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## Researchers Identify New Genetic Risk Factors for Type 2 Diabetes

### *Landmark Study Shows At Least 10 Genetic Variants Are Associated With Adult Onset Diabetes*



**BETHESDA, Md.**, Thurs., Apr. 26, 2007 – In the most comprehensive look at genetic risk factors for type 2 diabetes to date, a U.S.-Finnish team, working in close collaboration with two other groups, has identified at least four new genetic variants associated with increased risk of diabetes and confirmed existence of another six. The findings of the three groups, published simultaneously today in the online edition of the journal *Science*, boost to at least 10 the number of genetic variants confidently associated with increased susceptibility to type 2 diabetes – a disease that affects more than 200 million people worldwide.

"This achievement represents a major milestone in our battle against diabetes. It will accelerate efforts to understand the genetic risk factors for this disease, as well as explore how these genetic factors interact with each other and with lifestyle factors," said National Institutes of Health (NIH) Director Elias A. Zerhouni, M.D. "Such research is opening the door to the era of personalized medicine. Our current one-size-fits-all approach will soon give way to more individualized strategies based on each person's unique genetic make-up."

Led by Michael Boehnke, Ph.D., of the University of Michigan's School of Public Health, Ann Arbor; Francis Collins, M.D., Ph.D., of the National Human Genome Research Institute; Richard Bergman, Ph.D., of the University of Southern California, Los Angeles; Karen Mohlke, Ph.D. of the University of North Carolina, Chapel Hill; and Jaakko Tuomilehto, M.D., Ph.D. of the University of Helsinki and National Public Health Institute in Finland; the U.S.-Finnish team received major support from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and NHGRI's Division of Intramural Research, both part of the NIH. The laboratory analysis of genetic variants in the first stage of the study was conducted by the Center for Inherited Disease Research, using funding from NIH and The Johns Hopkins University in Baltimore.

The research was carried out in conjunction with the work of two other teams: the Diabetes Genetics Initiative, which is a collaboration of the Broad Institute of Harvard and MIT, Cambridge, Mass.; Lund University, Malmo, Sweden; and Novartis, Basel, Switzerland; and the Wellcome Trust Case Control Consortium/U.K. Type 2 Diabetes Genetics Consortium. The Diabetes Genetics Initiative was led by David Altshuler, M.D., Ph.D., Broad Institute; Leif Groop, M.D.,

Ph.D., Lund University; and Thomas Hughes, Ph.D., Novartis. The British team was led by Mark McCarthy, M.D., FRCP, Oxford University and Andrew Hattersley, D.M., FRCP, Peninsula Medical School, Plymouth.

"It's been a formidable challenge to identify the complex genetic factors involved in common diseases, such as type 2 diabetes. Now, thanks to the tools and technologies generated by the sequencing of the human genome and subsequent mapping of common human genetic variations, we finally are making significant progress," said NHGRI Director Collins, who led the NIH component of the Human Genome Project.

Type 2 diabetes affects nearly 21 million people in the United States and the incidence of the disease has skyrocketed in the U.S. and many other developed nations over the last 30 years. Diabetes is a major cause of heart disease and stroke, as well as the most common cause in U.S. adults of blindness, kidney failure and amputations not related to trauma.

NIDDK Director Griffin P. Rodgers, M.D., said, "These genetic findings are exciting news for diabetes research. While more work remains to be done, the newly identified genetic variants may point us in the direction of valuable new drug targets for the prevention or treatment of type 2 diabetes."

Previously known as adult onset or non-insulin dependent diabetes (NIDDM), type 2 diabetes usually appears after age 40, often in overweight, sedentary individuals. However, an increasing number of younger people and even children are developing the disease, which is characterized by the resistance of target tissues to respond to insulin and a gradual failure of insulin-secreting cells in the pancreas.

In addition to lifestyle factors like obesity, poor diet and lack of exercise, doctors have long known that heredity plays a significant role in the risk of developing type 2 diabetes. People who have a parent or sibling with type 2 diabetes face a 3.5-times greater risk than people without a family history of the disease. However, researchers have only recently begun to zero in on particular genetic variants that increase or decrease susceptibility to the disease.

To make their discoveries, researchers used a relatively new, comprehensive strategy known as a genome-wide association study. "Genome-wide association studies offer a powerful way to uncover the genetic variations that contribute to diabetes, as well as other common conditions, such as asthma, arthritis, heart disease, cancer and mental illnesses," Dr. Boehnke said. "Once susceptibility genes are identified, researchers then can use this information to develop better approaches to detecting, treating and preventing disease."

To conduct a genome-wide association study, researchers use two groups of participants: a large group of people with the disease being studied and a large group of otherwise similar people without the disease. Utilizing DNA purified from blood or cells, researchers quickly survey each participant's complete set of DNA, or genome, for strategically selected markers of genetic variation.

