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PRESS RELEASE

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SCIENTISTS FIND MAJOR SUSCEPTIBILITY GENES FOR CROHN'S DISEASE

**Discoveries reveal new genetic risk factors for the millions of people
with inflammatory bowel diseases**

Montreal, April 16, 2007 – A consortium of Canadian and American researchers led by Dr. John D. Rioux, PhD, Associate Professor of Medicine at the Montreal Heart Institute and the Université de Montréal, report in the April 15 online edition of Nature Genetics the results from a search of the entire human genome for genetic risk factors leading to the development of Crohn's disease. Specifically, using a novel approach, the authors identified that the PHOX2B, NCF4 and ATG16L1 genes constitute genetic risk factors for Crohn's disease. In addition, their study identified two regions of the genome where genetic risk factors are located but no known genes were implicated – further work will be necessary to identify the causal genes in these regions.

More than 1 million Americans and some 170,000 Canadians have Crohn's or colitis, known collectively as inflammatory bowel disease (IBD). The study's authors represent the IBD Genetics Consortium, which is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health. In addition to the Montreal Heart Institute and Université de Montréal, the Consortium's member institutions include the Cedars-Sinai Medical Center in Los Angeles, the University of Chicago, the Johns Hopkins University, the University of Pittsburgh, the University of Toronto, and Yale University.

Because IBD tends to run in families and is more frequent in certain ethnic 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. To identify additional genes that are

associated with IBD, the international team of researchers scanned the genome—all of 22,000 or so genes—by testing more than 300,000 single nucleotide polymorphisms, or SNPs, in people with Crohn's disease and in healthy controls. The comparison of these SNPs (common genetic variants) between patient and control groups identified multiple SNPs that were strongly associated with Crohn's disease. These findings were then tested in two additional sets of patients and healthy controls in order to confirm their results.

According to the corresponding author John D. Rioux, the findings highlight numerous biological pathways not previously thought to play a role in Crohn's disease. "The identification of the PHOX2B gene in this study, for example, may implicate a role for neuro-endocrine cells of the intestinal epithelium as having a role to play in Crohn's Disease. In addition, the identification of the NCF4 gene indicates that altered reactive oxygen species (ROS) production, important in the generation of an effective anti-microbial response, may lead to increased risk to developing Crohn's disease". The fact that the authors also found strong association of the ATG16L1 gene provides further evidence that an individual's response to microbes has an influence on susceptibility to Crohn's disease.

Specifically, in addition to demonstrating its association to disease, these authors have shown that ATG16L1 is essential for the normal autophagic process used to degrade worn-out cellular components and help eliminate some pathogenic bacteria. "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 both cellular and bacterial components, leading to inappropriate immune activation and increased risk of Crohn's disease" adds Dr. Rioux.

The findings reported in this study are expected to not only improve on the biological understanding of disease but should also have a long-term impact on clinical practice. According to Dr. Edmond-Jean Bernard, co-author and gastroenterologist at the Hôtel-Dieu Hospital in Montreal and the Université de Montréal "the multiple genetic risk factors we've identified provide important molecular targets for current functional studies aimed at understanding the disease and important targets for drug development to improve therapy of Crohn's disease in the future." Dr. Stephen P. James, M.D., director of the Division of Digestive Diseases and Nutrition at the National Institutes of Health's NIDDK continued by saying that "these important discoveries not only offer new hope for better therapies for patients with Crohn's disease, 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".

A complete list of authors and their affiliations can be found below.

About Dr. John D. Rioux

Dr. Rioux, PhD, is an Associate Professor of Medicine at the Université de Montréal and at the Montreal Heart Institute where he works as a researcher and director of the Laboratory in Genetics and Genomic Medicine of Inflammation (www.inflammgen.org), as well as visiting scientist at the Broad Institute of MIT and Harvard, and holder of the Canada Research Chair in Genetics and Genomic Medicine of Inflammation.

About the Montreal Heart Institute

Founded in 1954, the Montreal Heart Institute is Canada's largest and oldest institution dedicated to research, education and clinical care of cardiovascular diseases. It is affiliated with the Université de Montréal and constantly aims for the highest standards of excellence through its leadership in prevention, ultra-specialized care, professional training, clinical and basic research, and development of new innovative treatments. The MHI Research Centre officially came into existence in 1976 and has made enormous strides since its creation. Today, there are approximately 500 employees, students and researchers at the MHI Research Centre. 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. 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.

About the Université de Montréal

Deeply rooted in Montreal and dedicated to its international mission, the Université de Montréal is one of the top universities in the French-speaking world. Founded in 1878, the Université de Montréal today has 13 faculties and together with its two affiliated schools, HEC Montréal and École Polytechnique, constitutes the largest centre of higher education and research in Québec, the second largest in Canada, and one of the major centres in North America. It brings together 2,500 professors and researchers, accommodates more than 55,000 students, offers some 650 programs at all academic levels, and awards about 3,000 masters and doctorate diplomas each year.

Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis

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