Characterization of individuals at high risk of developing melanoma in Latin America: bases for genetic counseling in melanoma

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Purpose: CDKN2A is the main high-risk melanoma-susceptibility gene, but it has been poorly assessed in Latin America. We sought to analyze CDKN2A and MC1R in patients from Latin America with familial and sporadic multiple primary melanoma (SMP) and compare the data with those for patients from Spain to establish bases for melanoma genetic counseling in Latin America.

Methods: CDKN2A and MC1R were sequenced in 186 Latin American patients from Argentina, Brazil, Chile, Mexico, and Uruguay, and in 904 Spanish patients. Clinical and phenotypic data were obtained.

Results: Overall, 24 and 14% of melanoma-prone families in Latin America and Spain, respectively, had mutations in CDKN2A. Latin American families had CDKN2A mutations more frequently (P = 0.014) than Spanish ones. Of patients with SMP, 10% of those from Latin America and 8.5% of those from Spain had mutations in CDKN2A (P = 0.623). The most recurrent CDKN2A mutations were c.-34G>T and p.G101W. Latin American patients had fairer hair (P = 0.016) and skin (P < 0.001) and a higher prevalence of MC1R variants (P = 0.003) compared with Spanish patients.

Conclusion: The inclusion criteria for genetic counseling of melanoma in Latin America may be the same criteria used in Spain, as suggested in areas with low to medium incidence, SMP with at least two melanomas, or families with at least two cases among first- or second-degree relatives.

Key Words: CDKN2A; familial; Latin America; melanoma; MC1R

INTRODUCTION

Melanoma is the most aggressive of common skin cancers because of its tendency to metastasize. Its incidence is rapidly increasing, especially among Caucasian populations. Melanoma is the second most diagnosed cancer among patients younger than 30 years of age,1 and the 3-year survival rate for patients...
with metastases is around 15%. Identification of individuals at high risk of developing melanoma is necessary since an early diagnosis improves the disease prognosis.

Melanoma is caused by the interaction of environmental, phenotypic, and genetic factors. The main environmental risk factor for melanoma is sun exposure. Individuals with fair skin, red hair, and/or a high nevi count have an increased risk of developing melanoma. To date, CDKN2A, which encodes the tumor suppressor proteins p16INK4A and p14ARF, is the major high-risk gene involved in melanoma susceptibility. CDKN2A has been widely studied in melanoma patients from the United States, Europe, and Australia. The frequency of germline mutations in CDKN2A varies across populations (5–72%) and depends on the selection criteria used. Haplotype analysis indicates a founder effect for most of the recurrent mutations detected. Identification of the prevalence of CDKN2A mutations in patients at high risk for melanoma and the correlation of these mutations with clinical data has been crucial for establishing genetic counseling for melanoma. Melanoma risk may also be modulated by common genetic variants acting as low- to medium-penetrance variants. MC1R plays a key role in pigmentation and is responsible for phenotypic characteristics such as hair and skin color and the capacity of response to ultraviolet radiation. Several MC1R variants are associated with a moderately increased melanoma risk and also modulate the effect of CDKN2A mutations in carriers.

Genetic counseling and specific dermatological follow-up may be offered to patients at high risk for melanoma. In countries with a low to medium incidence of melanoma, genetic counseling is offered to patients with two primary melanomas and/or to families with two melanoma cases and/or one pancreatic adenocarcinoma and one melanoma in first- or second-degree relatives (the "rule of two"). In countries with a moderate to high incidence of melanoma, however, genetic counseling is offered to patients with three primary melanomas and to families with three cases of melanoma or pancreatic cancer in first- or second-degree relatives (the "rule of three"). It has been demonstrated that melanoma genetic counseling has a positive impact on the improvement of total body skin examination and self-examination of the skin in unaffected individuals carrying germline mutations after test reporting, whereas affected carriers maintain high levels of screening adherence.

Furthermore, after melanoma genetic counseling, unaffected members of high-risk melanoma families report improvements in daily routine sun protection, showing that genetic counseling may motivate sustained improvements in prevention behaviors. Thus it is very important for both melanoma patients and unaffected individuals from the family to be included in genetic counseling programs.

