Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis.

Multiple sclerosis is a common disease of the central nervous system in which the interplay between inflammatory and neurodegenerative processes typically results in intermittent neurological disturbance followed by progressive accumulation of disability. Epidemiological studies have shown that genetic factors are primarily responsible for the substantially increased frequency of the disease seen in the relatives of affected individuals, and systematic attempts to identify linkage in multiplex families have confirmed that variation within the major histocompatibility complex (MHC) exerts the greatest individual effect on risk. Modestly powered genome-wide association studies (GWAS) have enabled more than 20 additional risk loci to be identified and have shown that multiple variants exerting modest individual effects have a key role in disease susceptibility. Most of the genetic architecture underlying susceptibility to the disease remains to be defined and is anticipated to require the analysis of sample sizes that are beyond the numbers currently available to individual research groups. In a collaborative GWAS involving 9,772 cases of European descent collected by 23 research groups working in 15 different countries, we have replicated almost all of the previously suggested associations and identified at least a further 29 novel susceptibility loci. Within the MHC we have refined the identity of the HLA-DRB1 risk alleles and confirmed that variation in the HLA-A gene underlies the independent protective effect attributable to the class I region. Immunologically relevant genes are significantly overrepresented among those mapping close to the identified loci and particularly implicate T-helper-cell differentiation in the pathogenesis of multiple sclerosis.