PRESS RELEASE

For immediate release

International team analyzes human genetic variation in key immune region

In-depth analysis will enable scientists to identify genetic risk factors for common immune diseases.

Montreal, September 25, 2006 – An international group of researchers today unveiled a detailed map of human genetic variation within the major histocompatibility complex (MHC), the most important region of the human genome encoding the human response to infection, autoimmune disease and organ transplantation. The work represents a milestone in the analysis of genetic variability for this fundamental immune region and lays the scientific foundation for future efforts aimed at uncovering the genetic roots of immune-related diseases. The findings of this international team, which includes scientists from the Montreal Heart Institute (MHI), the Université de Montréal (UdeM), the Broad Institute of MIT and Harvard and several other research institutions, appear in the September 24 advance online edition of *Nature Genetics*.

"This new map will be a key resource for researchers to use to find genes affecting health, disease, and responses to medications," said senior author Dr. John D. Rioux, PhD, who is associate professor of medicine at the UdeM and at the MHI where he works as a researcher and director of the Laboratory in Genetics and Genomic Medicine of Inflammation (www.inflammgen.org), Visiting Scientist of the Broad Institute of MIT and Harvard, and holder of the Canada Research Chair in Genetics and Genomic Medicine of Inflammation. "It will provide the information necessary to design powerful studies to identify the genetic risk factors located within the MHC."

The MHC — specifically, the genes that comprise it — is associated with more diseases than any other region of the human genome. This includes common diseases such as atherosclerosis, arthritis, diabetes, HIV, lupus, multiple sclerosis and Crohn's disease. However, pinpointing the specific changes that are causative in these diseases has been complicated by two factors: the extremely high degree of genetic diversity that exists in the MHC among different individuals and the tendency for multiple genetic differences in this region to be inherited together in groups called "haplotypes."

To characterize the haplotype patterns of the MHC, the researchers analyzed the variability in its DNA sequence in more than 350 individuals from diverse geographic regions, including Africa, Europe, China and Japan. Specifically, the researchers "read" ~7,500 single-letter changes in the genetic code called single nucleotide polymorphisms (SNPs) together with short segments of DNA sequence from a set of highly variable genes within the MHC, called "HLA genes." These genes form a distinctive fingerprint that is recognized by an individual's immune system to

distinguish foreign tissues from "self" tissues and the genes' DNA sequences are frequently analyzed (a process called "HLA typing") in patients who receive organ transplants or suffer from autoimmune disease.

Importantly, the researchers' data and analyses, which are made available online to the entire scientific community, provide the tools needed to begin the initial efforts toward identifying genetic risk factors in the MHC for common immune-mediated diseases. Such endeavors, involving researchers at the Montreal Heart Institute, the University of California, San Francisco and the Broad Institute of MIT and Harvard, are now underway for several immune system diseases.

In addition, the results offer insights into the evolutionary history of the MHC region — its early origins and the evolutionary forces that have helped to shape it over time. The findings also suggest that analyzing select SNPs within the HLA genes may offer a more economical alternative for characterizing the most common genetic variants in the region than standard HLA typing methods.

Nearly three-quarters of the DNA samples that the scientists analyzed had been previously examined as part of the International Haplotype Map ("HapMap") Project, a worldwide scientific collaboration to catalogue human genetic variation on a genome-wide scale. The latest findings, particularly the analyses of the HLA gene region, provide new and complementary information that can be integrated with data from the recently completed HapMap Project as well as other genomic efforts, to provide a comprehensive view of genetic variability in the human MHC.

Data access

Data from the project will be made publicly available at the following websites:

http://www.inflammgen.org

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de Bakker P.I.W. *et al*. (2006) A high resolution HLA and SNP haplotype map for disease association studies in the extended human MHC. *Nature Genetics* doi:10.1038/ng1885

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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. 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

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 2,400 professors and researchers, accommodates nearly 55,000 students, offers some 650 programs at all academic levels, and awards about 3,000 masters and doctorate diplomas each year.

About the Broad Institute of MIT and Harvard

The Broad Institute of MIT and Harvard was founded in 2003 to bring the power of genomics to biomedicine. It pursues this mission by empowering creative scientists to construct new and robust tools for genomic medicine, to make them accessible to the global scientific community, and to apply them to the understanding and treatment of disease.

The Institute is a research collaboration that involves faculty, professional staff and students from throughout the MIT and Harvard academic and medical communities. It is jointly governed by the two universities.

Organized around Scientific Programs and Scientific Platforms, the unique structure of the Broad Institute enables scientists to collaborate on transformative projects across many scientific and medical disciplines.

For further information about the Broad Institute, go to http://www.broad.mit.edu.

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