

Multiple Sclerosis in Latin Americans: Genetic Aspects

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Abstract Latin Americans (LA) are a heterogeneous, multi-ethnic group of individuals who inhabit the continental countries in Latin America (LATAM), Caribbean islands and constitute the largest ethnic minority in the USA. Commonly used terminology and ethno racial classifications to define these groups may not be accurate. Risk for multiple sclerosis (MS) among LA is generally low to medium but frequencies are increasing in the American hemisphere. Genome-Wide Association Studies (GWAS) in LA show diverse variants and genetic proportions among Mestizos, the most representative ethnic population, who themselves are the product of centuries of interracial mixing between Native Americans (or Amerindians), White Caucasian Europeans, and Black Africans. Genetic distribution diversity appears to be related to migratory and historical and socio-political factors in LATAM. Epidemiologic studies show an extremely low prevalence of MS among non-mixed Amerindians; this has been attributed to protective ancestral Asian genetics and possibly, environmental factors. Mestizos and biracial LA of African ancestry have more susceptibility to MS apparently due to the historical introduction of the European HLA-DRB1*1501 gene. Contribution from HLA typing, GWAS, and ancestry informative markers (AIMs) has been determinant in the current LA genetic understanding but more regional studies are needed. The relationship between genetics and disease regional distribution is emphasized.

Keywords Multiple sclerosis · Latin Americans · Genetics · Amerindians · Mestizo

Introduction

Multiple sclerosis (MS) is a chronic, demyelinating, inflammatory, axonal degenerative disorder of the central nervous system (CNS). A distinct geographic distribution is recognized with the highest concentration of disease occurring in the northern portions of the globe. It is generally accepted that zonal presence of MS is closely linked to genetic factors providing susceptibility either directly or by interacting with environmental elements. The disease is fairly common in White Caucasians of northern European ancestry, but it is less common where non-Caucasians live, and in tropical zones. The prevalence in the Nordic region, the British Isles, and Canada is $\geq 220/100,000$ [1, 2] while the mean prevalence in the USA estimated among the commercially insured population is $149.2/100,000$ with regional variations [3]. MS has variable frequencies in the Americas with prevalence fluctuating from low to medium risk: $3.2/100,000$ (the lowest) in Ecuador, South America, and $30/100,000$ (the highest) in San Pedro Garza Garcia, a suburb of Monterrey, Mexico [4, 5]. Epidemiologic studies from Latin America (LATAM) indicate an increasing prevalence in these countries [6].

This phenomenon appears to be augmented by diverse factors including access to diagnostic tools and better diagnostic criteria, modern neurological education, increasing number of professionals in the region, and wider public information [7]. The continental LATAM mass extends from the southern frontier of USA with Mexico (32° north latitude) to the Patagonia (56° south latitude), includes 17 countries as well as the major island countries in the Caribbean. The LATAM population is estimated to be more than 560 million. The main languages in

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the region are Spanish, Portuguese, French, and indigenous languages and dialects. The National MS Society reports more than 400,000 individuals with MS in the USA [8]. Although epidemiologic studies on Latin American (LA) persons with MS residing in the USA are scarce [9, 10], recent estimations indicate there are about 25,000 to 30,000 ethnic LA with MS in this country [11].

The major histocompatibility complex (MHC) locus is the most consistent genetic determinant in MS. The MHC class II molecule serologically defined as the human leukocyte antigen (HLA) haplotype DRB1*1501-DQA1*0102-DQB1*0602 (HLA-DRB1) is the strongest genetic association affecting MS susceptibility [12]. This genetic signature is present in close to 70% of people with MS, mostly Caucasians of northern European descent living in the areas of the world exhibiting the highest concentration of this disease, with an odds ratio (OR) of ≥ 3 [13]. HLA-DRB1 is also present in healthy individuals although in a reduced proportion (25–30%), but is rare in healthy Black Africans, Asians, Amerindians, and LA groups [14].

More modern approaches to genetic predisposition utilizing Genome-Wide Association Studies (GWAS) identify DNA variants located across the genome, polymorphisms acting as surrogate markers of the loci associated with the trait of interest. These studies have reported more MS susceptibility in populations of European descent [15].