Few studies have assessed the prevalence of CDKN2A mutations or MC1R variants and phenotypic characteristics in patients at high risk for melanoma from Latin American countries. CDKN2A mutations have been identified in 13.6% of melanoma-prone families from São Paulo, Brazil, whereas one study reported no mutations in Porto Alegre, and in a different cohort the mutation frequency was 7%. In melanoma-prone families from Uruguay, 5/6 families had CDKN2A mutations. Phenotypic and genetic characterization of individuals at high risk for melanoma from Latin America may improve their management and implement genetic counseling in these countries. We present the molecular characterization of CDKN2A and MC1R genes in the largest set of patients at high risk for melanoma from distinct Latin American countries (Argentina, Brazil, Chile, Mexico, and Uruguay), and we compare the data with two sets of Spanish patients at high risk for melanoma to establish bases for genetic counseling in Latin America.

MATERIALS AND METHODS

The multicenter cross-sectional study included 1,090 patients at high risk for melanoma: 758 patients with familial melanoma (FM) and 332 patients with SMP from Latin American countries and Spain. Because Latin America is a region with a low incidence of melanoma (GLOBOCAN 2012, World Health Organization; http://globocan.iarc.fr), the inclusion criteria followed the rule of two.

Overall, 186 Latin American melanoma patients were recruited from Argentina (n = 10), Chile (n = 28), Mexico (n = 6), Uruguay (n = 25), and Brazil (n = 117), which included two sets of patients: Porto Alegre (Southern Brazil) (n = 58) and São Paulo (southeast region) (n = 59). The contribution of each country to the study resulted in a broad representation of a number of Latin American countries. A set of 904 Spanish patients with melanoma from Barcelona (n = 706) and Valencia (n = 198) also were included using the same selection criteria.

The number of primary melanomas, age at diagnosis, number of melanoma cases in the family, ancestral origin, and phenotypic data (hair and eye color, skin phototype, and nevi count) were recorded by dermatologists for most of the patients. Although the number of missing values was higher in the set of Spanish patients than in the Latin American patients, this did not introduce a bias, and the information recruited was informative for the whole cohort: Spanish patients were recruited consecutively, and missing data were distributed randomly; two different cohorts from Spain where used to minimize the bias due to the data collection procedure; and the variable with the greatest amount of missing data had information from at least 600 Spanish patients. Partial genetic information of the patients with melanoma from Spain and Brazil, and a subset of pedigrees from Uruguay, has been previously reported.

The study was approved by the ethical committee of the Hospital Clinic of Barcelona. The patients gave their written, informed consent.

CDKN2A and MC1R molecular screening

Molecular characterization of CDKN2A was performed in all patients. CDKN2A was sequenced in all patients, as previously described. MC1R was sequenced as described elsewhere. The MC1R genotype was available from all patients from Argentina and Chile, 57% (33/58) patients from Porto Alegre, Brazil, 92% (54/59) patients from São Paulo, Brazil, 96% (24/25)
patients from Uruguay, 59% (419/706) patients from Barcelona, Spain, and 94% (186/198) patients from Valencia, Spain. MC1R genotype data were not available for patients from Mexico.

Statistical analyses
For the statistical analyses, the most common MC1R variants were classified as r variants (not associated with red hair color: p.V60L, p.V92M, p.R163Q) or R variants (associated with red hair color: p.D84E, p.R142H, p.R151C, p.I155T, p.R160W, p.D294H).10

SPSS software version 17.0 (IBM, Chicago, IL) was used. Two-sided Pearson χ² or Fisher exact tests were used for categorical variables, as applicable. Student’s t-test was used for quantitative variables. Adjusted P values were calculated using the Bonferroni correction. The test was considered significant if the P value or adjusted P value (as applicable) was < 0.05.

RESULTS
The study included a set of 1,090 patients with melanoma from distinct Latin American countries and Spain. Latin America and Spain had similar frequencies of FM cases (67.7 and 69.9%, respectively) and SMP (32.3 and 30.1%, respectively; P = 0.600), and there were no gender differences (40.3% male and 58.7% female vs. 41.5% male and 58.5% female, respectively; P = 0.806). Since Latin America is a mixed population from European, Native, African and Asian origin as a result of the colonization process and migratory effects,4 we collected information regarding the patients’ ancestral origin. The four grandparents of more than 70% of Latin American patients were of European origin. Latin American and Spanish patients differed in pigmentation traits. Latin American patients had fairer hair color (adjusted P = 0.016) and skin phototype (adjusted P < 0.001) than Spanish patients. No differences were observed for nevi count or eye color (Table 1).

