Study discovers link between celiac disease risk and a noncoding RNA

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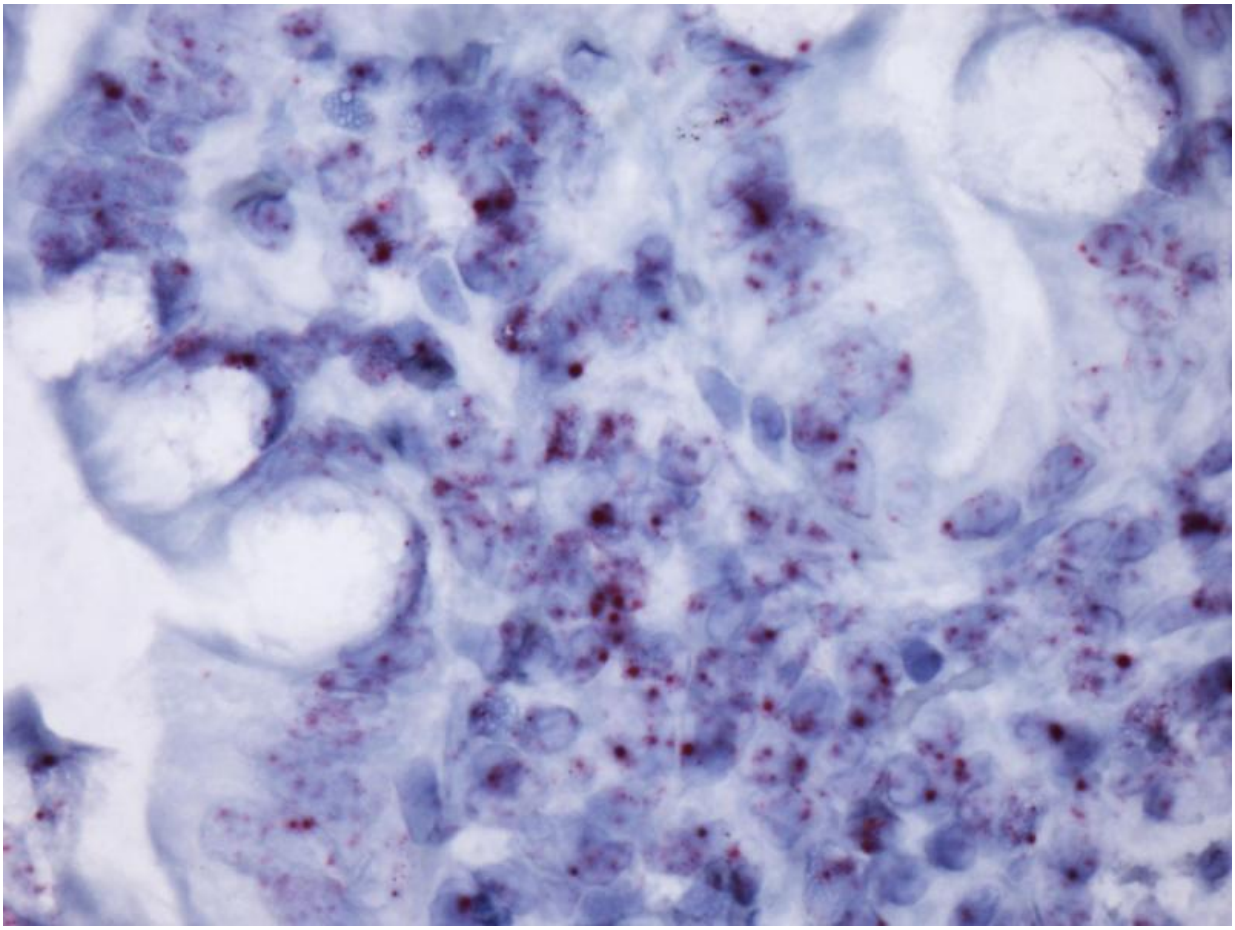


A photomicrograph showing the lnc13 RNA expression in an individual on a gluten-free diet. Credit: Lab of Dr. Sankar Ghosh/Columbia University Medical Center

