

## IBD

## GENOTYPES AND PHENOTYPES OF IBD

The findings of the largest phenotype–genotype study in IBD to date have been reported in *The Lancet*. The data point towards three distinct disease groups within IBD—ileal Crohn's disease, colonic Crohn's disease and ulcerative colitis—rather than simply a distinction between Crohn's disease and ulcerative colitis.

IBD is a heterogeneous disease in terms of disease course and therapeutic responses. Numerous IBD susceptibility loci have been identified, but how genetics influence disease biology and how this information can translate to clinical practice needs further investigations.

In the new study, Cleynen *et al.* analysed phenotype and genotype data from nearly 30,000 patients with IBD (16,902 with Crohn's disease and 12,597 with ulcerative colitis) from 49 centres across 16 different countries in Europe, North America and Australasia. Genotype–phenotype associations were tested across a total of 156,154 genetic variants, and genetic risk scores were calculated for particular disease phenotypes.

Only three main loci achieved genome-wide significance ( $P < 5 \times 10^{-8}$ ) for association with subphenotypes of IBD (mainly disease location): *NOD2*, *MHC* and *MST1 3p21*. Interestingly, no statistically significant associations were observed between subphenotypes and individual single nucleotide polymorphisms (including those robustly associated with disease susceptibility).

The calculated genetic risk score that accounts for all known risk alleles for IBD (163 known loci) was strongly associated with disease phenotype ( $P 1.65 \times 10^{-78}$ ), even after excluding *NOD2*, *MHC* and *3p21*. Given the importance of disease location found in this study, the risk score was then used to examine the genetic relationship between ileal Crohn's disease, colonic Crohn's disease and ulcerative colitis. The analysis revealed three genetically distinct groups within IBD, placing colonic Crohn's disease between ileal Crohn's disease and ulcerative colitis and supporting a continuum of disorders within IBD.

“These findings ... suggest that location is a fundamental biological aspect of a patient's disease, whereas behaviour (like surgery or treatment history) is a marker of disease progression,” write the study authors.

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**Original article** Cleynen, I. *et al.* Inherited determinants of Crohn's disease and ulcerative colitis: a genetic association study. *Lancet* doi:10.1016/S0140-6736(15)00465-1