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MC1R Variation in a New Mexico Population

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Abstract

Purpose: The Melanocortin 1 Receptor (*MC1R*) contributes to pigmentation, an important risk factor for developing melanoma. Evaluating single nucleotide polymorphisms (SNPs) in *MC1R* and association with race/ethnicity, skin type, and perceived cancer risk in a New Mexico population will elucidate the role of *MC1R* in a multi-cultural population.

Methods: We genotyped *MC1R* in 191 New Mexicans attending a primary care clinic in Albuquerque. We obtained individuals' self-identified race/ethnicity, skin type, and perceived cancer risk. We defined genetic risk as carriage of any one or more of the nine most common SNPs in *MC1R*.

Results: We found that one MC1R SNP, R163Q (rs885479), was identified in 47.6 percent of self-identified Hispanics and 12.9 percent of non-Hispanic whites, making Hispanics at higher "genetic risk" (as defined by carrying one of the MC1R common variants). When we deleted R163Q from analyses, Hispanics were no longer at higher genetic risk (33.3 percent) compared to NHW (48.3 percent), consistent with melanoma rates, tanning ability and lower perceived risk. Hispanics had a perceived risk significantly lower than non-Hispanic whites (NHW) and a non-significant better tanning ability than NHW.

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Conclusion: The R163Q variant in *MC1R* may not be a risk factor for melanoma among New Mexican Hispanics. This suggestion points to the need to carefully interpret genetic risk factors among specific populations.

Keywords

MC1R; skin cancer risk; Hispanics; New Mexico; non-Hispanic whites

Introduction

In 2019, it is estimated that 96,480 new cases of invasive melanoma, the most deadly form of skin cancer, will be diagnosed in the US, and 7,230 people are expected to die of the disease (1). The most recent data for the US indicates there were approximately 6,623 cases of melanoma among Hispanics in 2015 (2). While there are reports of increasing incidence among Hispanics from California (2) and Florida (3), data from 2003 to 2012 show an overall 1.4 percent decline in the incidence of melanoma in this population (2) with a stable frequency of deeper lesions. Overall, the lifetime risk of getting melanoma is about 2.6% (1 in 38) for whites and 0.58% (1 in 172) for Hispanics (1). Although fewer Hispanics are diagnosed with melanoma than non-Hispanic whites (NHW), they are more often diagnosed at an advanced stage (5) and at a younger age (56 versus 63) (4). Hispanics are one of the fastest growing populations in the United States, further highlighting that understanding their risk for melanoma is an important public health issue.

The major risk factor for melanoma is pigmentation. Melanin, a major determinant of pigmentation important in skin, hair, and eye color (6), is primarily located on the surface of melanocytes. Individuals with less eumelanin, the darker pigment, and more pheomelanin, the lighter pigment, are at highest risk for cutaneous malignant melanoma. Individuals with more pheomelanin generally tan poorly and potentially perceive themselves at high risk, whereas those with more eumelanin tan more easily (6) and potentially perceive themselves to be at lower risk for melanoma.

The melanocortin 1 receptor (*MC1R*), a G-protein coupled receptor, plays a major role in skin and hair pigmentation (7). *MC1R* is polymorphic, and some of these single nucleotide polymorphisms (SNPs) may alter the receptor's function (8). A number of SNPs have been associated with cutaneous melanoma, basal cell carcinoma and squamous cell carcinoma risk (9,10). Few studies have examined *MC1R* SNPs in U.S. Hispanic populations, where their frequency and impact are unknown, particularly in relation to phenotype.

New Mexico's population comprises 48% Hispanic (1.8% of all Hispanics in the US, the largest Hispanic statewide population nationally), and has a unique mixture of individuals who identify as Spanish and/or recent mixed Native American and European ancestry (11, 12). New Mexico therefore provides a distinctive study population for characterizing *MC1R* variants.

The current work aimed to determine whether presence of SNPs in *MC1R* genes, defined as higher than average genetic risk for melanoma, are associated with self-identified race/ethnicity, skin type, and perceived cancer risk in a New Mexico population. A better

understanding of genetic risk in the Hispanic population will guide the development of public health interventions to raise skin cancer awareness.

