Crohn's discovery could lead to better treatments for devastating condition

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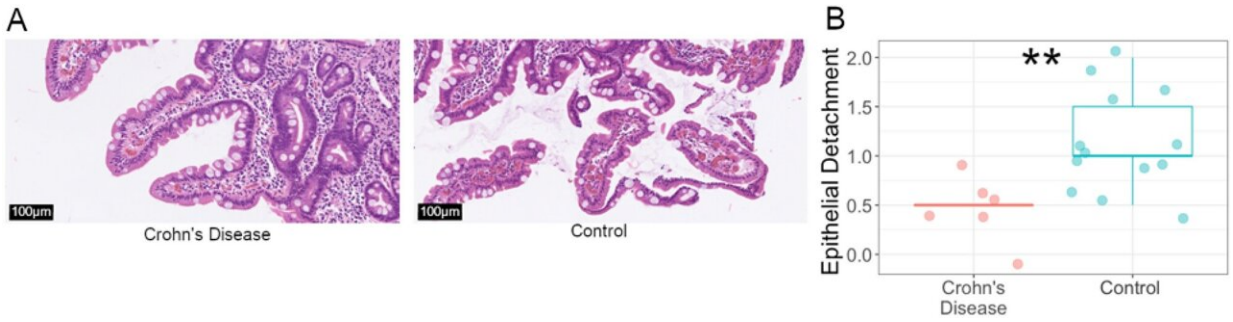

Decreased epithelial detachment in biopsy samples of patients with Crohn's disease compared with controls (**p = 0.006). Credit: *Scientific Reports* (2024). DOI: 10.1038/s41598-024-63299-y

Remarkable new research by a University of Virginia undergraduate may help explain recurrent Crohn's disease in children and open the door to new ways to treat or even cure the devastating condition. The work is published in the journal *Scientific Reports*.

Crohn's is a debilitating—and possibly life-threatening—inflammation of the digestive tract. Symptoms include abdominal pain, weakness, fatigue and malnutrition caused by the body's inability to absorb nutrients.

It's most common in adults but afflicts tens of thousands of children in

the United States alone. Many of those kids struggle to go to school and find their lives and childhoods greatly disrupted. These children can suffer stunted growth and delayed puberty and may need to have sections of their bowels surgically removed.

UVA's new research suggests answers to why children with relapsing Crohn's endure repeated bouts even after appearing to recover. Working under the guidance of the UVA School of Medicine's Chelsea Marie, Ph.D., undergrad Rebecca Pierce found that children with relapsing Crohn's had a persistent disruption of their microbiomes—the collection of microorganisms that lives in our guts—even after inflammation was successfully controlled by treatment.

"The relationship between dysbiosis and inflammation is a long-standing question in Crohn's disease. Rebecca leveraged a pediatric cohort at UVA to show dysbiosis was present even when gut inflammation was controlled," said Marie, of UVA's Department of Medicine and Division of Infectious Diseases and International Health. "Our study suggests that persistent microbial imbalances might be an important factor in the disease course in children."

That insight could be key to helping doctors develop better ways to treat or possible even cure Crohn's, said Ning-Jiun "Ninj" Jan, Ph.D., a senior scientist in Marie's lab who helped mentor Pierce.

"Currently, the main goal of most Crohn's disease treatments is to manage symptoms. This usually means taking different drugs to address inflammation and encourage healing," Jan said. "However, these are not cures, meaning these drugs need to be taken continuously to prevent relapse. Our study found that though the symptoms have been alleviated the bacterial composition in their guts did not return to normal, which may be why these patients relapse."

Crohn's Disease in children

Because Crohn's is most common in adults, most research has focused on adult patients. But UVA's new findings shed important light on Crohn's in children.

The researchers hypothesized that kids who suffer relapsing Crohn's had persistent inflammation, along with changes in the composition of the bacteria and other microbes in their guts. Scientists have increasingly come to appreciate the importance of these microbes in maintaining good health, and disruptions of the microbiome is increasingly suspected as a major contributor to disease.

Pierce, now a medical student at Georgetown University, and her collaborators compared biopsy samples collected from the intestines of children with Crohn's who had gone into remission with samples collected from a control group of children with no signs of Crohn's. The researchers found some big differences, with the children with Crohn's showing significant decreases in bacteria such as Streptococcus and increases in others, such as Oribacterium. (Oribacterium has previously been linked to gut microbiome disruptions.) Further, they observed notable changes in immune cells, such as an increase in the numbers of $CD4^+$ T cells, which play an important role in inflammation.

Perhaps counterintuitively, the children with Crohn's also had stronger barriers of epithelial cells lining their intestines. This suggests that existing Crohn's treatments are effective but not fully addressing the underlying issues that drive the disease, the researchers say.

"Even in our cohort of pediatric Crohn's patients in remission, we detected persistent microbial imbalances and subtle inflammatory changes," Pierce said. "Current therapeutics have focused on treating clinical symptoms which can leave patients vulnerable to relapse. Our

work suggests that incorporating therapies that target the root causes of dysbiosis could lead to improved treatments with fewer relapses."

That could lead to new and better Crohn's treatments for both children and adults, the researchers note. For example, doctors might seek to restore balance to the microbiome by using fecal transplants or by administering tailored cocktails of healthy microbes to replace those that have been lost.

"Our study suggests that returning the bacterial composition to normal might help prevent these patients from relapsing and possibly cure them of Crohn's disease," Jan said.

Marie noted that the new findings were made possible by the culture of collaboration at UVA.

"Clinical research is key for improving child health," Marie said. "Rebecca's work brought together experts in infectious disease, pediatric gastroenterology and bioinformatics to address a disease in our pediatric patients at UVA. We are excited to continue this model of collaboration."

Understanding the microbiome to prevent, treat and cure disease is a priority of UVA's TransUniversity Microbiome Initiative (TUMI), which brings together researchers from across the university to advance this cutting-edge field of biomedical research.

More information: Rebecca Pierce et al, Persistent dysbiosis of duodenal microbiota in patients with controlled pediatric Crohn's disease after resolution of inflammation, *Scientific Reports* (2024). DOI: 10.1038/s41598-024-63299-y

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