

Genes may exert opposite effects in diabetes and inflammatory bowel disease

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Pediatric researchers analyzing DNA variations in type 1 diabetes and inflammatory bowel disease have found a complex interplay of genes. Some genes have opposing effects, raising the risk of one disease while protecting against the other. In other cases, a gene variant may act in the same direction, raising the risk for both diseases.

Both type 1 diabetes (T1D) and [inflammatory bowel disease](#) (IBD) are autoimmune disorders—conditions in which the body's immune system overreacts, resulting in disease. Many such [autoimmune diseases](#) share genes in common, acting on shared biological pathways.

"This finding shows the genetic architecture of these diseases is more complex than previously thought," said study leader Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at The Children's Hospital of Philadelphia. "We knew that multiple genes that interact with each other and with environmental factors are needed to bring on these complex diseases, and we are still detecting these genes and uncovering those interactions. But we now see that some genes influence more than one disease, and sometimes in the opposite direction."

Hakonarson and colleagues, including collaborators from more than a dozen institutions in four countries, published the study online in an advance article on Feb. 22 in *Human Molecular Genetics*.

Inflammatory bowel disease consists of Crohn's disease (CD), which

may affect the entire [digestive tract](#), but especially the [small intestine](#), and [ulcerative colitis](#) (UC), mainly affecting the large intestine. Type 1 diabetes, also called insulin-dependent diabetes, occurs when the body produces little or no insulin because the immune system destroys insulin-producing cells.

The study team analyzed samples from 1,689 children and adolescents with CD, 777 with UC, and 989 with type 1 diabetes, as well as 6,197 control samples from healthy children. All the children were of European ancestry. The IBD and T1D samples were all from patients with early-onset disease, i.e., occurring by age 19.

The genome-wide association study (GWAS) identified multiple gene variants not previously reported for these diseases, in addition to evaluating genes previously discovered to be associated with one, two or all three diseases. The study team found overlaps among gene variants that conferred risk for both T1D and IBD. They also found four variants impacting the genes PTPN22, IL27, IL18RAP and IL10 that raised the risk of T1D while lowering the risk of Crohn's disease.

These opposing effects, said Hakonarson, could suggest a possible "genetic switch" on some biological pathways involved in both IBD and type 1 diabetes. "For these autoimmune disorders, the switch could be activated by specific infectious agents that trigger immune responses that are mediated by selective immunological pathways," he said. He noted that a pathogen could interact with a gene that raises the risk for [type 1 diabetes](#) at the same time it confers protection from Crohn's disease. "Infections cause a lot of adaptation within the immune system, and could be exerting selective pressure in driving genomes to evolve, where the resulting disease risk or protection is more of a bystander," Hakonarson added.

Hakonarson cautioned that the potential genetic switch is currently an

interesting hypothesis, requiring further investigation. Even the four gene variants (single nucleotide polymorphisms, or SNPs) that seem to cause opposing effects for these diseases may be markers for yet unknown causative genes that act in the same direction. "We won't know the exact impact of these variants until we have more sequencing data," he concluded.

More information: "Comparative genetic analysis of inflammatory bowel disease and type 1 diabetes implicates multiple loci with opposite effects," Human Molecular Genetics, advance access published Feb. 22, 2010. [doi:10.1093/hmg/ddq078](https://doi.org/10.1093/hmg/ddq078)

Provided by Children's Hospital of Philadelphia

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