Human leukocyte antigen Class II alleles associated with acral lentiginous melanoma in Mexican Mestizo patients: A case-control study

Rodrigo Roldan-Marin, Lucia Rangel-Gamboa[1], María E. Vega-Memije[2], Susana Hernández-Doño[3], Daniela Ruiz-Gómez[4], Julio Granados[3]

OncoDermatology Clinic, Faculty of Medicine, Universidad Nacional Autónoma de México, [1]Ecology of Pathogenic Agents, Division of Research, General Hospital Dr. Manuel Gea González, [2]Department of Dermatology, General Hospital Dr. Manuel Gea González, [3]Department of Transplant, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, [4]Department of Internal Medicine, Fundación Clínica Médica Sur A.C, Mexico

Abstract

Background: Melanoma is an aggressive cutaneous cancer. Acral lentiginous melanoma is a melanoma subtype arising on palms, soles, and nail-units. The incidence, prevalence and prognosis differ among populations. The link between expression of major histocompatibility complex Class II alleles and melanoma progression is known. However, available studies report variable results regarding the association of melanoma with specific HLA Class II loci.

Aims: The aim of the study was to determine HLA Class II allele frequencies in acral lentiginous melanoma patients and healthy Mexican Mestizo individuals.

Methods: Eighteen patients with acral lentiginous melanoma and 99 healthy controls were recruited. HLA Class II typing was performed based on the sequence-specific oligonucleotide method.

Results: Three alleles were associated with increased susceptibility to develop acral lentiginous melanoma, namely: HLA-DRB1*13:01; pC = 0.02, odds ratio = 6.1, IC95% = 1.4–25.5, HLA-DQA1*01:03; pC = 0.001, odds ratio = 9.3, IC95% = 2.7–31.3 and HLA-DQB1*02:02; pC = 0.01, odds ratio = 3.7, IC95% = 1.4–10.3.

Limitations: The small sample size was a major limitation, although it included all acral lentiginous melanoma patients seen at the dermatology department of Dr. Manuel Gea González General Hospital during the study period.

Conclusion: HLA-DRB1*13:01, HLA-DQB1*02:02 and HLA-DQA*01:03 alleles are associated with increased susceptibility to develop acral lentiginous melanoma in Mexican Mestizo patients.

Key words: Acral lentiginous melanoma, human leukocyte antigen Class II, human leukocyte antigen-DQA1*01:03, human leukocyte antigen-DQB1*02:02, human leukocyte antigen-DRB1*13:01, skin tumour, melanoma

Plain Language Summary

The incidence of skin cancers has been rising in recent decades and melanoma is the most aggressive among these. Melanomas include four genetic and clinical variants. One rare variant is acral lentiginous melanoma, a subtype arising from palms, soles, and nail units. The acral lentiginous melanoma incidence, prevalence and prognosis differ among populations. Melanoma

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Corresponding author: Dr. Lucia Rangel-Gamboa, Department of Ecology of Pathogenic Agents, Division of Investigation, Hospital General Dr. Manuel Gea González, México City, México. draluciaragel@yahoo.com.mx

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progression has been linked to different expression of major histocompatibility complex class II proteins. However, the available literature reports variable findings regarding the melanoma association with specific HLA Class II loci. This study compares HLA Class II allele frequencies in acral lentiginous melanoma Mexican Mestizo patients with the frequencies presented in healthy individuals. Three alleles (HLA-DRB1*13:01, HLA-DQA1*01:03 and HL-DQB1*02:02) were found to confer susceptibility to develop acral lentiginous melanoma in Mexican Mestizo patients. HLA susceptibility alleles differ among melanoma subtypes, which suggests differences in the immunopathological mechanism. Potentially, HLA typing could be useful to discriminate between melanoma subtypes and could possibly help in guiding the treatment plan.