Considering all patients, CDKN2A mutation prevalence was 19% in Latin America and 12% in Spain. CDKN2A mutation frequency in SMP was similar in Latin America (10%) and Spain (8.5%) (P = 0.623). However, the prevalence of CDKN2A mutations in Latin American melanoma-prone families was higher than in Spain (24 and 14%, respectively; P = 0.019). The frequency of mutations varied among countries. Whereas southern Brazil had a low mutation prevalence, Chile and Uruguay showed a high prevalence of mutations in both SMP and FM (Table 2).

The CDKN2A mutations differed in each country (Table 3). Overall, 74% (23/31) of Latin American CDKN2A mutation carriers had a mutation also found in Spanish patients with melanoma. The most prevalent mutations in Latin America (c.-34G>T and p.G101W (c.301G>T)) were among the most recurrent mutations in Spain, which are p.G101W (33%), p.V59G (c.176T>G) (7%), c.-34G>T (6%), p.A36RfsX17 (c.106delG) (6%), and p.E120fsX145 (c.358delG) (5%) (Table 3). Mutation c.-34G>T was present in 90% of families from Chile, and families from São Paulo (Brazil) and Uruguay with CDKN2A mutations. Mutation p.G101W was present in families from Argentina, São Paulo (Brazil), and Uruguay. The other mutations detected in Latin America were restricted to a few pedigrees.

CDKN2A mutations have been previously associated with a lower age at diagnosis, number of primary melanomas, and the number of cases in the family.1 The whole set of patients also showed these associations (Table 4). Latin American patients with melanoma carrying a CDKN2A mutation had an increased number of cases in the family and a lower age at diagnosis, but the number of personal primary melanomas did not reach significance.

We sequenced MC1R to assess the distribution of MC1R variants across countries (Table 5). We observed differences in the number and type of variants between Latin America and Spain. We detected MC1R variants in 80.5% of Latin American and 67.9% of Spanish patients (P = 0.003), with a similar R variant frequency (39.6 vs. 36.3%, respectively; P = 0.514) but a higher r variant prevalence in Latin America (40.9 vs. 31.6%, respectively; P = 0.033). We analyzed the frequencies of the most common R and r variants, comparing Latin America and Spain (Supplementary Table S1 online). When adjusting using the Bonferroni correction, we found a significantly increased presence of p.R160W (17.4 vs. 7.5%; adjusted P < 0.005) and p.R163Q (14.1 vs. 5.2%; adjusted P < 0.005) in Latin America, but we should take into consideration that all patients carrying the p.R163Q variant in this study were from only three study sites: Brazil (São Paulo), Chile, or Uruguay. The p.D294H variant was more frequent in Spain (5.4 vs. 13.3%; adjusted P = 0.045). The presence of MC1R variants and R variants correlated with phenotype (Supplementary Tables S2 and S3 online).

DISCUSSION
Latin America has a low incidence of melanoma (GLOBOCAN 2012). The characterization of melanoma genes has allowed other areas with low to medium incidence of melanoma, such as Spain, to recommend genetic counseling for patients with melanoma.12,25 To date, only a few specialized centers in Latin America offer melanoma genetic counseling, and there is little knowledge of the implication of high-risk genes in melanoma susceptibility. This study presents the clinical and molecular characterization of CDKN2A and MC1R in the largest set of Latin American patients at high risk for melanoma.