The genetic influences affecting LA susceptibility to MS, including the identification of “regional” variations outside the inheritance influence of the HLA-DRB1*1501, the presence of protective genes conferring “resistance” to acquire the disease, data from GWAS, and the epigenetic and environmental factors contributing to the development of disease in the region, deserve discussion. This review will focus in available genetic reports in LA with MS.

Challenges to Ethnic Definitions of LA Populations

Inaccurate terminology describing ethnic and racial groups may affect inclusion criteria in genetic and epidemiologic studies; hence, the final results and appropriate conclusions may be at risk [16]. The term *Hispanic* and *Latino* are used interchangeably in the USA (the latter referring to LA). The terms are utilized to define this large and heterogeneous ethnic conglomerate. In 1980, the US Census Bureau introduced the term *Hispanic* in view of increasing difficulties defining these groups (“persons of Spanish surname”) [17], adding in 2010 the optional demonym *Latino* referring to a person “of Cuban, Mexican, Puerto Rican, Central or South American origin, regardless of race” [18]. While the LA denomination is based on historical and socio-political concepts dating back to the nineteenth century (people from the American continent who speak a Latin-derived language and share common cultures),

the term has a broader connotation and is more inclusive than the term *Hispanic* which factually excludes people of Portuguese extraction including Brazilians, many African Caribbean groups, and non-Spaniard Caucasians of European origin born or residing in Latin America (LATAM). The US Census estimates the Hispanic (LA) population in the USA (September 14, 2015) at 57 million or 17.3% of the nation’s total population [19], thus is the nation’s largest ethnic minority. Mexicans constitute the majority of this segment (64%). People of Puerto Rican background represent about 9.5% of the LA population, while Cubans along with Salvadorans, other Central and South American groups, compose the rest of the LA conglomerate in the USA [20].

The term *Hispanic* commonly employed in the USA is not utilized in LATAM countries whose populations typically identify themselves according to their nationality (i.e., Mexican, Argentinean, Brazilian, etc.) or as *Latin Americans* when described as an ethnic hemispheric group. The terms *Native Americans*, *American Indians*, *Amerindians*, and customarily in Canada, *Aboriginals*, are utilized interchangeably referring to the descendants of the indigenous populations of the Americas.

LA Populations, Genetics, and MS

American Indians

All theories on the early peopling of the Americas point to a seminal Asian origin [21] when groups migrated from the Beringian region, moving down south by land to Mesoamerica, and also some by sea along the Pacific coast reaching the southern tip of South America. This unique multipath human migration phenomenon occurred during an epoch estimated between 16,000 to 20,000 years after the last *Glacial Maximum* period [22].

Analysis of the genetic and anthropological links between East Asian *Mongoloid* groups and Native Americans or Amerindians, resulting from migration and dispersal routes of their ancestral populations, has identified several alleles present in these large groups including HLA-B*3901-DRB1*1406-DRB1*0301 and HLA-A*6801 [23•] as well as multiple mitochondrial haplotypes [24, 25]. These findings indicate that native populations from North America, Mexico, Central and South America share *Mongoloid* genetic markers with Asian groups.

MS prevalence in Far East Asian areas is very low, with reports consistently showing frequencies of less than 5/100,000, i.e., Yakutsk Natives from Siberia, 0.1/100,000, and populations from the Yunnan Province in China, 2/100,000 [26]. The low MS prevalence in Asia, along with the ancestral genetic Asian congruency with Amerindians, supports the generalized concept that these groups are seldom

affected by the disease. MS was initially not identified among the major Amerindian groups of central Mexico in a general epidemiological study performed in 1996 [27•]; further observations have been carried out in northern Mexico [28, 29], and in the southernmost region of the country, bordering with Guatemala. This last observation was from a specifically designed epidemiological study to confirm the absence of MS and other demyelinating diseases in native populations in Mexico. It was carried on-site among Lacandonian people, an isolated, "pure" (non-mixed) Amerindian ethnic group living in the sierras of Chiapas. This study explored generational antecedents and current health status and did not find clinical evidence of demyelinating disease [30••]. Studies in other areas of the Americas including Colombia [31], Brazil, Peru, Chile [32], Panama [33], and Ecuador [34] have coincided with lack of identification in non-mixed Amerindians. A consensus in this respect has been emitted by the Latin American Committee for Treatment and Research in MS (LACTRIMS) [35].