Introduction

Cutaneous melanoma is a relatively common skin cancer with different clinical subtypes that vary with respect to progression and clinical presentation.[1,2] The rarest type of melanoma is acral lentiginous melanoma; this melanoma variant occurs mainly on the palms, soles, and nail units.[3] It begins as a flat patch of discoloured skin that may enlarge slowly over time; it can become invasive and spread as the condition advances. Usually, this entity is diagnosed at advanced stages. Thus, prognosis tends to be worse than with other subtypes of melanoma.[4-6]

Melanoma is considered an immunogenic malignancy. In an idyllic state, antigen-presenting cells lead to the activation of effector memory T-cells in the lymph nodes that mediate anti-tumour effects at the cancer site, producing new antigens from destroyed malignant cells and creating a tumour-immunity cycle.[7] One of the contributory factors to melanoma progression is the failure of melanoma cells expressing HLA Class II molecules to process oxidised or cysteinylated peptides.[8] This phenomenon leads to a modified epitope presentation to CD4+ T-cells and a resultant absence of immune response against the tumour.[9] HLA-DR mediated signalling is another factor that plays a role in melanoma progression, increasing the migration and invasion of melanoma cells.[10]

HLA-DR mediated signalling is strongly influenced by the high polymorphism of these molecules.[10] Importantly, the variability and richness of HLA molecules in Mexican Mestizos are strongly influenced by admixture;[11] and in many cases, the introduced and fixed alleles have been responsible for susceptibility to different diseases. However, the specific alleles which generate susceptibility and change signalling in melanoma cells are not yet described for acral lentiginous melanoma. Consequently, this work aims to determine the frequencies of major histocompatibility complex Class II alleles, namely, HLA-DRB1, HLA-DQB1 and HLA-DQA1 in Mexican Mestizo patients with acral lentiginous melanoma and compare them with ethnically matched healthy controls.

Methods

Subjects

Eighteen ethnically Mexican Mestizo patients with acral lentiginous melanoma were included. Mestizos are the result of admixture, mostly between Amerindians and Spaniards; currently, they represent practically 93% of Mexican population.[12] The diagnosis of acral lentiginous melanoma was based on clinical evaluations as well as histologic criteria. Tumour site and histology were coded according to the World Health Organization classification of tumours.[13] Recruited patients had a histologic diagnosis of acral lentiginous melanoma; ICD code 8744.[5] The presence of other cancers or diseases already linked to HLA alleles, mainly autoimmune diseases, was considered an exclusion criterion. All patients were above 18 years old, and they were recruited during a three-year period between 2004 to 2007, from the dermatology outpatient clinics at Dr. Manuel Gea González General Hospital in Mexico City. As a control group, 99 healthy unrelated Mexican admixed individuals were studied.

Ethics statement

The Institutional Review Board of Dr. Manuel Gea González General Hospital approved the protocols for genetic studies (registration number 06-39-2006). All subjects were informed about the research objectives and procedures related to this study and provided written informed consent before recruitment to this study. Declining to participate did not affect their medical treatment. All procedures were performed with due respect for human rights in keeping with the Helsinki declaration.[14]

HLA typing

Genomic DNA from all study subjects was obtained and purified from peripheral blood leukocytes, according to Miller's salting-out method.[15] Blood was collected by a single peripheral venipuncture, according to the current guidelines and procedures approved by the Internal Review Boards of the Dr. Manuel Gea González General Hospital. The HLA-DRB1, -DQB1 and -DQA1 loci were genotyped based on the hybridisation of labelled single-stranded polymerase chain reaction products to sequence-specific oligonucleotides. The LifeCodes HLA typing kit using the Luminex platform (GenProbe Transplant Diagnostics, Inc., Stamford, CT, USA) was used, in accordance with the manufacturer's recommendations. Data were analysed using the Quicktype for LifeCodes version 3.0 software to determine the HLA alleles.

Statistical analysis

Each allele was evaluated separately with the X^2 method using the Epi Info™ v7.2, Stat Calc, tables (2×2×N) option. Epi Info™ software is provided by the Center for Disease Control and Prevention, Atlanta, USA.[16] A P-value < 0.05 was considered

indicative of a statistically significant difference between HLA allele frequencies in patients compared to healthy individuals. The *P*-values were also corrected using the Bonferroni method (for allele frequencies, multiplying the original *P*-value by the number of alleles, included in the EpiInfo algorithm). The risk factors were expressed as odds ratios.