Materials and Methods:

Data were collected as part of a randomized controlled trial () examining interest, uptake, and outcomes associated with an offer of testing for *MC1R* gene variants associated with increased melanoma risk (10). Study enrollment methods have been described previously (13, 14). In brief, 600 participants were recruited from a primary care clinic in Albuquerque, New Mexico (Table S1). They were randomized 5:1 to an intervention group which received an invitation to assess their genetic risk for melanoma using *MC1R* genotyping compared to a control group where the participants were not offered genetic assessment until after the follow-ups in the intervention group were complete (n=499 in the intervention arm; n=101 in the control arm). Participants in the intervention arm were balanced across self-reported Hispanic (n = 242) versus NHW ethnicity (n = 220; 36 reported “Other” ethnicity; 1 did not report ethnicity). Participants in the control group were evenly distributed across self-reported Hispanic (n = 44) versus NHW ethnicity (n = 44;13 reported “Other”). Each participant provided informed consent as approved by the University of New Mexico Health Sciences Center Institutional Review Board.

Baseline surveys were completed in-person and have been published. Measures used in this study included [1] phenotype (ability to tan (15), history of sunburn), [2] demographics (ethnicity, race, age, income, and education level), [3] family and personal history of skin cancer, and [4] perceived skin cancer risk compared to persons of the same age and sex. Participants in the intervention arm were given access to the study website with information about skin cancer prevention and genetic testing (232, or 46%, accessed the website and 166 of those sent saliva samples for genetic testing). The controls were offered access to the study website, and the potential for genetic testing, after the final follow up assessment (25 sent saliva samples for genetic testing). Genetic risk was assigned based on the nine most common and most-studied MC1R genotypes (10). These included V60L, D84E, V92M, R142H, R151C, I155T, R160W, R163Q and D294H. The entire *MC1R* gene was sequenced, but only these genotypes were used to assess risk. If an individual had one or more of the nine SNPs, they were told that they had a “higher risk” variant. If a participant had none of the nine, then they were told that they were at “average” risk. Results from the genetic tests were sent by email or mail to participants. Two weeks after receiving their results, those in the intervention arm were contacted to complete a survey regarding their responses to receiving their results.

MC1R genotyping.

Saliva samples were mailed to the University of New Mexico Molecular Epidemiology Laboratory. *MC1R* genotypes were described in Kanetsky et al.(16). Genomic DNA was isolated from buccal cells using a version of the QIAamp DNA Mini Kit protocol by Qiagen (Qiagen, Inc., Valencia, CA). Using standard PCR technique, an Eppendorf Mastercycler gradient thermocycler was used to amplify the entire 951-nucleotide *MC1R* coding region. All amplified products were directly sequenced on a 3730 Series Genetic Analyzer (Applied

Biosystems, Foster City, CA) using BigDye Terminators (Applied Biosystems) according to the manufacturer's specifications. PCR primers consisted of a set of two oligonucleotides: 5′-GCCATGAGCACCAGCATAG-3′ and 5′-GACCACACAAATATCACCACCT and a set of four sequencing primers: 5′-TCGTCTTCAGCACGCTCTTC-3′, 5′-TTTAAGGCCAAAGCCCTGGT-3′, 5′-AACCTGCACTCACCCATGTA-3′, and 5′-CTGCAGGTGATCACGTCAAT. *MC1R* chromatograms were read aided by Finchtv sequencing software version 1.5 (Geospiza Inc., Seattle, WA). All *MC1R* genotypes were double entered into a customized Excel sheet and a RedCAP database. We used the *MC1R* consensus sequence (GenBank accession no. AF326275) nomenclature and definitions suggested by Pasquali et al. (10) to group *MC1R* variants by risk.

Univariate associations [odds ratios (OR)] were evaluated for *MC1R* variants and self-reported race and ethnicity. Unconditional logistic regression was used to obtain adjusted estimates. Models were adjusted for age, sex, and family history of skin cancer. Both unadjusted and adjusted ORs and corresponding 95% confidence intervals are presented. Analyses were carried out in SAS 9.4 (SAS, Cary, NC). We restricted analyses to Hispanics and NHW given the "Other" category (Asian, American Indian or Alaskan Native, Native Hawaiian/Pacific Islander, African American, or other) that provided a sample for genotyping represented a small group (n=12).

Results

Characteristics of those genotyped, based on 63 Hispanic and 116 NHW individuals (159 from the intervention group and 20 from the control group who requested genetic testing, excluding "Other" category n=12) show that in this analysis Hispanics compared to NHW are more likely to be female, have less education beyond high school, have a lower income (borderline significant), and be of similar age (Table 1).

