

# Discovery of new family of genetic mutations involved in inflammatory intestinal disease

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The discovery of new genetic mutations involved in inflammatory intestinal disorders could lead to a better understanding of these common conditions, two scientists told the annual conference of the European Society of Human Genetics today (Monday 2 June).

Dr. Alexandra Zhernakova, from the Utrecht University Medical Centre, Utrecht, the Netherlands, and Dr. Eleonora Festen, from the University of Groningen, Groningen, the Netherlands, both working in the group of Professor Cisca Wijmenga, said that they had found common origins for two inflammatory diseases of the bowel, and that understanding the genetic profiles of these diseases will lead to better diagnosis, prevention, and, in the longer term, treatment. The research provides further support for the theory that common genetic factors are involved in a range of auto-immune and inflammatory diseases

Dr. Zhernakova and colleagues set out to study genetic mutations involved in coeliac disease. Coeliac disease is characterised by inflammation of the intestines leading to diarrhoea and, in children, failure to thrive through malnutrition. It is caused by an immune reaction to gluten, a protein found in wheat, rye, and barley in people who are genetically susceptible. When the immune system encounters gluten in the body, it cross-reacts with the bowel tissue and causes an inflammatory reaction. In the long-term this leads to flattening of the lining of the small intestine, which in turn hampers the absorption of nutrients. Currently, the only effective treatment is a totally gluten-free diet. The disease affects about 1% of the population in developed

countries.

Using a genome-wide search, the team, in collaboration with researchers from Ireland and the UK, analysed genetic variants in 778 coeliac cases, and in 1422 controls from the UK. In phase II of this study the extensive collection of more than 5000 coeliac cases and controls from the UK, Ireland and the Netherlands were followed up for the top 1000 variants detected in phase I. The researchers found genetic mutations in eight new areas, seven of which contained genes involved in controlling immune responses.

"Three of these areas are also involved in Type 1 diabetes", said Dr. Zhernakova, "and, most interestingly, one overlaps with another intestinal inflammatory condition, Crohn's disease. This seems to show that common genes for inflammatory disease such as coeliac disease are not specific to the disease. It appears that these shared genetic mutations point to common molecular pathways."

Dr. Festen's team analysed the genetic variants in the immune pathway in a three-step design in a group of 1851 patients with inflammatory bowel disease (IBD) and 1936 controls. The two most common manifestations of this condition are Crohn's disease and ulcerative colitis. Crohn's disease can be found throughout the digestive tract, but most commonly affects the lower part of the small intestine. It causes extensive inflammation leading to swelling of the bowel lining and the formation of scar tissue; this results in pain and weight loss. In developed countries the disease affects around 45 people in every 100,000.

Ulcerative colitis causes inflammation and ulcers in the top layer of the lining of the large intestine, leading to diarrhoea and bleeding. The incidence is lower than that of Crohn's disease, with about 15 people in every 100,000 affected in developed countries. Both diseases affect men and women equally and run in families, suggesting a genetic cause.

"In spite of the large number of studies on the heritability of IBD", said Dr. Festen, "only very few of the genes responsible have been identified to date. Interestingly, one of the new genes we found for IBD is also involved in coeliac disease, lending more weight to the theory that the genetics of these inflammatory intestinal disorders are shared.

"We will continue looking for more genes that are implicated in IBD, without which it is hard to full understand the causes and disease mechanisms involved. This in turns leads to difficulties in identifying effective treatments – whether a drug will work on not for a certain patient is hard to predict, which means that patients often have to try out a number of different medicines, sometimes with unpleasant side-effects, before they find one that works for them."

The scientists hope that identifying more of the genes involved in inflammatory intestinal disease will give them a better insight into the mechanisms of the disease and therefore the possibility of developing new therapies, as well as enabling them to use existing therapies more effectively. The team will now follow up their work by looking for the exact mutation responsible for disease development in each of the new areas identified, and then to define the mechanism of genetic effect on disease development.

Effective prevention is also a target. "In coeliac disease, for example, genetic studies such as these will allow us to define genetically high-risk children where we could delay or prevent the onset of disease by introducing a diet that avoided the foods which provoke an inflammatory response", said Dr. Zhernakova.

Source: European Society of Human Genetics

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