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IBD

The IBD genome—new study findings contribute to an ever-growing gene catalogue

A comprehensive catalogue of common genetic variants associated with the development of IBD has been put together in a collaborative effort between international researchers. The report, published in *Nature*, is one of the largest genetic studies to date of a complex disease, helping to dissect the biology of IBD and providing fundamental insights into the underlying pathogenetic mechanisms.

"Prior to this study, nearly 100 loci had been associated with IBD; the present study increases this number to 163," explains author Judy Cho from Yale University, USA. "These additional loci provide important new clues to the earliest steps that drive increased susceptibility to IBD," she adds.

Genome-wide association studies (GWASs), and associated meta-analyses, have proved to be a powerful method to identify common genes associated with disease. Previous GWASs had already highlighted considerable overlap and common loci between several immune-mediated diseases, including IBD, rheumatoid arthritis and type 1 and 2 diabetes mellitus.

> "...genetic variants that provide protection against infectious diseases ... might confer increased risk of immune-mediated diseases, such as IBD"

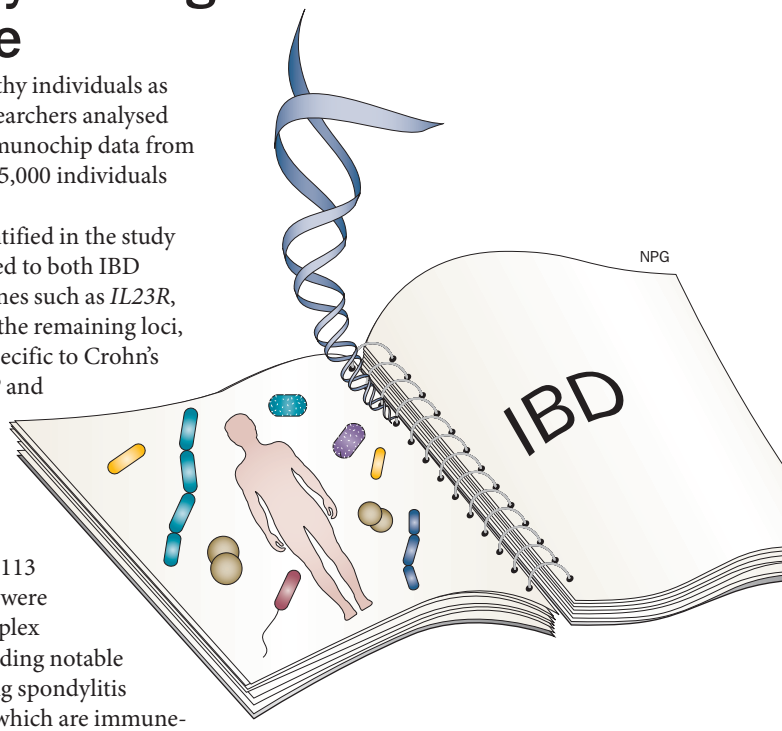
Now, Cho *et al.* have expanded on this knowledge by performing a meta-analysis of data from 15 existing GWASs in patients with Crohn's disease or ulcerative colitis—the two most common forms of IBD with increasing prevalence worldwide. The major findings from the GWASs data were validated against an independent genotype dataset (obtained using Immunochip) comprising 14,763 patients with Crohn's disease, 10,920 patients with ulcerative colitis and 15,977 healthy individuals as controls. Thus, the researchers analysed combined GWAS–Immunochip data from a combined total of >75,000 individuals with IBD or controls.

Most of the loci identified in the study (110 of 163) contributed to both IBD subtypes, including genes such as *IL23R*, *MUC19* and *JAK2*. Of the remaining loci, 30 were classified as specific to Crohn's disease (such as *NOD2* and *ATG16L1*) and 23 as specific to ulcerative colitis (such as *IRF5* and *TNFRSF14*).

Validating previous work, just under 70% (113 of 163) of the IBD loci were shared with other complex diseases or traits, including notable overlap with ankylosing spondylitis and psoriasis, both of which are immune-mediated diseases. Furthermore, IBD loci were also enriched in genes involved in primary immunodeficiences, particularly genes involved in T-cell responses (such as *STAT3* and *CARD9*).

One of the more intriguing findings by Cho and colleagues is that many of the IBD loci identified overlap with susceptibility to various infectious diseases—most notably mycobacterial infections (such as tuberculosis and leprosy)—with genetic pathways shared between host response to mycobacteria and predisposition to IBD. "This finding suggests that genetic variants that provide protection against infectious diseases, as a secondary consequence in a different environment, might confer increased risk of immune-mediated diseases, such as IBD," clarifies Cho.

"This study provides a comprehensive catalogue of common genetic variants that contribute to disease, and have identified key cells and signalling pathways that may be targeted for therapeutic benefit," notes Cho. The authors do acknowledge that even the large number of IBD loci identified in the study explains only a minority of variance in disease risk, suggesting that other factors (such as environmental exposure or rarer genetic variation) make substantial contributions to IBD pathogenesis.



Ongoing studies will examine the possible contributions of these rare genetic variants in subsets of patients with IBD. How DNA variation affects gene expression (for instance, at the RNA level) and precisely modulates cellular composition in health and disease will also be examined further. "Defining the early and key control points in order to most effectively prioritize therapeutic targeting is a major goal of future research," foresees Cho.

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Original article Jostins, L. *et al.* Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* **491**, 119–124 (2012)

Further reading Manichanh, C. *et al.* The gut microbiota in IBD. *Nat. Rev. Gastroenterol. Hepatol.* **9**, 599–608 (2012)