MULTIPLE SCLEROSIS

*HLA B*44* is protective in multiple sclerosis

Both genetic and environmental factors are strongly implicated in the etiology of multiple sclerosis (MS), but relatively little is known about which genes affect disease progression. Researchers at Brigham and Women's Hospital and Harvard Medical School, Boston now show that the class I MHC alleles human leukocyte antigen (*HLA*) *A*02* and *HLA B*44* are independently associated with a reduced risk of developing MS, and that *HLA B*44* attenuates disease progression.

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MS is a chronic inflammatory–demyelinating disease of the CNS that is generally considered to result from deficits in immune system function. MHC class I and class II molecules are integral components of the immune system, and the MHC class II allele *HLA DRB1*1501* is a known genetic risk factor for MS development. Several class I MHC loci have also been associated with MS susceptibility, and three class I MHC alleles—*HLA A*02*, *HLA B*44* and *HLA C*05*—are known to influence MS susceptibility independently of *HLA DRB1*1501*.

To evaluate the contributions of these three class I MHC alleles to the development of MS, Healy *et al.* determined their frequencies in 532 patients with MS or clinically isolated syndrome and 776 healthy controls. The researchers found that, as expected,the frequency of the *HLA DRB1*1501* allele was higher in the patient group than in the control group. By contrast, the frequencies of the *HLA A*02*, *HLA B*44* and *HLA C*05* alleles were lower in patients with MS than in healthy individuals, indicating that these alleles decrease an individual's risk of developing MS. Furthermore, an analysis of the data indicated that the *HLA A*02* and *HLA B*44* alleles had independent effects on MS susceptibility, whereas the effects associated with the *HLA C*05* allele were not independent of *HLA B*44*.

To investigate the association between the *HLA A*02* and *HLA B*44* alleles and disease progression, the researchers assessed Expanded Disability Status Scale scores and MRI measures of disease progression from patients with MS. Analysis of these data revealed that the *HLA A*02* allele did not markedly affect disease progression. By contrast, patients with MS who had the *HLA B*44* allele were shown to have lower T2 lesion volumes and higher brain parenchymal fractions than individuals with other variants of the *HLA B* gene. Thus, "we showed that the *HLA B*44* allele, but not the *HLA A*02* allele, not only diminishes your risk of getting MS but also, once you have this condition, appears to protect you, since people who have it have fewer lesions and larger brains," explains principal investigator Philip De Jager. "Understanding how the *HLA B*44* allele affects the immune system might aid the development of neuroprotective drugs that, hopefully, could reduce disease burden and brain atrophy in patients who have MS".

Nick Jones

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