

Invited editorial

Genetic burden mirrors epidemiology of multiple sclerosis

Kelly Hilven, An Goris

Laboratory for Neuroimmunology, Department of Neurosciences, KU Leuven – University of Leuven, Herestraat 49 bus 1022, 3000 Leuven, Belgium

Corresponding author:

an.goris@med.kuleuven.be, phone +32-16-330772

The prevalence of multiple sclerosis (MS) varies worldwide and, within Europe, decreases with latitude from Scandinavia to the Mediterranean populations. Several explanations have been offered for the prevalence gradient including environmental factors such as sunlight exposure. However, differences in the frequency of genetic risk factors may well explain an important fraction of variation in prevalence of MS¹. The Italian island of Sardinia, one of the highest risk regions worldwide with an MS prevalence of 224/100,000 inhabitants, is a notable exception on the north-south gradient and is characterized by a genetic background distinct from other European populations and long isolation². In two papers in the current issue of *Multiple Sclerosis Journal*, Hadjixenofontos *et al.* and Barizzone *et al.* investigate the combined role of known MS genetic risk factors in this special population^{3,4}.

The current list of known MS risk variants includes several independent HLA alleles and 110 non-HLA variants, most of which have been identified in the context of the International Multiple Sclerosis Genetics Consortium, with contributions from continental Europe, the UK, US and Australia^{5, 6}. Combining data from the current studies in Sardinia^{3, 4} with previous work in Europeans^{5, 6} and African Americans⁷ demonstrates that common MS risk variants tend to be shared across populations even though their population frequencies can vary. Indeed, the vast majority (89%) of non-HLA risk variants detected in a mixed European population show over-representation of the risk allele also in Sardinian cases versus controls, with 42% reaching nominal significance as expected in a single study population of this size⁴.

A summary measure, the multiple sclerosis genetic burden (MSGB), counts the total number of MS risk alleles a person carries, weighted by the risk effect size of each variant. As expected and as seen in other European populations⁸, the average genetic burden in patients is higher than in controls^{3,4}. More remarkably, the genetic burden in Sardinian controls is significantly elevated compared to continental Italian or US controls and approximately equals the burden observed in patients in the latter populations^{3,4}. This increased burden is not due to a few variants with exceptionally deviating frequencies in Sardinia but rather to a subtle increase in frequency for many risk variants. This is seen in the median difference of 1% between the frequency of non-HLA risk variants in Sardinia and continental Italy⁴ or the average difference of 2 out of a total possible of 218 risk alleles between US controls and both US cases and Sardinian controls³. Barizzone *et al.* further extend this observation by reporting a correlation between the burden of known genetic variants and the prevalence of MS throughout Europe⁴. Genetic scores capturing general trends in epidemiology have already been shown for other immune-related diseases⁹.

Both studies report some degree of heterogeneity between the Sardinian and mixed European population in the percentage of the variance explained by known variants and the distribution of the non-HLA burden stratified by the HLA burden^{3,4}. This may once again relate to differences in the frequency of shared risk variants, which are even more pronounced for the HLA region compared to non-HLA variants. Indeed, all of the five classical HLA alleles originally reported in mixed European^{5,6} or Sardinian¹⁰ populations are significantly associated with MS in both continental Italy and Sardinia⁴ but frequencies and consequently the power to detect these effects in different study populations vary. The DRB1*1501 allele is common in northern Europe, less common in southern Europe and rare

in Sardinia, where the DRB1*0301 allele takes over as predominant HLA risk allele. The DRB1*0405-DQB1*0301 risk haplotype, on the other hand, is only seen in Sardinia, continental Italy and Italian minorities but is virtually absent elsewhere¹¹. Further fine-mapping of the regions of association, especially the HLA region for which non-additive effects and interactions have been suggested^{10, 12}, will improve models of how a different frequency spectrum contributes to disease risk in Sardinia versus other European populations.

Components of the genetic burden contribute not only to risk but also the phenotype of the disease. The HLA burden, especially the DRB1*1501 allele, corresponds on average to a younger age at onset^{5, 8} and higher antibody production in the cerebrospinal fluid^{8, 13}, and there are indications that a higher non-HLA burden, based on the up-to-date list of known variants in mainly immunological genes, correlates with higher relapse rate⁸. Hence, an intriguing question remains whether the increased MS genetic burden or the different frequency spectrum of especially HLA alleles within this burden reflects distinct features of the disease phenotype in Sardinia.

Acknowledgments

AG is supported by the Research Fund KU Leuven (OT/11/087 and CREA/14/023) and the Research Foundation Flanders (G073415N).

References

1. Dean G, Yeo TW, Goris A, et al. HLA-DRB1 and multiple sclerosis in Malta. *Neurology*. 2007; 70: 101-5.
2. Sardu C, Cocco E, Mereu A, et al. Population based study of 12 autoimmune diseases in Sardinia, Italy: prevalence and comorbidity. *PLoS One*. 2012; 7: e32487.
3. Hadjixenofontos A, Gourraud PA, Bakthavachalam V, et al. Enrichment for Northern European-derived multiple sclerosis risk alleles in Sardinia. *Mult Scler*. 2015.
4. Barizzone N, Zara I, Sorosina M, et al. The burden of Multiple Sclerosis variants in continental Italians and Sardinians. *Mult Scler*. 2015.
5. The International Multiple Sclerosis Genetics Consortium and The Wellcome Trust Case Control Consortium 2. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature*. 2011; 476: 214-9.
6. The International Multiple Sclerosis Genetics Consortium. Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. *Nat Genet*. 2013; 45: 1353-60.
7. Isobe N, Madireddy L, Khankhanian P, et al. An ImmunoChip study of multiple sclerosis risk in African Americans. *Brain*. 2015; 138: 1518-30.
8. Hilven K, Patsopoulos NA, Dubois B and Goris A. Burden of risk variants correlates with phenotype of multiple sclerosis. *Mult Scler*. 2015.
9. Kiryluk K, Li Y, Sanna-Cherchi S, et al. Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. *PLoS Genet*. 2012; 8: e1002765.
10. Cocco E, Sardu C, Pieroni E, et al. HLA-DRB1-DQB1 haplotypes confer susceptibility and resistance to multiple sclerosis in Sardinia. *PLoS One*. 2012; 7: e33972.
11. Gonzalez-Galarza FF, Takeshita LY, Santos EJ, et al. Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations. *Nucleic Acids Res*. 2015; 43: D784-8.
12. Barcellos LF, Sawcer S, Ramsay PP, et al. Heterogeneity at the HLA-DRB1 locus and risk for multiple sclerosis. *Hum Mol Genet*. 2006; 15: 2813-24.
13. Goris A, Pauwels I, Gustavsen MW, et al. Genetic variants are major determinants of CSF antibody levels in multiple sclerosis. *Brain*. 2015; 138: 632-43.