Results

Clinical and socio-demographic characteristics of acral lentiginous melanoma patients

Eighteen patients with acral lentiginous melanoma were diagnosed by clinical [Figure 1] and histopathological criteria [Figure 2]. The mean age at diagnosis was 56 years; females outnumbered males with a ratio of 2.6:1. Lesions were most often located on the lower extremities, in 10/18 of cases (55.5%).

HLA-DRB1*13:01, -DQA1*01:03 and -DQB1*02:02 are susceptibility alleles for acral lentiginous melanoma

The HLA alleles, which showed higher frequencies among acral lentiginous melanoma patients compared with healthy individuals, were HLA-DQA1*01:03 (pC = 0.001, odds ratio = 9.3, IC95% = 2.7–31.3), HLA-DQB1*02:02 (pC = 0.01, odds ratio = 3.7, IC95% = 1.4–10.3) and HLA-DRB1*13:01 (pC = 0.02, odds ratio = 6.1, IC95% = 1.4–25.5 [Tables 1-3].

Previous studies have not found a linkage disequilibrium among these three susceptibility alleles which we found increased in acral lentiginous melanoma patients.[17] This implies that each allele confers risk separately and the risks are additive. Thus, patients who have more than one susceptibility allele been at a correspondingly greater risk of developing acral lentiginous melanoma, which does not happen when alleles are in linkage disequilibrium. Importantly, any of these alleles are not from native Amerindians.[18]

Discussion

Melanoma in Mexico has a prevalence of 0.4 per 100 thousand inhabitants.[19] However, acral lentiginous melanoma prevalence is not known and limited information has been published about acral lentiginous melanoma and HLA susceptibility alleles. Acral lentiginous melanoma is included as a rare disease in the National Institute of Health Database and Genetic and Rare Diseases Information Center.[20] Its severity is often the result of the delayed diagnosis or misdiagnosis and the fundamental cause of acral lentiginous melanoma is poorly understood. It is not related to sun exposure, unlike other forms of skin cancer.[21,22] Major histocompatibility complex expression is known to influence melanoma severity and its response to anti-cancer therapy. However, only few associations have been described between HLA-specific alleles and melanoma and even less is known in this regard for acral lentiginous melanoma.

Table 1: Allele frequencies of HLA-DQA1 gene in Mexican Mestizo patients with acral lentiginous melanoma

HLA-DQA1 Alleles	Patients N=18 *n*=36		Healthy Individuals N=99 *n*=198		pC[a]	OR	95% IC	
	N	af	n	af				
DQA1*03	12	0.333	51	0.258	0.460	1.4	0.67	3.09
DQA1*01:03	7	0.194	5	0.025	0.0001	9.32	2.77	31.31
DQA1*04:01	5	0.139	33	0.167	0.865	0.8	0.29	2.23
DQA1*01:01	3	0.083	11	0.056	0.791	1.5	0.41	5.84
DQA1*01:02	3	0.083	14	0.071	1.000	1.2	0.33	4.39
DQA1*05:02	3	0.083	5	0.025	0.206	3.5	0.80	15.39
DQA1*05:01	2	0.055	32	0.162	0.160	0.3	0.07	1.33
DQA1*02:01	1	0.028	22	0.111	0.215	0.2	0.03	1.75

N: Number of individuals, n: Number of alleles, af: Allele frequency, *pC[a]: Corrected *P* value by Bonferroni method, correction factor 8, OR: Odds ratio, CI: Confidence interval, ns: No statistical significance, HLA: Human leukocyte antigen

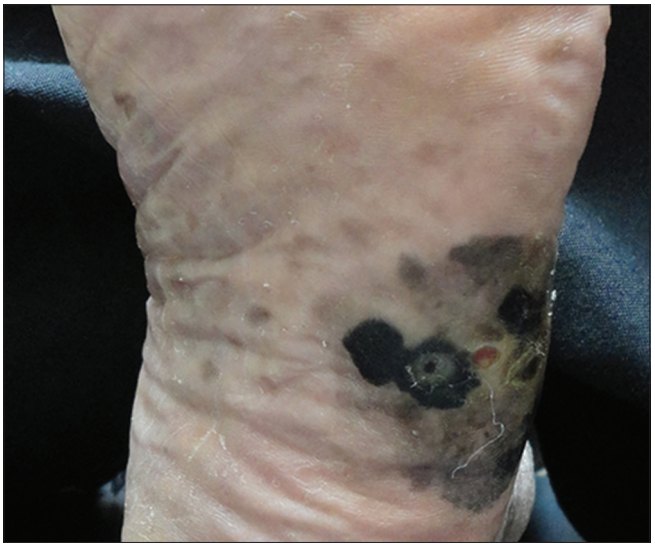

Figure 1: Acral lentiginous melanoma on the lateral aspect of the left foot showing irregularly bordered and variable pigmentation with a slightly centre ulcerated lesion

