Genetic pleiotropy between multiple sclerosis and schizophrenia but not bipolar disorder: differential involvement of immune-related gene loci.

Converging evidence implicates immune abnormalities in schizophrenia (SCZ), and recent genome-wide association studies (GWAS) have identified immune-related single-nucleotide polymorphisms (SNPs) associated with SCZ. Using the conditional false discovery rate (FDR) approach, we evaluated pleiotropy in SNPs associated with SCZ (n=21,856) and multiple sclerosis (MS) (n=43,879), an inflammatory, demyelinating disease of the central nervous system. Because SCZ and bipolar disorder (BD) show substantial clinical and genetic overlap, we also investigated pleiotropy between BD (n=16,731) and MS. We found significant genetic overlap between SCZ and MS and identified 21 independent loci associated with SCZ, conditioned on association with MS. This enrichment was driven by the major histocompatibility complex (MHC). Importantly, we detected the involvement of the same human leukocyte antigen (HLA) alleles in both SCZ and MS, but with an opposite directionality of effect of associated
HLA alleles (that is, MS risk alleles were associated with decreased SCZ risk). In contrast, we found no genetic overlap between BD and MS. Considered together, our findings demonstrate genetic pleiotropy between SCZ and MS and suggest that the MHC signals may differentiate SCZ from BD susceptibility.