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IBD

Key genetic regulators of IBD identified by genomic network modelling

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A new study uses genomic, transcriptomic and clinical data from patients with IBD to model the network of genes regulating the disease, revealing conserved, central genetic regulators of immune-related gene expression in tissue.

Genome-wide association studies (GWAS) have been widely used to find genetic variants associated with Crohn's disease and ulcerative colitis. However, despite >200 associated loci being identified to date, these variants only explain a small proportion of the heritability of IBD. The identities of causal relationships between genes at these loci are also unclear. As a result, there is a need to combine data from GWAS with tissue-specific functional genetic data and disease pathology. Causal network models that integrate genomic and transcriptomic data derived from tissue samples from patients with IBD are a potential method for uncovering new genetic regulators important to the pathophysiology of the disease.

On the basis of previous genetic research that identified a regulatory network in IBD enriched for genes related to inflammation and immune function, Lauren Peters and colleagues sought to construct a model of the conserved inflammatory component of IBD, using data derived from samples of intestinal tissue taken from patients at different disease stages: treatment-naive paediatric patients, patients refractory to anti-TNF therapy and patients with advanced IBD. Data on single-nucleotide polymorphisms, expression quantitative trait loci (loci associated with altered mRNA expression) and *cis*-regulatory elements associated with IBD were integrated to identify candidate causal IBD genes. This information was then combined with gene co-expression networks derived from tissue gene expression levels in each patient group, and prior data on immune-related genes associated with IBD, to define a core immune activation module (IAM) representing a set of immune genes conserved across the studied IBD populations.

After projecting the core IAM onto Bayesian networks constructed for tissue gene expression in each of the three patient groups, creating three group-specific networks of the IBD conserved immune component (CIC), the investigators identified key driver genes (KDGs) able to substantially alter the transcriptional state of each network. 133 KDGs were identified, of which five had not been previously validated as associated with IBD: *DOCK2*, *NCKAP1L*, *AIF1*, *GPSM3* and *DOK3*. These five KDGs were upregulated in inflamed patient intestine samples, and their expression correlated with clinical parameters, including disease duration.

Given the enrichment of macrophage-specific genes in the core IAM, the researchers defined an IBD network specific to macrophages by projecting a macrophage-specific gene signature onto the patient network with greatest enrichment of macrophage signatures. Eleven KDGs were identified that were present in an independent human macrophage signature set and also correlated with clinical IBD variables, including *GPSM3*, *DOK3*, *NCKAP1L* and *AIF1* from the non-cell-specific IBD CIC. The relevance of these KDGs was then explored by knocking out each gene in mice and examining the response to induced colitis. These experiments validated the role of the KDGs in IBD pathophysiology; for instance, knockout of *Dock2*, *Gpsm3* and *Nckap1l* exacerbated colitis induced by dextran sulfate sodium, whereas knockout of *Aif1* and *Dok3* reduced colitis severity assessed by weight loss. Further molecular validations showed that intestinal gene expression changes, predicted by the IBD network model after KDG knockout, were observed experimentally for each of the KDGs.

Concluding the paper, the authors promote the potential of IBD network modelling to explore the different molecular mechanisms associated with specific disease subsets. Such approaches could be used to define the regulatory genes implicated in early or late IBD stages, or in patients refractory to therapy.

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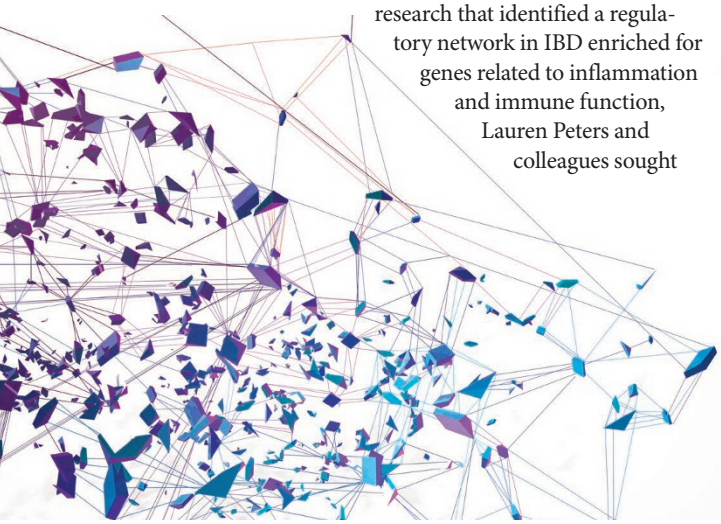

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ORIGINAL ARTICLE Peters, L. A. *et al.* A functional genomics predictive network model identifies regulators of inflammatory bowel disease. *Nat. Genet.* http://dx.doi.org/10.1038/ng.3947 (2017)

FURTHER READING de Souza, H. S. P., Fiocchi, C. & Iliopoulos, D. The IBD interactome: an integrated view of aetiology, pathogenesis and therapy. *Nat. Rev. Gastroenterol. Hepatol.* http://dx.doi.org/10.1038/nrgastro.2017.110 (2017)