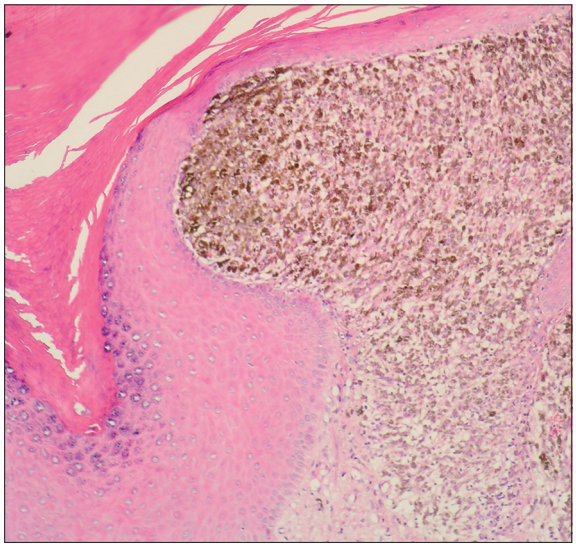

Figure 2: Acral lentiginous melanoma, showing epidermis with acanthosis, in papillary dermis atypical melanocytes with melanin granules and large nuclei. (H&E, ×100)

Table 2: Allele frequencies of HLA-DQB1 gene in Mexican Mestizo patients with acral lentiginous melanoma

HLA-DQB1 Alleles	Patients N=18 *n*=36		Healthy Individuals N=99 *n*=198		pC[a]	OR	95% IC	
	n	af	*n*	af				
DQB1*04:02	9	0.250	33	0.167	0.336	1.7	0.72	3.87
DQB1*02:02	7	0.194	12	0.060	0.01	3.7	1.36	10.28
DQB1*03:02	5	0.139	48	0.242	0.251	0.5	0.19	1.37
DQB1*03:01	3	0.083	33	0.166	0.306	0.5	0.13	1.57
DQB1*06:03	3	0.083	4	0.020	0.130	4.4	0.94	20.60
DQB1*05:01	2	0.055	9	0.045	1.000	1.2	0.26	5.97
DQB1*06:01	2	0.055	2	0.011	0.216	5.8	0.79	42.32
DQB1*06:02	2	0.055	12	0.060	1.000	0.9	0.20	4.26
DQB1*02:01	2	0.055	31	0.156	0.180	0.3	0.07	1.39
DQB1*06:09	1	0.028	0	0.000				

N: Number of individuals, *n*: Number of alleles, af: Allele frequency, *pC[a]: Corrected *P* value by Bonferroni method, correction factor 10, OR: Odds ratio, CI: Confidence interval, ns: No statistical significance, HLA: Human leukocyte antigen

Table 3: Allele frequencies of HLA-DRB1 gene in Mexican Mestizo patients with acral melanoma

HLA-DRB1 Alleles	Patients N=18 *n*=36		Healthy Individuals N=99 *n*=198		pC[a]	OR	95% IC	
	N	af	*n*	af				
DRB1*08:02	9	0.250	30	0.150	0.224	1.9	0.80	4.36
DRB1*07:01	7	0.194	22	0.111	0.262	1.9	0.76	4.93
DRB1*04:07	5	0.138	21	0.106	0.773	1.4	0.48	3.87
DRB1*13:01	4	0.111	4	0.020	0.02	6.1	1.40	25.50
DRB1*15:01	4	0.111	9	0.045	0.235	2.6	0.76	9.03
DRB1*14:01	3	0.083	6	0.030	0.293	2.9	0.69	12.21
DRB1*01:01	2	0.055	7	0.035	0.913	1.6	0.32	8.06
DRB1*03:01	2	0.055	9	0.045	1.000	1.2	0.26	5.97

