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Largest gene study of childhood IBD identifies 5 new genes

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In the largest, most comprehensive genetic analysis of childhood-onset inflammatory bowel disease (IBD), an international research team has identified five new gene regions, including one involved in a biological pathway that helps drive the painful inflammation of the digestive tract that characterizes the disease.

A research team led by Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at The Children's Hospital of Philadelphia, says that the findings advance the scientific understanding of how IBD develops. "This is an evolving story of discovering what genes tell us about the disease," said Robert N. Baldassano, M.D., a co-first author of the study and director of the Center for Pediatric Inflammatory Bowel Disease at Children's Hospital. "Pinpointing how specific genes act on biological pathways provides a basis for ultimately personalizing medicine to an individual's genetic profile."

The study appears online today 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 GI tract, and half have ulcerative colitis, which is limited to the large intestine.

Most gene analyses of IBD have focused on adult-onset disease, but the Center for Applied Genomics—one of the world's largest pediatric

genotyping programs—at Children's Hospital has concentrated on childhood-onset IBD, which tends to be more severe than adult-onset disease. The researchers performed a genome-wide association study on DNA from over 3,400 children and adolescents with IBD, plus nearly 12,000 genetically matched control subjects, all recruited through international collaborations in North America and Europe.

In a genome-wide association study, automated genotyping tools scan the entire human genome seeking gene variants that contribute to disease risk.

The study team identified five new gene regions that raise the risk of early-onset IBD, on chromosomes 16, 22, 10, 2 and 19. The most significant finding was at chromosome locus 16p11, which contains the IL27 gene that carries the code for a cytokine, or signaling protein, also called IL27. "This cytokine acts on a biological pathway, the T-helper 17 pathway, which plays a key role in causing intestinal inflammation," said Hakonarson. T helper 17 cells are recently discovered cells that lead to severe inflammation and tissue injury in autoimmune diseases. IBD is an autoimmune disease, in which a person's immune system runs out of control and attacks the body.

"There are many cytokines in our immune system, but our research strongly suggests that IL27 has a primary causative role in IBD," added Hakonarson. "This gene discovery makes sense in terms of our functional understanding of the disease."

Some current IBD drugs are monoclonal antibodies that act on another cytokine, called tumor necrosis factor, which contributes to inflammation. Although much research remains to be done, the current study may provide a basis for developing drugs that target the cytokine IL27's action, for patients with the disease-causing IL27 gene variant.

One strength of the current study, in addition to its large sample size, is the collaboration of many leading pediatric IBD research programs. In addition to The Children's Hospital of Philadelphia, other centers with principal investigators who played key roles were the Hospital for Sick Children of the University of Toronto; the University of Edinburgh, UK; Cedars Sinai Medical Center, Los Angeles; Emory University, Atlanta; and the IRCCS-CSS Hospital, S. Giovanni Rotondo, Italy.

More information: "Common variants at five new loci associated with early-onset inflammatory bowel disease," *Nature Genetics*, published online Nov. 15, 2009 dx.doi.org/10.1038/ng.489

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