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Gene combinations and interactions affect risk of Crohn's disease

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A statistical model accounting for dozens of different genes in combination—and the interactions between them—is an important step forward in understanding the genetic factors affecting the risk of Crohn's disease (CD), reports a study in *Inflammatory Bowel Diseases*, official journal of the Crohn's & Colitis Foundation of America (CCFA).

It's not just how many risk genes are present but how those genes interact with each other that determines the inheritance of CD risk, suggests the report by a research group from the Cleveland Clinic and University of Pittsburgh. The study is the first to show that information on genetic interactions can improve the ability to predict CD risk and explain its genetic heritability.

New Model of 'Cumulative Genetic Effects and Interactions' Crohn's disease is a chronic inflammatory bowel disease affecting up to 700,000 Americans. Although the exact cause is unknown, CD appears to result from an "inappropriate persistent immune response." In addition to genetics, microbial and environmental factors likely play important roles in the development of CD.

Using modern genetic research methods, called genomewide association studies (GWAS), researchers have identified at least 71 genes that appear to affect CD risk. However, individual genes have only small effects on CD risk. Even after accounting for the combined effects of CD risk genes, less than one-fourth of CD heritability can be explained.

To address this issue, the researchers developed a new model exploring "higher-order genetic interactions" among known CD risk genes. The model was designed to evaluate not only the additive effects of having multiple CD risk genes, but also the possible impact of interactions between genes.

Using data from two large genomewide association studies of CD patients, the model showed "good CD risk predictability." People with a higher "cumulative allele score"—reflecting more CD risk genes present—were at higher risk of having CD. However, there wasn't a major difference in the average total risk score for patients with CD versus healthy people. Based on combinations of risk genes only, the model's ability to explain genetic inheritance of CD was 24 percent.

But after information of potential interactions between genes were added to the model, explained heritability increased to 27 percent. A model of interactions among five particularly important risk genes was confirmed using an independent patient dataset.

While an increase of three percentage points may seem small, the new results show that heritability is related not only to the number of CD risk genes present but also to the interactions among them. The researchers hope their model will contribute to understanding the genetic contribution to CD risk.

They plan further studies to confirm the model's performance in larger groups of patients. In addition, future studies will attempt to pinpoint the specific interactions occurring between CD risk genes—and possibly to identify environmental factors that interact with genes in contributing to the development of CD.

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