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Large meta-analysis finds new genes for type 1 diabetes

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The largest-ever analysis of genetic data related to type 1 diabetes has uncovered new genes associated with the common metabolic disease, which affects 200 million people worldwide. The findings add to knowledge of gene networks involved in the origin of this complex disorder, in which patients depend on frequent insulin injections to control their blood sugar levels.

"Genome-wide association studies, as we used here, have been extremely powerful in identifying gene locations involved in the pathogenesis of complex, common diseases," said study leader Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at The Children's Hospital of Philadelphia. "The larger the cohort used, the more discoveries we can make, and the more we find intriguing biological pathways offering insight into causes of disease."

The study appears online today in PLoS Genetics.

The genome-wide association study (GWAS), in which Hakonarson collaborated with Constantine Polychronakos, M.D., director of Pediatric Endocrinology at McGill University, was a meta-analysis, investigating combined DNA data from six large publicly available datasets of type 1 diabetes. The six studies included data from approximately 10,000 individuals with the disease and 17,000 control subjects. The databases contained single nucleotide polymorphisms (SNPs)—single-base changes in DNA sequence that serve as signposts for gene mutations associated with them.

SNPs are not disease-causing mutations, but they reside in gene regions associated with the disease, and set the stage for more detailed sequencing studies to pinpoint causative mutations. Previous studies by Hakonarson and colleagues over the past four years had already discovered SNPs related to type 1 diabetes.

In addition to validating results from previous studies, the current research identified, then replicated, three novel SNPs located in regions of considerable biological interest, being involved in protein-protein interactions, inflammation and cell signaling activity. "Our study found SNPs that we had not expected to have any connection to type 1 diabetes," said Hakonarson. "The strongest association among the three SNPs was in the region of the LMO7 gene on chromosome 13. We previously associated another member of the LMO gene family with the childhood cancer neuroblastoma. This gene family plays an important role in protein-protein interactions, but it would not have occurred to anyone that it may be active in type 1 diabetes. GWAS continues to turn up surprising biological associations."

Hakonarson added that follow-up studies will focus on resequencing the regions linked to the SNPs to narrow down causative mutations. Further research will concentrate on investigating how specific mutations function in the development of type 1 diabetes.

More information: "A genome-wide meta-analysis of six type 1 diabetes cohorts identifies multiple associated loci," *PLoS Genetics*, published online Sept. 29, 2011, freely available at www.plosgenetics.org/article/i … journal.pgen.1002293

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