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Genetics of Multiple Sclerosis

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The quest to define the mechanisms underlying the genetic predisposition to develop MS has long been the focus of considerable research. Observations on the distinct prevalence of MS in certain areas of the world and in different populations, combined with familial aggregations and other epidemiological investigations, provided the first clues to the genetic factors that increase the risk of MS. As the techniques of molecular biology have improved and international collaborations have been established, the genetics of MS are being unraveled. As might be expected, the emerging picture indicates that no single gene is causative but that certain alleles of the HLA-complex are major players in the genetic susceptibility to MS. Other genes with altered transcription also appear to be contributing factors. The potential of targeting those genes in treatment options is the result of the many long and difficult studies that have been performed on the underlying causes of MS.

Key Words: genetics, human leukocyte antigen, multiple sclerosis

Abbreviations Used: DNA, deoxyribonucleic acid; HLA, human leukocyte antigen; IL, interleukin; MHC, major histocompatibility complex; mRNA, messenger ribonucleic acid; MS, multiple sclerosis; SNP, single nucleotide polymorphism

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In the United States, neurologists in clinical practice often are asked the cause of MS and the risk of relatives for contracting the disease. Extensive studies have been conducted to address these questions, and advances in biotechnology have improved the accuracy of the answers. This article reviews the results from recent studies addressing the genetics of MS.

Epidemiology of MS

The first suggestion that individuals may have a genetic predisposition to develop MS was based on epidemiological observations at the population level from almost a century ago. The disease is practically unknown in some African states, and its incidence is very low in China and other regions of the Far East. Its highest expression is in northern European countries. The prevalence of MS in distinct ethnic groups in the same areas of the world supports the interpretation that genetic makeup is a factor in an individual's susceptibility to MS. For example, the prevalence of MS is relatively high for Sardinians, Lapps in Finland, Gypsies in central Europe, and Maoris in New Zealand.[12,19,23] Beyond the simple assessment of disease prevalence across ethnic groups, the results of several migration studies suggest that the interaction of environmental factors with genetic susceptibility affects the expression of MS. Furthermore, the risk for developing MS is modified if individuals migrate during childhood.[9]

Epidemiological surveys have indicated that MS occurs in a familial fashion. A direct relationship between degree of kinship and risk for MS was

established by assessing the recurrence rate of MS in offspring of one or both affected parents and its prevalence in conjugal cases compared to its recurrence rate in half siblings, second-degree relatives, or adopted individuals.[6,9-11] Moreover, the concordance rate in monozygotic twins varies between 10 and 30% in different populations, while the concordance rate in dizygotic twins approaches the recurrence rate in other biological siblings.[9,22]

These data support a genetic role in the development of MS. However, they leave ample room for environmental factors to influence the expression of the genetic component. This relationship can be calculated to yield a ratio, known as lambda (λ), by dividing the recurrence rate in families by the population prevalence.[21] For MS the value of λ is about 20 based on a risk for family members of about 2% and a population prevalence of 100 per 100,000. For comparison, the value of λ for type I diabetes is 15. That is, the overall genetic susceptibility to MS is greater than that for diabetes, for which the genetic contribution has been established.[1]

Linkage Analyses

The large epidemiological literature on MS accumulated over the last few decades indicates the relevance of genetics and raises the question of which genes account for the observed predisposition to develop the disease. The availability of rapidly evolving techniques from molecular biology has sparked interest in applying those methods to test samples from MS patients. Familial clustering indicated a mode of inheritance consistent with a complex trait involving many genes.[28] Linkage studies in multigenerational families were infeasible and of limited utility with MS.[29] With adequate samples, however, testing siblings for linkage (sib-pair analysis) was anticipated to be sufficiently powerful to detect genes exerting moderate-to-high effects.[20]

In the attempt to improve the detection of genes with lower effects, another modality was investigated. The transmission disequilibrium test allows genetic markers to be assessed in both parents and an affected child to identify preferential transmission of markers. Over large numbers of families, a transmission rate expected to be greater than 50% by chance is indicative of both linkage and association with the disease.[26]

However, the hope of resolving the genetics of MS by these methods of linkage analysis was not fulfilled. Despite efforts to increase the numbers of samples to increase statistical power, the results were unjustly considered unsatisfactory. Ultimately, a meta-analysis of the studies performed in many different populations led to more disappointment. One problem identified was the inconsistency of good quality data across studies.[24,27] However, those investigations set the stage for future experiments that have improved our understanding of the etiology of MS.

More than three decades ago the pathogenic relevance of the HLA class II molecules in MS was reported. The contribution of the extended haplotype of the DR2 and DR4 alleles has been confirmed repeatedly in linkage and association studies in every tested population. At this point, the presence of this haplotype should be considered an established risk factor for MS.