N: Number of individuals, *n*: Number of alleles, af: Allele frequency, *pC[a]: Corrected *P* value by Bonferroni method, correction factor 8, OR: Odds ratio, CI: Confidence interval, ns: No statistical significance, HLA: Human leukocyte antigen

In this study, we found, three HLA Class II susceptibility alleles, namely, HLA-DRB1*13:01, HLA-DRQB1*02:02 and HLA-DQA1*01:03, which confer high risks for the development of acral lentiginous melanoma in Mexican Mestizos. HLA-DQA1*01:03 was previously associated with melanoma in the Japanese population.[23] However, it is the first time that HLA-DQB1*02:02 and HLA-DRB1*13:01 have been associated with melanoma in any population. Remarkably, each one of these three alleles confers an independent risk for the development of acral lentiginous melanoma. More importantly, these alleles are not recognized as native of Mexican Amerindians; this fact adds an anthropological angle to the results, which in turn influences the biomedical traits. Therefore, the biomedical, clinical, and anthropological importance of the results is discussed.

The complex ethnic background of Mexicans contributes to the unusual situation where alleles such as HLA-DRB1*13:01 and HLA-DRB1*02:02, found in haplotypes mainly from African and Caucasian populations, respectively, increase the susceptibility of Mexican patients to develop acral lentiginos melanoma. Mexicans are among the population groups with the highest richness of admixture worldwide. This fact affects the biomedical traits and consequently, favours the development of diseases and altered immunological responses in Mexicans,[23] as has been seen in other diseases and autoimmune conditions.

The biomedical repercussions chiefly concern the aberrant participation of HLA-DR in melanoma cell signalling, allowing, and enhancing melanoma cell migration and invasion, which has been previously demonstrated.[8-10,24] But hitherto, not much was known regarding specific HLA Class II susceptibility alleles for acral lentiginous melanoma in Mexicans. Quite possibly the acral lentiginous variant shares the invasion mechanism modified by HLA-DR that has been described in common melanoma. Besides, recently it has been demonstrated that major histocompatibility complex proteins are determinants of both melanoma prognosis[25] as well as its sensitivity to different anti-CTLA-4, anti-PD-1 and MAPK inhibitors.[26, 27]

Some studies about HLA alleles and susceptibility to melanoma have been inconclusive.[28,29] But recently, a Genome-Wide Association Study has confirmed the role of HLA in melanoma.[28] In this study, HLA-DQA1*01:03 has been associated with susceptibility to develop acral lentiginous melanoma, which has also been confirmed in Japanese patients ($P = 0.013$, odds ratio = 2.4).[23] Moreover, the HLA-DQA1 locus has been associated with melanoma in Spaniards,[30,31] but the risk alleles found were different from those found in Mexicans. In our study, HLA-DQA1*01:03 presented a strong statistical association with acral lentiginous melanoma patients with carriers having a more than nine-fold risk of developing the disease.

The second allele which presented a significant statistical association with acral lentiginous melanoma in our study was HLA-DQB1*02:02, imparting an almost four-fold increased risk of developing this type of melanoma. HLA-DQB1 locus has been studied in Italian melanoma patients; some alleles were found more frequently in patients, but the results were not statistically significant.[31] Interestingly, other studies have observed that patients with localised melanoma who carried HLA-DQB1*03:01 presented an increased risk of developing recurrent disease compared with stage-matched patients who lacked this allele.[33-35]

The third allele which presented strong statistical association with acral lentiginous melanoma in our studied patients was HLA-DRB1*13:01, conferring a more than six-fold increased risk of developing the disease. Studies about the -DRB1 locus have been performed in different groups of melanoma

patients. A study involving Italian melanoma patients found an increased frequency HLA-DRB1*11:01 but without reaching statistical significance.[32] Nevertheless, another study noticed that HLA-DRB1*11:01 was the strongest predictor of melanoma recurrence. In addition, these patients showed increased levels of IFN-gamma compared with patients lacking this allele,[36] which could be contributory to recurrence.

