

PTPN22, CTLA4, MIF-1, IL6 and TCF7 Polymorphisms and Type 1 Diabetes

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The risk of developing Type 1 Diabetes (T1D) is clearly influenced by one's genetic makeup. While the strongest association with the disease is found in the HLA gene region, single nucleotide polymorphisms (SNPs) in other genes have also been found to be associated with T1D. Because events in the development of T1D involve the immune-mediated destruction of pancreatic islet cells, we have begun a study to analyze SNPs in genes involved in immune regulation. We have recently analyzed SNPs in the coding region of PTPN22 (C1858T) and CTLA4 (A49G), and in the promoter regions of MIF-1 (G-173C) and IL6 (C-174G). Our subjects included 1711 individuals from 341 Caucasian families who have at least two children affected with diabetes. PTPN22 encodes Lyp, a lymphoid-specific phosphatase, which functions as a downregulator of T-cell signaling. Our results reveal a significant association of the PTPN22 1858 T allele with T1D, consistent with previously reported data. However, transmission of the T allele is significantly increased only in our patients who also carry at least one copy of the TCF7 883A allele, another important regulator of T-cell activation that is associated with T1D. In our study, both the CTLA4 49G allele and the GG genotype are seen at a greater frequency in subjects with T1D who do not carry the DR3/DR4 high risk HLA genotype than in those who are DR3/DR4 positive. MIF-1, a proinflammatory factor produced by cells in both the immunological and the neuroendocrine system, has not previously been identified as a susceptibility gene for T1D. Our data show a significant undertransmission of the less common MIF-1 -173C allele from parents to diabetic male offspring. The same allele, which has been reported to increase MIF-1 protein production, was also found to be underrepresented in a group of rheumatoid arthritis patients (BMC Genetics 2004 5:1). Our initial assessment of the IL6 C-174G SNP does not indicate an association with T1D in our population.

We are currently analyzing our data for epistatic interactions between the SNPs described above and plan to carry out further SNP analysis on selected genes. These studies will lead to a better predictive assessment of the susceptibility to T1D and a greater understanding of the important pathways involved in the development of this autoimmune disease.