Genetic results comparing Hispanics and NHW showed carriage of several different variants. The variant R163Q (rs885479) was more common among Hispanic individuals and V92M (rs2228479) and R160W (rs1805008) were more common among NHW (Table 2).

Only 22.2% of Hispanics perceived themselves to be at increased risk of skin cancer; in contrast, 46.6% of NHW felt themselves to be at increased risk of skin cancer. Based on the genotyping of the nine *MC1R* variants, 63.5% of Hispanics and 56.4% of NHW are at increased genetic risk. When R163Q was excluded from genetic risk assessment, the number of Hispanics with a higher risk variant was reduced by almost half to 33.3% compared to a small reduction to 48.3% among NHW (Table 3).

There was no significant difference in genetic risk, that is, between those with any *MC1R* variant compared to those with no variants, between Hispanics and NHW who reported a family history of skin cancer ($P = 1.00$) (Table S2). In NHW participants, there was a borderline association between family history and high risk genotypes (OR = 2.00, 95% CI = 0.93, 4.30, $P = 0.08$). (Table S2)

Even after adjusting for family history of skin cancer, Hispanics still perceived themselves to be at a lower skin cancer risk than NHW (P=0.004) (Table 3). The majority of genetic risk in

Hispanics was due to the contribution of R163Q (Table 3). In this sample, *MC1R* risk variants were associated neither with tanning ability ($P = 0.60$) nor with perceived risk ($P = 0.82$). (Table S2)

Discussion

Few studies have examined the frequency and impact of *MC1R* SNPs in the U.S. Hispanic population. *MC1R* risk variants have been considered major determinants of sun sensitivity, conferring a 2-to-3-fold increase in melanoma risk in the general population, including those who report increased ability to tan. Interestingly, *MC1R* variants predict melanoma risk in darker-skinned European populations more strongly than those with lighter skin (17). As Hispanics are a phenotypically diverse group with marked variations in tanning ability (17), one might expect relatively wide variation in *MC1R* SNPs.

A genome-wide association study (GWAS) of pigmentation SNPs in more than 6,000 subjects in Latin America found a very strong association of R163Q with Native American populations (17). As many Hispanics in New Mexico have approximately 24 to 37 percent Native American ancestry, our results regarding R163Q are not surprising (18).

New Mexican Hispanics may have a significant contribution of Native American genes (18), and as Native Americans have genetic ties to Northeast Asia (17) where R163Q does not appear to increase risk for melanoma (19), it is critical to continue to evaluate the role of R163Q in NM Hispanics in relationship to melanoma risk. Other studies have found similarly divergent associations for risk SNPs in populations looking at different diseases (e.g., 20). There have been no specific explanations proposed explaining why the particular SNP variant is not associated with melanoma risk in Native Americans. It is likely that pigmentary risk in relationship to melanoma will differ by population and that there are a variety of as yet unstudied interactions among pigmentary genes in Native Americans and Europeans to produce different risk profiles (21). Relationships among *MC1R* genotype, ethnicity/race, self-reported skin cancer, family history of skin cancer and tannability all contribute to skin cancer risk and warrant further investigation in Hispanic populations.

Our study is the first to evaluate *MC1R* variants with self-identified ethnicity in a diverse NM population. Results indicate that when participants are categorized by self-reported ethnicity, the most common *MC1R* variant in Hispanics is R163Q compared to NHW who had increased risk with R151C and R160W. As the Hispanics in our study perceive their skin cancer risk to be lower, understanding how or if the R163Q variants contribute to genetic risk for melanoma among NM Hispanics could inform public health initiatives. A relatively small sample size limits generalizability of our results; they should be investigated in a larger group of Hispanics and NHWs in NM. As the incidence rate of melanoma among New Mexican Hispanics is low and steady, the role of *MC1R* may be more complex than originally thought. New Mexico is a unique setting to further evaluate the role of *MC1R* and other genetic factors in its multi-cultural population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

MC1R	melanocortin-1 receptor
UNM	University of New Mexico
NM	New Mexico
NHW	non-Hispanic white
Hw	Hisapnic white
GWAS	Genome-wide association study

References:

