The heritability of Crohn's disease better understood

17 December 2010

A University of Liege GIGA-Research Unit team has discovered new particular genetic mutations which influence hereditary predisposition to Crohn's disease, a chronic inflammatory disease of the bowel. The rare variants discovered by the researchers prove to protect against the disease and turn out not to be risk variants.

Crohn's disease is not fatal but is currently incurable and very incapacitating, characterised by intense abdominal pain, gastrointestinal bleeding, weight loss and persistent fever. It is a multifactorial disease: an individual's predisposition depends on both environmental factors (food consumption, physical activity, etc.) as well as genetic ones. The heritability of Crohn's disease is in the order of 80%.

Research into human genetics aims at identifying the genes which underpin this heritability, as such discoveries allow new therapeutic targets to be defined and contribute to the development of more personalised medicine.

Thanks to the technologies of large scale genotyping ('Genome Wide Association Studies') which have been available for around three years, dozens of genes (or more precisely loci) involved in hereditary predisposition to multifactorial pathologies such as cancer, Alzheimer's disease, cardiovascular an inflammatory diseases etc. have been discovered. For Crohn's disease 100 genomic regions have already been discovered, containing genetic variants affecting predisposition to this disease, and the development of new medicines on the basis of these results is under way.

Nevertheless the genes identified to date only explain a low proportion of the heritability of the complew pathologies studied (around 10%). Geneticists have thus puzzled over this 'missing heritability.' Several hypotheses are being studied, including that of 'rare variants.' In this case an array of 'private' rare variants is to be added to the risk variants for standard diseases commonly found in the population as a whole.

It was the task of bringing to light these rare Crohn's disease variants that the ULg's GIGA-Research Unit team set itself. The new technologies of high throughput sequencing that the GIGA Unit has available have enabled the genomes of hundreds of patients to be analysed. This ultra-fine exploration of the genome has permitted the discovery of rare variants which have an influence on predisposition to Crohn's disease. Nevertheless these variants play more of a protective role against the disease than a risk factor role.

More precisely these newly observed mutations reduce the activity of the IL23 receptor, a hormone which plays a vital role in the activation of the immune system. This suggests that Crohn's disease results in part at least from an exaggerated immune response to intestinal bacterial flore. Individuals who have slightly deficient IL23 receptors (due to the presence of rare variants in the corresponding gene) would cetainly be disadvataged, for example, in the 'hunter-gatherer' environment which prevailed some hundreds of years or tens of thousands of years ago, but are on the other hand advantaged in our ultra-hygienic environment.

'In this publication we confirm that rare variants indeed contribute to Crohn's disease heritability, and we define the procedures to follow in order to identify them,' explains Professor Michel Georges (GIGA-Research Unit). 'But our calculations also show that if these rare variants exist, they do not in themselves explain all of the missing heritability. Other hypotheses remain to be explored in order to understandin a detailed manner why we are not all equal before certain diseases, such as Crohn's disease.'

More information: Resequencing of positional candidates identifies low frequency IL23R coding variants protecting against inflammatory bowel disease, *Nature Genetics*, Advance Online Publication 12/12/2010 doi:10.1038/ng.733

Source: University of Liege