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Identification of genetic markers for ulcerative colitis could lead to treatment

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An international consortium of researchers, including major contribution from a team led by Dr. John D. Rioux, a professor of medicine at the Université de Montréal and the Montreal Heart Institute, has identified genetic markers associated with risk for ulcerative colitis. The findings, published in the advance online journal *Nature Genetics*, bring researchers closer to understanding the biological pathways involved in the disease and may lead to the development of new treatments that specifically target them.

"Our identification of some of the genes that lead to ulcerative colitis are giving us a first look into the causes of this debilitating disease and provides strong leads as to improved diagnosis and treatment," says Dr. Rioux, one of the lead researchers of the study.

Ulcerative colitis is a chronic, relapsing disorder that causes inflammation and ulceration in the inner lining of the rectum and large intestine. The most common symptoms are diarrhea (oftentimes bloody) and abdominal pain. Ulcerative colitis and Crohn's disease, another chronic gastrointestinal inflammatory disorder, are the two major forms of inflammatory bowel disease (IBD).

"Ulcerative colitis and Crohn's disease are chronic conditions that impact the day-to-day lives of patients," says senior author of the study Richard H. Duerr, M.D., associate professor of medicine and human genetics at the University of Pittsburgh School of Medicine and Graduate School of Public Health. "IBD is most often diagnosed in the teenage years or early

adulthood. While patients usually don't die from IBD, affected individuals live with its debilitating symptoms during the most productive years of their lives."

Because IBD tends to run in families, researchers have long thought that genetic factors play a role. Technology developed in recent years has enabled systematic, genome-wide searches for gene markers associated with common human diseases, and the discovery of more than 30 genetic risk factors for Crohn's disease has been one of the major success stories in this new era of research.

While some genetic factors associated with Crohn's disease also predispose individuals to ulcerative colitis, markers specific for ulcerative colitis had yet to be found. To do so, researchers performed a genome-wide association study of hundreds of thousands of genetic markers using DNA samples from 1,052 individuals with ulcerative colitis and pre-existing data from 2,571 controls, all of European ancestry and residing in North America.

Several genetic markers on chromosomes 1p36 and 12q15 showed highly significant associations with ulcerative colitis, and the association evidence was replicated in independent European ancestry samples from North America and southern Italy.

Nearby genes implicated as possibly playing a role in ulcerative colitis include the ring finger protein 186 (RNF186), OTU domain containing 3 (OTUD3), and phospholipase A2, group IIE (PLA2G2E) - genes on chromosome 1p36, and the interferon, gamma (IFNG), interleukin 26 (IL26), and interleukin 22 (IL22) genes on chromosome 12q15 that play an important role in inflammation. RNF186 and OTUD3 are members of gene families involved in protein turnover and diverse cellular processes. PLA2G2E, IFNG, IL26 and IL22 are known to play a role in inflammation and the immune response.

The study also found highly suggestive associations between ulcerative colitis and genetic markers on chromosome 7q31 within or near the laminin, beta 1 (LAMB1) gene, which is a member of a gene family known to play a role in intestinal health and disease, and confirmed previously identified associations between ulcerative colitis and genetic variants in the interleukin 23 receptor (IL23R) gene on chromosome 1p31 and the major histocompatibility complex on chromosome 6p21.

Source: University of Montreal