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New gene-searching method uncovers possible new targets for Crohn's disease drugs

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Discovering the different genes that contribute to a complex disease is like searching in the proverbial haystack for an unknown number of needles--some much smaller than others, often blending into the background, and many of them widely separated from each other. But if some needles are linked to each other by fine threads, you might pull out clumps of them together.

Using a novel approach that combines a statistical tool that identifies genes interacting on the same biological pathways with highly automated gene-hunting techniques that scan the whole genome, an international team of researchers has discovered new genes involved in Crohn's disease. Crohn's disease is a chronic and painful condition caused by inflammation of the gastrointestinal tract. The researchers, led by scientists at The Children's Hospital of Philadelphia, say their approach broadens the power of gene discovery studies to ferret out potential targets for disease treatments.

In a complex disorder such as Crohn's disease, many different genes interact to cause the illness. Research over the past few years have identified many of the genes with the strongest effects, but many other genes with important roles may produce weaker or ambiguous signals in the large-scale studies, and go overlooked. "Our pathway-based approach aggregates information from multiple sources to detect modest effects from genes associated with each other," said study leader Hakon

Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at Children's Hospital.

The study appeared online today in the *American Journal of Human Genetics*. It will be published in the journal's print edition on March 13.

Currently the workhorse of gene-hunting is genome-wide association (GWA), which uses automated analytic equipment to sweep through the full range of all 23 human chromosomes and detect the most significant gene variants associated with a given disease. Those variants, each a change in a single DNA base, are called single nucleotide polymorphisms (SNPs).

However, individual GWA studies often do not have the statistical power to detect subtle but important variants that are involved in disease development. By using an algorithm developed by Kai Wang, Ph.D., at the Center for Applied Genomics, Hakonarson's study team created a pathway-based approach that seeks out interacting or related genes along the same biological pathway. "We applied our pathway-based approach to GWA data for Crohn's disease, but conducted the search without starting with a hypothesis focused on a specific suspected pathway," said Hakonarson. "Among hundreds of known biological pathways, the one that surfaced from the analysis as being most significant included genes already known to be relevant to the biology of Crohn's disease."

That pathway, the interleukin 12 (IL12) pathway, governs cell receptors involved in the development of Crohn's disease. Hakonarson added that the IL12 pathway might be more correctly referred to as the IL12/IL23 pathway, since IL12 receptor signaling converges with signaling on another receptor, IL23. Previous work by other researchers had shown that monoclonal antibodies that block the IL12 or IL23 receptor show some clinical success in treating Crohn's disease.

"As we better understand the gene pathways operating in Crohn's disease, we are uncovering more potential targets for effective drug treatments," said pediatric gastroenterologist Robert Baldassano, M.D., a study co-author and the director of the Center for Pediatric Inflammatory Bowel Disease at Children's Hospital. He added that developing targeted therapies based on gene pathways might allow doctors to tailor treatments to a patient's genetic profile.

The study team performed the initial analysis in DNA from 1,758 patients with Crohn's disease and 1,480 control subjects, all of European ancestry. They repeated the study in three additional groups, of both European and African American ancestry, and were able to replicate their results. Their study was the first to use a pathway-based approach to analyze GWA, without deciding beforehand to concentrate on a specific pathway.

For children and adults with Crohn's disease, who suffer the debilitating effects of chronic gastrointestinal inflammation, the emerging gene data may open the doors to more effective treatments. "Blocking cell receptors at some points on a biological pathway may produce clinical improvements, but with side effects to the immune system," said Baldassano. "If we can block other molecules further downstream on a pathway, we may achieve better treatments that may be more specific to an individual patient, with fewer side effects."

More information: Wang et al, "Diverse Genome-wide Association Studies Associate the IL12/23 Pathway with Crohn's Disease," The American Journal of Human Genetics, 84, pp. 1-7, March 13, 2009.

Source: Children's Hospital of Philadelphia