CDKN2A mutation frequency in melanoma-prone families was higher in Latin America than Spain, using the same selection criteria. By contrast, both areas had similar SMP CDKN2A mutation prevalence, consistent with that reported in other studies (8.2–9%).25,26 The age at diagnosis and number of primary melanomas were associated with the presence of mutations in CDKN2A, as previously reported.6 Otherwise, we did not find associations between CDKN2A mutation and nevi count, suggesting that other genes could play a role in nevogenesis.27,28 Most CDKN2A mutations identified had been previously detected in European or North American patients with melanoma. The most prevalent mutation in Latin America was c.-34G>T. This mutation occurs at a high
## Table 1 Characteristics and phenotypic data of patients with melanoma, by country (region)

|                          | Argentina (Porto Alegre) | Brazil (São Paulo) | Chile | Mexico | Uruguay | Spain (Barcelona) | Spain (Valencia) | Latin America | Spain | Adjusted | Total |
|--------------------------|--------------------------|--------------------|-------|--------|---------|-------------------|-----------------|---------------|-------|-----------|-------|
| Patients with melanoma   |                          |                    |       |        |         |                   |                 |               |       |           |       |
| FM                       | 5                        | 50.0               | 45    | 77.6   | 37      | 62.7              | 16              | 57.1          | 3     | 50.0      | 20    |
| SMP                      | 5                        | 50.0               | 13    | 22.4   | 22      | 37.3              | 12              | 42.9          | 3     | 50.0      | 20    |
| Total                    | 10                       | 58                 | 59    | 28     | 26      | 6                 | 25              | 706           | 198   | 186       | 904   |

### Phenotypic characteristics

#### Hair color

|         | n | %  |
|---------|---|----|
| Red     | 1 | 10.0 |
| Blond   | 2 | 20.0 |
| Dark    | 7 | 70.0 |
| Missing | 0 | 0    |
| Total   | 10| 58   |

#### Eye color

|         | n | %  |
|---------|---|----|
| Fair    | 5 | 50.0 |
| Dark    | 5 | 50.0 |
| Missing | 0 | 0    |
| Total   | 10| 58   |

#### Skin color

|         | n | %  |
|---------|---|----|
| Fair    | 7 | 70.0 |
| Dark    | 3 | 30.0 |
| Missing | 10| 35   |
| Total   | 10| 58   |

#### Nevi count

|         | n | %  |
|---------|---|----|
| <50     | — | —   |
| 50–100  | — | —   |
| >100    | — | —   |
| Missing | 10| 35   |
| Total   | 10| 58   |

### Ancestral origin

|         | n | %  |
|---------|---|----|
| European| 8 | 88.9 |
| Latin   | 1 | 11.1 |
| Amerindian| 0 | 0 |
| African| 0 | 0 |
| American| 1 | 1 |
| Missing | 1 | 2 |
| Total   | 10| 58   |

Statistically significant P values are given in bold. SmP, sporadic multiple primary melanoma.

*P* values were obtained comparing Latin America with Spain. Bonferroni correction was used to obtain the adjusted *P* values. In the familial melanoma (FM) category we included families with at least two melanoma cases.

Skin color was classified according to the Fitzpatrick phototype classification: fair (phototypes I or II) and dark (phototypes III–V). The ancestral origin of the Latin American patients with melanoma is indicated according to the origin of their grandparents. “European” means all grandparents were born in a European country. “Latin,” “Amerindian,” and “African American” indicate that at least one of the grandparents was born in Latin America (but had Spanish or Portuguese ancestors), was a descendent of natives, or had an African-American origin, respectively. In the case that the grandparents were of different origins, for example, African American and Amerindian, the ancestral origin was indicated taking into consideration the darkest skin color: African American/Amerindian/Latin. There were no individuals with Asian origin.
Table 2  
CDKN2A mutation distribution between families according to the number of melanoma cases by country (region)

