

# The genetics of multiple sclerosis in Latin America

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## Abstract

**Background:** In today's globalised world, the heterogeneity of diseases such as multiple sclerosis has been studied since it has been suggested that ethnic differences, in conjunction with geographical and environmental factors, influence its incidence and prevalence.

**Aim:** Based on this, an attempt has been made to identify the genetic factors that may confer risk or protection, not only for developing multiple sclerosis but also for determining the course of its evolution.

**Results:** In Latin America we have some data about this, which have been replicated in different populations in the entire region, with very different results compared with other regions, which could explain not only the different frequencies in some populations, such as Caucasians, but also the course of the disease and the response to actual treatments. However, in addition to these findings, other associated epigenetic mechanisms have also been found in our populations, such as levels of vitamin D, parasitic diseases, and indigenous populations. Therefore, the study of epigenetics plays a crucial role in understanding the physiopathology of multiple sclerosis. It must be studied in each population, especially in Latin America, due to its broad heterogeneity.

**Conclusion:** It is very important to understand not only the genetic and external factors with these very specific effects in multiple sclerosis patients, but also the way they interact and are able to explain the frequency and some specific phenotypes of the disease in our populations besides the possibility to be a very specific treatment target.

**Keywords:** Multiple sclerosis, genetics, Latin America, epigenetics

Date received: 16 May 2017; accepted: 25 July 2017

## Introduction

In today's globalised world, cultural diversity and genetics are permanently being studied. There is repeated mention of the influence of environmental factors and population-based genetic susceptibility, cultural-genetic pluralism and multiculturalism, hybrid populations and their influence on the heterogeneity of diseases such as multiple sclerosis (MS).

The first cultures on the American continent appeared approximately 45,000 years ago and belonged to a nomadic group of hunter-gatherers who migrated from north to south in successive waves. They originated in the Asiatic steppes before crossing the Bering Strait. The unity of the human species is a scientifically irrefutable fact and American regions were populated over tens of thousands of years, as were other parts of the world,

starting from a common origin that is possibly located in Africa.

In Mesoamerica, the 'high civilisations' (Incas, Mayans, Aztecs) appeared and were characterised by a diversified economy, impressive urban and ceremonial centres, and unique regional exposure to environmental factors that certainly contributed to the susceptibility of suffering from certain diseases in our time.

Autoimmune diseases, especially MS, are classified as organ specific and may involve components of the humoral and cellular response.<sup>1</sup>

In MS, genetic factors play a very important role in disease susceptibility.<sup>2</sup> It has been suggested that ethnic differences, in conjunction with geographical



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**Table 1.** Indigenous population estimates in certain countries in Latin America.

Country	Indigenous population	% of total population
Argentina	360,000	1.1
Belize	27,000	14.7
Bolivia	5,600,000	81.2
Brazil	1,500,000	1.0
Colombia	744,000	2.2
Chile	1,000,000	10.3
Ecuador	3,800,000	35.3
El Salvador	400,000	7.0
Guatemala	4,600,000	50.0
Honduras	50,000	1.3
Mexico	10,900,000	12.6
Nicaragua	67,000	1.8
Panama	194,000	8.3
Paraguay	30,000	0.7
Peru	9,000,000	40.0
Venezuela	315,000	1.0

**Source:** CEPAL, “Etnicidad, ‘raza’ y equidad en América Latina y el Caribe,” Doc. LC/R.1967, March 2000; ML González, “How many indigenous people?” in Psacharopoulos G and Patrinos HA (Eds.), *Indigenous People and Poverty in Latin America*, 1994.

and environmental factors, influence the incidence and prevalence of the disease.<sup>3</sup> There is little published information available in Latin America (LATAM) and the Caribbean on the indigenous component of our populations (Table 1).

It is very important that we know about the genetic risk and protection factors for populations like ours.<sup>1,4</sup> To date, more than 100 loci have been identified as being related to the disease; genetic studies have identified the participation of DRB\*15:01 in Caucasian populations as the main susceptibility allele in MS.<sup>5</sup>

This geographical region has an incidence between 0.85 and 21.5 cases per 100,000 inhabitants and is estimated to be between 1.0 and 7.1 for Central America and the Caribbean.<sup>6</sup>

### MS genetics in LATAM

Based on these data, an attempt has been made to identify the genetic factors that may confer risk or protection, not only for developing MS but also for determining the course of its evolution.