For an immune-mediated disease like MS, the involvement of the MHC makes intuitive sense. However, the actual mechanisms by which certain alleles confer the predisposition to the disease are not completely understood. A widely accepted theory suggests that the HLA-class II molecules are responsible for presenting the processed antigen derived from myelin basic protein, a putative target antigen for MS. A connection between HLA and Epstein-Barr virus was proposed on the basis of molecular mimicry involving HLA class II alleles.[16] Convincing data support the association between Epstein-Barr virus and MS. Several pathogenetic mechanisms could explain the genetic predisposition with this environmental agent.[2,7,17]

A recent case-control study of the MS population in Malta supports an interaction between the environment and genetic background in the expression of MS. Almost all MS patients residing in the Maltese isles were genotyped for the prevalence of the HLA-DRB alleles, and their frequencies were compared to anonymous samples from Maltese donors. The well-known association of MS with the allele HLA-DRB*1501 was confirmed. However, its frequency was unexpectedly high considering the low prevalence of the disease in Malta. The prevalence of MS is much higher on the neighboring island of Sicily than on Malta, but the incidence of HLA-DRB1 alleles is lower in Sicily. These findings indicate that the environment is indeed a key co-factor in the development of MS.[8]

Single Nucleotide Polymorphisms

The application of the most advanced biotechnology, combined with an international effort to render available the largest set of DNA samples from MS patients, resulted in a landmark publication that allows fundamental conclusions to be made about the mechanisms underlying MS.[14] The International MS Genetic Consortium led by a group in Cambridge, England used a microarray-based method to test a large number of SNPs across the entire genome to look for associations with the disease. The SNPs were selected as informative and statistically associated in a stepwise fashion through test and validation sets of several hundred samples. Combining all samples achieved maximal statistical power and allowed about 5,000 patients to be compared to 12,000 controls.

In addition to the overwhelming role played by the allele DRB1*1501, two other polymorphisms were identified.[14] The first was the nonsynonymous mutation in the exon 6 of the IL-7 receptor, whose relevant role in the regulation of the immune system was subsequently addressed.[13] The functional importance of the alternative splicing of the IL-7 receptor mRNA caused by this gene polymorphism influenced the occurrence of autoimmunity.[13]

The other SNP associated with MS was the coding sequence of the IL-2 re-

ceptor gene. IL-2 is a cytokine with a fundamental role in the maturation of T lymphocytes. An alteration of signaling through its receptor affects the regulation of the immune response. That IL-2 is a key player in MS is underscored by the encouraging results from a clinical trial with a monoclonal antibody that targets the IL-2 receptor (anti-CD25, daclizumab).[25]

A possible interpretation of these findings is that the presence of at least one DRB1*1501 allele in Caucasians confers a 20% increase in the risk of developing MS compared to noncarriers. Moreover, an additional risk with a dose effect is detected in carriers of two alleles.[4] Conversely, other alleles in the MHC-class I seem to confer a protective effect.[30] Recent unpublished data from our group confirmed the association of the disease with the HLA-DRB2 locus when DNA samples from 250 MS patients and 250 controls were tested for about 500,000 SNPs across the genome. No other genetic markers were significantly associated with MS.

Role of Other Genes in MS

The next questions are whether other genes predispose individuals to the disease and, if so, what is their relevance? The fundamental concept is that MS is a heterogeneous disease with variable phenotypic presentation that likely reflects distinct pathogenic mechanisms. Phenotypes of some disorders, including Mendelian traits, can be caused by different gene mutations either in the same or alternative metabolic pathways (e.g., tuberous sclerosis, Parkinsonian syndromes, and Alzheimer's disease). As in MS, all complex traits may manifest as a consequence of an abnormal regulation at one of many "check points" that is not under genetic influence alone. For example, an association between MS and a mutation in the promoter of the CD45 gene was detected in some families from Northern Europe.[15] The potential pathogenic role of that particular polymorphism is likely an uncommon cause of a predisposition to MS. In fact, other family members, also carriers of the polymorphism, have not developed the disease. In a subsequent study,[3] no other MS patients were found to bear the mutation. This evidence supports the view that many different pathways may lead to a similar manifestation or disease phenotype.

The second consideration refers to the influence of the environment, namely, nutritional and toxic exposures, on gene expression. Consider phenylketonuria, a Mendelian disorder whose phenotypic expression can be abrogated dramatically by diet restrictions. The complexity that allows synchronous orchestration of all components of the immune system can be disrupted at any level to produce dysregulation of function, especially for immune-mediated diseases.

Although HLA exerts the strongest influence on genetic susceptibility to MS, it only does so for some people who carry those alleles. Yet many individuals who do not have these alleles still develop MS. Most likely they inherit a predisposition to the condition via a distinct set of genes, or they encounter an environmental factor, such as the Epstein-Barr virus, with the potential to initiate an abnormal immune response. In other words, some individuals may have little genetic predisposition to an autoimmune disease, but an environmental factor can still act as a strong trigger. This scenario could underlie the remarkable variation in the disease expression observed clinically and the variations in disease concordance in twins in northern or southern European populations.[9,22]

Conclusion

Studies on the genetics of MS have tended to test as many individuals as possible to increase the statistical power of the analysis. However, MS is a heterogeneous condition in which the involved genes may be different in different subsets of patients. Consequently, combining data may actually be counterproductive leveling off and masking the role of the different genes. Analyzing a homogeneous population is ideal to identify a potential founder effect or common pathogenic mechanism underlying MS. In fact, the cleanest results on the genetics of MS with high statistical significance were obtained in a population of Caucasian ancestry. The next step is to identify homogeneous subsets of patients that may share the same genetics and test them as separate groups. This approach has already been successful in African-American patients with MS whose genetic susceptibility is associated with alleles of the HLA-class II that are different from the ones in Caucasians.[5]

The genetic aspects of a complex disease like MS must be analyzed and understood to improve treatments. The path to a cure is anticipated to be long. Nonetheless, the results of the many ongoing efforts by the scientific and medical community are encouraging.[18]

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