Regarding anthropological aspects, the presence of three foreign HLA Class II alleles in Mexicans could be explained on the basis that these susceptibility alleles were introduced and fixed because of an advantage against infections. However, antigen presentation by these alleles is not favourable and probably permits acral lentiginous melanoma cells to escape immune responses.

Human migration dynamics could explain the increased frequency of the susceptibility alleles in Mexican Mestizo acral lentiginous melanoma patients. The HLA region is commonly used in anthropology studies because the allele and haplotype distributions at these loci vary widely among ethnic groups.[37,38] Thus, according to the data available in allele frequency net database,[18] the allele HLA-DQA1*01:03 is most prevalent in the region along the ancient commercial route called the "*Silk Road*,"[37,39] which is depicted in Figure 3. In contrast, HLA-DQA1*01:03 is found in low frequencies in Amerindian natives [Table 4]. This allele was

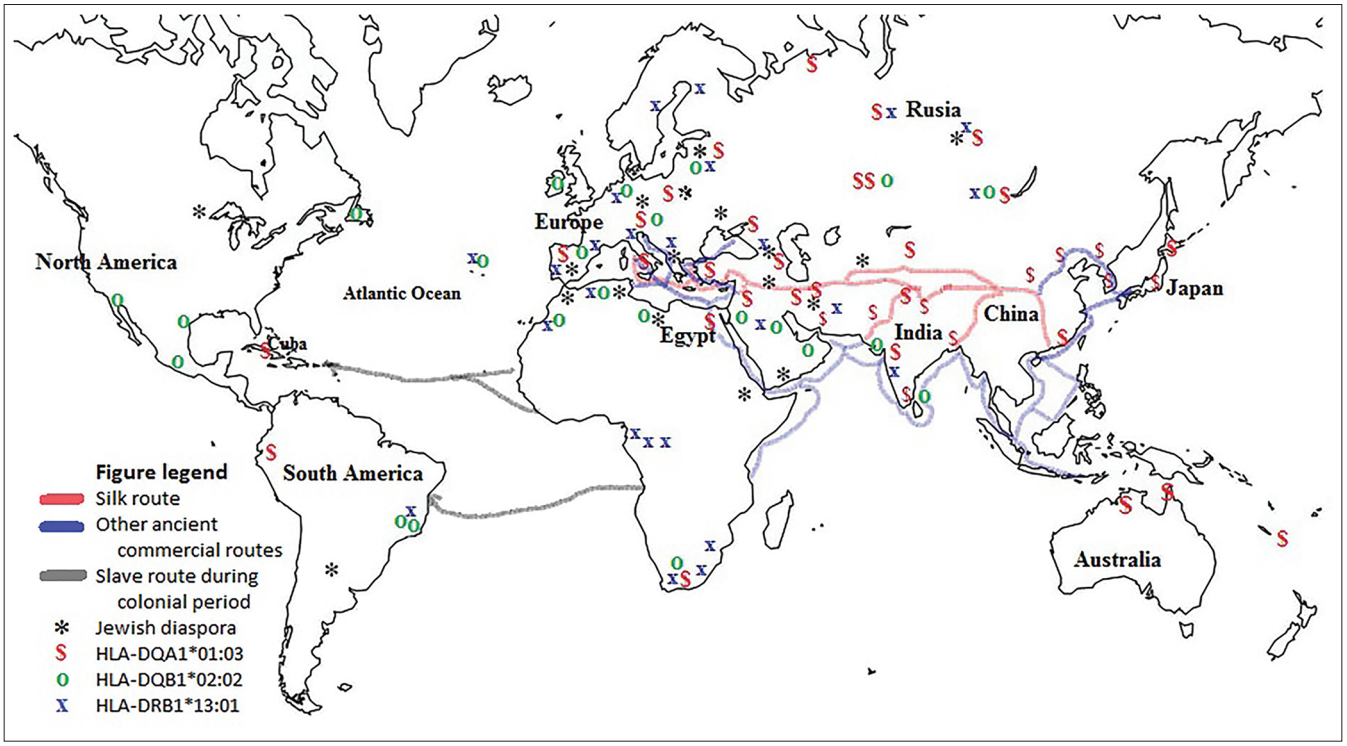

Figure 3: World map showing the Silk Road and other ancient commercial routes from east to west and some slave routes from Africa to America used in the colonial period. Also marked are regions populated by the Jewish diaspora and regions with high prevalence (≥9%) of HLA-DQA1*01:03, HLA-DQB1*02:02 and HLA-DRB1*13:01 alleles