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2019. CA Cancer|Clin 2019 69:7–34.
2. Garnett E, Townsend J, Steele B, Watson M. Characteristics, rates, and trends of melanoma incidence among Hispanics in the USA. Cancer Causes Control. 2016;27:647–59. [PubMed: 27021339]
3. Pollitt RA, Clarke CA, Swetter SM, Peng DH, Zadnick J, Cockburn M. The expanding melanoma burden in California hispanics: Importance of socioeconomic distribution, histologic subtype, and anatomic location. Cancer2011;117:152–61. [PubMed: 20737564]
4. Rouhani P, Pinheiro PS, Sherman R, Arheart K, Fleming LE, Mackinnon J, et al. Increasing rates of melanoma among nonwhites in Florida compared with the United States Arch Dermatol. American Medical Association; 2010
5. Harvey VM, Oldfield CW, Chen JT, Eschbach K. Melanoma Disparities among US Hispanics: Use of the Social Ecological Model to Contextualize Reasons for Inequitable Outcomes and Frame a Research Agenda. J Skin Cancer 2016:4635740. [PubMed: 27651954]
6. Brenner M, Hearing VJ. The protective role of melanin against UV damage in human skin. Photochem Photobiol 2008;84:539–49. [PubMed: 18435612]
7. 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 Melanoma Res. 2003;16:266–72.
8. Beaumont KA, Shekar SL, Newton RA, James MR, Stow JL, Duffy DL, et al. Receptor function, dominant negative activity and phenotype correlations for MC1R variant alleles. Hum Mol Genet. 2007
9. Tagliabue E, Fargnoli MC, Gandini S, Maisonneuve P, Liu F, Kayser M, et al. MC1R gene variants and non-melanoma skin cancer: a pooled analysis from the M-SKIP project. Br J Cancer. 2015;113:354–63. [PubMed: 26103569]
10. Pasquali E, García-Borrón JC, Fargnoli MC, Gandini S, Maisonneuve P, Bagnardi V, et al. *MC1R* variants increased the risk of sporadic cutaneous melanoma in darker-pigmented Caucasians: A pooled-analysis from the M-SKIP project. Int J Cancer. 2014;136:618–631. [PubMed: 24917043]
11. Hunley K, Edgar H, Healy M, Mosley C, Cabana GS West F. Social Identity in New Mexicans of Spanish-Speaking Descent Highlights Limitations of Using Standardized Ethnic Terminology in Research. Hum Biol.2017

12. Rana BK, Hewett-Emmett D, Jin L, Chang BH, Sambuughin N, Lin M, et al. High polymorphism at the human melanocortin 1 receptor locus. Genetics 1999;151:1547–57. [PubMed: 10101176]
13. Hay JL, Berwick M, Zielaskowski K, White KA, Rodríguez VM, Robers E, et al. Implementing an Internet-Delivered Skin Cancer Genetic Testing Intervention to Improve Sun Protection Behavior in a Diverse Population: Protocol for a Randomized Controlled Trial. JMIR Res Protoc. 2017;6:e52. [PubMed: 28442450]
14. Hay JL, Zielaskowski K, Meyer White K, Kaphingst K, Robers E, Guest D, et al. Interest and Uptake of *MC1R* Testing for Melanoma Risk in a Diverse Primary Care Population. JAMA Dermatology. 2018[;154:684. [PubMed: 29801061]
15. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol. 1988;124:869–71. Arch Dermatol. 1988;124:869-71. [PubMed: 3377516]
16. Kanetsky PA, Ge F, Najarian D, Swoyer J, Panossian S, Schuchter L, et al. Assessment of polymorphic variants in the melanocortin-1 receptor gene with cutaneous pigmentation using an evolutionary approach. Cancer Epidemiol Biomarkers Prev. 2004;13:808–19. [PubMed: 15159314]
17. Adhikari K, Mendoza-Revilla J, Sohail A, Fuentes-Guajardo M, Lampert J, Chacón-Duque JC, et al. A GWAS in Latin Americans highlights the convergent evolution of lighter skin pigmentation in Eurasia. Nat Commun. 2019;10:358. [PubMed: 30664655]
18. Healy M, Edgar H, Mosley C, Hunley K. Associations between ethnic identity, regional20and genomic ancestry in New Mexicans of Spanish-speaking descent. Biodemography and Social Biology 2018; 64:152–170. [PubMed: 30570413]
19. Motokawa T, Kato T, Hongo M, Ito M, Takimoto H, Katagiri T, et al. Characteristic MC1R polymorphism in the Japanese population. J Dermatol Sci. 2006 ;41:143–5. [PubMed: 16309897]
20. Zabaleta J, Schneider BG, Rychman K, Hooper PF, Camargo MC, Piazuelo MB et al. Ethnic differences in cytokine genet polymoprhisms: potential implications for cancer development. Cancer Immunol Immunother. 2008;57:107–114. [PubMed: 17618436]
21. Quillen EE. Bauchet M, Bigham AW, Delgado-Burbano ME, Faust FX, Limentidis YC, et al. *OPRM1* and EGFR contribute to skin pigmentaiton differences between Indigenous Americans and Europeans. Hum Genet. 2012; 131:1073–10 [PubMed: 22198722]