Specific studies have been carried out in LATAM to this end, with findings in many cases that are distinct to those previously described in Caucasian and even Asian populations (although studies exist in countries such as Mexico, where certain genetic characteristics are shared with the latter populations).<sup>2</sup>

Currently, more than 100 loci have been associated with MS. The human leukocyte antigen (HLA) on chromosome 6 is the locus with the highest association to date,<sup>2,7,8</sup> or at least has been replicated most consistently in different populations around the world.

A genome-wide association study has confirmed the participation of the DRB\*15:01 allele as a primary susceptibility factor for MS; however, throughout the world differences have been noted even among countries within the same region, but mainly in European populations, where the HLA-DRB1\*15:03 haplotype is more frequent.<sup>5</sup>

For example, Mexican studies on ancestry as a potential risk factor for MS have found that Mexican mestizo patients have different proportions of genetic mixtures than healthy mestizos in the general population, suggesting that susceptibility to the disease may be related to a higher European component.<sup>2</sup> In this case, the most frequent allele found in individuals with relapsing–remitting multiple sclerosis (RRMS) was DR\*15 ( $P=0.006$ , odds ratio (OR) 2.2, 95% confidence interval (CI) 1.3–3.6), and the DR\*13 allele was more frequent among healthy individuals than among MS patients ( $P=0.050$ ), even though it has a protective OR 2.6 (95% CI 1.3–5.2,  $P=0.050$ ), suggesting a protective factor among the Mexican Mestizo population. This study compared the progression index (PI) in RRMS patients who were carriers of the DR13 allele (PI 0.63), slightly above that expected (0.4–0.6) and the mean PI of all patients (0.94), showing a less aggressive disease course in HLA-DR13 patients, but without statistical significance (Table 2). Subsequent studies looked for specific alleles in patients versus controls.

In other countries such as Brazil, which has one of the highest rates of documented MS patients in LATAM, other studies have been published with interesting findings on haplotypes that had not previously been described and that initially presented with statistical significance. However, after making the necessary statistical corrections, not all of them presented with relevant values;<sup>9</sup> the lack of significance may be due to the number of patients or to the

**Table 2.** Genetic findings described in Latin American countries.

Country	Year	Alleles	Protective	Risk	<i>P</i> value
Mexico (7)	2015	DR*15		*	0.006
		DR*13	*		0.05
Brazil (9)	2017	DQB1*02:03		*	0.0027
Brazil (10)	2014	DRB1*1501		*	0.002
Argentina (11)	2009	DRB1*1501		*	<0.001
		DR*14	*		0.07
Colombia (12)	2015	DR*15		*	<0.001
		DR*14	*		0.001

regions where the samples were obtained. However, a previous study found a significant association with HLA-DRB1\*1501 but with a higher incidence in female patients, which may be explained by the gene interactions that code the oestrogen receptor and the vitamin D receptor and the said allele, with a consequent increase in the risk of developing MS.<sup>10</sup> Also, the same study found that the CIITA polymorphism of rs4774\*C (the gene regulating HLA-D expression) is associated with higher disease frequency in combination with the haplotype above.<sup>10</sup>

In another study from Argentina, the finding on HLA-DRB1\*1501 was replicated, and it is notable that HLA-DRB1\*14 is reported to tend to be a protective factor, although it was not statistically significant ( $P = 0.07$ ).<sup>11</sup> However, it becomes relevant when a subsequent study was published on the Colombian population that found the latter association with a reliable statistical significance.<sup>12</sup>

It is important to mention that the genetic studies were not carried out solely to look for specific associations with HLA, although they are clearly those with the most descriptions around the world. It is also important to remember that in the context of a multifactorial disease with a physiopathology that is still in the process of being understood, such as MS, other genetic factors become important.

One of the best examples that has been studied in our population are the findings in Brazilian studies regarding mutations in the vitamin D receptor (VDR). More recently, they have been described in a study carried out in Mexico,<sup>8</sup> in which 120 patients and 180 controls manifested a positive association of polymorphism specific to VDR, TaqI (rs731236) and BsmI (rs1544410) with MS in adult patients. There

are various theories for this interaction; the main theory clearly explains how this gene regulates the transcription of HLA-DRB1-15, which has consistently emerged as the main genetic factor in MS.<sup>13</sup>

Despite these findings, it must be noted that the differences in results among different populations highlight the need for more studies based on the ethnic and genetic differences present in each country.

