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Crohn's Disease: One Gene Copy Too Few Leads to Weakened Defense

Patients with Crohn's disease of the colon have one copy less than healthy persons of the beta-defensin 2 gene, a gene coding for an important defense molecule of the body. An international research team comprising scientists of the Robert Bosch Hospital in Stuttgart and the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in Heidelberg have discovered a possible cause of the chronic inflammations.

Crohn's disease (CD) is a chronic inflammatory disease of the intestinal tract affecting most commonly the lower part of the small bowel, called the ileum, and the colon. The cause of the disease is unknown; genetic and environmental factors have been suggested to play a role.

Defensins are part of the arsenal of defense weapons used by the human immune system. The peptides consist of only about 30 protein building blocks and act like our body's own antibiotics that protect the mucous membranes from bacterial invasion. Patients with Crohn's disease of the colon (colonic CD) have a lower level of beta-defensins in the mucous membranes. In a collaborative research project headed by Dr. Klaus Fellermann and Professor Eduard F. Stange, Robert Bosch Hospital, Stuttgart, researchers from the German Cancer Research Center and the Universities of Vienna and Davis, California, have now discovered that the number of defensin gene copies has a crucial influence on the development of the disease.

Defensin genes are arranged in nests, called clusters, on chromosome 8. The number of clusters varies considerably across the population; this is technically called a polymorphism. The research team has now shown that patients with colonic CD have on average only three copies of the gene encoding beta-defensin 2, whereas healthy control persons as well as patients with small bowel CD or ulcerative colitis, another inflammatory bowel disease, have an average of four copies of this gene per cell.

The researchers showed that a lower number of gene copies is indeed associated with reduced production of the endogenous antibiotic, which explains the known low defensin level. They presume that this causes the defense of the intestinal mucous membrane to become porous so that bacteria can attach to and invade the mucous membrane, which leads to the typical inflammatory hot spots of Crohn's disease.

The disease, which is named after American physician Dr. Burrill Bernhard Crohn, is characterized by recurring episodes of active disease. It affects approximately 150,000 people in Germany; five new cases per 100,000 inhabitants are diagnosed each year. There has been a substantial rise in incidence rates in recent years. Patients suffering from Crohn's disease also have an elevated risk of developing bowel cancer.

Klaus Fellermann, Daniel E. Stange, Elke Schaeffeler, Hartmut Schmalzl, Jan Wehkamp, Charles L. Bevins, Walter Reinisch, Alexander Teml, Mattias Schwab, Peter Lichter, Bernhard Radlwimmer and Eduard F. Stange: A chromosome 8 gene cluster with low human beta-defensin copy number predisposes to Crohn's disease of the colon. The American Journal of Human Genetics, e-pub ahead of print

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