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Team unearths genetic risk factors for diabetes

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Scientists have discovered three unsuspected regions of human DNA that contain clear genetic risk factors for type 2 diabetes, and another that is associated with elevated blood triglycerides.

The findings stem from the work of the Diabetes Genetics Initiative (DGI), a public-private partnership between the Broad Institute of MIT and Harvard, Novartis and Lund University, and they also reflect a close partnership with two other diabetes research groups.

The three groups' studies, which appeared together in a recent advance online edition of Science, are among the first to apply a suite of genomic resources to clinical research. These genomic resources include the Human Genome Project, the SNP and HapMap Projects, and genome-scale laboratory and analytical tools.

"For the first time, it is possible to look across the human genome and discover new clues about the root causes of common, devastating diseases that arise from a combination of genes, environment and behavior," said senior author David Altshuler, a principal investigator of DGI, director of the Broad Institute's program in medical and population genetics and a professor at Massachusetts General Hospital and Harvard Medical School.

"The confirmed genetic contributors we and our collaborators have found open surprising new avenues for disease research, treatment and prevention," he said.

With the aging of the population and the frequent excesses of modern lifestyles, type 2 diabetes and cardiac risk factors constitute a looming threat to human health, particularly in industrialized nations. Solutions to this burgeoning problem must include new, more effective treatments and the ability to identify "at risk" individuals--each of which requires innovative directions for future research.

The DGI study is one of the first large-scale studies of human genetic variability, aiming to reveal genetic connections to type 2 diabetes and other cardiovascular risk factors such as blood insulin levels, cholesterol levels, blood pressure and body weight. Each of these traits is considered "complex" because it involves a mix of inherited, environmental and behavioral factors.

The scientists' approach, known as a "genome-wide association study," involves scanning thousands of individuals' genomes for single letter changes, called single nucleotide polymorphisms (SNPs). Due to the block-like nature of the human genome, certain SNPs can serve as signposts, highlighting pieces of nearby DNA that may play a causal role in disease.

Using this approach, the DGI team and their collaborators identified and confirmed three novel regions of the genome that influence the risk of type 2 diabetes, as well as a genomic region that is linked with blood triglyceride levels. Perhaps the most intriguing result involves a DNA region that lies far from any known annotated genes. Such genomic "outsiders" would have been incredibly difficult to find by traditional hypothesis-driven approaches.

The other regions linked to diabetes lie near genes with known biochemical functions, but ones never before connected to the disease. Interestingly, the region implicated in triglyceride levels involves a gene that has long been known to play a role in modulating blood glucose.

Based on initial results, the DGI scientists turned to replicating the most promising findings in independent samples--a critical aspect of the genomic method. The scientists worked together with two other groups that performed similar genomic analyses of type 2 diabetes: the Wellcome Trust Case Control Consortium/UK Type 2 Diabetes Genetics Consortium (WTCCC/UKT2D) and the Finland-United States Investigation of NIDDM (non-insulin-dependent diabetes mellitus) Genetics (FUSION).

By virtue of their close collaboration, DGI, WTCCC/UKT2D and FUSION researchers identified at least eight clear genetic risk factors for type 2 diabetes, including three that had never before been found, as well as several other probable risk factors that warrant further study.

Source: MIT