The Current State of Multiple Sclerosis Genetic Research

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Abstract

Introduction*: Multiple sclerosis (MS) is the most common genetic disease of the nervous system with onset usually in young adulthood. Four genome-wide searches in different Caucasian populations for MS susceptibility loci have been performed, but none reported any linkage at a level that would be regarded as significant according to current criteria. Significant linkage of MS to allelic variants of the major histocompatibility (MHC) locus on chromosome 6p21 has been established although its overall contribution to MS susceptibility has proven difficult to quantify. The objective of this review is not only to provide the reader with an update of MS genetics research, but also to provide a basic knowledge of the techniques being employed to map MS susceptibility genes. The different methodologies are discussed, and specific studies are reviewed in context. *Methods*: This review is based on findings from original articles, however, the results of recent candidate gene studies are intended to update previous review articles. *Results*: There remains no concrete non-MHC locus for MS, although there are enough findings of sufficient interest to warrant further investigation and optimism. Stratification of genome scan data based on MHC class II suggests that it interacts differentially with non-MHC loci and that it contributes moderately to disease susceptibility. Candidate gene studies have continued to return negative and ambiguous results, and follow-up fine mapping of suggestive linkages from the UK genome scan has proven unsuccessful in identifying significant linkages. Genetic analysis of crosses between mouse strains that are differentially susceptible to experimental allergic encephalomyelitis (EAE) has yielded linkages corresponding to putative MS susceptibility loci. However, recent successes in transgenic mice may provide an alternative to EAE, regarded by some as a poor model of MS. *Conclusion*: The first whole genome search for a common human disease was performed over five years ago, and it is now clear, from the lack success in this field, that the genetic complexity of these traits has been underestimated. The genome-wide searches for MS susceptibility genes have suffered from insufficient statistical power, which has probably been compounded by disease and genetic heterogeneity. Studies in isolated populations and better laboratory and clinical definitions of disease are both steps in the right direction to solving these problems. Not withstanding the negative effects of genetic heterogeneity, pooling of resources for meta-analyses may provide the increase in statistical power required for detection of loci that exert a moderate or small effect on disease predisposition.

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