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Genetic variant newly linked to Crohn's disease also associated with altered gut microbiome composition

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An international team led by researchers at the University of Pittsburgh, Cedars-Sinai Medical Center and the University of California Los Angeles discovered that a genetic variation previously linked to obesity, cholesterol levels, blood pressure and schizophrenia also is associated with Crohn's disease, a chronic inflammatory condition of the gastrointestinal tract that is estimated to cost the U.S. $6 billion annually.

In addition, the genetic variant is associated with changes in the composition of the gut microbiome—which is made up of potentially billions of microbes that help people digest food, synthesize nutrients and perform myriad other essential functions—in healthy people, overweight people and people with Crohn's disease. The findings are reported online and scheduled for the October issue of the journal *Gastroenterology*, and the research was funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and Helmsley Charitable Trust, among others.

"We knew from previous studies that there is reduced diversity of the gut microbiome in patients with Crohn's disease," said co-senior and corresponding author Richard Duerr, M.D., a professor in Pitt's School of Medicine, and co-director and scientific director of the UPMC Inflammatory Bowel Disease Center. "But that left us with a question: Does Crohn's disease alter the composition of the gut microbiota, or do pre-existing changes in the gut microbiota confer risk for Crohn's

disease? Our study found that there is a reduction in the abundance of hundreds of minor species of gut bacteria in healthy, overweight and Crohn's disease-affected people who carry this genetic variant, suggesting that the genetic variant may increase risk for disease by altering the gut habitat. This is an important step toward understanding how the disease works so we can develop therapies or a cure in the future."

Under the leadership of Dr. Duerr and co-senior author Dermot McGovern, M.D., Ph.D., F.R.C.P. (Lon), director of Translational Medicine in the Cedars-Sinai F. Widjaja Foundation Inflammatory Bowel and Immunobiology Research Institute, the team focused their analysis on 10,523 blood samples from people with inflammatory bowel disease (half had been diagnosed with Crohn's disease) and 5,726 samples from healthy people. They discovered that a variation in the SLC39A8 gene is associated with Crohn's disease.

"This finding is another important example of how a particular genetic variant can have a role in the development and course of many diseases. Our study of this variant suggests that therapies effective in treating one disease also may benefit the treatment of some patients with other illnesses," said Dr. McGovern, who also is director of Precision Medicine at Cedars-Sinai.

Taking it a step further, the team identified healthy people, overweight people and Crohn's disease-affected people with the genetic variant and analyzed their gut microbiomes under the leadership of co-senior author Jonathan Braun, M.D., Ph.D., chair and professor of pathology and laboratory medicine in the David Geffen School of Medicine at UCLA. That is how they discovered that the genetic variant is not just linked to Crohn's and other conditions, but also to a reduction in hundreds of species of gut bacteria.

"Many of these species are believed to play roles in protecting the intestine against Crohn's disease, and also in preserving a lean body physiology," said Dr. Braun. "So, this may be an example where the gene increases risk for disease via its effect on types of bacteria we need to preserve our health."

The findings have sparked additional questions and potential research avenues, but therapies are still quite a ways off, said Dr. Duerr, also a professor in the Pitt Graduate School of Public Health Department of Human Genetics. However, the recent establishment of the University of Pittsburgh Center for Medicine and the Microbiome will help accelerate this research and bring potential therapies—which may involve the center's clinical fecal transplantation program—to patients.

"This study illustrates the remarkable interaction between our proper genome and our symbiome—the organisms and environment inside and outside of us that influence our well-being—in the setting of inflammatory bowel disease," said Mark T. Gladwin, M.D., chair of medicine and Dr. Jack D. Myers Professor of Internal Medicine at Pitt. "Insights from this study are likely to guide the development of microbiome modulating therapies that hold the promise to alleviate patient suffering."

More information: Ling-Shiang Chuang et al. A Frameshift in CSF2RB Predominant Among Ashkenazi Jews Increases Risk for Crohn's Disease and Reduces Monocyte Signaling via GMCSF, *Gastroenterology* (2016). DOI: 10.1053/j.gastro.2016.06.045

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