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Genetic Defect Promotes Development of Crohn's Disease

The DMBT1 gene helps to fight off pathogenic agents that affect the intestines. If this gene is absent or defective, the affected individual has an increased risk of developing Crohn's disease, a chronic inflammation of the digestive tract. This was found out by researchers of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) within the framework of a European collaboration.

Tiredness, abdominal pain and diarrhea are the most common first symptoms of Crohn's disease. Crohn's disease is a chronic inflammatory bowel disease (CIBD) and occurs most often in people between the ages of 16 and 35. Any area of the gastrointestinal tract, from the mouth to the anus, can be affected by inflammation, but it most commonly affects the mucous lining of the large intestine (colon) and the small intestine.

Crohn's disease can be regarded as an immune system disorder. Research suggests that a weakened immune system promotes the chronic invasion of the mucous membrane by pathogens. Another theory is that the immune cells are unable to control the body's own intestinal bacteria. The body can only defend itself against these 'invaders' using means that damage the mucous membrane of the intestines – the result is chronic inflammation. Researchers suspect that environmental factors such as bacteria or viruses, specific substances in foods or smoking may play a role in Crohn's disease. Inherited defects in risk genes can also promote the development of Crohn's disease.

Defensins are a group of genes whose defects are associated with the development of Crohn's disease. Defensins act like natural antibiotics and fend off infectious bacteria in the mucosa. A similar role of the DBMT1 gene was found by researchers headed by Associate Professor Jan Mollenhauer and Professor Annemarie Poustka.

Like the defensins, the gene product of DMBT1 is found in intestinal mucosa where it may play an important role in the defense against viruses and bacteria. In their current work, DKFZ researchers collaborating with colleagues from five European countries found out that in CIBD patients the activity of DMBT1 is particularly high in inflamed tissue areas of the intestines. The researchers then investigated whether defects in the gene might lead to an increased risk of developing chronic bowel inflammations. To this end, they compared the genetic information of CIBD patients and of healthy study subjects. Indeed, they found a defect in the DMBT1 gene that occurs significantly more frequently in patients with Crohn's disease than in healthy individuals.

In order to show that a defect in DMBT1 has a direct influence on disease risk, Mollenhauer and colleagues deactivated the gene for DMBT1 in mice. The researchers irritated the intestines of the mice with a chemical. Mice whose DMBT1

gene was switched off showed stronger inflammatory reactions than animals with an intact copy of the gene. The scientists deduced that DMBT1 counteracts chronic bowel inflammations. If this gene is absent or defective, the risk of developing Crohn's disease is increased. Other diseases found to be associated with DMBT1 by the DKFZ scientists are cancers of the breast, lung, brain and the gastrointestinal tract.

Marcus Renner, Gaby Bergmann, Inge Krebs, Caroline End, Stefan Lyer, Frank Hilberg, Burkhard Helmke, Nikolaus Gassler, Frank Autschbach, Floris Bikker, Olga Strobel–Freidekind, Sabine Gronert–Sum, Axel Benner, Stephanie Blaich, Rainer Wittig, Melanie Hudler, Antoon J. Ligtenberg, Jens Madsen, Uffe Holmskov, Vito Annese, Anna Latiano, Peter Schirrmacher, Arie V. Nieuw Amerongen, Mauro D'Amato, Petra Kioschis, Mathias Hafner, Annemarie Poustka und Jan Mollenhauer: DMBT1 Confers Mucosal Protection In Vivo and a Deletion Variant Is Associated With Crohn's Disease. *Gastroenterology*, vol. 133, p. 1499, November 2007