Interferons-? (IFN-?) are the most widely used immunomodulatory drugs for treatment of multiple sclerosis (MS). The development of neutralizing antibodies (NABs) against IFN-? is one of the main reasons for treatment failure. While formulation of the drug has a proven impact on the development of NABs, the genetic predisposition to develop antibodies is poorly understood. We performed genome-wide single-nucleotide polymorphism (SNP) genotyping in 362 MS patients of whom 178 had developed and 184 had not developed antibodies on IFN-? therapy. Four candidate SNPs were validated in an independent cohort of 350 antibody-positive and 468 antibody-negative MS patients. One SNP within the human leucocyte antigen (HLA) region (rs9272105, P-value: \( 3.56 \times 10^{-10} \)) and one SNP in an intergenic region on chromosome 8q24.3 (rs4961252, P-value: \( 2.92 \times 10^{-8} \)) showed a genome-wide significant association with the anti-IFN-? antibody titers. We found no interaction between the genome-wide significant SNPs (rs9272105 and rs4961252) in our study and the previously described HLA-DR(*)0401 or (*)0408 alleles, indicating an additive effect of SNPs and HLA alleles. Testing for these SNPs and the HLA-DR(*)0401 or (*)0408 alleles allows to identify...
patients at risk to develop antibodies to IFN-? and may provide helpful information for individual
treatment decisions.