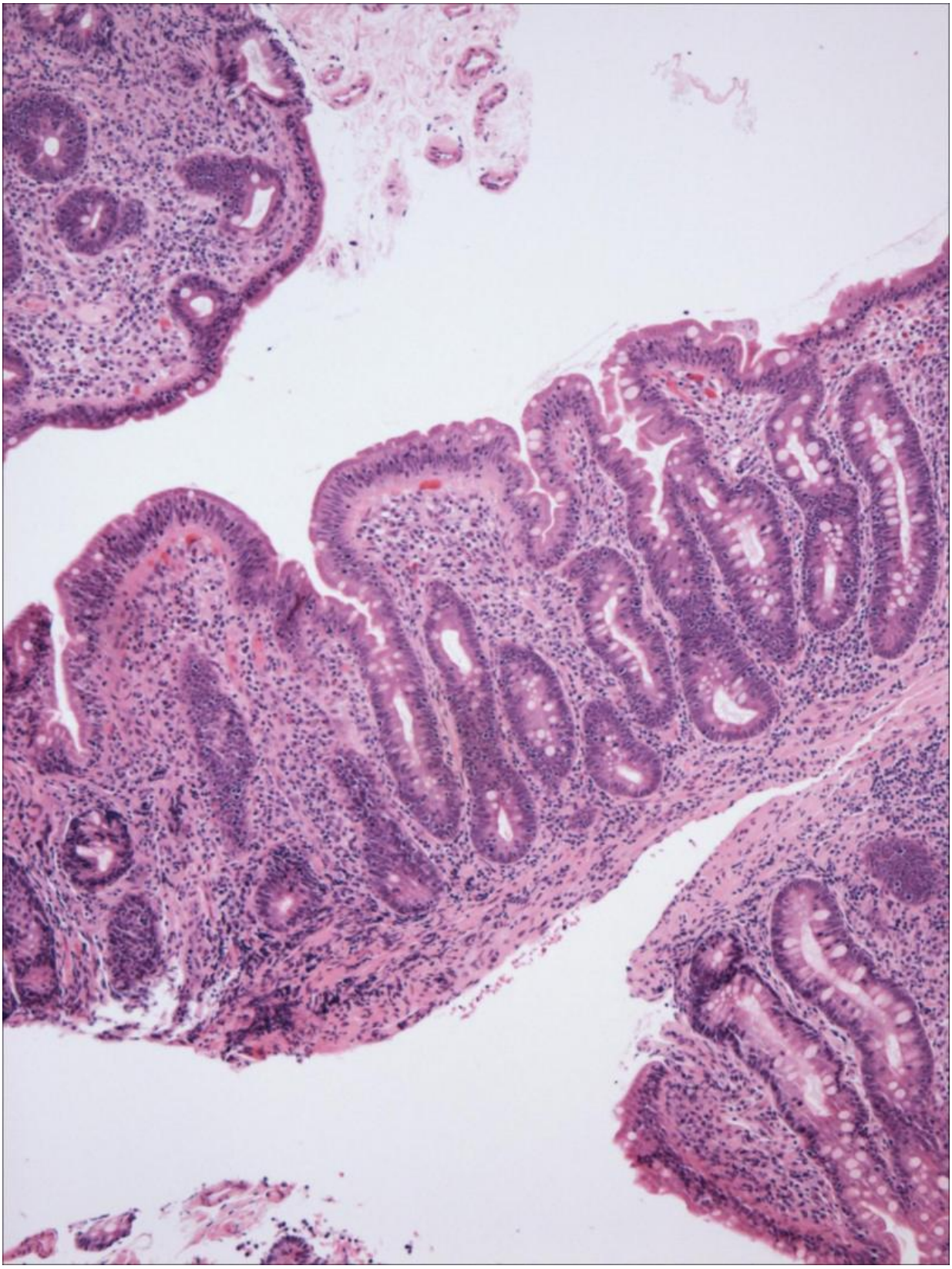
Researchers have identified a common variant in a non-coding RNA that may contribute to the intestinal inflammation that occurs in people with celiac disease. The findings point to a possible new risk factor for developing celiac disease in people with celiac disease risk genes.

The study was reported today in *Science*.

Celiac disease is an autoimmune digestive disorder in which genetically predisposed individuals develop an immune response to gluten, a protein found in cereal grains, wheat, rye, and barley. An estimated 40 percent of the population has the primary gene variant associated with celiac disease, but only 1 percent of people with these genes go on to develop intestinal inflammation and damage—the hallmarks of the disease—after ingesting gluten.

"We don't know why only a fraction of individuals with genetic risk factors for celiac disease actually become gluten intolerant," said Peter Green, MD, the Phyllis and Ivan Seidenberg Professor of Medicine at Columbia University Medical Center (CUMC), Director of the Celiac Disease Center at Columbia University and co-author on the study. "It is only through the dedicated work of translational scientists that we can begin to uncover the mechanisms that unleash the symptoms of celiac disease."

Recently, researchers have focused on the ability of noncoding RNA, the portion of our genome that does not encode for the production of proteins, to regulate a variety of biological processes. Long noncoding RNA (lncRNA), which contains more than 200 nucleotides, are thought to play a role in autoimmune diseases and cancers by interacting with other RNA, DNA, and proteins. However, it was not clear whether changes in lncRNA genes could put people at risk of developing complex diseases in the same way that changes in protein-coding genes do.



Stained photomicrographs of small intestinal biopsies from newly diagnosed celiac disease patients showing marked architectural distortion that comprise total villous atrophy, crypt hyperplasia and increased intraepithelial lymphocytes. Credit: Lab of Dr. Sankar Ghosh/Columbia University Medical Center

Through a variety of experiments, the researchers demonstrated that lnc13 dampens the expression of celiac-associated genes by binding to a common family of proteins. The celiac-associated variant of lnc13 binds poorly to these proteins, leading to increased expression of inflammatory genes. The researchers then discovered that patients with celiac disease had unusually low levels of lnc13 in their intestines, suggesting that downregulation of this gene may contribute to the inflammation seen in celiac disease.

"These findings add an important detail to our understanding about how celiac disease develops," said Sankar Ghosh, PhD, the Silverstein and Hutt Family Professor of Microbiology and Immunology, Chairman of the Department of Microbiology and Immunology at CUMC, lead author of the paper. "Given that the majority of the population consumes these grains, understanding the factors that put certain individuals at greater risk for the development of celiac disease will have a broad impact. In future studies, we hope to investigate factors that lead to suppression of lnc13, which may cause celiac disease in people who were previously able to tolerate gluten."

More information: "A long noncoding RNA that is associated with susceptibility to celiac disease," *Science*, DOI: 10.1126/science.aad0467