| Country (region)    | All pedigrees included (N) | Patients with SMP | All melanoma-prone families | Families with two cases | Families with three cases | Families with four or more cases | P value<sup>a</sup> | CDKN2A mutation | P value<sup>b</sup> | CDKN2A mutation | P value<sup>b</sup> | CDKN2A mutation | P value<sup>b</sup> | CDKN2A mutation | P value<sup>b</sup> | CDKN2A mutation | P value<sup>b</sup> |
|---------------------|----------------------------|-------------------|-----------------------------|-------------------------|--------------------------|-------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                      |                            | n     | %     | n     | %     | P value | n     | %     | n     | %     | P value | n     | %     | n     | %     | P value | n     | %     | n     | %     | P value |
| Argentina            | 10                         | 5     | 50.0  | 0     | 0     | 4.893  | 4     | 80.0  | 0     | 0     | 0.019  | 1     | 20.0 | 0     | 0     | 0.567  | 0     | 0     | 0     | 0     | 0.007  |
| Brazil (Porto Alegre)| 50                         | 13    | 26.0  | 0     | 0     | 1.219  | 37    | 74.0  | 3     | 8.1   | 0.019  | 27    | 73.0 | 1     | 3.7   | 0.623  | 21    | 60.0 | 1     | 4.8   | 0.007  |
| Brazil (São Paulo)   | 57                         | 22    | 38.6  | 1     | 3.6   | 0.095  | 35    | 61.4  | 8     | 22.4  | 0.019  | 21    | 60.0 | 1     | 4.8   | 0.007  | 13    | 37.1 | 7     | 53.8  | 0.007  |
| Chile                | 27                         | 12    | 44.4  | 3     | 25.0  | 0.019  | 15    | 55.6  | 7     | 46.7  | 0.019  | 27    | 73.0 | 1     | 3.7   | 0.007  | 13    | 37.1 | 7     | 53.8  | 0.007  |
| Mexico               | 5                          | 3     | 60.0  | 0     | 0     | 0.007  | 2     | 40.0  | 1     | 50.0  | 0.007  | 2     | 100  | 0     | 0     | 0.007  | 0     | 0     | 0     | 0     | 0.007  |
| Uruguay              | 20                         | 5     | 25.0  | 1     | 20.0  | 0.007  | 15    | 75.0  | 8     | 40.0  | 0.007  | 4     | 26.7 | 3     | 75.0  | 0.007  | 1     | 2.9   | 0     | 0     | 0.007  |
| Spain (Barcelona)    | 564                        | 234   | 41.5  | 20    | 8.5   | 0.007  | 330   | 58.5  | 47    | 14.2  | 0.007  | 47    | 14.2 | 11    | 23.4  | 0.007  | 14    | 4.2   | 6     | 42.9  | 0.007  |
| Spain (Valencia)     | 147                        | 38    | 25.9  | 3     | 7.9   | 0.007  | 109   | 74.1  | 15    | 13.8  | 0.007  | 79    | 72.5 | 8     | 10.1  | 0.007  | 22    | 20.2 | 5     | 22.7  | 0.007  |
| Missing              | 0                          | 0     | 0     | 0     | 0     | 0.007  | 0     | 0     | 0     | 0     | 0.007  | 0     | 0     | 0     | 0     | 0.007  | 0     | 0     | 0     | 0     | 0.007  |
| Latin America        | 169                        | 60    | 35.5  | 6     | 10.0  | 0.023  | 109   | 64.5  | 26    | 39.3  | 0.019  | 77    | 70.6 | 12    | 15.6  | 0.007  | 26    | 23.9 | 11    | 42.3  | 0.007  |
| Spain                | 711                        | 272   | 38.3  | 23    | 8.5   | 0.019  | 439   | 61.7  | 62    | 14.1  | 0.019  | 348   | 79.3 | 38    | 10.9  | 0.007  | 69    | 15.7 | 16    | 23.2  | 0.007  |
| Total                | 880                        | 332   | 37.7  | 29    | 8.9   | 0.019  | 548   | 62.3  | 88    | 16.1  | 0.019  | 425   | 77.6 | 50    | 11.8  | 0.007  | 95    | 17.3 | 27    | 28.4  | 0.007  |

Statistically significant P-values are given in bold.

<sup>a</sup>P-values to assess differences in mutation frequency among families with sporadic multiple primary melanoma (SMP) and among all melanoma-prone families were obtained by comparing the global result of Latin America versus Spain.  
<sup>b</sup>P-values to assess differences in mutation frequency among families according to the number of melanoma cases were assessed separately in Latin America, in Spain, and in the entire set of patients (total).
Table 3  CDKN2A genetic results

