The major cause of multiple sclerosis is environmental: genetics has a minor role - Yes

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Proposal

It is clear that multiple sclerosis (MS) has a complex aetiology that involves both genetic and environmental factors and that both make a significant contribution to causation. However, the weight of evidence would favour a significantly greater role for the environment over genetics. There is now ample evidence for a profound effect of the environment on MS causality, with at least four and probably more factors directly contributing, with the reported effect sizes significantly greater than any identified genetic factor.

1. latitude, sunlight exposure (UVR), and vitamin D (odds ratio [OR] ≈ 20);¹
2. prior Epstein–Barr Virus (EBV) infection timing and adaptive immune response to EBV (OR = 12.5);²
3. cigarette smoking (OR = 1.4);²
4. the hygiene hypothesis (OR ≈ 3).³

The actual heritability of MS is not clearly delineated, as defining heritability in a polygenic disease can be very difficult. Most studies state that the genetic component of MS risk is around 25% largely based on the concordance rates of mono-zygotic twins.⁴ The rates for female mono-zygotic twins being significantly higher than male mono-zygotic twins and the rate for di-zygotic twins being similar to that for non-twin siblings.⁴ The actual sibling relative risk (λₙ) is also used to characterize the level of heritability (λₙ is calculated by dividing the risk for siblings by the population risk (population prevalence)); for MS this figure is 20–40 indicating that the risk for siblings is 20–40 times the background population MS risk.⁵ The effect of environmental exposure may also act by multiple processes at the genomic level including epistasis, changes in methylation, gene–environment interactions and/or directly on the adaptive immune system.

Currently despite massive genome-wide association studies (GWASs),⁶,⁷ we can only explain 20–30% of the perceived heritability of MS. Perhaps the other 70–80% is not yet to be found but represents an individual’s environmental lifetime exposure affecting how genes are expressed or methylated and thereby influence perceived heritability.

It would seem at odds that the remaining 70–80% of unexplained MS heritability is made up of thousands of genes with a small effect ORs <1.1 or rare variants (none have been found to date). For example in Crohn’s disease the percentage of heritability contributed by multiple small risk alleles has been calculated for ever-increasing GWAS size and demonstrated that for a near infinite sized GWAS that the common variance hypothesis can only describe less than 40% of the perceived heritability.⁸

Therefore, if the upper estimate of MS heritability from twin studies is 25% and the amount of heritability that we can explain at present represents only 25% of this we may only be explaining 5% of the causation of MS by known genetic variants. After human leukocyte antigen (HLA) DRB1*15:01 the next most significant genetic locus described, IL2RA, only contributes <1% to overall MS heritability.⁶

It is important to note that there does not appear to be a genetically MS immune population, with MS reported in many ethnic groups and in all locations around the globe. Indicating that even in the absence of all known genetic causative and putative ethnic/genetic protective factors, MS still occurs.¹

In contrast the environmental causative factors all have well-established and well-supported roles in MS causation and have significant and large effects on MS causation.

Latitude. The latitude gradient may be the most obvious example of how the environment affects the risk of MS. The gradient is now well established as a true MS geodemiological association, with MS prevalence increasing from very low levels near the equator of 5–10 per 100,000 to levels around 200 per 100,000 population at latitude 59° N, an increase of more than 20 fold.¹⁹ A similar gradient has been found for first episodes of central nervous system
(CNS) demyelination. Adjusting for the frequency of the most powerful genetic association HLA DRB1*15:01 does not have a significant influence on the gradient in Europe, indicating that the gradient is driven by environmental rather than genetic factors. The best explanation for the gradient may be decreased UVR exposure and subsequent decreased vitamin D particularly in winter.

**EBV infection.** Studies consistently show that people with MS are more likely to be EBV seropositive (≥99%) than healthy controls (85–95%), suggesting that prior EBV infection may be a prerequisite for the development of the disease process. In recent meta-analyses, the summary OR for MS based on being EBV seropositive (versus seronegative, 8 studies) was 13.5 (95% confidence interval [CI] 6.3–31.4), while being EBV seronegative (versus seropositive, 13 studies) was associated with a marked decrease in MS risk (OR = 0.06, 95% CI 0.03–0.13). Timing of EBV infections also plays an important role in MS causation. Early EBV infections, although associated with an increased risk of MS, are not as strongly associated as late EBV infections particularly those associated with clinical infectious mononucleosis (IM). Previous hospital admission with IM was associated with a four-fold increase in MS risk compared with a comparison cohort in the Oxford Record Linkage Study, with a mean interval to MS onset of 14 years. The most consistent EBV serological finding in relation to increased MS risk is elevation of antibodies to the Epstein–Barr nuclear antigen (EBNA) complex, particularly anti-EBNA-1 titres. In a recent meta-analysis (n = 30 studies) the summary ORs for MS risk in relation to anti-EBNA-1 IgG, OR = 12.1 (95% CI 3.1–46.9).

**Smoking, personal UVR exposure, vitamin D and the hygiene hypothesis.** Smoking and the hygiene hypotheses are also well-established environmental risk factors that significantly alter the risk of developing MS. Vitamin D deficiency clearly has a role in the causation of MS and is now well established as a risk factor for MS with lower vitamin D prior to MS onset associated with a significant increase in the risk of developing MS.

**Gene–environment interactions.** Several instances of clear gene environment interaction have been described in MS nearly always interacting with HLA DRB1*15:01. For example, the combined effect of HLA-DRB1*15:01 positivity and low infant sibling exposure on MS (OR = 7.88, 95% CI 3.43–18.11) was 3.9-fold greater than expected. When combined with high EBNA titres the OR increased to >19, indicating how a modifiable environmental factor can significantly interact with a modest effect fixed genetic factor.

**Conclusions**

The weight of evidence would support the assertion that the environment is more important than genetics in the causation of MS. Environmental factors may provide >75% of the risk of developing MS. Although genetic factors are important and may play a significant role in the development of MS in individuals not exposed to the discussed environmental factors, they are by no means the major driver of MS causation in the vast majority of MS cases.

**References**