Scientists find new genes for Crohn's disease

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Just a few months after their landmark article in Science magazine reporting the discovery of strong links between variations in a gene that codes for a cellular receptor involved in controlling inflammation and Crohn's disease, a consortium of U.S. and Canadian researchers is reporting in today's online issue of *Nature Genetics* that they have discovered several more genetic variations that are strongly linked to an increased risk for the disease.

The discovery of these Crohn's disease-associated genetic variants has identified several key biological pathways that will be the focus of further research to understand how the debilitating inflammatory process is initiated and maintained in many cases of the disease.

"As we collect more and more data from these genome-wide association studies, we continue to discover susceptibility genes for Crohn's and other inflammatory bowel diseases (IBDs). More importantly, those genes are leading us to the biological pathways that relate to IBD pathogenesis. By understanding these pathways, we may be better able to develop more effective therapies for IBD," said consortium member Richard H. Duerr, M.D., associate professor of medicine and human genetics at the University of Pittsburgh, co-director of the Inflammatory Bowel Disease Center and director of the IBD Genetics Program.

These latest results are helping to fill in the gaps in knowledge about Crohn's and other IBDs, which affect more than 1 million Americans. Because IBDs tends to run in families and are more frequent in certain ethnic populations, especially Ashkenazi Jews, scientists have long

suspected that they have a significant genetic component.

Previous genetic studies have found strong links between Crohn's disease and mutations in two genes, one known as CARD15, and, more recently, a gene known as IL23R, which codes for the immune cell receptor for interleukin-23, an important biochemical mediator of inflammation in the body.

However, mutations in these two genes alone cannot account for the entire genetic component of the disease. To identify additional genes that are associated with Crohn's, the researchers scanned more than 300,000 single nucleotide polymorphisms, or SNPs, in the genomes—all of 22,000 or so genes—in people with Crohn's disease and in healthy controls. SNPs are subtle variations in the genetic code found in all genes. Some variations can be harmful, while others may be helpful or have no effect at all.

The comparison of these SNPs between patients with Crohn's disease and people without the disease identified multiple variations in several genes that were strongly associated with Crohn's disease. These findings were then retested in two additional sets of patients and healthy controls in order to confirm their significance. After all of the comparisons, the consortium identified variations in three genes — PHOX2B, NCF4 and ATG16L1 — as contributing significantly to the risk for Crohn's disease.

According to corresponding author John D. Rioux, Ph.D., associate professor of medicine at the Montreal Heart Institute and at the Université de Montréal, the identification of the PHOX2B gene in this study suggests that neuroendocrine cells of the intestinal epithelium have a key role to play in Crohn's. In addition, the identification of the NCF4 gene indicates that the production of altered reactive oxygen species, which are important in the generation of a protective response against

microbes, may lead to an increased risk of developing the condition.

Particularly interesting to the authors was the association between Crohn's and variations in the ATG16L1 gene, which they found is essential for the cell's normal mechanism for degrading worn-out cellular components and helping to eliminate some pathogenic bacteria—a pathway known as autophagy (pronounced AU-TOF-A-GEE).

Finding ATG16L1's involvement in Crohn's disease provides confirmatory evidence for what doctors have long suspected: that an individual's ability to respond effectively to harmful microbes influences his or her susceptibility to the disease.

"We propose that genetic variation in the ATG16L1 gene leads to alterations in how the body uses autophagy and therefore may result in increased persistence of [toxic] cellular and bacterial components. This may lead to an inappropriate immune activation and increased risk of Crohn's disease," says co-author Dr. Ramnik Xavier, a gastroenterologist at the Massachusetts General Hospital's (MGH) Center for the Study of IBD and a researcher at the MGH Center for Computational and Integrative Biology.

This study's findings are expected not only to improve on the biological understanding of disease but also should have a long-term impact on clinical practice, according to Dr. Steven Brant, co-author and gastroenterologist at Johns Hopkins University.

"The multiple genetic risk factors we've identified provide important targets for current functional studies aimed at understanding the disease. These will be important targets for drug development to improve therapy of Crohn's disease in the future," he said.

Stephen P. James, M.D., director of the division of digestive diseases

and nutrition at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) agreed, saying that "these important discoveries not only offer new hope for better therapies for patients with Crohn's disease, but they also highlight the promise of the human genome project and subsequent investments by the NIH in large-scale, collaborative research projects to unravel the causes of, and hopefully better treatments for complex, enigmatic diseases".

In addition to finding the additional Crohn's disease susceptibility genes, the researchers got strong signals for genetic risk factors located in areas of the genome where there are no known genes. "Further work will be necessary to identify the causal genes in these regions," the authors said.

Source: University of Pittsburgh Schools of the Health Sciences