| Exon  | cDNA change | Protein change | p14ARF | p16INK4A | Argentina (Porto Alegre) | Brazil (São Paulo) | Chile | Mexico | Uruguay | Spain (Barcelona) | Spain (Valencia) | Latin America | Spain | Total |
|-------|-------------|----------------|--------|----------|---------------------------|-------------------|-------|--------|---------|------------------|----------------|---------------|-------|-------|
|       |             |                | n %   | n %      | n %                       | n %               | n %   | n %    | n %     | n %              | n %            | n %           | n %   |       |
| 1/8   | c.127G>C    | p.V43L         | 0 0   | 0 0      | 0 0                       | 1 11.1            | 0 0   | 0 0    | 0 0     | 0 0              | 0 0            | 1 3.4         | 0 0   | 1 0.9 |
| 1α    |             |                |       |          |                           |                   |       |        |         |                  |                |               |       |       |
|       | c.-34G>T    |                | 0 0   | 1 33.3   | 0 0                       | 0 0              | 1 12.5| 5 7.5  | 0 0     | 14 45.2          | 5 5.9          | 19 16.2       |       |       |
|       | c.106delG   |                | 0 0   | 0 0      | 0 0                       | 0 0              | 0 0   | 5 7.5  | 0 0     | 0 0              | 5 5.9          | 5 4.2         |       |       |
|       | c.142C>A    |                | 0 0   | 0 0      | 0 0                       | 0 0              | 0 0   | 0 0    | 0 0     | 0 0              | 0 0            | 4 12.9        | 0 0   | 4 3.4 |
|       | c.146T>C    |                | 0 0   | 0 0      | 0 0                       | 0 0              | 1 100 | 0 0    | 0 0     | 0 0              | 1 3.2          | 0 0            | 1 0.9 |       |
| 2     | c.159G>C    | p.D68H         | 0 0   | 0 0      | 0 0                       | 0 0              | 0 0   | 0 0    | 0 0     | 0 0              | 0 0            | 1 3.2         | 0 0   | 1 0.9 |
|       | p.M53I      |                |       |          |                           |                   |       |        |         |                  |                |               |       |       |
|       | c.176T>G    | p.S73R         | 0 0   | 0 0      | 0 0                       | 0 0              | 0 0   | 2 3.0  | 4 22.2  | 0 0              | 6 7.0          | 6 5.1         |       |       |
|       | p.V59G      |                |       |          |                           |                   |       |        |         |                  |                |               |       |       |
|       | c.262G>T    | p.G102V        | 0 0   | 0 0      | 0 0                       | 0 0              | 2 25.0| 2 3.0  | 0 0     | 2 6.5            | 2 4.2          | 4 3.4         |       |       |
|       | p.E88X      |                |       |          |                           |                   |       |        |         |                  |                |               |       |       |
|       | c.301G>T    | p.R115L        | 1 100 | 0 0      | 1 11.1                     | 0 0              | 0 0   | 5 62.5| 24 35.8 | 4 22.2           | 7 22.6         | 28 32.9       | 35 29.9|       |
|       | p.G101W     |                |       |          |                           |                   |       |        |         |                  |                |               |       |       |
|       | c.358delG   |                | 0 0   | 0 0      | 0 0                       | 0 0              | 0 0   | 1 1.5  | 3 16.7  | 0 0              | 4 4.7          | 4 3.4         |       |       |
|       | p.E120fsX45 |                |       |          |                           |                   |       |        |         |                  |                |               |       |       |
|       | c.430C>T    | p.R144C        | 0 0   | 0 0      | 0 0                       | 0 0              | 1 10  | 0 0    | 0 0     | 0 0              | 1 3.2          | 0 0            | 1 0.9 |       |
| 3     | IVS2-105A>G |                |       |          |                           |                   |       |        |         |                  |                |               |       |       |
|       |             |                | 0 0   | 0 0      | 0 0                       | 1 11.1            | 0 0   | 0 0    | 0 0     | 0 0              | 1 3.2          | 0 0            | 1 0.9 |       |
|       | All exons   | Other¹        | 0 0   | 0 0      | 0 0                       | 0 0              | 0 0   | 28 41.7| 7 38.9  | 0 0              | 35 41.2        | 35 29.9       |       |       |
| Total |             |                | 1 3   | 9 10     | 1 1                        | 8 67             | 18    | 31     | 85 117  |                 |               |               |       |       |

| p16INK4A Polymorphism | Yes | — | 7 | 12.1 | 5 | 8.6 | 1 | 4.0 | — | — | 3 | 12 | 65 | 9.2 | 15 | 7.6 | 16 | 9.6 | 80 | 8.9 | 96 | 9.0 |
| p.A148T              | No  | — | 51 | 87.9 | 53 | 91.4 | 24 | 96.0 | — | — | 22 | 88 | 638 | 90.8 | 183 | 92.4 | 150 | 90.4 | 821 | 91.1 | 971 | 91.0 |
| Missing              | 10 | 0 | 1 | 3 | 6 | 0 | 3 | 0 | 20 | 3 | 23 |
| Total                | 10 | 58 | 59 | 28 | 6 | 25 | 706 | 198 | 186 | 904 | 1,090 |

