of phenotypic characteristics, absence of back nevi (OR = 1.68, 95% CI = 1.12–2.53; $P = .01$) and a sun-sensitive phenotypic index (OR = 1.44, 95% CI = 1.03–2.01; $P = .03$) remained statistically significant, but not presence of many freckles or *MC1R*. Attenuation of the association with *MC1R* was explained by the addition of freckles and phenotypic index to the model. Despite the attenuation, the point estimate for the r/r, R/r, R/R variants was similar to that for freckling and phenotypic index.

Results for individual phenotypic characteristics and separate *MC1R* genotypes are in Table S1. Table S2 shows *MITF* E318K was not associated with amelanotic melanoma in our study (OR = 0.86, 95% CI = 0.22–2.37; $P = .82$).

Incident and Prior Melanoma Pigmentation

Table 3 shows associations of incident amelanotic melanoma with the pigmentation state of the previous melanoma in 527 MPM participants with pigmentation scored for each melanoma. Of 24 patients with incident amelanotic melanomas, 5 (20.8%) had prior amelanotic melanomas. For 503 patients with incident pigmented melanomas, 27 (5.4%) had prior amelanotic melanomas. Patients with an incident amelanotic melanoma were more likely to have a prior amelanotic melanoma than those with an incident pigmented melanoma (OR = 4.62, 95% CI = 1.25–14.13; $P = .01$).

Discussion

Our findings suggest that patients with prior amelanotic melanomas remain at risk of pigmented melanoma, but have increased odds of developing subsequent amelanotic melanomas. Further, we found independent associations of absence of back nevi, presence of many freckles, and a sun-sensitive phenotypic index with amelanotic melanoma. *MC1R*, a genetic determinant of phenotype (especially freckling and red hair),[9] was also associated with amelanotic melanoma. This association lost statistical significance in a model with phenotype, but the point estimate for the r/r, R/r, R/R variants was similar to that for the correlated phenotype variables. Thus, the association of *MC1R* with amelanotic melanoma may not be entirely accounted for by phenotype.

Although clinicians may expect that patients with sun-sensitive phenotypes or history of amelanotic melanoma are more likely to develop amelanotic melanoma, we are unaware of another study examining amelanotic melanoma's associations with phenotype or prior amelanotic melanoma. One report consistent with GEM described three amelanotic melanomas in a patient with red hair, fair skin, many freckles, and few nevi.[6] Also similar to GEM, Ghiorzo et al.[7] found an association of *MC1R* with amelanotic melanoma.

Strengths of our study include the large, international, population-based study design; centralized dermatopathology review; and objective definition of pigmentation. A limitation is that melanoma pigmentation may be misclassified due to interobserver variability. While we did not have pre-biopsy pigmentation, we previously reported that the clinical, pre-biopsy impression of pigmentation extracted from pathology reports was significantly associated with histopathologic pigmentation in a subset of GEM patients.[2]

Conclusions

Increased index of suspicion for melanoma in presenting non-pigmented lesions and careful periodic screening for signs of amelanotic and pigmented melanoma in patients at increased odds of amelanotic melanoma might lead to earlier diagnosis and improved survival. Dermoscopy and confocal microscopy, useful for diagnosis of amelanotic melanoma,[12,13] could be helpful. Research to determine whether other genetic polymorphisms associated with pigmentary characteristics and/or nevi[14,15] are associated with amelanotic melanoma is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

Are phenotypic characteristics, *MC1R* variants, and prior amelanotic melanoma associated with amelanotic melanoma?

Findings

Absence of back nevi, presence of many freckles, a sun-sensitive phenotype, and prior amelanotic melanoma were associated with development of amelanotic melanoma. *MC1R* was associated with amelanotic melanoma but this association lost significance in a model with phenotype.

Meaning

Prior amelanotic melanoma and the phenotypes associated with it should raise clinicians' index of suspicion for amelanotic melanoma when examining a suspicious but non-pigmented skin lesion, and clinicians might also use these characteristics to prompt periodic, meticulous screening of non-pigmented as well as pigmented skin lesions.

Table 1

Characteristics of 2914 Primary Melanomas from 2387 Patients Scored for Histopathologic Pigmentation in the GEM Study

	Incident Primary Melanoma	Prior Primary Melanoma
Characteristic	**(n=2387)[a]**	**(n=527)[a]**
Sex		
Male	1322 (55.4)	354 (67.2)
Female	1065 (44.6)	173 (32.8)
Age at diagnosis, y		
Mean (±SD)	58.3 ± 16.1	65.9 ± 12.9
< 50	712 (29.8)	62 (11.8)
50–69	966 (40.5)	222 (42.1)
≥ 70	709 (29.7)	243 (46.1)
Race/Ethnicity		
Caucasian	2380 (99.7)	526 (99.8)
Non-Caucasian	7 (0.3)	1 (0.2)
Country		
Australia (New South Wales & Tasmania)	1096 (45.9)	394 (74.8)
Canada (British Columbia & Ontario)	547 (22.9)	76 (14.4)
Italy (Torino)	75 (3.1)	2 (0.4)
United States (NC, NJ, MI, and CA)	669 (28.0)	55 (10.4)
Histopathologic pigmentation		
Pigmented	2209 (92.5)	495 (93.9)
Amelanotic	178 (7.5)	32 (6.1)
Histologic subtype		
Superficial Spreading	1551 (65.0)	353 (67.0)
Nodular	182 (7.6)	40 (7.6)
Lentigo maligna	286 (12.0)	87 (16.5)
In-situ	161 (6.7)	0 (0.0)
Unclassified/other[b]	207 (8.7)	47 (8.9)
Anatomic Site		
Head, neck	437 (18.3)	84 (15.9)
Trunk, pelvis	1040 (43.6)	248 (47.1)
Upper extremities	424 (17.8)	94 (17.8)
Lower extremities	486 (20.4)	101 (19.2)
Breslow thickness, mmc	(n=2,380)	(n=525)
Median (IQR), mm	0.6 (0.8)	0.7 (0.7)
In-situ	167 (7.0)	0 (0.0)
0.01 to 1.00	1518 (63.8)	365 (69.5)