Clinical and genetic differences between Native Americans in the hemisphere have been reported. Genetic analysis in Canadian aboriginals of Algonkian background in Manitoba [36] diagnosed with MS has shown DRB1 and DQB1 loci with analysis HLA alleles "previously not associated with the development of MS." Some of the cases reported in this study however had predominance of opticneuritis, longitudinally extensive cervical cord lesions (>5 levels) by the MR images displayed in the report, along with atypical brain lesions and histopathological findings suggestive of NMO. Nevertheless, MS has been recognized among native populations from Canada and the USA, albeit exhibiting a very low prevalence. The MS frequencies in First Nations people in Alberta, Canada [37] and aboriginals living in British Columbia (First Nations, Inuit and Métis) [38] are similar to the prevalence found among Native American, Veterans from the US Gulf War era ($\geq 3/100,000$) [39]. Even though ancient Mongoloid roots are shared by the Native US and Canadian populations with the Native American or Amerindian groups from the rest of the continent, the genetic frame appears to have evolved differently between these groups. While Native Canadian and Native US populations have for generations tended to a more flexible intermixing with White Caucasians and other ethnic groups, i.e., Mexicans in the US Southwest [40–42], the opposite situation has occurred with actual native peoples in the rest of the continent who remain essentially non-mixed and perennially isolated.

A multinational cooperative analysis involving patients with diverse forms of *Idiopathic Inflammatory Demyelinating Disease (IID)* from Argentina, Brazil, Paraguay, and Venezuela, did not identify Amerindians in any of the 1474 cases collected from 22 centers contributing to this cross-sectional descriptive study [43].

Latin American Mestizos

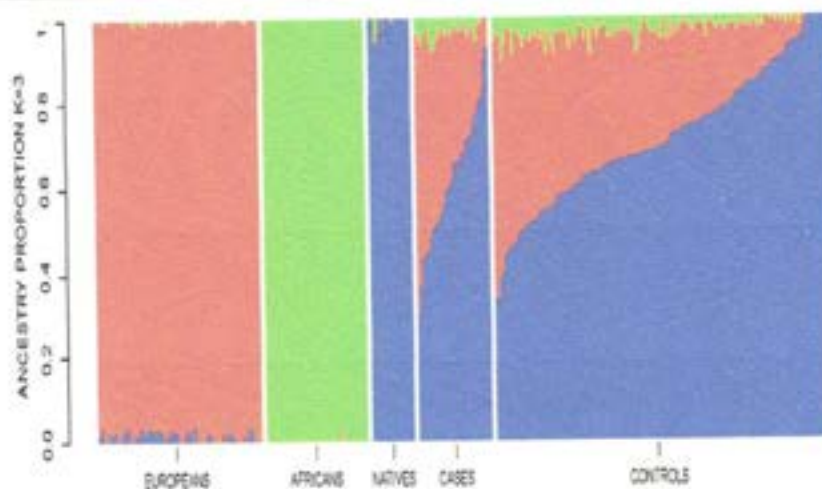
Mestizos constitute the largest ethnically diverse group in LATAM, a complex racial admixture resulting from five centuries of intermixing genetics from Amerindians, White Caucasian Europeans, and the eventual incorporation of genetics from Black Sub-Saharan Africans [44]. While the fundamental racial structure of the LA Mestizo remains uniform in the American continent, the distribution of the diverse genetic proportions has had substantial regional differences even within the territory of a region as shown by panels of *ancestry informative markers* (AIMs) based on GWAS [45]. Variants in genetic proportions in LA Mestizos most likely reflect historical and migratory developments in the American continent. Puerto Rican and Dominicans have the largest proportion of African ancestry while Mexicans have a significant larger genetic proportion of Native American heritage than other LA groups [46]. Mexicans also have the lowest contribution from African genetics (1%) as determined by studies derived from the Mexican genome [47].

Analysis of HLA class II genotypes in Mexican Mestizos with familial and non-familial MS showed a predominant association with HLA-DR2 (the common MS European inherited genetic marker), while controls had frequencies of less than 0.05 of these haplotypes [48]. Additional observations on familial MS (including twin studies) among LA populations are lacking in LATAM.

