

## Genetics of Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system. It is presumed to be an autoimmune disorder, causing severe neurological disability as a result of demyelination. For the majority of affected individuals, the disease begins as episodic and then over a period of time becomes progressive. In early stages, cognitive dysfunction, such as impairment of memory, inhibition, conceptualization, verbal fluency, and learning is common.<sup>1</sup> Impairment of attention, information processing speed, and ambulatory disability are common as the disease progresses.<sup>1</sup> The median time to severe disability is approximately 33 years.

The causes of MS are mostly unknown, although twin and sibling pair studies point to a genetic component.<sup>2</sup> The concordance rate among identical twins is approximately 30%,<sup>1,3</sup> and the clinical course of MS among related individuals seems to be similar. However, there is a large environmental component to MS as well, complicating efforts to identify the genes responsible for increasing susceptibility and affecting clinical outcome.

The most promising candidate gene associated with MS is *HLA-DRB1*. Studies of the Human Leukocyte Antigen (HLA) chromosomal region consistently show evidence for a link to MS susceptibility. HLA proteins play an important role in immune recognition of self vs. non-self.<sup>3</sup> The \*1501 allele of HLA is present in approximately 48% of MS patients, indicating that it is likely involved in the pathogenesis of the disease.<sup>4</sup> The individual risk for developing MS is about twice as high in individuals who carry two copies of the \*1501 allele. Interestingly, the HLA region is implicated in almost all autoimmune diseases.<sup>4</sup>

Another promising candidate gene that may impact development of MS is the *Interleukin 7 Receptor  $\alpha$  subunit (IL7R $\alpha$ )*. IL7R $\alpha$  is involved in the homeostasis of the memory T-cell pool and in generation of autoreactive T cells.<sup>5</sup> For those carrying a variant form of *IL7R $\alpha$* , it is thought that there is an increase in the amount of soluble versus membrane-bound receptor, affecting signaling through the Interleukin pathway.<sup>4</sup> Approximately 30% of MS cases may be explained by having the *IL7R $\alpha$*  variant.<sup>4</sup>

In addition to investigating the genetic control of the risk of developing MS, is current investigation into the genetics of MS clinical outcome. MS clinical outcome is widely variable among patients. However, it has been observed that age at onset, disease course, and rate of acquisition of disability are similar in siblings and twins, suggesting a genetic component to phenotypic expression.<sup>2</sup> Several genes are being studied for their effects on the clinical outcome of MS.

Although genetic testing cannot yet accurately identify those at risk of developing MS, research is advancing rapidly. Genome-wide association studies are increasingly identifying candidate genes for a number of disorders including MS,<sup>6</sup> and it's possible that they may help to unravel the genetic mysteries of MS.

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