

Multiple sclerosis as a universal disease and the challenges to immigrants in high prevalence countries

doi:10.1111/ene.13574

Multiple sclerosis (MS) frequencies are increasing globally affecting populations which traditionally were considered to have a low risk for the disease. MS is common among white Caucasians of northern European ancestry, displaying a very high prevalence in Scandinavia and the British Isles and in the areas where their genetically descendant and migratory groups live: Canada, USA, Australia and New Zealand [1]. Whilst genetic susceptibility appears to be the most significant consequential factor in MS development, it is generally accepted that interaction with some environmental and exogenous elements will assemble the complex multifactorial immunopathogenic process leading to disease.

Genome-wide association studies (GWAS) identified specific HLA *DR/DQ* genes in MS. The allele HLA *DRB1*1501 (DRB1)* exerts the largest genetic contribution to Caucasian, African American, Asian and Latin American populations with MS; hence these groups account for more than 70% of the world's people affected by the disease [2]. The *DRB1* genotype is rare amongst groups with low (or reportedly nil) MS presence such as non-mixed Māori in New Zealand, the Sámi people living in the northernmost areas of the Scandinavian countries, the Inuit in northern Canada and Alaska, and 'pure' Native Americans (Amerindians) [3].

The *DRB1* genetic tag, however, is not an exclusive determinant for disease susceptibility. 'Regional' HLA variations have also been described, i.e. African Brazilian MS patients exhibit a stronger association with HLA *DQB1*0602* [4]. The widely utilized observation that groups migrating from a low to a high MS prevalence area condition the new arrivals to acquire the local risk (particularly if the immigrants are younger than 15 years of age or born in the new country) continues to be debated. However, studies assessing phenotype characterizations and long-term prognosis in migratory groups are scarce.

In this issue, a study by Alsaed *et al.*, analyzing the long-term outcomes in ethnic minorities (EM) with MS from a UK-population-based registry (Wales), identified 83 EM individuals with MS and compared their clinical course over time with the

outcomes of 1866 Caucasian patients [5]. The EM groups originated from areas with theoretically a low MS prevalence. Although in 21 individuals information on country of birth was not available, in the patients where this datum was identified, one-third (32.5%) were born in Europe upholding the consideration of environmental influences favoring their susceptibility to the disease. The EM populations included Afro-Caribbean, Indian, Pakistani, Bangladeshi, Chinese, Gulf and North African Arabs, partially representing present time migratory tendencies to the UK. These patients were younger at disease onset (28.6 vs. 32.8 years, $P = 0.001$) and reached early levels of disability more rapidly than their British Caucasian counterparts. These findings mirror observations on Latin Americans (LAs) in the USA. LA immigrants with MS acquire the highest level of disability faster whilst LAs born in the USA experience the onset of symptoms at an earlier age (28.5 vs. 39.2 years, $P < 0.001$) [6]. LA Mestizos constitute the most representative ethnic population on the American continent. This complex genetic group is the product of five centuries of interracial admixture between Amerindians and white European Caucasians, primarily Spanish, Portuguese and French, evolving in the areas constituting at present the LA region: Mexico, Central America, South America and the major Caribbean island countries.

The proportion of black African genetics contributing to the LA Mestizo genomic profile is associated with historical and migratory events occurring throughout time in the different areas of the Americas. GWAS performed in Mexican Mestizos from the general population showed a minimal proportion of African ancestry (<3%) whilst the European and Amerindian components occupied the genetic metrics data almost equally. On the other hand, the GWAS genotyping assessment on Mexican Mestizos with MS showed a significant enrichment of the European proportion ancestry ($P = 0.00005$) in the HLA *DRB* region. An intriguing aspect in LA MS epidemiology is the 'resistance' and apparent extreme low risk to MS demonstrated by non-mixed Amerindians which has been associated with their predominantly ancestral

Asian genetics [7], considering that MS is rare amongst Far Eastern Chinese and Siberian groups.

Whilst MS prevalence remains low amongst some ethnic groups, its frequency is notably increasing in the subtropical arid climate Middle East countries, as well as LA countries mostly located in the tropics, some near the Equator [8]. In this era, multipath human migration and genetic dissemination have contributed to the globalization of MS affecting populations relatively resistant to this disorder. Exposure to new, although still mostly unknown, environmental factors may also be a causal generator. The concern of possibly ineffective access to adequate care for EM in industrialized countries (which usually exhibit high prevalence) is provoked by the findings from the UK and studies in US Latinos. Whether this represents an unfavorable societal situation affecting these groups residing in a new environment or a real biological phenomenon deserves to be further studied.

Disclosure of conflicts of interest

The author declares no financial or other conflicts of interest.

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