

Early onset gene for inflammatory bowel diseases identified

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A study of Crohn's disease and ulcerative colitis in children has identified a gene that influences whether children get these diseases early in life, and points to a potential new target for treatment. The findings of the international team that performed the study were published online this week by the journal *Nature Genetics*.

Crohn's disease and ulcerative colitis are chronic inflammatory diseases that affect the intestines, resulting in pain, severe diarrhea, intestinal bleeding, weight loss and fever. In ulcerative colitis, the inner lining of the colon is inflamed, while in Crohn's disease the inflammation extends deeper into the intestinal wall and can involve both the small and large intestine.

While several genes that influence susceptibility to the two diseases have been found previously, this study is the first to focus on inflammatory bowel disease (IBD) with childhood onset, says co-first author Subra Kugathasan, MD.

Kugathasan recently was recruited to Emory University School of Medicine's Department of Pediatrics from the Medical College of Wisconsin to head the Pediatric Inflammatory Bowel Disease program. Dr Kugathasan's future research will focus on discovery of additional IBD genes and in depth study of how these genes influence disease onset and progression.

"Our novel candidate gene is in the same inflammatory pathway as some

other susceptibility genes, so it may represent an accessible target for treatment," Kugathasan says.

Kugathasan's co-first author is Robert Baldassano, MD, director of the Center for Inflammatory Bowel Disease at Children's Hospital of Philadelphia. The study's senior author is Hakon Hakonarson, MD, director of the Center for Applied Genomics at Children's Hospital of Philadelphia and associate professor of pediatrics at University of Pennsylvania School of Medicine.

Both genetics and the environment have an effect on the risk of getting inflammatory bowel disease, Kugathasan says. If one identical twin suffers from Crohn's disease, the other has a 60 percent probability of getting it too. However, the incidence of disease has drastically increased over the last half century, he notes, suggesting a key role of the environment in disease development. Smoking is an environmental factor that is particularly strong in increasing the risk of Crohn's disease.

"We have to conclude that the interactions between genetics and environment are responsible for most cases," he says.

The study compared the DNA of more than 1,000 children diagnosed with inflammatory bowel diseases at the average age of 11 with 4,250 controls (disease-free children), and confirmed the findings in a larger set of patients established by the British Wellcome Trust Case Control Consortium.

The authors used gene chip microarray technology to scan thousands of one-letter alternative genetic "spellings" -- known to geneticists as single nucleotide polymorphisms (SNPs)-- spread throughout the patients' DNA. Most of the SNPs made little difference when it came to affecting the risk of inflammatory bowel disease, but a few stood out, and two had not been seen before.

One new SNP led the scientists to a gene called tumor necrosis factor receptor superfamily member 6B (TNFRSF6B), whose activity they found was associated with the degree of inflammation in the colon. The function of the second SNP is still under investigation.

TNFRSF6B encodes a protein that lengthens the duration of an immune response by regulating the longevity of activated white blood cells.

Kugathasan notes that a related protein, tumor necrosis factor alpha, is the target of an existing antibody treatment for inflammatory bowel disease. This suggests that antibodies to TNFRSF6B could also be helpful in controlling the disease, he says.

Source: Emory University

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