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Virus works with gene to cause Crohn's-like illness

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Scientists have shown that a specific virus can interact with a mutation in the host's genes to trigger disease. The observation may help explain why many people with disease risk genes do not actually develop disease.

Researchers at Washington University School of Medicine in St. Louis found that three factors were necessary in mice to create a condition similar to the human bowel disorder Crohn's disease: a mutated gene, exposure to a damaging chemical and infection with a specific virus. The report appears in *Cell*.

Complex diseases like Crohn's are influenced by both genetic and environmental factors; other examples include cancer, heart disease, diabetes, Alzheimer's disease, multiple sclerosis and Parkinson's disease.

Studies of these conditions have shown that having a gene linked to disease does not always lead directly to that disease. This has prompted searches for other factors that interact with genes to trigger complex diseases, including exposure to toxins or infection with microorganisms. Researchers say the new findings suggest that viruses may provide some of the missing links between genes, environment and disease.

"We've provided a very specific example of a virus triggering a complex disease — if the mice don't have the virus, they don't get the symptoms," says co-senior author Herbert W. "Skip" Virgin, MD, PhD, the Edward Mallinckrodt Professor and head of Pathology and Immunology. "Many viruses infect nearly 100 percent of people, and when their genes

interact with our genes, they may be contributing to such diseases."

Virgin and co-senior author Thaddeus S. Stappenbeck, MD, PhD, associate professor of pathology and immunology and of developmental biology, also found evidence that viruses' roles in complex diseases may be difficult to detect.

Crohn's disease, which affects approximately 500,000 Americans, causes diarrhea, abdominal pain and infections, and can lead to complications requiring surgery. Some people with Crohn's have mutations in their Atg16L1 gene, but the mutations are much more prevalent than the disease.

"In Western society, about half of all copies of Atg16L1 contain the mutation linked to Crohn's," Stappenbeck says. "That means both copies of this gene are mutated in about one in every three persons. And yet Crohn's occurs in a small fraction of these individuals."

In an earlier study, Stappenbeck and Virgin learned that mice with mutated Atg16L1 have abnormalities in Paneth cells, which help regulate the gut microbial communities that aid digestion.

When the model was recreated in a more stringently controlled environment, the Paneth cell abnormalities did not reoccur until researchers infected the mice with a mouse norovirus. Versions of this virus that infect humans are infamous for causing difficult-to-control outbreaks of diarrhea on cruise ships, and cause a significant portion of gastroenteritis cases worldwide.

When they also fed the mice dextran sodium sulfate (DSS), a chemical used to simulate gut injury, additional Crohn's-like pathologies appeared, but only in the presence of the mouse norovirus.

"We don't know the details of why DSS works with the virus to help create the model, and we have no evidence as yet that dietary toxins play a similar role in the creation of human Crohn's disease," Stappenbeck says. "Given how similar the model's symptoms and responses to treatment are to human disease, though, those are issues we will be investigating."

Stappenbeck notes that the study also doesn't prove that human noroviruses cause Crohn's disease.

"It suggests that they might be a place to look," he says. "But it's worth emphasizing that we needed the additional damage from DSS, together with the virus and the mutant gene, to trigger the symptoms."

Scientists have found several genes that influence risk of Crohn's disease. Stappenbeck suggests that there are likely to be several paths to developing the disease that include multiple environmental risk factors.

When scientists gave the mice a broad-spectrum antibiotic, their symptoms stopped. Researchers speculate that the virus and the gene's effects on Paneth cells may be changing the gut microbial community in harmful ways, triggering Crohn's-like pathology. It's possible that the antibiotic, which does not affect viruses, clears out the maladjusted community of gut microbes.

"More immediately, this tells us that how a complex disease responds to antibiotics can't be used to rule out a part for viral contributors in causing that disease," Virgin says. "If we hadn't already been aware of the virus' role as a trigger for symptoms, the model's response to the antibiotic would have led us to pin the blame on gut microbes and stop looking at viruses."

A closely related strain of mouse norovirus with only slight genetic

differences could not cause symptoms. According to Virgin, the two strains would have been indistinguishable to conventional tests for viral infection, which are based on the types of antibodies found in the blood.

"Our results show that we can't rely on these tests to determine if a particular strain of virus helps trigger a complex disease," Virgin says.

Virgin and Stappenbeck plan multiple follow-up investigations, including a more detailed look at how norovirus infection alters the microbial community in the gut of the mice and continued efforts to identify new viruses that infect humans.

"Viruses are extra genes present in the host," Virgin says. "Until we understand how those extra genes interact with our own DNA, we may not be able to assemble a complete picture of how what's in our genes affects what happens to our health."

Provided by Washington University School of Medicine