Shared Genetic Basis for Type 1 Diabetes, Islet Autoantibodies, and Autoantibodies Associated With Other Immune-Mediated Diseases in Families With Type 1 Diabetes

Type 1 diabetes (T1D) is a polygenic autoimmune disease that is often present with autoantibodies directed against pancreatic islet proteins. Many genetic susceptibility loci are shared with other autoimmune or immune-mediated diseases that also cosegregate in families with T1D. The aim of this study was to investigate whether susceptibility loci identified in genome-wide association studies (GWAS) of T1D were also associated with autoantibody positivity in individuals with diabetes. Fifty single nucleotide polymorphisms (SNPs) were genotyped in 6,556 multiethnic cases collected by the Type 1 Diabetes Genetics Consortium (T1DGC). These were tested for association with three islet autoantibodies—against autoantibodies to GAD (GADA), IA-2 (IA-2A), and zinc transporter 8 (ZnT8A)—and autoantibodies against thyroid peroxidase (TPOA) in autoimmune thyroid disease, gastric parietal cells (PCA) in autoimmune gastritis, transglutaminase (TGA) in celiac disease, and 21-hydroxylase (21-OHA) in autoimmune hypoadrenalism. In addition to the MHC region, we identify SNPs in five susceptibility loci (IFIH1, PTPN22, SH2B3, BACH2, and CTLA4) as significantly associated with more than one autoantibody at a false discovery rate less than 5%. IFIH1/2q24 demonstrated the most unrestricted association, as significant association was demonstrated for PCA, TPOA, GADA, 21-OHA, and IA-2A. In addition, 11 loci were significantly associated with a single autoantibody.