

Gene identified for Crohn's disease in children

July 18 2007

Pediatrics researchers have identified a gene variant that raises a child's risk of Crohn's disease, a chronic and painful condition attributed to inflammation of the gastrointestinal tract.

The research reinforces previous results by German researchers, who found the same gene variant associated with the adult form of Crohn's disease.

Researchers from The Children's Hospital of Philadelphia and The University of Pennsylvania reported their results in a letter in the August issue of the journal *Gut*.

"Because Crohn's disease is complex, with multiple genes interacting with each other and with environmental factors, it's important to sort out specific genes and to replicate previous findings," said the study's first author, Robert N. Baldassano, M.D., director of the Center for Pediatric Inflammatory Bowel Disease at Children's Hospital. "There are different types of Crohn's disease, so classifying types by genetic profiles may help us select the most appropriate treatments for each patient."

The study compared the genomes of 143 children with Crohn's disease to genomes of 282 matched control subjects. The study team found that 64 percent of children with Crohn's disease had a specific variant form of the gene ATG16L1, compared with 52 percent of the healthy children. The odds ratio for children with the gene variant was 1.62 compared to control children, meaning that those who have the variant

were 62 percent more likely to have Crohn's disease than children with the more common allele.

A separate test that analyzed trios (a Crohn's patient and both parents) also found an association between the ATG16L1 gene variant and disease symptoms. This finding strengthened the results of the pediatric case-control study.

The genome-wide association study, which used highly automated analytic equipment to scan each patient's DNA for more than half a million genetic markers, 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 among the first that our center has published on a gene associated with a complex childhood disease, but we have many projects under way,” said senior author Hakon Hakonarson, M.D., Ph.D., the director of the Center for Applied Genomics. “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 for translating those discoveries into successful treatments.” Earlier this month, Hakonarson collaborated with researchers in Montreal to identify a gene associated with insulin-dependent diabetes in children. Other projects at the Center are seeking genes associated with pediatric asthma, allergy, obesity, attention-deficit hyperactivity disorder, autism, hypertension, juvenile rheumatoid arthritis and the pediatric cancer neuroblastoma.

The gene implicated in the current research, ATG16L1, plays an important role in the autophagosome pathway, a sequence of biological

events involved in processing bacteria within cells. While the mechanisms are not fully understood, said Baldassano, a mutation in the gene may weaken a cell's ability to degrade cellular waste products, including bacteria. When unprocessed waste products pile up within the cell, they may stimulate the inflammatory response that characterizes Crohn's disease.

Although much research remains to be done, he added, better understanding of the disease process may guide doctors to new and improved therapies. "If an excess of bacteria is the problem, we may find antibiotics effective in treating this type of Crohn's disease. Other approaches may be to use immune-boosting drugs to blunt the inflammation, or determining whether particular foods interact with genetic susceptibilities to affect disease symptoms. Understanding gene influences gives us a more targeted way to look at disease physiology, and also may suggest targets for treatment." Baldassano and Hakonarson said that they will continue to search for other gene variants associated with Crohn's disease and the closely related bowel disorder ulcerative colitis.

Source: Children's Hospital of Philadelphia

Citation: Gene identified for Crohn's disease in children (2007, July 18) retrieved 2 May 2024 from <https://medicalxpress.com/news/2007-07-gene-crohn-disease-children.html>

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