Populations in LATAM differ genetically based on their ancestry, because of the indigenous genetic and European components, since the colonising populations differed by country and region. Currently, ancestry studies are being performed to locate specific regions where specific susceptibility antigens are manifested.

### Epigenetics and MS in LATAM

There has been a notable increase in the number of cases of MS in LATAM; for example, in Mexico, the incidence rose from 1.6 to 12 patients per 100,000 inhabitants.<sup>4,14</sup> The study of MS in LATAM is, therefore, a highly interesting task because it involves population characteristics that are very complex because of the mixture of native and European genes. The addition of genes from other ethnicities such as Asian and African, as the result of voluntary and involuntary migration, also combine with the region's own environmental factors.

As mentioned previously, MS is subject to genetic and environmental factors. This has given rise to a special interest in understanding which external factors influence the manifestation, behaviour, and prognosis of the disease. It is also important to identify the molecular changes produced at the cellular level and their implications in genetic expression.<sup>15</sup> Specifically, epigenetics is the link between these environmental and genetic factors, as it is

characterised by the identification of reversible molecular processes that are responsible for modifying the cellular phenotype as a response to external stimuli.<sup>16,17</sup> These changes may be as small as the addition or removal of chemical groups of DNA or their histones, which result in gene expression or deactivation.<sup>18,19</sup> In specific relation to MS, known for its complex immune physiopathology, the suppression or activation of the production of certain proteins derived from genetic expression is a key feature of immune modulation, which may be beneficial in limiting or increasing disease activity. With these points in mind, it is very clear how epigenetics becomes a key factor in the risk of suffering from MS and affect its evolution, prognosis, and therapy.

One of the most well-known epigenetic mechanisms in MS is methylation. At the nuclear level of the virgin T lymphocyte, methylation is a decisive process in the differentiation of T helper 1 and T helper 2 cells. In addition, the hypomethylation of IL-17, one of the most important pro-inflammatory interleukins in MS, stimulates the differentiation of more lymphocytes, which speaks to us of a regulatory process. Other molecular mechanisms that have been studied as the result of epigenetic changes are histone acetylation and transcriptional regulation by micro RNA.<sup>19,20</sup>

Diet also influences the processing of the genome through macronutrients, because it may generate reversible changes to DNA that may generate protection or damage. This occurs with isoflavonoids, omega 3 and six polyphenols, food contents, which molecular action protects from oxidative stress and reduces the risk of degenerative conditions in MS.<sup>21</sup> Taking in certain vegetables may unleash a process that influences transcription factors, which directly influence intranuclear receptors. These, in turn, inhibit the acetylation of certain histones, producing a protective effect on DNA aging. In particular, in our populations the diet is absolutely different from other countries where the frequency of the disease is greater, not only in the ingredients, but also in the processing of the same, as well as the traditions in their preparation, which also has not been well established, and is a possible factor of dietary epigenetic changes.

Other factors that may produce molecular genetic changes that have been studied are associated with the Epstein–Barr virus and the varicella zoster virus (VZV); for example, in Mexico VZV was the most frequent virus to be identified in relapses of MS

patients,<sup>22–24</sup> as well as hormones, ultraviolet radiation,<sup>25</sup> levels of vitamin D serum, smoking and exposure to metals, among others.

In addition, the hygiene factor theory differentiates between developed and developing countries in reference to parasitic diseases that may confer, through immune mechanisms, certain protection against developing the disease.<sup>26,27</sup>

Despite the large number of studies on these factors worldwide, the different populations in LATAM have a different response pattern, secondary to the complexity of their genetic inheritance as a population and their environmental diversity. For example, a study of indigenous populations that have maintained endogamy that was carried out in the Lacandona region in Chiapas, Mexico, did not find MS or neuromyelitis optica in the population.<sup>28</sup>

Generalisations about risk factors based on studies of European or Anglosaxon populations are not always reproducible in LATAM. For example, the assertion that low levels of vitamin D constitute a risk factor for MS was applicable in a country like Argentina, but not in tropical countries in LATAM such as Mexico and Brazil, where vitamin D levels were low in both patients and control cases, and where not only the environment may be influencing these results, but also the genetics of the population, due to the differences present in Argentina, in relation to those in Brazil or Mexico.<sup>29–34</sup>

Therefore, the study of epigenetics plays a crucial role in understanding the physiopathology of MS. It must be studied in each population, especially in LATAM, due to its broad heterogeneity of the population and environmental levels.

### Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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