A GWAS genotyping assessment performed on Mexican Mestizos with MS showed significant difference ($p = 0.0045$) in the European proportion ancestry between MS cases and controls. In that study, imputation analysis showed a signal with significant level ($p = 0.00005$) in the HLA-DRB region [49••]. These findings suggest enriched European ancestry is a risk factor to develop MS in Mexican Mestizo populations while indigenous ancestry of Asian origin seems to confer protection. In this study, the African genetic component (as previously established by other observations) was similarly negligible in both the MS cases and controls (Fig. 1).

Typing HLA class II polymorphisms on Colombian Mestizos showed the alleles DRB1*1503, DQB1*0602, and DRB1*1501 were risk factors to develop MS [50]. Studies in Argentina confirmed the strong association of HLA-DRB1*15 in patients with MS (33.9%) comparison to controls (13.5%), $p < 0.001$ [51]. A caveat posed by genetic epidemiological assessments in this South American country is that majority of the Argentinean population is Caucasian with Italian, Spanish, English, German, and other European ancestries intermixing prominently over the last two centuries while native and African genetic influences are very low.

Fig. 1 Proportions of European, African, and Amerindian ancestry in Mexican Mestizo MS cases and controls: higher European ancestry in MS cases (reprinted from Ordoñez et al. [49]), with permission from Elsevier)



Observations in Brazil, a country constituted by a complex multiethnic population, show the allele HLA-DRB1*15 to be the most common MS marker association in White and Mulatto groups [52]. The term Mulatto is commonly used in LATAM referring to individuals derived from the biracial mixture of White Caucasians with Black Africans.

The US census reports the majority of ethnic Hispanics (66.2%) are of White race [53]. This group is most representative of the LA Mestizo population in the USA. Racial denominations in LATAM countries are utilized in national census and epidemiological studies, but rarely constitute a sociological discussion.

Latin Americans of African Ancestry

African groups arrived to the American continent during centuries XVI to XIX adding to the complex genetic admixture of the peoples in the Americas. Despite the substantial contribution of African genetics to the population fabric of many areas in the hemisphere, very few studies exist on the genetic characterization of LA of African ancestry with MS in the LATAM region. Studies in African Americans with MS in the USA have provided important data in incidence and risk variants [54–56]; however, similar information from the rest of the continent is lacking. Large groups of biracial African LA contribute to the population structure in the Caribbean islands, most Central American countries, and the South American countries of Colombia, Venezuela, Ecuador, Peru, areas in northern Chile and western Paraguay, and Brazil.

African LA are customarily identified or self-proclaimed according to their nationality, i.e., African Cubans, African Brazilians, African Peruvians, etc. Genetic studies in Brazilian MS patients from Rio de Janeiro (22.9° south latitude) showed the HLA-DQ1*0201-0301 to be prominent in Whites ($p = 0.003$) and DRB*03-1503 in African Brazilians. In these series, DRB1*1501 allele conferred ethnicity independent MS susceptibility in White patients while

DQB1*0602 conferred susceptibility regardless of ethnicity [57]. Other genetic/epidemiologic studies performed in the area of Curitiba, State of Paraná (25.6° south latitude), did not identify any African Brazilian in a series of 86 MS patients although 3.6% were identified as biracial individuals and 96.6% as Whites. Despite the relative geographic approximation of these locations, the authors conclude that diverse genetic backgrounds influence ethnic distribution in the Brazilian populations [58]. Nevertheless, racial categories in Brazil are traditionally based on skin color. The last census (2010) showed that 50.7% of the population define themselves as Black or mixed race or *Pardo* (“brown”) [59]. Formal DNA or genome studies in this multi-ethnicity country have not been completed.

MS has been reported in Martinique (French West Indies) [60], island situated in the easternmost area of the Caribbean with a very small White population (5%); the rest of Martinicans are Non-Caucasian conformed by a racial blend of people of African ancestry and French heritage (French Afro-Caribbean). Even though Martinicans are not commonly included within the concept of the LA population, their French language roots, genetics, and culture could include them within this broad ethnic connotation. A genetic study in African Martinicans with MS demonstrated an association of disease with alleles DRB1*15 and DRB1*07, the former clearly of European origin. In this study however, the allele subtype *1503 was more common in this population [61].

While the HLA-DRB1 gene appears to be the major primary genetic introduction into the MS susceptibility frame in LA, multiple variants are noted in the diverse populations of the Americas (Table 1).

