Influence of the HLA-DRB1 Genotype on Antibody Development to Interferon Beta in Multiple Sclerosis.

Abstract: To determine relevant HLA-DRB1 alleles associated with the susceptibility of anti-interferon beta antibody development in a large patient cohort. In a case-control study, HLA-DRB1 genotyping was performed in a discovery cohort (n = 268) and a validation cohort (n = 825). Patients were recruited in Germany by primary care physicians and neurologists and were mainly of Northern European heritage. All patients had a diagnosis of multiple sclerosis and were receiving long-term interferon beta therapy. The antibody status to interferon beta was determined in all patients by capture enzyme-linked immunosorbent assay and in vivo myxovirus protein A assay and correlated with the HLA-DRB1 genotype. In the discovery and validation cohorts, HLA-DRB1*04:01, *04:08, *16:01 were identified as genetic markers that are associated with an increased risk of anti-interferon beta antibody development (P< .05). In addition, alleles with a protective potential were identified, including HLA-DRB1*03:01, *04:04, *11:04. However, after correction for multiple testing, protective alleles did not reach statistical significance. The HLA alleles identified in this study seem to be the major genetic determinant of antibody development, allowing the prediction of the individual risk of patients before initiation of therapy.