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## Researchers Discover New Genetic Culprit in Type 2 Diabetes

Researchers at the Howard Hughes Medical Institute (HHMI) at the University of Chicago have identified a new genetic culprit in type 2 diabetes.

The scientists say their findings offer new insight into the origins of type 2 diabetes, a major public health problem that affects more than 135 million people worldwide. The incidence of type 2 diabetes is on the rise, and it currently accounts for about 90 percent of cases of diabetes. If untreated, type 2 diabetes can cause blindness, kidney and heart disease, stroke, loss of limbs and reduced life expectancy.

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The multi-institution research team, which included HHMI investigator Graeme Bell and his colleagues at the University of Chicago, announced their discovery in an article published in the October 2000 *Nature Genetics* and in a second article published in the October 2000 *Journal of Clinical Investigation*.

The *Nature Genetics* report details the scientists' discovery that small genetic variations, called single-nucleotide polymorphisms (SNPs), in the gene for calpain-10 are associated with type 2 diabetes in a long-studied population of Mexican Americans who are susceptible to the disease. The report also implicated the gene in diabetes in an isolated population of people from Finland.

In the *Journal of Clinical Investigation* article, the scientists showed that a group of Pima Indians at high risk for diabetes also had the calpain-10 polymorphism. This group had insulin resistance and showed reduced levels of calpain-10 gene expression, demonstrating that the polymorphism relates to the disease. That study was also led by co-authors from the National

Institutes of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health, who were also co-authors on the *Nature Genetics* paper.

The search for a specific genetic defect underlying type 2 diabetes began after Bell and University of Texas at Houston researcher Craig Hanis led a 1996 screening study that localized a diabetes susceptibility gene in a population of highly diabetes-susceptible Mexican Americans in Texas. That population had been studied by Hanis — a co-author of the *Nature Genetics* paper — and his colleagues for more than two decades. The screening study statistically linked increased diabetes risk to an unknown gene on chromosome 2, which the scientists named *NIDDM1*.

"This was the first genome-wide screen for susceptibility genes for type 2 diabetes," said Bell. "It actually demonstrated that one could map susceptibility genes for this disorder." The finding launched Bell, Hanis and their colleagues on a search to pinpoint the specific gene and its variants that caused increased diabetes susceptibility in this population.

"Such an identification had never been done before for a genetically complex disorder such as type 2 diabetes," said Bell. "It was extraordinarily difficult because the gene location is not precisely defined by recombination events, as it is for a single-gene disorder. Rather, it is only a probability that the gene will be in a particular region, so the region that you have to search is much larger than for a single-gene disorder."

By sequencing DNA samples from the Mexican-American population under study and performing statistical analysis on the DNA sequences, the researchers narrowed their search for the gene from a vast region of chromosome 2 to a much more manageable region of 66,000 DNA base pairs. Further analysis led them to SNPs in a previously unknown gene called *CAPN10*. The gene codes for calpain-10, a protein-snipping enzyme called a protease, said Bell.

"This protease was not on anyone's list of favorite genes for affecting either insulin secretion or insulin action or hepatic glucose production," said Bell. "People were focusing on the insulin receptor and insulin receptor pathway; on insulin-responsive tissues or the secretory mechanism that regulates glucose metabolism of the pancreatic beta cell. They weren't thinking about proteases."

What's more, the SNPs were not even in the protein-coding portions of the *CAPN10* gene, but in non-coding regions of the gene called introns. Introns are gene segments that are edited out when a gene is copied to messenger RNA (mRNA) to make the functioning protein. According to Bell, their studies suggest that the SNPs they found somehow decrease the level of *CAPN10* expression, thus contributing to the diabetes susceptibility in affected populations. Bell emphasized that an enormous amount of work lies ahead to understand the role of calpain-10 and its variants in diabetes susceptibility.

"Clearly, once we understand more about the pathway, it could lead to new therapeutic approaches for treating diabetes," said Bell. "But we don't know enough about the pathway right now to predict whether or not that realization will come to pass. This discovery is certainly an important piece of the puzzle, but having gotten this far, we now end up with many more challenges ahead," he said.

For example, the researchers would like to understand how the different versions of the gene, or alleles, they found might interact to increase diabetes susceptibility. Their current hypothesis is that diabetes susceptibility is achieved through a "two-hit" effect:

"The two-hit notion is that one allele affects calpain-10 expression in, for example, the pancreatic beta cell," said Bell. "And the other allele would affect expression in an insulin-responsive tissue. Thus, it would require a defect in both tissues to lead to type 2 diabetes."

The *CAPN10* expression study in Pima Indians is important, Bell said, "because we demonstrated that variations in *CAPN10* do indeed affect expression of the gene in skeletal muscle, as we predicted. Also, individuals who are at greatest risk of diabetes, have lower levels of calpain-10 mRNA in skeletal muscle.

"In addition, the Pima study shows a nice correlation between calpain-10 mRNA levels in skeletal muscle, and glucose metabolism by skeletal muscle. So, it begins to provide some understanding of the mechanism of this defect."

More broadly, Bell said that he hopes that the success of their search for type 2 diabetes susceptibility genes will inspire other scientists to tackle other complex genetic diseases. "Of course, we're still at the beginning, but our success so far with type 2 diabetes means that those investigators looking for genes for asthma, schizophrenia and other disorders that also have a complex genetic basis are going to have a high likelihood of success as well," he said.