Type 2 Diabetes (T2D) and Quantitative Trait (QT) Association Analysis of MODY Genes in Finns


1NHGRI-NIH, Bethesda, MD
2U. Michigan, Ann Arbor, MI
3U. Southern California, Los Angeles, CA
4Nat'l Public Health Inst., Helsinki, Finland
5U. North Carolina, Chapel Hill, NC

T2D is a multifactorial polygenic metabolic disorder characterized by defects in both insulin action and secretion. In contrast, maturity-onset diabetes of the young (MODY), an autosomal dominant form of diabetes, is primarily due to impaired insulin secretion as a result of variations in one of at least 6 genes: HNF4A, GCK, TCF1, IPF1, TCF2 and NEUROD1. Several of the MODY genes are part of a transcription factor network regulating gene expression in the pancreas and liver. Reports of T2D association with variants in HNF4A, GCK, TCF1 and IPF1 support the hypothesis that subtle genetic variants in MODY genes may confer susceptibility to T2D. To complement our ongoing studies of HNF4A, we have undertaken a comprehensive gene-based association study to determine the relevance of 5 other MODY genes in T2D in Finns. For each gene and its flanking regions (20 kb 5' and 5 kb 3'), we selected non-redundant SNPs (r^2<0.8 with other SNPs) either from the HapMap database (www.hapmap.org) or a private LD map source (D. Altshuler, personal communication). Thus far we have tested 77 SNPs on 795 index cases from T2D families, and 655 normal glucose-tolerant controls. We performed permutation tests to derive empirical p-values that account for multiple testing within each SNP. Associations with NEUROD1, TCF1 and TCF2 have been identified, with p-values of 0.0007, 0.02, and 0.01 respectively. We also examined whether MODY gene SNPs were associated with diabetes-related QTs. For 6 SNPs in 3 genes (IPF1, GCK and TCF2), we found significant (p< 0.05) trait associations in the glucose-tolerant individuals. One SNP in TCF2 exhibited association with both T2D and QTs. Our data suggest that one or more of these MODY genes may also play a role in T2D pathogenesis.