

Gene mutation weakens virus-fighting protein in the gut, causing rare inflammatory bowel disease

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Johns Hopkins Medicine researchers, in collaboration with national and international researchers, have identified a genetic mutation in a small

number of children with a rare type of inflammatory bowel disease. The discovery of the mutation, which weakens the activity of a protein linked to how the immune system fights viruses in the gut, may help researchers pinpoint the cause of more common bowel diseases, investigators say.

The study, published June 29, 2021 in *Human Genetics*, may also suggest new ways to target the immune system's role in gut diseases.

"We aimed to see if children have a greater genetic susceptibility for this type of inflammatory [bowel disease](#) because they develop it so young," says Anthony Guerreiro Jr., M.D, Ph.D., M.S., director of the Very Early Onset Inflammatory Bowel Disease Clinic and assistant professor of pediatrics at the Johns Hopkins University School of Medicine.

Unlike other inflammatory bowel diseases, very early onset inflammatory bowel disease is diagnosed in patients before the age of 6, occurring in four out of every 100,000 births worldwide. In such young patients, the disease does not often respond to anti-inflammatory medications, and sometimes requires surgery to remove all or parts of the colon.

Inflammatory bowel diseases are chronic, inflammatory conditions—including Crohn's disease and ulcerative colitis—that occur when immune cells in the intestines are over-activated and cause sustained inflammation in the gut. These diseases are thought to be caused by multiple [genetic mutations](#) and environmental factors, such as diet and pollution as well as disruptions to the makeup of gut bacteria. Treatments usually include prescription drugs that curb inflammation.

Since the most common characteristic of bowel diseases is inflammation, scientists have long suspected genetic ties between the immune system and bowel disease. Inflammation is the immune system's response to damaged tissue.

For the current study, the scientists collected tissue samples from 24 patients with very early onset inflammatory bowel disease seen at The Johns Hopkins Hospital and Johns Hopkins Children's Center and performed whole exome sequencing, a method that looks at the protein-producing areas of a gene to identify [mutations](#).

Among the 24 patients, the scientists found mutations in four patients in parts of a gene called IFIH1, which produces a protein involved in the virus-fighting branch of the immune system. Other genetic sequencing studies have also linked the IFIH1 gene to inflammatory bowel diseases, and the current research provides new evidence for its involvement in very early onset inflammatory bowel disease.

Because of the small number of patients in the first round of sequencing, the researchers turned to a Johns Hopkins-developed online database called GeneMatcher, which contains genetic variations from people worldwide. Guerrero and GeneMatcher co-founder Nara Sobreira, M.D, Ph.D, assistant professor of genetics and pediatrics at the Johns Hopkins University of Medicine, found an additional 18 patients with very early onset inflammatory bowel disease being studied at both the NIH and in Padova, Italy.

The combined research teams found IFIH1 mutations in four of the 18 new patients, bringing the total of IFIH1 mutations found to 8 out of the 42 patients. Among the IFIH1 mutations, the researchers discovered nine mutations which resulted in abnormal production of a protein called MDA5. In the eight patients with the mutations, MDA5 function was much lower than normal.

When functioning properly, MDA5 is a part of the inborn immune system that helps fight off viruses in the gut. Using protein assays that mimicked the activity of normal and abnormal MDA5, the researchers found that in each patient with the IFIH1 mutation, the MDA5 proteins

only partially worked, but not enough to do their job of battling viruses. The researchers suspect this loss of function in the protein causes the improper activation of the immune system, triggering the inflammation that leads to very early onset [inflammatory bowel disease](#).

The researchers also believe that the partially functioning MDA5 proteins protect patients from more severe and rare immune diseases, such as Singleton-Merton syndrome and Aicardi-Goutières syndrome, that are associated with no MDA5 production.

"When you look at the physical changes associated with IFIH1 mutations, there are a wide range and they are really very different," says Sobreira. "It's crucial to know that these different variations in the same gene can cause these different characteristics."

Guerrerio and Sobreira hope their findings will help other clinicians and patients pinpoint the genetic cause of their disease and inform treatment options. They also believe the research provides additional evidence of the link between inflammatory bowel diseases and the virus-fighting part of the body's immune response.

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More information: Mara Cananzi et al, IFIH1 loss-of-function variants contribute to very early-onset inflammatory bowel disease, *Human Genetics* (2021). [DOI: 10.1007/s00439-021-02300-4](https://doi.org/10.1007/s00439-021-02300-4)

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