Table 4: Allele frequencies of HLA-DQA1*01:03, HLA-DQB1*02:02 and HLA-DRB1*13:01 alleles in Mexican Mestizo patients with acral melanoma, Mexican Mestizo control group, plus various Amerindian populations, and some Asian, European, and Jewish references populations

Allele	Populations									
	Acral lentiginous melanoma patients	Mexican Mestizo (control group)	Maya Mazatecans Mixtec Nahuas Tarahumara[17,20,21,26,27,33]	Aymaras (Bolivia), Mapuche (Araucanian Chile) and Urros (Titikaka lake, Peru) [34,35]	Japanese[31]	Italian Spain[29,30]		Finland[36]	Jewish[22-25]	
									Ashkenazi	Non-Ashkenazi
DQA1*01:03	0.194	0.025	0.035	?	0.272	0.059–0.113	0.074–0.104	?	0.174–0.181	**0**.149†–0.225
DQB1*02:02	0.194	0.000	0.000	0.000	0.110	0.077	0.175	0.029	0.333[a]	0.423[a]
DRB1*13:01	0.11**1**	0.020	0.000–0.011	0.005	0.000	0.053	0.083	0.090	0.035–0.075	0.089†–0.092

†Moroccan Jews. [a]In these cases just HLA-DQB1*02 information was available, HLA: Human leukocyte antigen

introduced by Europeans during migrations processes to the Americas.[40,41]

As for HLA-DQB1*02:02, it is common in Europe. High allele frequencies are observed in Portugal and Spain, ranging from 0.175–0.178. In Mexican Mestizos, this allele has been previously identified in haplotypes of Caucasian origin.[17] In this study, the frequency of this allele in Mexican Mestizo acral lentiginous melanoma patients is 0.194, which is like its frequency in the Caucasian population. However, the allele frequency is diminished in Mexican Mestizo healthy individuals being 0.060.[17,42]

The third allele of interest, HLA-DRB1*13:01 has been reported at a lower frequency of 0.020 in the native Amerindian population. HLA-DRB1*13:01 appearance in Amerindians is considered to be a product of admixture with Spaniard conquerors.[39,43] However, the highest frequencies of this allele have been found in African haplotypes.[17]

Acral lentiginous melanoma is the rarest type of melanoma, but is most common in non-Caucasian ethnicities, with 15% presenting in Hispanics and only 2–8% in Caucasians. However, it is interesting that one of the main alleles imparting susceptibility to Mexicans is Caucasian, which suggests a genetic interaction with Mexican genes resulting in disease, which manifests much less often in Caucasians. Importantly, the Mexican Americans do not develop acral lentiginous melanoma.

More significantly, the medical implication of this study is that, although informally, medicine in Mexico is increasingly taking the ethnic aspect more seriously in suspecting a disease involving a genetic component. Gradually, ethnicity is taking its place as a novel criterion in the screening and decision algorithm of some diseases.[44]

Limitations

The main limitation of this study is the small sample size. However, this study included every single acral lentiginous melanoma patient seen at the outpatient dermatology clinic at Dr. Manuel Gea González General Hospital during the three-year study period. Moreover, this dermatology department is a national referral centre for dermatological diseases for southern and central states of Mexico.

Conclusion

This study shows the role of HLA alleles in susceptibility to develop acral lentiginous melanoma in Mexican Mestizos. The presence of HLA-DQA1*01:03, HLA-DRB1*02:02 and HLA-DRB1*13:01 increased the risk of acral lentiginous melanoma in this study. These differ from the alleles found in other studies of HLA and common melanoma. The differences in susceptibility alleles could indicate important differences in the immunopathological mechanisms; or besides the differences could be attributable to the ethnic and admixture background. Adding the determination of HLA Class II to the battery of genetic studies conducted on acral lentiginous melanoma in Mexican patients when there are doubts about the melanoma diagnosis could be beneficial.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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