New genes found for inflammatory bowel disease in children

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Researchers have discovered two new genes that increase the risk of developing inflammatory bowel disease (IBD) in childhood.

While further study is needed to identify the specific disease-causing mutations in these new genes, the researchers say the genes are particularly strong candidates to be added to the list of genes already known to affect IBD. "As we continue to find genes that interact with each other and with environmental influences in this complex, chronic disease, we are building the foundation for personalized treatments tailored to a patient's genetic profile," said co-first author Robert N. Baldassano, M.D., director of the Center for Pediatric Inflammatory Bowel Disease at The Children's Hospital of Philadelphia.

"We will resequence the gene regions we have identified to pinpoint the causative mutations in these genes," added study leader Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at Children's Hospital. "We strongly suspect one gene will provide a compelling target for drug development, given what's known about its biology."

Both authors direct research programs at Children's Hospital and are also faculty members of the University of Pennsylvania School of Medicine. Their study, performed in collaboration with researchers from the Medical College of Wisconsin, The University of Utah, Cincinnati Children's Hospital and two research hospitals in Italy, appears in advance online publication Aug. 31 in *Nature Genetics*.

IBD is a painful, chronic inflammation of the gastrointestinal tract, affecting about two million children and adults in the United States. Of that number, about half suffer from Crohn's disease, which can affect any part of the gastrointestinal tract, and half have ulcerative colitis, which is limited to the large intestine.

IBD that begins in childhood tends to be more severe than adult-onset disease, and is more likely to affect the colon than other areas of the GI tract. Those age-related differences in IBD spurred the current research team to do their gene hunting in childhood-onset disease. "Although the gene variants we found may have a stronger signal in pediatric IBD than in adult-onset IBD, we do not believe them to be limited to varieties of the disease that begin in childhood," said Baldassano.

The researchers performed a genome-wide association study, searching for genetic variations in DNA samples from 1,000 patients with childhood-onset IBD, compared to samples from 4,250 healthy subjects. Both patients and controls were of European ancestry.

In addition to finding gene variations previously reported by other groups, the study team identified two novel gene variants, one on chromosome 20 and the other on chromosome 21. They then replicated their findings with studies using additional samples from other sources.

The researchers say that the TNFRSF6B gene on chromosome 20 is a compelling candidate, because it is already known to participate in the biological pathway of a protein called tumor necrosis factor (TNF). TNF is a cytokine, a chemical messenger that plays a key role in the harmful inflammation characteristic of IBD.

Some current treatments for IBD use monoclonal antibodies that selectively bind to a type of TNF involved in the disease (Among those drugs are infliximab, adalimumab and certolizumab). "As we better

understand the complex gene interactions in IBD, we may be able to diagnose patients by their genetic profile to predict who will better respond to anti-TNF drugs," said Hakonarson. Anti-TNF medications such as those mentioned above are currently given intravenously or as injections, said Baldassano, who added, "If better knowledge of the disease pathway enables pharmaceutical companies to develop anti-TNF drugs in pill form, the medications will be easier to deliver as well as more customized to each patient."

The study team also found an association between ulcerative colitis and genes on the major histocompatiblity complex (MHC) on chromosome 6. The MHC is a large group of genes with important roles in the immune system, and this finding may help refine diagnostic techniques that would allow physicians to administer more specific therapies to their patients.

Source: Children's Hospital of Philadelphia