CANADIAN AND AMERICAN SCIENTISTS FIND GENE TARGET THAT MAY PROTECT AGAINST CROHN’S DISEASE AND ULCERATIVE COLITIS

Discovery offers hope of better-targeted therapy
for millions of people with inflammatory bowel diseases

Montreal, October 26, 2006 – The discovery by a six-member Inflammatory Bowel Disease (IBD) Genetics Consortium of a genetic risk factor for IBD has been reported in Science Express, the online publication of the journal Science. According to one of the Canadian principal investigators, director of the Laboratory in Genetics and Genomic Medicine of Inflammation at the Montreal Heart Institute, Dr. John D. Rioux, “This discovery may lead to a paradigm shift in our thinking from ‘genetics of diseases to genetics of health’, particularly as concerns Crohn’s Disease and Ulcerative Colitis.” This discovery was, in part, due to the contributions of the gastroenterologists of the Quebec IBD Genetics Consortium led by Dr. Rioux and Dr. Alain Bitton of the McGill University Health Centre.

Inflammatory bowel disease, or IBD, describes two similar yet distinct conditions called Crohn's disease and ulcerative colitis. These diseases affect the digestive system and cause the intestinal tissue to become inflamed, form sores and bleed easily. Symptoms include abdominal pain, cramping, fatigue and diarrhea.

Crohn's disease may affect the gastrointestinal tract, from the mouth to the anus, and while Crohn's disease can not be cured by drugs or surgery, either may relieve symptoms.

In Canada, an estimated 170,000 Canadian men and women suffer from IBD, most frequently between the ages of 15-25, or 45-55. It is particularly difficult for children and young adults since it often affects a person's self-concept. IBD is found throughout the world. However, it appears to be most common in North America and northern Europe; Canada having one of the highest incidence rates of IBD in the world. (1) In the U.S., more than 1 million Americans have Crohn’s or colitis.

Since IBD tends to run in families and is more frequent in certain populations, especially Ashkenazi Jews, scientists have long suspected a significant genetic component. Although previous genetic studies found a link between Crohn’s disease and mutations in a gene known as CARD15, those mutations alone are not considered to account for the entire genetic component of disease.

According to senior author Judy H. Cho, M.D., associate professor in the departments of Medicine and Genetics at Yale School of Medicine, the findings highlight a major inflammatory

(1) Source: Crohn’s & Colitis Foundation of Canada
pathway and may change our thinking about disease-associated genetic variation. “This pathway is particularly intriguing because we appear to have identified a gene variant that protects against development of IBD,” said Dr. Cho, who is also director of the Inflammatory Bowel Disease Center at Yale.

While mutations of the gene which codes for a receptor in a major inflammatory pathway are strongly associated with Crohn’s disease, surprisingly, Consortium researchers report that one type of mutation may confer significant protection and identify potential targets for drugs therapies for the management of Crohn’s disease and ulcerative colitis.

To identify additional genes that are associated with IBD, the international team of researchers scanned the genome – some 22,000 – by testing more than 300,000 nucleotide polymorphisms, or SNPs, in people with Crohn’s disease, and a similar number of people without IBD. The scan led to an unexpected discovery.

Although several polymorphisms were associated with a significantly increased risk of developing IBD, one appeared to confer a very strong protection against IBD.

“Of all the SNPs we studied in people with and without IBD, this protective SNP was the most statistically significant finding in our study. So, it took us a bit by surprise,” said first author, Richard H. Duerr, M.D., associate professor of medicine and human genetics, University of Pittsburgh. “What it means in terms of improving treatments for IBD patients, we are not sure yet.”

Nonetheless, members of the Consortium are attempting to tease out the specific downstream effects of this protective polymorphism. Yet, because IL-23 plays an important role in activating inflammation, including in the organs of the digestive tract, it could be an extremely important target for improving the management of Crohn’s disease and other IBDs.

“Recent studies in mice in which the gene for IL-23 was deleted demonstrated that it is essential for triggering chronic intestinal inflammation. Such evidence, combined with the current discovery, suggests therapies that target the IL-23 pathway may lead to more individualized, better-directed therapies for IBDs. In fact, blocking the activity of IL-23 or manipulating its pathway may be an effective way to manage IBD,” said Dr. Rioux. “I am confident that the future genetic studies by this collaborative group will continue to improve our understanding of these and other chronic inflammatory diseases,” he added.

Dr. John D. Rioux, PhD, one of the six principal investigators of the Consortium, is associate professor of medicine at the Université de Montréal and at the Montreal Heart Institute where he is the director of the Laboratory in Genetics and Genomic Medicine of Inflammation (www.inflammgen.org). He is also visiting scientist of the Broad Institute of MIT and Harvard and holder of the Canada research chair in Genetics and Genomic Medicine of Inflammation.

The Inflammatory Bowel Disease (IBD) Genetics Consortium is funded by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health. Consortium member institutions include the Cedars-Sinai Medical Center in Los Angeles, the University of Chicago, the Johns Hopkins University, Montreal Heart Institute & Université de Montréal, the University of Pittsburgh, the University of Toronto, and Yale University.
Title of the report:
A Genome-wide Association Study Identifies IL23R as an Inflammatory Bowel Disease Gene.

For a complete list of the study’s authors and their affiliations please see:
http://www.sciencemag.org/sciencexpress/recent.

About the Montreal Heart Institute
Founded in 1954, the Montreal Heart Institute constantly aims for the highest standards of excellence in the cardiovascular field through its leadership in prevention, ultra-specialized care, training of professionals, clinical and fundamental research, and assessment of new technologies. It is affiliated with the Université de Montréal and its clinical outcomes are among the best in the world. The MHI Research Centre officially came into existence in 1976 and has made enormous strides since its creation. Today, there are approximately 450 employees, students and researchers at the MHI Research Center. The MHI’s outstanding feature is the balance it achieves between basic research, clinical research and clinical care. Its prime focus areas of research are vascular diseases, myocardial function and electrophysiology. Genetics, genomics (including pharmacogenomics), biomarkers and preventive cardiology are other areas of focus. To learn more about the Institute, please visit our website at www.icm-mhi.org.

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