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Researchers discover gene that increases susceptibility to Crohn's disease

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Researchers at McGill University, the Research Institute of the McGill University Health Centre (RI MUHC) and the McGill University and Génome Québec Innovation Centre, along with colleagues at other Canadian and Belgian institutions, have discovered DNA variations in a gene that increases susceptibility to developing Crohn's disease. Their study was published in the January issue of the journal *Nature Genetics*.

The study was led by McGill PhD candidate Alexandra-Chloé Villani under the supervision of Dr. Denis Franchimont and Dr. Thomas Hudson. Dr. Franchimont, now with the Erasme Hospital in Brussels, Belgium, was a Canada Research Chair formerly affiliated with the Gastroenterology Dept. of the MUHC. Dr. Hudson, former Director of the McGill University and Génome Québec Innovation Centre, is now the President and Scientific Director of the Ontario Institute for Cancer Research (OICR), located in Toronto.

The researchers pinpointed DNA sequence variants in a gene region called NLRP3 that are associated with increased susceptibility to Crohn's disease. Crohn's is a chronic relapsing inflammatory disease of the digestive system that can affect any part of the gastrointestinal tract. Patients can suffer from a number of different symptoms in various combinations, including abdominal pain, bloody diarrhea, fever, vomiting and weight loss. Rarer complications include skin manifestations, arthritis and eye inflammation.

"Although the exact cause of Crohn's disease is still unknown, both

environmental and genetic factors are known to play a critical role in the pathogenesis of the disease," Dr. Franchimont said.

Crohn's disease is found throughout the world. However, it appears to be most common in North America and northern Europe, and Canada has one of the highest incidence rates in the world. Crohn's affects between 400,000 and 600,000 people in North America.

The 400 square metres of the intestinal absorptive area is the largest single surface in or on the human body, and it is covered by billions of bacteria of the intestinal microflora living in the gastrointestinal tract.

"The single layer of cells lining your intestinal digestive tract is thus constantly exposed to high levels of bacteria and pathogens," Villani explained. "These cells must recognize and respond appropriately to the harmful bacteria while maintaining tolerance to the non-pathogenic 'good' bacteria that make up your intestinal microbial flora. This is the central challenge of the digestive immune system, which needs to balance defence versus tolerance."

"The protein encoded by the Crohn's disease susceptibility gene NLRP3, cryopyrin, is an intracellular bacteria sensor that plays a key role in initiating immune response," explained Villani. Based on their results, researchers theorize the bacterial sensor cryopyrin is probably defective in some patients, and doesn't correctly recognize the presence of harmful bacteria.

"When the digestive immune system's counter-attack is insufficient to clear the threat," Ms. Villani continued, "there is a bacterial infiltration in the intestinal wall through the first line of defence mechanisms. The digestive immune system will again try to repel the threat, but the effort may not be sufficient, and this usually leads to a vicious cycle that results in chronic inflammation in the intestinal wall. And that is Crohn's

disease."

"This gene also plays a central role in the regulation of fever, which is one of the most primitive defence mechanisms that exists in humans to fight the surrounding pathogenic bacteria," Dr. Hudson added. "DNA sequence variations in the NLRP3 gene are also known to be responsible for hereditary periodic fever syndromes."

"Previously published genome-wide association studies have already detected more than 30 distinct Crohn's genetic factors, but these only explain about one-fifth of Crohn's disease heritability", said Dr. Franchimont.

Though these results will not lead to any new short-term treatments for Crohn's, Dr. Franchimont is confident that in the longer term it will benefit patient care. "Studies like this one give us a better understanding of key pathways and pathogenic mechanisms involved in Crohn's disease," he said. "Now that we are aware of the role of bacterial sensors in the disease, steps can be taken to develop a new treatment strategy."

Source: McGill University