The other CDKN2A mutations identified in the Spanish population affecting only p14ARF were p.R21RfsX46 (c.60ins16), p.G32R (c.94G>A), and p.A121T (c.318G>A); those affecting p16INK4A were p.A5T (c.13G>A), p.P11T (c.31C>G), p.G35E (c.104G>A), p.N395 (c.116A>G), p.Y44X (c.131dup), p.Q50R (c.149A>G), p.G55V (c.164G>T), p.L65P (c.194T>C), p.N715 (c.212A>G), p.R80X (c.238C>T), p.R87W (c.259C>T), p.R399W (c.295C>T), p.G101R (c.301G>A), p.A102V (c.305C>T), p.R112P (c.335G>C), p.E120fsX21 (c.359_365del), p.G122R (c.364G>C), p.A127S (c.379G>A), and p.D153N (c.457G>A).
Table 4 Clinical and phenotypic characteristics of melanoma patients according to the presence of a CDKN2A mutation, by country

| CDKN2A mutation carriers | Brazil | Brazil | Chile | Mexico | Spain (Barcelona) | Spain (Valencia) | Latin America | Adj. P | Spain | Adj. P | Total | Adj. P |
|--------------------------|--------|--------|-------|--------|-------------------|------------------|---------------|--------|-------|--------|-------|--------|
| Red                      | 0      | 0      | 0     | 0      | 0                 | 0                | 0             | 0      | 0     | 0      | 0     | 0      |
| Blond                    | 0      | 0      | 0     | 0      | 2                 | 7.7              | 37.5          | 0      | 0     | 0      | 0     | 0      |
| Dark                     | 1      | 14.3   | 1     | 8.3    | 9                 | 29.0             | 17.0          | 13.1   | 11.1  | 27     | 30.7  | 78     |
| Missing                  | 0      | 2      | 0     | 0      | 0                 | 0                | 1             | 20     | 2     | 3      | 22    | 25     |
| Total                    | 1      | 3      | 12    | 10     | 2                 | 10               | 11            | 101    | 19    | 39     | 120   | 159    |
| Hair color               |        |        |       |        |                   |                  |               |        |       |        |       |        |
| Eye color                |        |        |       |        |                   |                  |               |        |       |        |       |        |
| Skin colora             | 1      | 14.3   | 3     | 5.4    | 11                | 21.6             | 5             | 19.6   | 7     | 75.0   | 20.0  |
| Nevi count               |        |        |       |        |                   |                  |               |        |       |        |       |        |
| No. of MMs               | 1      | 0      | 1     | 3.7    | 4                 | 16.7             | 5             | 35.7   | 1     | 100    | 43    | 12.3   |
| No. of A148T carriers with melanoma |        |        |       |        |                   |                  |               |        |       |        |       |        |
| Age at diagnosis of first melanoma$^b$ |        |        |       |        |                   |                  |               |        |       |        |       |        |
| CDKN2A mutation          | 39.0   | 40.3   | 18.0  | 43.7   | 10.6              | 43.4             | 9.8           | 47.5   | 3.5   | 36.3   | 15.0  |
| CDKN2A wild type         | 44.9   | 13.6   | 50.0  | 13.6   | 45.7              | 13.2             | 16.4          | 39.2   | 6.8   | 51.8   | 17.3  |
| Total                    | 44.3   | 12.9   | 49.5  | 13.8   | 45.3              | 12.6             | 49.2          | 42.0   | 6.9   | 44.1   | 17.7  | 64.1   |

$^a$Skin color was classified according to the Fitzpatrick phototype classification: fair (phototypes I or II) and dark (phototypes III–V). $^b$The age at diagnosis of first melanoma was not available in 1/28 (3.4%) of Chilean, 2/20 (10%) of Uruguayan, 64/707 (9.1%) of Barcelonan, and 3/195 (1.5%) of Valencian patients.

