Fighting gut infections helps prevent Crohn's disease and ulcerative colitis

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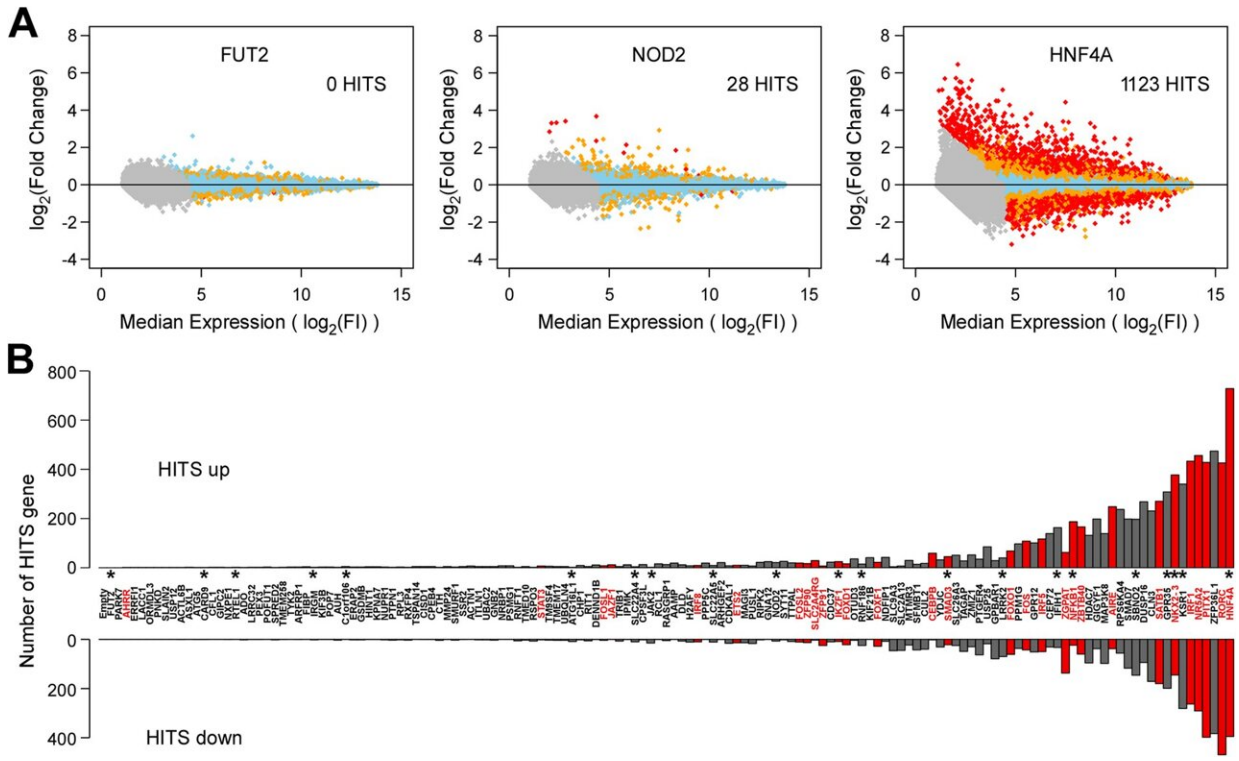

Impact of IBD gene candidate ORFs on the HT-29 transcriptome. A Selected examples illustrating the impacts observed on the transcriptome of HT-29 cells following the expression of different ORFs for IBD gene candidates. HITS are identified as genes with probes from either microarray platform showing detectable expression in HT-29 (endogenously or following ORF expression) for which the fold effect in response to the expression of a given ORF is greater than two compared to the baseline and shows expression outside the expected range. As examples, FUT2 (left), a terminal enzyme in a metabolic pathway, had no impact on the transcriptome (0 HITS); NOD2 (middle), an intracellular

PAMP receptor, had only marginal impact on the transcriptome (28 HITS) in the absence of its ligand, and HNF4A, a transcription factor known to have a central role in intestinal epithelial cells, had the strongest effect (1123 HITS). Each dot represents a single detectable probe from the genome-wide array tagging a specific gene in the HT-29 transcriptome. The x-axis shows the log2-transformed median expression across all conditions (baseline). The y-axis represents the effect of transduction of a given ORF, as the log2-transformed fold-induction compared to baseline. Sky blue dots are probes with expression value within expected range of variation ($|Z| \leq 2$), orange dots represent probes suggestively outside the range ($|Z| > 2$), and red dots represent probes outside the range ($|Z| > 4$). Gray dots are probes with expression value below detection threshold. B Impact of the expression of all IBD gene candidates on the transcriptome of HT-29 cells. ORFs are ordered along the x-axis by increasing total number of HITs (see Additional file 1: Table S5), with number of upregulated and downregulated HITs gene shown along the y-axis. Starred ORFs are previously reported IBD candidate causal genes and ORFs listed in red indicate known transcription factors (as defined by Lambert et al. [38]). Credit: DOI: 10.1186/s13073-021-00996-7

A research team at the Montreal Heart Institute and Université de Montréal has shown that genes present in specific intestinal cells protect against the development of inflammatory bowel diseases. Published today in the scientific journal *Genome Medicine*, the study results show that more than a dozen of these genes, which contribute to the development of Crohn's disease and ulcerative colitis, help fight viral and bacterial infections.

Crohn's disease and ulcerative colitis, known as inflammatory bowel diseases, are characterized by chronic digestive system inflammation. The research team screened 145 genes associated with inflammatory bowel diseases (IBD) risk in human digestive system cells, called intestinal epithelial cells, and found that many of these genes are significant in helping these cells detect bacteria or viruses and set up the

appropriate defensive response to control such infections. Thus, researchers have identified genes that make people more likely to develop chronic gut inflammation, characteristic of IBD when disrupted by genetic variants.

"Most of the current medical therapies used to treat Crohn's disease and ulcerative colitis target the functions of immune system cells," said Dr. John D. Rioux, an MHI researcher, medical professor at UdeM and Canada Research Chair in Genetics and Genomic Medicine. "This study demonstrates the importance of developing therapeutic approaches aimed at strengthening the protective functions of the digestive system for the benefit of patients with inflammatory bowel disease."

10,000 new cases a year

More than 270,000 people suffer from IBD in Canada and almost 10,000 new cases appear every year, resulting in estimated annual economic costs of $2.6 billion. IBD is characterized by the body's own immune system attacking parts of the digestive system. The exact causes of these diseases are still unknown, and there is currently no cure.

Previous genetic studies had already identified some differences in the genetic code associated with the development of IBD, but for most of them no actual disease-causing gene has been found.

"The challenge was how to use this genetic information to better understand the biological pathways leading to IBD," said Jessy Carol Ntunzwenimana, a doctoral student at the Rioux Lab and co-lead author of the study. Her research team had therefore to develop a new approach to identify which genes are likely to be involved in IBD and reveal their biological functions.

"The findings from this study provide an important piece to the puzzle in

understanding how the body's interactions with the gut flora can predispose an individual to develop IBD," said Kate Lee, vice president in charge of the research and patient program at Crohn's and Colitis Canada. "This is a great example of how genomic research can advance our understanding of health and disease, with a potential impact on patients who will be treated in the future," added Stéphanie Lord-Fontaine, Vice President, Scientific Affairs of Génome Québec.

More information: Jessy Carol Ntunzwenimana et al, Functional screen of inflammatory bowel disease genes reveals key epithelial functions, *Genome Medicine* (2021). DOI: 10.1186/s13073-021-00996-7

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