If certain genetic variations are found more frequently in people with the disease compared to healthy people, the variations are said to be associated with the disease. The associated genetic variations can serve as a strong pointer to the region of the genome where the genetic risk factor resides. However, the first variants detected may not themselves directly influence disease susceptibility, and the actual causative variant may lie nearby. This means researchers often need to take additional steps, such as sequencing every DNA base pair in that particular region of the genome, to identify the exact genetic variant that affects disease risk.

In the latest work, researchers began by scanning the genomes of more than 2,300 Finnish people who took part in the Finland-United States Investigation Of NIDDM Genetics (FUSION) and Finrisk 2002 studies. About half of the participants had type 2 diabetes and the other half had normal blood glucose levels.

"We thank all the Finnish citizens who participated in this study. Their generosity has created a lasting legacy that will help to reduce the terrible toll that diabetes is taking on the world's health," said Dr. Tuomilehto of the Diabetes Unit in Finland's National Public Health Institute.

To validate their findings, the researchers compared their initial results with results from genome scans of 3,000 Swedish and Finnish participants in the Diabetes Genetics Initiative and 5,000 British participants in the Wellcome Trust Case Control Consortium, led by Peter Donnelly, D.Phil., Oxford University. After identifying promising leads through this approach, the three research teams jointly replicated their findings using smaller, more focused sets of genetic markers in additional groups totaling more than 22,000 people from Finland, Poland, Sweden, the United Kingdom and the United States. All told, the genomes of 32,554 people were tested for the study, making it one of the largest genome-wide association efforts conducted to date.

"This is a phenomenal accomplishment, in terms of both the breadth and depth of the research. By pulling together and sharing their data, these three groups were able to achieve far more than any one of them could have done alone," said Eric D. Green, M.D., Ph.D., director of NHGRI's Division of Intramural Research. "This is scientific collaboration at its best."

Ultimately, the researchers identified four new diabetes-associated variations, as well as confirmed previous findings that associated six other genetic variants with increased diabetes risk. The newly identified diabetes-associated variations lie in or near:

- *IGF2BP2*. This gene codes for a protein called insulin-like growth factor 2 mRNA binding protein 2. Insulin-like growth factor 2 is thought to play a role in regulating insulin action.
- *CDKAL1*. This gene codes for a protein called CDK5 regulatory subunit associated protein1-like1. The protein may affect the activity of the cyclin dependent kinase 5 (CDK5) protein, which stimulates insulin production and may influence other processes in the pancreas's insulin-producing cells, known as beta cells. In addition, excessive activity of CDK5 in the pancreas may lead to the degeneration of beta cells.
- *CDKN2A* and *CDKN2B*. The proteins produced by these two genes inhibit the activity of cyclin-dependent protein kinases, including one that has been shown to influence the growth of beta cells in mice. Interestingly, these genes have been heavily studied for their role in cancer, but their contribution to diabetes comes as a complete surprise.
- Chromosome 11. One intriguing association is located in a region of chromosome 11 not known to contain any genes. Researchers speculate that the variant sequences may regulate the activity of genes located elsewhere in the genome, but more work is needed to determine the exact relationships to pathways involved in type 2 diabetes.

The genetic variants associated with diabetes that were confidently confirmed by the new research are: *TCF7L2*, *SLC30A8*, *HHEX*, *PPARG*, *KCNJ11* and *FTO*. A variant in *FTO* was recently associated with increased risk of obesity. (T. Frayling *et al.* A Common Variant in the *FTO* Gene Is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity. *Science Express*, Published online April 12, 2007) The latest study found that variations in or near the *FTO* gene are also associated with greater risk of type 2 diabetes, which is likely related to an increased predisposition to obesity.

When the genomes of the Finnish participants were scanned for all 10 diabetes-associated genetic variants, researchers could identify individuals whose genetic profiles placed them at increased risk for type 2 diabetes – including one subset of people who faced a risk four times higher than those at the lowest genetic risk. This "could potentially have value in a personalized preventive medicine program," the researchers wrote.

However, the researchers emphasized that their predictions of disease risk need to be interpreted with caution because the diabetes group in their sample was "enriched" with people who had affected siblings and because the healthy group excluded people who had impaired glucose tolerance or impaired fasting glucose.

For more information about genome-wide association studies, go to <http://www.genome.gov/20019523>. For more information about diabetes, go to: <http://diabetes.niddk.nih.gov/dm/pubs/overview/index.htm>.

NHGRI and NIDDK are two of the 27 institutes and centers at the National Institutes of Health, which is an agency of the Department of Health and Human Services. The NHGRI Division of Intramural Research develops and implements technology to understand, diagnose and treat genomic and genetic diseases. Additional information about NHGRI can be found at [www.genome.gov](http://www.genome.gov). The NIDDK conducts and supports research in diabetes and other endocrine and metabolic diseases; digestive diseases, nutrition, and obesity; and kidney, urologic and hematologic diseases. Additional information about NIDDK can be found at [www.niddk.nih.gov](http://www.niddk.nih.gov).

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