Scientists link genes to diet in inflammatory bowel disease

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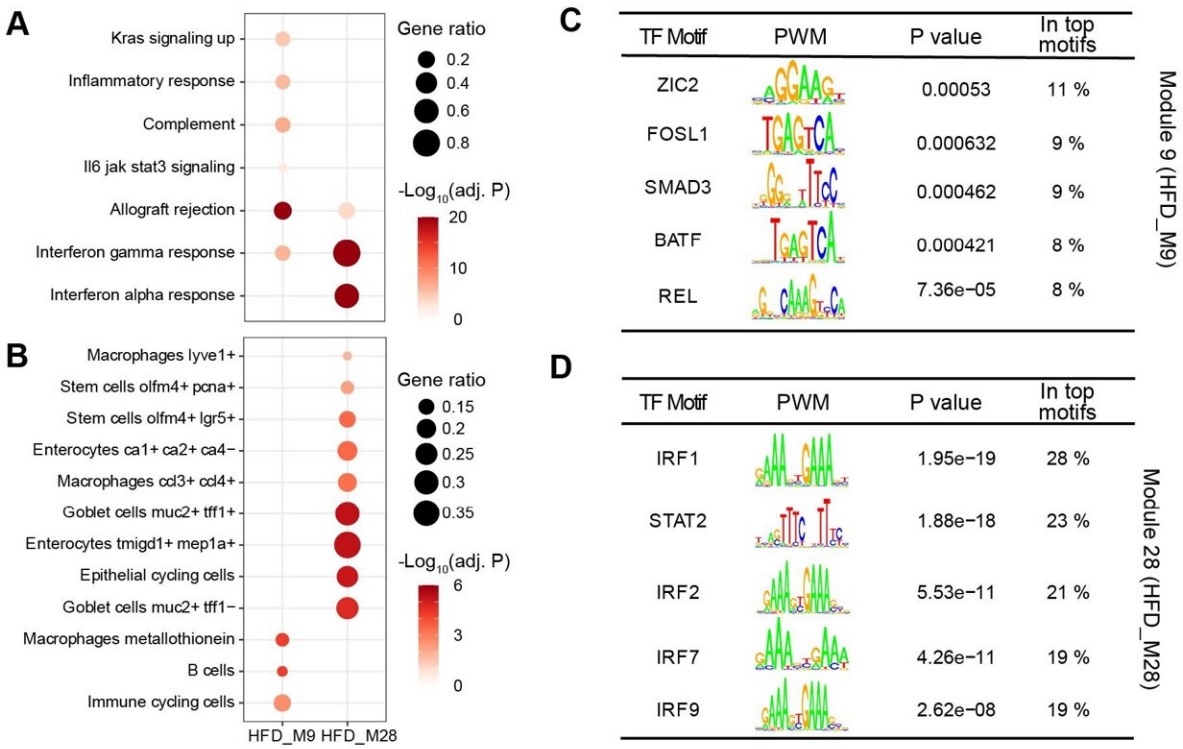

Biological interrogation of identified IBD-related modules.(A, B) Dot plots showing the enrichment of IBD-related modules in hallmark genesets (A) and cell-type gene signatures of inflamed colon in Crohn's disease patients (B). Gene ratios higher than 0.1 are shown and represented by dot size. Dots are colored by -$\log_{10}$(BH-adjusted P values). (C, D) The enriched motifs for promoters of the genes involved in module HFD_M9 (C) and HFD_M28 (D). The significantly enriched motifs (P value eLife (2023). DOI: 10.7554/eLife.87569.2

A study of the genetic variation that makes mice more susceptible to bowel inflammation after a high-fat diet has identified candidate genes which may drive inflammatory bowel disease (IBD) in humans. The findings are published as a Reviewed Preprint in *eLife*.

Described by the editors as a fundamental study, the work provides a framework for using systems genetics approaches to dissect the complex mechanisms of gut physiology. The authors show how it is possible to use genetically diverse but well-characterized mice to interrogate intestinal inflammation and pinpoint genes influenced by the environment—in this case, a high-fat diet—and identify potential treatment targets for IBD in mice and humans. The editors describe the strength of the analyses as compelling and add that, as a resource, it will be useful for linking genetic variations and diet to gut-related disorders.

It is well established that a high-fat diet can increase the risk of IBD. However, the impact of diet varies between individual people, suggesting an interplay with genetic factors. More than 200 risk genes have been identified for IBD, but there is still no effective treatment, and it is therefore important to understand the gene-by-environment interactions underpinning the inflammation that eventually evolves into IBD.

"Differences in the clinical presentation of IBD among patients, as well as diversity in diet and lifestyle, render human genetic studies challenging," explains lead author Xiaoxu Li, a Doctoral Research Assistant at the Institute of Bioengineering, École Polytechnique Fédérale de Lausanne (EPFL), Switzerland. "Genetically diverse populations of mice allow us to mirror the differences in human populations, while controlling several environmental factors, such as temperature and diet, when exploring the genetic modulators of IBD in the laboratory."

Li and colleagues used mouse genetic reference populations (GRPs) to

map the genetic factors that are important in IBD induced by a high-fat diet. They measured the levels of gene expression in the colons of 52 mice fed with either a chow or a high-fat diet and identified a subset of mice that were more susceptible to high-fat-diet-induced intestinal inflammation.

Moreover, they found that levels of a pro-inflammatory cytokine called interleukin-15 were increased in the mice more likely to develop IBD, while levels of the anti-inflammatory cytokine, Interleukin-10, were decreased. This indicates that changes in the levels of genes associated with IBD reflect the general inflammatory status of mice.

After classifying different mouse strains based on their likelihood of developing IBD-like genetic signatures, the team explored this further using gene co-expression network analysis. This identified two distinct modules (clusters) of genes that are related to known genetic signatures of human IBD.

Next, they looked at the function of these genes and how they are controlled. Both IBD-associated modules largely consisted of immune response-related genes, including those known to be involved in Crohn's disease, and the team identified the likely regulators of the expression of these genes. But the genetic drivers behind the different susceptibility in the mice were still elusive.

To find the candidate genes that influence gut inflammation specifically following a high-fat diet, they performed QTL analysis to identify quantitative trait loci (QTL)—regions of genes that interact with the environment to impact the observable trait data. This revealed a QTL that is related to chronic intestinal inflammation in mice.

To see whether genes under this QTL could play a role in human IBD, the team then cross-checked their findings with risk genes for IBD by

conducting an analysis using genome-wide association study data from UK Biobank. They identified two plausible gene candidates, called EPHA6 and MUC4. In addition, using publicly available genetic variation data for IBD, Crohn's disease and ulcerative colitis, they found evidence to suggest that increased expression of the MUC4 gene in part of the colon may increase the risk of IBD in humans.

A limitation of this analysis is that there were no mechanistic investigations or studies that directly provide a causative link between the candidate genes and IBD. The results are primarily observational and correlative, but they provide a dataset that generates hypotheses that can be studied further.

"Our results point to important potential roles of two gene candidates in gut chronic inflammation that may lead to inflammatory disorders," says senior author Johan Auwerx, a Professor at the Institute of Bioengineering, EPFL. "Our systems genetics approach using GRP mice where the genetic backgrounds are known and the environment can be controlled enables the prioritization of candidate genes in a complex disease which, when combined with human genome-wide association studies from UK Biobank, are generalizable to human patients and may have clinical value."

More information: Xiaoxu Li et al, Genetic and dietary modulators of the inflammatory response in the gastro-intestinal tract of the BXD mouse genetic reference population, *eLife* (2023). DOI: 10.7554/eLife.87569.2

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