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Review Article

The Relation between Human Leukocyte Antigen and Multiple Sclerosis

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Abstract: HLA genes are associated with more than 100 diseases, including infectious diseases like HIV, and some cancers. Some autoimmune conditions, including diabetes and multiple sclerosis, are also linked to specific variations in the HLA. In MS, the immune system fails to distinguish between the body's tissues and foreign proteins resulting in it attacking myelin as if it were foreign. Several HLA genes have been found to influence the risk of developing MS. Some variants make an individual more likely to develop MS, whereas others may have a protective effect and decrease the risk. Although the precise genes involved in the development of multiple sclerosis are still not fully understood, research has identified one HLA gene that is more prevalent in women with MS and may be part of the explanation why more women than men get the condition.

Keywords: HLA, Multiple sclerosis, disease susceptibility, genetic factor.

INTRODUCTION

Multiple sclerosis (MS) has been associated with HLA-DR2 for more than 20 years, and a large number of studies have addressed the relation between MS and the HLA class II genes, which are our major immune-response genes. This has produced a complex and confusing picture that is difficult to interpret. With the advent of reliable and comprehensive DNA-based typing techniques, it is now possible to extract a coherent pattern from this mass of data. The associated haplotype has been specified to HLA-Dw2 in cellular typing nomenclature, which equals DR15, DQ6 by serology, and DRB1*1501, DQA1*0102, DQB1*0602 in sequence-based terminology. This haplotype is increased among groups of MS patients worldwide, although most strongly in North and West Europeans, and it is the only haplotype with a clear importance in MS. Attempts to map this association within the haplotype have not been successful [1].

This condition corresponds to an autoimmune pathology with a predominant immune cell response characterized by the presence of autoreactive T cells that react against the myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), and the proteolipid protein (PLP). The HLA-DRB1*15:01 and HLA-DQB1*06:02 alleles, which are in LD, are the main alleles associated with risk for MS in Caucasians and Latin Americans [2]. Recently, in a large combined multinational cohort in the International Multiple Sclerosis Genetics Consortium (IMSGC) GWAS study, the HLA-DRB1*13:03 allele was also identified as being associated with MS (OR=2.43). Furthermore, HLA-DRB1*01:08 (OR=1.18) and HLA-DRB1*03:01 (which is strongly linked to HLA-DQB1*02:01; OR=1.26) showed significant associations. Evidence of an additive effect for each additional allele was also described [3]. In the Sardinia region of Italy, where MS prevalence is high, HLA-DRB1*04, HLA-DRB1*03:01, and HLA-DRB1*13:01 (in addition to HLA-DRB1*15:01) positive associations with MS have been reported [4].

Several studies have explored phenotype-genotype correlation for associated HLA alleles in MS and reported that HLA-DRB1*15 has been associated with younger age at onset and a worse Expanded Disability Status Scale (EDSS) score as well as severe morbidity in patients with primary progressive MS [5]. Both the carriage of HLA-DRB1*15 and the presence of oligoclonal bands in the cerebrospinal fluid have been reported to hasten disease progression [6]. An association between MS and alleles of the major histocompatibility complex (MHC) was found in the 1970s, notably

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involving the class II human leukocyte antigen HLA-DR2 [7]. This was later fine-mapped to the extended haplotype HLA-DRB5*0101-HLA-DRB1*1501-HLA-DQA1*0102-HLA-DQB1*0602 [8] (to briefly explain HLA nomenclature, the first two digits of an allele describe its serological antigen (called an allelotype) while the third and fourth digits are used to list the allele subtypes. Alleles with different numbers in these first four digits must differ by at least one non-synonymous nucleotide substitution). This extended haplotype confers a relative risk of approximately 3, but much larger effects are seen if haplotypic and diplotypic (both haplotypes in combination) information is taken into account, and the odds ratio for risk spanned by variation in the class II HLA region is thought to exceed 30.

Genome-wide association studies have highlighted the fact that the HLA class II region exerts by far the strongest genetic effect on risk [9], but exactly how it alters the risk of developing MS is not yet fully understood. As HLA-DRB1 alleles have different structural capacities for antigen presentation depending on their amino acid sequence, the MS MHC association has been used to support the concept that disease pathogenesis is the result of an autoimmune reaction, perhaps against myelin-related antigens in the restricting context of HLA-DRB1*1501. However, it has become clear only very recently that it is now untenable that all MHC related disease risk is due to the DRB1*1501 allele, as was originally thought. This conclusion may be unwelcome for those who have made large investments in the transgenic animal models that depend on it, as these models are now clearly uninformative to truly understand disease pathogenesis.

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