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In Search of the Holy Grail: Linking Genotype to Clinical Phenotype in Multiple Sclerosis

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The clinical heterogeneity associated with progression to disability remains one of the mysteries surrounding multiple sclerosis (MS) and can be a source of consternation to patients and physicians alike. Patients who appear neurologically comparable at diagnosis often have widely divergent disease courses: some progress rapidly and require assistance to ambulate within a few years, while others experience few relapses and remain almost neurologically intact for decades. Many have hypothesized that the phenotypic variability of MS stems from underlying genetic differences between patients.

The major histocompatibility complex (MHC) was identified as a contributor to MS risk in the 1970's (1). Subsequently, the sequencing of the human genome and generation of the haplotype map were followed by the development of technologies that allowed rapid interrogation of the genome to ascertain genetic variants associated with disease risk. This provided a roadmap to examine the pathogenesis of MS in a “non-hypothesis limited” fashion. Although the risk attributable to most individual nucleotide variants is modest, comprehensive study of risk variants with genome wide association studies (GWAS) provides an unbiased view of the biological pathways disrupted across human autoimmune diseases. This allowed, in 2007, the first identification of variants outside of the MHC linked to disease risk (2). Subsequent genomic interrogation of over 45,000 patients with MS and 60,000 control subjects led to the elucidation of 194 genetic variants associated with disease risk (3)(International MS Genetics Consortium (IMSGC), unpublished data). These data clearly demonstrate that the genetic variants associated with MS are primarily related to immune genes. MS clusters with other autoimmune disorders, forever answering the question as to whether MS is an immunologic disease or a neurodegenerative disease with secondary inflammation. The cumulative effect of these genetic variants may explain up to 60% of MS incidence (3, 4)(IMSGC, unpublished).

Genetic mapping of quantitative traits, including gene expression, is a complementary approach to epigenomic annotation of functional genomic elements. We find that the causal variants in 88% of GWAS loci are noncoding. The majority map to immune-cell specific enhancers, many of which transcribe enhancer-associated ‘eRNAs’ and increase histone acetylation upon immune activation. Moreover, genetic variants in MS tend map to histone acetylation sites with open chromatin in both B cells, regulatory T cells, and Th1/Th17

populations. These genetic studies have provided deep information regarding the immune pathways and cell types underlying risk of developing MS without regard to prior hypotheses.

Despite these advances in our genetic understanding of MS pathogenesis, the contribution of genetics to MS clinical course has not yet been elucidated. In this issue, Isobe and colleagues leverage the wealth of genetic data produced via the IMSGC datasets to evaluate the genetic contributions of the human leukocyte antigen (HLA) alleles to MS phenotype among a cohort of European-ancestry MS patients (5). Study of the MHC is complicated, because the four megabases comprising the HLA complex have very long-range linkage disequilibrium. That is, genetic variants within this large complex tend to be inherited as a block, making it difficult to determine the likely causative gene within the region. This is of importance since the HLA complex is the strongest genetic modifier of MS (6), and robust data support increased susceptibility to MS among patients carrying the *HLA DRB1*15:01* allele (7). Modern genetic analyses have identified a number of other HLA polymorphisms that are independently associated with MS risk. The *HLA DRB1* locus carries the most genetic weight; in addition to the **15:01* allele, **03:01*, **13:03*, **04:04*, **04:01*, **14:01*, and **15:01* are independently associated with MS risk (8). MHC class I alleles, including *HLA-A*02:01*, *HLA-B*44:02* and *HLA-B*38:01* have a protective effect (6, 8, 9). A number of interactions have also been identified, specifically between *HLA-DQA1*01:01* and *HLA-DRB1*15:01* as well as *HLA-DQB1*03:01* and *HLA-DQB1*03:02* (6). In addition to affecting an individual's risk for developing MS, several studies have demonstrated that the *HLA-DRB1*1501* allele is associated with phenotypic features of the disease including female sex and presence of CSF-restricted oligoclonal bands (10, 11). The phenotypic effects of the other HLA haplotypes independently associated with MS risk have not yet been fully characterized.

Previous investigations of the HLA region did not support a strong influence on the clinical course of MS. That is, many studies found no effect of HLA genotype on MS subtype, disease progression, relapse rate, or clinical severity (10, 12, 13). Many of these studies specifically evaluated *HLA DRB1*15*, however, without incorporating other risk variants. Interestingly, work by Okuda and colleagues, demonstrated that patients with *HLA DRB1*15:01* had an increased volume of white matter lesions, decreased normalized brain parenchymal volume and decreased N-acetyl-aspartate concentration within normal appearing white matter when compared to patients without this allele (14). These data suggested that although the effects of HLA subtype may not be detectable using coarse measures of disability such as the estimated disability status scale (EDSS) or multiple sclerosis severity scale (MSSS), there may be a subtle effect on disease progression that can be identified using sensitive MRI metrics.

Isobe (5) used the most recent IMSGC data to create a composite HLA-specific genetic burden score which incorporates all known HLA risk variants for MS. They correlate this score with clinical disease course and MRI measures of disease severity. Using this method, they are able to reproduce and validate the previously reported associations of HLA alleles with MS risk and sex. Due to baseline differences in HLA genetic burden between men and women, Isobe et al stratify their results by sex and subsequently demonstrate the sexual

dimorphism of HLA genetic contributions to MS. They found that women with a high HLA genetic burden developed MS at a younger age than those with a low HLA genetic burden, which may help explain previous discrepancies in the literature (10, 12). Women with a clinically isolated syndrome and a high HLA genetic burden also developed clinically definite MS more rapidly than women with a low genetic burden. Baseline MRI scans demonstrated that women with a high HLA genetic burden had a lower subcortical gray matter volume than those with a low genetic burden, and this finding was reproduced on follow-up MRI a year later. The effect was driven by *HLA DRB1*1501*. Interestingly, HLA genetic burden was not associated with brain MRI metrics among men.

As mentioned above, studies of HLA contributions to MS are complicated by the high degree of linkage disequilibrium present within the MHC locus. This makes it challenging to unequivocally determine whether a causal relationship exists between a genetic polymorphism and MS phenotype. The high degree of LD leads to numerous common HLA haplotypes, and some have suggested that MHC haplotype, rather than specific alleles, should be considered as the fundamental unit of MS risk (15). Thus by dissecting the *HLA DLRB1*1501* haplotypes associated with subcortical gray matter volume on MRI Isobe found that only the *HLA-A*24:02-HLA-B*07:02-HLADRB1*1501* haplotype was associated with loss of subcortical gray matter; the other four common **1501* haplotypes did not relate to this MRI metric of disease, despite accounting for more than half of the *HLA DRB1*1501* patients in the study. These findings will need to be replicated with larger patient numbers; the exact number of *HLA-A*24:02-HLA-B*07:02-HLADRB1*1501* patients is not reported, but only 194 of the female relapsing MS patients in the cohort carried the *HLADRB1*1501* allele. Nevertheless, this is an exciting development in the ongoing effort to elucidate the link between genetics and MS phenotype. This work underscores the power of large genetic datasets to aid discovery of clinically meaningful genetic markers.

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