P values were obtained by comparing carriers vs. noncarriers individually in Latin America, Spain, and the total sample. Adjusted P values were calculated using the Bonferroni correction. Statistically significant P values are given in bold. MM, primary melanoma.
Table 5. MC1R variant distribution

| Country         | Total | Brazil (Porto Alegre) | Brazil (Sao Paulo) | Chile               | Argentina       | Mexico          | Spain (Valencia) | Spain (Barcelona) | Latin America | Spain | Total |
|-----------------|-------|-----------------------|--------------------|---------------------|-----------------|----------------|------------------|-------------------|---------------|-------|-------|
| n               | %     | n                     | %                  | n                   | %               | n              | %                | n                 | %             | n    | %    |
| MC1R WT         | 7      | 222                   | 29.6               | 10                  | 30.3            | 16             | 11.1             | 13                | 21.4          | 9    | 21.4 |
| MC1R ≥1 variant| 9      | 222                   | 29.6               | 10                  | 30.3            | 16             | 11.1             | 13                | 21.4          | 9    | 21.4 |
| MC1R variant    | 9      | 222                   | 29.6               | 10                  | 30.3            | 16             | 11.1             | 13                | 21.4          | 9    | 21.4 |
| Other variants  | 3      | 222                   | 29.6               | 10                  | 30.3            | 16             | 11.1             | 13                | 21.4          | 9    | 21.4 |

Values were obtained comparing Latin America versus Spain. Statistically significant p-values are given in bold.

MC1R WT, p.R160W, and other rare missense variants not associated with red hair or phenotype change. p.R160W variants were considered MC1R ≤10%.

p.R163Q variant in Latin America, although its frequency in a control Latin American population is unknown.

To date, genetic testing in patients at high risk for melanoma is restricted to CDKN2A and CDK4. More studies of patients with melanoma and red hair color. The prevalence of MC1R variants varies between populations. In this study, specific variant frequencies differed between Latin American and Spanish patients with melanoma. Latin American patients with melanoma had an increased presence of p.R160W and p.R163Q. However, controls would be needed to assess the melanoma risk associated with carrying these variants in Latin America. p.R160W is associated with an increased risk for melanoma and red hair color. By contrast, p.R163Q, which is not associated with pigmentation or tanning response, favors the development of chronic sun exposure melanomas in the Mediterranean population and increases the risk for melanoma in areas with high ultraviolet radiation. These reports suggest that a possible interaction between p.R163Q and a high ultraviolet radiation dose could favor melanoma development. Most Latin American countries receive a huge amount of ultraviolet radiation compared with northern latitudes; this could explain the increased frequency of SMP and FM with the p.R163Q variant in Latin America, although its frequency in a control Latin American population is unknown.

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study, the inclusion criteria for genetic counseling for patients with melanoma in Latin America should also follow this rule because it allows the detection of CDKN2A mutations in a significant number of patients, except for southern Brazil, where the rule of three should be used. Genetic testing allows us to identify mutation carriers in families with a high risk of developing the disease. Carriers can be included in specific follow-up programs that allow the detection of melanomas at early stages, which improves the disease prognosis.13,37,38 Digital follow-up with specific dermatologic techniques, including total-body photography and digital dermoscopy, allow early detection of melanomas with a low rate of excision.38 Early melanomas in patients carrying MC1R variants may be difficult to diagnose definitively using dermoscopy, and an integrated approach including clinical history and dermoscopic data should be used when evaluating them.39 Thus, MC1R sequencing could also help to choose the best screening methods. The experience of genetic counseling in Spain over 10 years shows that melanomas can be diagnosed at any time, so the follow-up of individuals at high risk for melanoma should be maintained over time.52

In conclusion, Latin American patients with melanoma and at high risk for melanoma had fair skin and European origin. The mutations found also had been detected in Spanish, European, or North American populations, suggesting that they could have a single origin and that there could be a founder effect. Finally, inclusion criteria for genetic counseling in Latin American patients with melanoma should follow the rule of two: two primary melanomas in an individual or families with at least one invasive melanoma and one or more other diagnoses of melanoma or pancreatic cancer in first- or second-degree relatives.

SUPPLEMENTARY MATERIAL
Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

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DISCLOSURE
The authors declare no conflict of interest.

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