Latin American Populations’ Resistance to MS

The notable absence of MS in non-mixed Amerindians (Table 2) has been adjudicated to a large extent to their

Table 1 Genetic markers in populations with MS in the Americas

Allele groups	Populations
HLA-DRB1*1501-DQB1*0302	Mexican Mestizos, Chihuahua [28]
HLA-DRB1*1501-DQA1*0102-DQB1*0602	
HLA-DRB4*0103-DQB1*0302	
HLA-DRB1 and DQB1	Canadian Aboriginals [36]
HLA-DR2	Familial MS in Mexican Mestizos [48]
HLA-DRB1*1503	Colombian Mestizos [50]
HLA-DQB1*0602	
HLA-DRB1*1503	
HLA-DRB1*15	Argentines [51]
HLA-DRB1*15	White and Mulatto Brazilians [52]
HLA-DQ1*0201-0301	White Brazilians [57]
HLA-DRB1*1501	White Brazilians [idem]
HLA-DRB*03-1503	African Brazilians [idem]
HLA-DQB1*0602	Independent of ethnicity [idem]
HLA-DRB1*1503	Afro-Caribbean (Martinique) [61]

References: Velazquez et al. [28]; Mirsattari et al. [36]; Alvarado-de la Barrera et al. [48]; Rojas et al. [50]; Patrucco et al. [51]; Bram et al. [52]; Alves-Leon et al. [57]; Quélvenec et al. [61]

ancestral Asian roots. Low MS prevalence is consistently reported among the peoples in the Far East. At present time, the population impact of native groups in the Americas is variable. Amerindian groups are practically extinguished in Cuba and Puerto Rico after being racially incorporated into the other segments of the population. Amerindians have a very small demographic representation in Argentina and Uruguay but in other countries, particularly Mexico, with a population of 123 million inhabitants, Amerindians constitute 21.5% (26 million) of the population. The demographics of the most remotely located and isolated groups in Mexico are dwindling, becoming increasingly urbanized and mixed with the Mestizo population [62]. The theoretical effect of this sociological phenomenon in the prevalence of MS in these areas remains to be established.

In an analytical typing study, healthy Mexican Mestizos had an HLA-DR1 presence showing a significant difference to a comparative cohort of patients with relapsing-remitting MS ($p = 0.050$). It is deduced by this finding that certain genes may confer protection for MS to certain Mestizo groups [63]. Epistatic studies have not been performed in LATAM.

The report of high incidence of parasitism among Amerindian groups [64] and its purportedly immunologic regulatory effect in MS would suggest the effect of potential environmental factors providing additional protection to these groups. Phylogenetic trees suggest Amerindians that live in similar ecosystems, i.e., Seris Indians from Sonora, northwestern Mexico, and Waro Indians from Venezuela, are more closely related than Mexican Lacandones who live in the jungle in southwestern Mexico [65].

Table 2 Latin American areas not identifying Amerindians groups with MS

Mexico
Central Mexico [27]
Chihuahua [28]
Monterrey [29]
Chiapas [30]
Colombia [31]
Medellin
Chile [32]
Santiago
Peru [32]
Lima
Brazil [43]
Goiânia
Mato Grosso
Minas Gerais
Pará
Paraná
Pernambuco
Rio de Janeiro
Santa Catarina
Sao Paulo
Paraguay [43]
Asunción
Venezuela [43]
Caracas
Maracaibo
Argentina [51]
Buenos Aires

References: Corona et al. [27]; Velázquez et al. [28]; De la Maza Flores et al. [29]; Flores et al. [30]; Sánchez et al. [31]; Rivera et al. [32]; Pappas-Alvarenga et al. [43]; Patrucco et al. [51]

Other contributing external elements and epigenetic factors have not been studied.

Conclusions

Studies in the LATAM region show the major susceptibility factor for MS is the historical introduction of the primary European HLA-DRB1 into the genetic composition of the population. Diverse allelic and haplotypic varieties have been identified among the LA Mestizo groups and people of African ancestry with MS in the Americas. Epistatic and epigenetic factors have not been assessed. The ineluctable relationship between disease distribution and the genetic frame of populations of the Americas is emphasized by the available data. Studies on the apparent resistance to MS from Amerindians and more regional genetic ascertainties

utilizing advanced methods, i.e., GWAS and molecular AIMS techniques, are needed in LA.

Compliance with Ethical Standards

Conflict of Interest Victor M. Rivera declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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