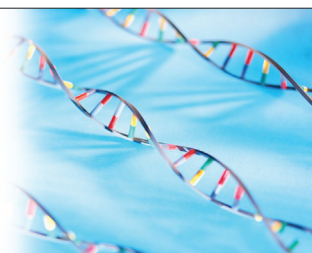


Prognostic Markers:

GENES



Substantial progress has been made in localizing regions on the human genome most closely linked to genetic susceptibility for MS.⁵⁵ Most analyses suggest that multiple genes are involved. The set of genes that increase susceptibility to MS may not be the same set of genes that influence the severity of MS or its rate of progression. Some familial haplotypes associated with increased risk of MS appear to predict disease expression, such as age at onset or disease severity.^{56,57}

An analysis of MS genotype was published by an international genetic consortium.⁵⁸ In a dataset created by 730 families of Northern European descent, 4,506 markers were evaluated in 2,692 individuals. There was a highly significant linkage with the major histocompatibility complex (MHC) on chromosome 6p21 with suggestive linkages on chromosomes 17q23 and 5q33. The log of odds (LOD) score was substantially higher in this study for these linkages than those of previous analyses.^{59,60} When the dataset was stratified by carriage of the MS-associated DRB1*1501 allele, no other region of linkage was identified that had genome-wide significance.

Genetic variability is an attractive explanation for the marked heterogeneity in the course of MS. Gene activation

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may confer relative protection against or facilitate molecular events that characterize disease progression. For example, several teams of investigators have discovered an association between the presence of the APOE-4 allele and a relatively aggressive disease course.^{61,62} Conversely, the APOE-3/4 genotype has been associated with slow progression from RRMS to SPMS.⁶³

As more sophisticated analyses of the human genome are conducted, genetic polymorphisms may be identified that not only reveal risk of MS but help explain disease progression in the context of molecular events influenced but not directly related to MS. Preliminary studies to evaluate MS severity in the context of genes influencing such factors as TNF and IL-1 have been initiated.⁶⁴

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There are potential limitations of genetics to account for risk of MS or the severity of its expression. The limited concordance for MS among monozygotic twins is one example. In discordant twins, there can be abnormal MRI findings in the clinically unaffected twin, suggesting that clinical expression requires some additional nongenetic mechanism.¹⁰ Large surveys suggest that only about 20% of MS patients can be linked to another first-degree relative with MS.⁴⁴

In pharmacogenomics, therapies are individualized for the patient in regard to genetic influences on the efficacy and toxicity of available drugs. Some of the variability in response to disease-modifying agents, and the subsequent effect on disease course, may be related to inherited differences in metabolizing enzymes or receptors targeted by these agents. The current efforts to better characterize individual differences in gene activation could prove instrumental in tailoring treatment for diseases with highly heterogeneous expression. □

Clinical Summary: Current Status of Genetic Factors for Prognosis

- Multiple genes are likely to be involved in MS.
- Genes that increase susceptibility to MS may differ from those that impact disease course.
- Genetic variability may explain the heterogeneity seen in the course of MS.
- Identification of genetic variabilities that influence response to disease-modifying therapies may help tailor individualized treatments.