Table 1.

Comparison of key demographic characteristics between Hispanics (HW) and Non-Hispanic Whites (NHW) who were genotyped (n = 179).

Variable	HW n (%)	NHW n (%)	Odds Ratio	95% CI	*P*-value
Gender					
Male	6 (9.5)	34 (29.3)			
Female	57 (90.5)	82 (70.7)	0.25	(0.10, 0.64)	0.0003
Age					
Median (IQR)	54 (23)	56 (17)			0.28
Education					
Less than HS	14 (22.2)	7 (6.0)			
HS or greater	49 (71.8)	109 (94.9)	0.22	(0.09, 0.39)	0.0003
Income					
< $50,000	41 (65.8)	22 (34.9)			
≥$50,000	58 (50)	58 (50)	0.54	(0.29, 1.01)	0.06

“Other” participants (n=12) were excluded from analysis due to small sample size

Table 2.

Comparison of *MC1R* genotype in Hispanic (HW) and Non-Hispanic White (NHW) **

Variable	HW (n=63)	NHW (n=116)	Odds Ratio	95% CI	*P-value*
MC1R Genotype					
V60L	10 (15.9)	18 (15.5)	1.03	0.44, 2.38	0.93
D84E	*0*	*2 (1.7)*	*Not estimable*		
V92M	1 (1.6)	12 (10.3)	0.14	0.02, 1.10	0.06
R142H	*0*	2 (1.7)	*Not estimable*		
R151C	6 (9.5)	16 (13.8)	0.66	0.24, 1.78	0.41
I155T	2 (3.2)	4 (3.5)	0.92	0.16, 5.16	0.92
R160W	2 (3.2)	15 (12.9)	0.22	0.49, 0.99	0.03
R163Q	30 (47.6)	15 (12.9)	6.12	2.94, 12.75	<0.0001
D294H	1 (1.6)	1 (0.9)	1.86	0.11, 30.17	0.66

** Includes those from control group who asked for genetic testing (n = 25) and those responding to the invitation for testing in the intervention group (n = 166). We excluded “Other” ethnicity participants (n=12) due to the small sample size.

Table 3:

Tanning ability, perceived risk and genetic risk among Hispanics (HW) and Non-Hispanic White (NHW).

Variable			**Bivariate Association**			**Multivariable Association** [#]		
Tanning Ability [**]	Poor	Good	OR	95% CI	P-value	OR	95% CI	P-value
HW	16 (28.6)	40 (71.4)						
NHW	41 (38.3)	66 (61.7)	0.64	(0.37, 1.30)	0.22	0.66	(0.32, 1.39)	0.27
Perceived Risk	High Risk	Average Risk						
HW	14 (22.2)	49 (77.8)						
NHW	54 (46.5)	62 (53.5)	0.32	(0.16, 0.66)	0.0014	0.34	(0.16, 0.70)	0.004
Genetic Risk [***]	High Risk	Average Risk						
HW	40 (63.5)	23 (36.5)						
NHW	66 (56.4)	50 (48,1)	1.32	(0.70, 2.78)	0.39	1.58	(0.80, 3.13)	0.19
Genetic Risk Without R163Q	High Risk	Average Risk						
HW	23 (33.3)	42 (66.7)						
NHW	56 (48.3)	60 (51.8)	0.54	(0.28, 1.01)	0.06	0.59	(0.30, 1.16)	0.13

[#] Controlling for age, sex and family history of skin cancer

[**] Tanning ability was answered as “don’t know” by 7 Hispanics and 9 NHW.

[***] Genetic risk is based on having any one *MC1R* variants (V60L, D84E, V92M, R142H, R151C, I155T, R160W, R163Q, D294H)