Genetic similarity suggests Crohn's disease and ulcerative colitis form a continuum of subtypes in the bowel

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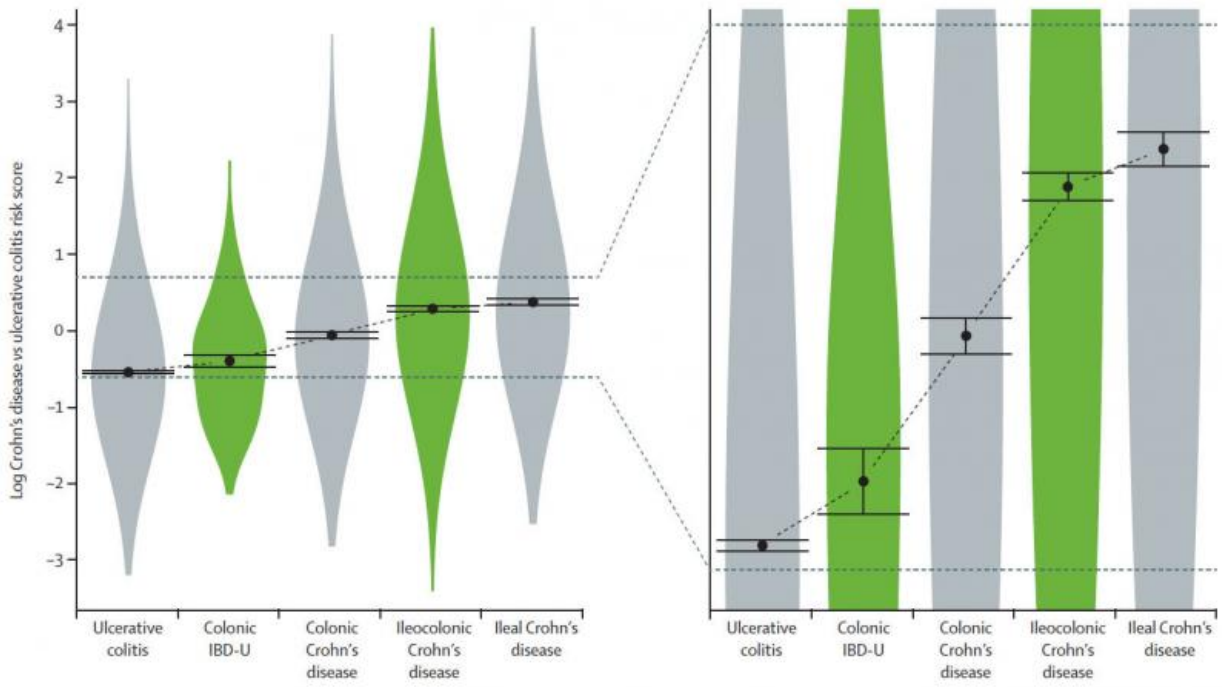

Violin plot showing the genetic substructure of inflammatory bowel disease location. Credit: The Lancet

A new understanding of inflammatory bowel diseases has been prompted by the analysis of genetic and clinical data from more than 30,000 patients. This study reveals that genetic factors affect the location of the

inflammation in the gut, with implications for diagnosis and treatment of patients.

The largest study of its kind, this research uncovers a continuum of inflammatory bowel diseases, and shows that genetic information could be used to reveal misdiagnoses. The research demonstrates the importance of worldwide clinical collaborations and using information about symptoms to better understand the genetics of complex diseases.

Inflammatory bowel disease (IBD) is an umbrella term for two related immune diseases: Crohn's disease, which can affect any part of the digestive tract, and ulcerative colitis, which affects only the colon, or large bowel. However this research shows that a binary diagnosis of disease is oversimplified. Genetic data indicate that IBD is a complex continuum of disorders heavily influenced by the site of inflammation. While disease location in Crohn's have long been recognised as important, the new observation that large bowel Crohn's disease is half-way between ulcerative colitis and small bowel Crohn's disease on this genetic spectrum suggests that important aspects of disease biology are associated with location.

"Patients who initially present with similar IBD symptoms progress in drastically different ways. Some experience a mild course of disease while others need invasive surgery," says Dr Isabelle Cleynen, a first author from the Wellcome Trust Sanger Institute and KU Leuven. "Our current symptom-led system of classification doesn't clearly predict which path a particular patient is likely to take. Our genetic data reflect this same uncertainty."

Previous research on IBD had shown that the genes involved are largely shared between Crohn's disease and ulcerative colitis, with only a small number of genes specific to each disease. The new study married this genetic information with clinical symptoms to try to understand the

biology behind the disease.

Diagnosis is based on clinical evidence and symptoms, with different medication and surgery indicated for Crohn's and ulcerative colitis. For some patients, clinicians find it difficult to diagnose which of these two diseases is presented. The genetic continuum between the two ends of the spectrum explains some of this difficulty in diagnosis and patients could benefit from re-classification.

At extreme ends of the continuum, genetic markers may have some diagnostic utility. Clinicians reassessed the records of outlier patients, who had genetic factors that strongly pointed to Crohn's disease but had been originally diagnosed with ulcerative colitis, or vice-versa. They found that doctors had raised doubts about the diagnosis three times more often than for randomly chosen patients.

"For a small subset of patients, genetics can uncover a misdiagnosis. Working with clinicians we hope this will help prevent costly and traumatic unnecessary surgery," says Dr Jeffrey Barrett, a corresponding author from the Wellcome Trust Sanger Institute and Director of the Centre for Therapeutic Target Validation. "However, in the vast majority of cases, the genetic scores we've identified for each condition are not different enough to be used diagnostically. Further research, pairing genetic data with patient responses to treatment over time will help us to better understand what's happening on a molecular level in patients with different forms of IBD."

To treat complex diseases, physicians need to understand the underlying biology. Genetic information could be used to inform treatment guidelines, or which patients to include in a clinical trial to obtain the clearest results. It is possible that certain trials may be appropriate for colonic Crohn's disease and ulcerative colitis patients. Genetics could also be used as another piece of evidence to catch rare mistakes in

diagnosis, which could prevent unnecessary surgery.

Dr Charlie Lees, a corresponding author, consultant gastroenterologist and senior lecturer at the University of Edinburgh. "In order to personalise treatments, we need to be open-minded about the clinical categories we have constructed by observing symptoms in isolation. It is crucial that clinicians and researchers continue to work closely together and to share comprehensive data that will help to solve this complex puzzle."

More information: Cleynen I, et al. Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: a genetic association study. *The Lancet* 2015 DOI: 10.1016/S0140-6736(15)00465-1

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