Gene discovered for type 1 diabetes in children

July 15 2007

Pediatrics researchers at The Children's Hospital of Philadelphia and McGill University in Montreal have identified a gene variant that raises a child's risk for type 1 diabetes, formerly called juvenile diabetes. As investigators continue to pinpoint genes contributing to diabetes, they have their eyes on providing a scientific basis for designing better treatments and preventive measures for the disease.

The research adds a new gene and new knowledge to the four genes previously discovered for type 1 diabetes, in which the immune system destroys insulin-producing beta cells in the pancreas and makes patients dependent on frequent insulin injections to keep the body's blood sugar under control. As the project continues, the study team expects to identify additional genes (perhaps as many as 15 or 20) thought to interact with each other in the disease.

The study appeared July 15 in an advance online letter in the journal *Nature*.

"The genotyping technology we now have available has revolutionized the way we can ask and answer research questions," said the study's lead author, Hakon Hakonarson, M.D., Ph.D., the director of the Center for Applied Genomics at The Children's Hospital of Philadelphia. "Unlike the previous technology, which was quite limited and dealt largely with relatively rare gene variants, we can now detect common genetic variants that are important in large numbers of individuals, and begin to understand how multiple genes interact in complex diseases such as

diabetes."

In the discovery phase of the study, the investigators examined the genomes of 1,046 children with type 1 diabetes. These DNA samples came from patients and families followed in pediatric diabetes clinics in Philadelphia and four Canadian cities. Specifically, the researchers compared the genomes of 563 patients with type 1 diabetes with those of 1,146 matched control subjects. Those results were combined with those obtained from an independent analysis of 483 family trios, in which the genomes of a child with the disease and both parents were examined.

The researchers confirmed the four previously identified locations for genes contributing to type 1 diabetes, but also uncovered a new type 1 diabetes locus on chromosome 16, occupied by a gene called KIAA0350. The team then replicated this discovery in yet another independent cohort of 1,333 children with the disease from the Type 1 Diabetes Genetics Consortium, which includes children of European descent in Europe, North America and Australia, as well as in 390 additional type 1 diabetes family trios from Canada.

Constantin Polychronakos, M.D., director of Pediatric Endocrinology at McGill University and senior author of the study, said that better knowledge of genes that predispose to type 1 diabetes may later enable physicians to screen newborns to predict those at high risk for the disease.

The gene implicated in the current research, KIAA0350, is known to be active almost exclusively in immune cells. Although scientists do not currently know the exact function of the protein the gene encodes, other research has predicted that it produces a protein called C-type lectin that is located on the surface of immune cells and binds to groups of sugars in the body.

“The role of KIAA0350 needs to be investigated,” said Hakonarson. “However, a special cell type called a natural killer (NK) cell expresses this gene abundantly, although at different levels based on these gene variants. Our hypothesis is that a special mutation in KIAA0350 may influence the sugar binding of the protein, and trigger an autoimmune response that activates these NK cells in such a way that they attack and destroy the islet cells in the pancreas, resulting in type 1 diabetes. A particular version of the gene protects against this inappropriate autoimmune response, while a different version of the gene makes it more likely to happen. ”

Although much research remains to be done, better understanding of the disease process may guide doctors to new and improved therapies. “If we know the gene pathways that give rise to type 1 diabetes, we hope to intervene early in life with targeted drugs or cell therapies to prevent the disease from developing,” said Polychronakos.

The current research used a technique called genome-wide association, in which highly automated analytic equipment rapidly scans each patient’s DNA for more than half a million genetic markers. It was performed at the Center for Applied Genomics at Children’s Hospital. The Center’s tools spell out a patient’s genotype—the specific pattern of variations among an individual’s 30,000 genes. Established in the summer of 2006, the center is taking on one of the largest genotyping projects in the world, and is the largest one dedicated to genetic analysis of childhood diseases.

“This study is the first one that our center has published on a gene associated with a complex childhood disease, but we have many projects under way and several other papers in press,” said Hakonarson. “Our goal at the Center is to discover the major disease-causing variants and genes that influence complex pediatric diseases, thus providing a scientific foundation that is based in biology for translating those

discoveries into successful treatments."

Among its current projects, the Center's investigators are focused on identifying genes involved in pediatric asthma, allergy, obesity, attention-deficit hyperactivity disorder, autism, inflammatory bowel disease, hypertension, juvenile rheumatoid arthritis and the pediatric cancer neuroblastoma. The Center recently contributed 4,000 DNA samples to an industry-hosted database that serves as a free repository of control samples for researchers seeking gene variations in diseases.

Source: Children's Hospital of Philadelphia