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

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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.