	Incident Primary Melanoma	Prior Primary Melanoma
Characteristic	**(n=2387)[a]**	**(n=527)[a]**
1.01 to 2.00	405 (17.0)	95 (18.1)
2.01 to 4.00	195 (8.2)	49 (9.3)
>4.00	95 (4.0)	16 (3.1)

Abbreviations: GEM = Genes, Environment, and Melanoma; IQR = interquartile range; SD = standard deviation.

[a] Data are given as number (percentage) of melanomas.

[b] Other includes acral lentiginous, spindle cell, nevoid, and Spitzoid melanomas.

[c] Counts do not sum to the total number of study subjects due to missing data.

Table 2

Phenotypic Characteristics and MC1R Status in Relationship to Histopathologic Pigmentation in Incident Primary Melanomas from 2387 patients in the GEM Study

			Amelanotic vs. Pigmented Melanoma					
	Pigmented Melanoma	Amelanotic Melanoma	Study Design Features[b]		Study Design Features + Phenotype[c]		Study Design Features + Phenotype + MC1R[d]	
Characteristics	**(n = 2209)[a]**	**(n = 178)[a]**	**OR (95% CI)**	***P* Value[e]**	**OR (95% CI)**	***P* Value[e]**	**OR (95% CI)**	***P* Value[e]**
Phenotype								
Back nevi								
Present	1904 (86.2)	139 (78.1)	1 [Reference]	0.006	1 [Reference]	0.01	1 [Reference]	0.01
Absent	305 (13.8)	39 (21.9)	1.76 (1.18–2.65)		1.71 (1.14–2.57)		1.68 (1.12–2.53)	
Freckles								
None to few	1912 (86.6)	143 (80.3)	1 [Reference]	0.007	1 [Reference]	0.03	1 [Reference]	0.10
Many	297 (13.4)	35 (19.7)	1.76 (1.17–2.65)		1.58 (1.04–2.39)		1.44 (0.93–2.22)	
Phenotypic index[f]								
Sun-resistant phenotypic index	989 (47.1)	68 (38.2)	1 [Reference]	0.006	1 [Reference]	0.02	1 [Reference]	0.03
Sun-sensitive phenotypic index	1109 (52.9)	110 (61.8)	1.57 (1.14–2.18)		1.48 (1.07–2.07)		1.44 (1.03–2.01)	
Genetics								
MC1R[g]								
wt/wt	357 (16.2)	23 (12.9)	1 [Reference]		-	-	1 [Reference]	
r/wt or R/wt	980 (44.4)	69 (38.8)	1.17 (0.71–1.93)		-	-	1.16 (0.70–1.92)	
r/r, R/r, or R/R	872 (39.5)	86 (48.3)	1.70 (1.04–2.78)		-	-	1.43 (0.86–2.39)	
P value for trend				0.01	-	-		0.13

Abbreviations: CI, confidence interval; GEM, genes, environment, and melanoma; MC1R, melanocortin 1 receptor; MPM, multiple primary melanoma; OR, odds ratio; SPM, single primary melanoma.

[a] Data are given as number (percentage) of melanomas unless otherwise specified.

[b] Adjusted for study design features: sex, age, study center, and lesion status (SPM or index MPM)

[c] Adjusted for study design features, freckling, back moles, and phenotypic index.

[d] Adjusted for study design features and all characteristics displayed in the table.

[e] *P* values were calculated according to logistic regression models and *P* values for trend were calculated including MC1R categories as ordinal variables.

[f] Phenotypic index was calculated by additively combining: hair color (black or dark brown=0; light brown or blonde=1; red=2), eye color (brown=0; grey, green, or hazel=1; blue=2), and ability to tan (deeply or moderately=0; occasionally or none=1). Those with index scores of 0,1, or 2 were categorized as having a sun-resistant phenotypic index. Patients with index scores of 3, 4, or 5 were categorized as having a sun-sensitive phenotypic index.

[g] *MC1R* "R": D84E, R142H, R151C, R160W, and D294H, all nonsense and insertion/deletion; "r": all other variants; "wt": consensus.

Table 3

Association of Histopathologic Pigmentation Between Incident and Prior Melanomas in 527 Multiple Primary Melanoma Patients in the GEM Study[a]

	Incident Primary Melanoma			
	Pigmented Melanoma	**Amelanotic Melanoma**	**Amelanotic vs. Pigmented Prior Primary Melanoma**	
Prior Primary Melanoma	n (%)[b]	n (%)[b]	OR (95%CI)	*P* Value[c]
Pigmented Melanoma	476 (94.6)	19 (79.2)	1 [Reference]	0.01
Amelanotic Melanoma	27 (5.4)	5 (20.8)	4.62 (1.25–14.13)	

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Includes only patients with second or higher order primary melanomas scored for histopathologic pigmentation

[b] Data are given as number (percentage) of melanomas.

[c] *P* value was calculated using an exact logistic regression model.