Crohn's disease, protective genetic mutations

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The genes with a predisposition to Crohn's disease identified up until now allow an explanation of a small part of the heritability of this inflammatory digestive system disease. In dissecting the genomes of healthy people and of people suffering from this pathology, with the aim of looking for rare genetic variants, ULg researchers have discovered genetic mutations which protect human beings against Crohn's disease.

Since the complete sequencing of the human genome, in 2003, scientists the world over have been getting down to the task of putting their fingers on the genes, or rather the genetic variants, which predispose human beings to the various diseases with their origins in our DNA. In 2007, a team of ULg researchers, directed by Edouard Louis
and Michel Georges, discovered the mutation of a gene linked to Crohn’s disease (read the article, *The identification of a Crohn’s disease gene*). The fruit of close joint work between the team of specialists in gastroenterology and the one with specialists in genetics and genomics since 2002, this study brought to light a genetic variant found in 20% of patients suffering from this disease. Following this discovery the researchers decided to venture further amongst the meanders of the genetics of this chronic inflammatory disease of the digestive system. In 2008, thanks to a large meta-analysis carried out jointly with the National Institute of Health (NIH) in the United States, the Wellcome Trust in England and the Belgian university hospitals Erasme, UZ Gent and UZ Leuven, the Liège scientists succeeded in bringing to light around 40 genes linked to Crohn’s disease. Despite this great step forward in understanding the genetic origins of the disease, these genes as a whole only enable 20 to 30% of the heritability of this complaint to be explained.

**Looking for rare genetic variants**

'We thus said to ourselves that there could exist rare mutations which are not picked up by the type of analysis used up until now because their detection requires an integral reading of the genes,' points out Edouard Louis, ex FNRS (National Scientific Research Fund) Senior Research Associate and currently Senior Lecturer at the ULg and Head of the Gastroenterology at the Liège University Hospital Centre (CHU). In order to verify this hypothesis, Edouard Louis, Michel Georges - who runs the Animal Genomics Unit at the GIGA-Research Unit - and their colleagues carried out the complete sequencing of some forty genes identified as well as of other genes suspected of being involved in Crohn's disease occurring. 'We carried out analyses based on samples from larger and larger patient cohorts in order to confirm the results,' continues Edouard Louis. 'Here as well the Erasme, UZ Gent and UZ Leuven hospitals as well as other European centres took part in gathering blood samples in order to obtain a powerful databank.'
If this study enabled confirmation of the presence of rare genetic variants in the genomes of people suffering from Crohn's disease, it also revealed that they were only responsible in a very small way for the disease's heritability. Another of this study's conclusions nevertheless merits greater explanation. In effect the scientists discovered that, instead of offering a predisposition for Crohn's disease, certain of the rare genetic variants detected over the course of this analysis indeed protected against it! It concerns notably variants of the gene coding for the IL23 receptor, a cytokine which plays an essential role in the activation of the immune system. The results of this study have been published in the *Nature Genetics* journal (1).

**An exaggerated immune response**

The aforementioned variants are found on chromosome 1, in one of the three zones linked to Crohn's disease brought to light during the genetic screening study of 2007. *These mutations are observed in 2 to 3% of 'healthy' individuals and in 0.5 to 0.8% of people affected by Crohn's disease; they are thus ten times less frequent in the latter,* adds Edouard Louis. *From this springs the hypothesis that these variants..."
invalidates the inflammatory cascade's activation capacities,' he continues. In people who carry these rare variants the IL-23 receptors are thus thought to have reduced activity, which prevents the appearance of an exaggerated immune response against intestinal bacterial flora. Because if the precise causes of Crohn's disease today remain unknown scientific studies show that part of the response could in effect be found in the way the body reacts to the bacteria which colonise the digestive system. Around ten years ago or so scientists agreed that the inflammations of the bowel which arise in Crohn's disease were due to a hyperactivity of the immune system. Today new studies tend to show that the cause of this disease is a defence system which is too weak, or in any case at first. The idea is the following: as the body reacts in an insufficient manner against intestinal bacteria they proliferate and cause inflammations. Subsequently the immune system tries to counter the consequences of its too weak initial reaction and becomes hyperactive.


**Tobacco, a risk factor**

Described in the United States in 1932 by Doctor Burnill Bernard Crohn, the disease of the same name affects around 15,000 people in Belgium. In a person affected, all the parts of the digestive tract can be subjected to permanent inflammation. Nevertheless it is more frequently the colon and the small intestine which are affected. The symptoms which result are diarrhoea, abdominal pains, weight loss, fever and fatigue. If genetic factors play an important role in the outbreak of the disease, environmental factors are equally involved. Since the 1930s Crohn’s disease has become more and more frequent in western countries. This evolution suggests that our lifestyles favour the development of this disease. Amongst the environmental factors identified by scientists is notably counted tobacco. Smoking in effect multiplies the risk of developing Crohn's disease by two.

'For identical twins, if one of the twins has Crohn’s disease, the other has a 50% chance of developing the disease. For brothers and sisters this percentage is 5%,' explains Edouard Louis. These are figures which irregardless underline the great influence of our genes on the probability of suffering from this disease. It is thus vital to continue scanning the genome to detect within it the genes which have a predisposition for this disease.
'Michel George’s Animal Genomics Unit is cutting edge in terms of developing techniques and concepts in genetics, so working with him allows us to be at the summit of the research into the genetics of Crohn’s disease,’ enthuses Edouard Louis. ‘The discovery of rare protective genetic variants has no value in terms of diagnostics but a great deal for an understanding of the disease and the search for new therapeutic pathways. It confirms that the search for substances which can act on the level of the cascade of mechanisms linked to IL23 is pertinent,’ he concludes.