Genetic epidemiology of multiple sclerosis

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Multiple sclerosis (MS) is a chronic autoimmune disease characterized by demyelination of nerves in the central nervous system. MS has no known singular cause, but onset is affected by genetic traits, environmental factors, immune dysregulation, and viral infections, particularly by Epstein-Barr Virus (EBV). None of these causes always leads to development of MS, and they interact in complex ways.

# MS is not always hereditary, but some genetic risk factors are.

While MS is not hereditary in a classical Mendelian sense like some other neurological disorders (e.g. Huntington’s), having a relative with MS is a risk factor, although families with many occurrences of MS are uncommon. Identical twins show the highest prevalence of familial MS, with prevalence decreasing along with genetic relatedness [1,2]. MS affects over 200 different genetic loci, so quantifying the heritability of all traits which can increase MS susceptibility is impossible with current methodology. The effect of any given single polymorphism on MS susceptibility is unclear, so understanding how all of these traits interact to determine MS heritability is difficult [3].

The prevalence of MS has historically been accepted to be higher in populations with European ancestry than in other racial or ethnic groups, which may be due to the environmental effect of latitude, or due to the distribution of certain genetic haplotypes across racial and ethnic groups. Recent findings with the prevalence of MS in Australia, and the lack of data from Africa and the Middle East complicates this finding, however [4]. Furthermore, Black Americans also have a higher risk of MS than indigenous American populations, or African and Asian populations. So attributing MS heritability to either an environmental effect of latitude or to allelic variants associated with specific ethnic groups is quite difficult, and MS susceptibility likely arises as the interaction of both effects [3,5,6].

# Polymorphisms in important immune system genes are associated with MS pathophysiology.

The first genetic risk factors discovered for MS were multiple alleles in human leukocyte antigen (HLA) genes, which encode the major histocompatibility complex (MHC) [7]. MHC plays a vital role in the immune response, and is important in both identifying infectious agents, as well as auto-immune responses. Since MS involves the immune system attacking the myelin sheath of CNS nerves, involvement of a critical immunogenetic locus in MS pathophysiology makes sense. Several HLA allelles area ssociated with increased susceptibility to MS, although not all individuals with MS have these HLA alleles, nor does the presence of a given HLA allele imply the incidence of MS.

Since the 1970s when the HLA complex was discovered to be involved with MS, MS has been accepted as a polygenetic trait where many individual polymorphisms all contribute a small amount of risk towards developing MS [1]. There are two hypothesis with regards to the genetic component of MS. The “common disease” hypothesis suggests that only a few frequent gene variants affect disease susceptibility, and these variants have high prevalence but a weak effect [8,9]. The heterogeneity hypothesis posits a genetic predisposition to a disease is due to many rare variants which sporadically occur in the population, but individually have very strong effects [8,10]. However, genome-wide association studies (GWAS) have suggested that a mixture of these two hypotheses is an underlying mechanism for the development of MS, and the interaction between prevalent, weak genes and rare, strong genes is important. MS has over 200 loci which have been identified as risk factors [3], which is more than expected under the common disease hypothesis, but less than expected purely from the heterogeneity hypothesis [8,11].

Multiple different HLA alleles are associated with MS, empirically supporting a blend of strong and weak genetic effects on MS susceptibility. While one major HLA allele is associated with the majority of MS cases in Caucasian populations (specificaly HLA-DRB1\*15:01), this allele is not necessary or sufficient for the development of MS. Other HLA genotypes have also been associated with MS, and different genotypes are associated with other ethnic groups as well. So while some HLA alleles have a stronger impact on MS than others, the relative strength and frequency of these effects vary across different populations, likely because of gene-gene and gene-environment interactions [12].

# Viral infection is closely linked to MS incidence.

In addition to HLA and other genetic signals, several viral infections are linked to MS susceptibility. Individuals who are seropositive to cytomegalovirus [13], varicella-zoster virus [14], other herpesviruses [13], acinetobacter [8], or pseudomonas [8] were more likely to develop MS, among other pathogens. The most prominent pathogenic culprit in the development of MS is Epstein-Barr Virus (EBV) [8,13,15]. Notably, herpesviruses are incredibly common in human serosurveys, even in individuals who have never had symptomatic infections. For example, EBV is ubiquitous, even in individuals who report never having infectious mononucleosis.

The ubiquity of herpesviruses has made testing causal hypothesis of the relationship between herpesviruse serostatus and other diseases difficult, because such studies typically have very low power. However, a recent cohort study conducted by Greer et al using residual serum samples from the Department of Defense Serum Repository demonstrated that risk of MS incidecence was 32 times higher in participants who were EBV-negative prior to enrollment [15]. The same study found that other viruses, including cytomegalovirus, did not show the same effect. Given that not every EBV-negative individual eventually developed MS, while it seems likely that adult contraction of EBV can be important in the development of MS, genetic and environmental markers cannot be disregarded, and likely interact with the effect of EBV infection.

# Environmental and genetic traits have interacting effects on MS susceptibility.

# Future directions

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