Complexity of Crohn's disease revealed as 'gene' count tops 30

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New research has trebled the number of genetic regions known to be implicated in Crohn's disease, a form of inflammatory bowel disease, to over thirty. The research, published today in the journal *Nature Genetics*, has identified a number of potential new targets for drug development as well as providing surprising new links between the condition and other common diseases including asthma.

Crohn's disease affects between 1 in 500 and 1 in 1000 people within the UK, causing inflammation of gastrointestinal tract and leading to pain, ulcers and diarrhoea. The disease can strike at any age, but onset is typically between 15 and 40 years old. As many as 80% of people suffering from the disease will require surgery at some point.

Previous studies have already identified 11 genes and loci (regions of the genome typically including one or more genes) that increase susceptibility to the disease. Now an international collaboration of researchers has identified a further 21 new genes and loci. The team of scientists and clinicians involved used DNA samples from almost 12,000 people. Many were from UK patient collections and analysed originally in the Wellcome Trust Case Control Consortium – the largest study ever undertaken into the genetics underlying common diseases – with others coming from European and North American collections.

"We now know of more than thirty genetic regions that affect susceptibility to Crohn's disease," says Dr Jeffrey Barrett from the Wellcome Trust Centre for Human Genetics at the University of Oxford,

lead author of the study. "These explain only about a fifth of the genetic risk, which implies that there may be hundreds of genes implicated in the disease, each increasing susceptibility by a small amount.

"Whilst this study shows the power of genome wide association studies to reveal the genetics behind common diseases, it also highlights the complexity of diseases such as Crohn's."

Genome wide association studies have led to an explosion in the number of genes known to be implicated in complex diseases such as diabetes, heart disease and Crohn's disease. The first two Crohn's disease susceptibility genes were discovered in 2001, followed by a third in 2006. The Wellcome Trust Case Control Consortium and parallel studies took that number above ten the following year using genome wide association studies. This number has now almost trebled to thirty-two.

Amongst the findings are loci containing genes known to be implicated in a number of other common diseases including diabetes, rheumatoid arthritis and psoriasis. However, the genetic relationship between Crohn's and these other diseases is not always straightforward. For example, the genetic variant PTPN2 appears to increase susceptibility to both Crohn's disease and type 1 diabetes. But the similarly named PTPN22 increases the risk of developing type 1 diabetes, yet appears to offer protection from Crohn's.

Although some of the disease connections were unsurprising – there is already a known epidemiological correlation between Crohn's disease and psoriasis, for example – the ORMDL3 gene on chromosome 17 provided the most unexpected link. ORMDL3 was already known to be a genetic risk factor for childhood asthma, but until now, no epidemiological link had ever been seen between asthma and Crohn's disease.

"It's too early for us to say how Crohn's disease and many of these other diseases, including asthma, are linked at a biological level," says Dr Miles Parkes, Consultant Gastroenterologist at Addenbrooke's Hospital and the University of Cambridge, who also worked on the study. "However, we are building up a picture of the biology underlying Crohn's disease, and the more we understand about the underlying biology of these diseases, the better equipped we will be to treat them.

"Studies such as this are not about developing diagnostic tests, but about identifying targets for new drugs therapies. Crohn's disease can be a very serious condition, often requiring surgery, and the sooner we can understand the underlying causes, the sooner we will be able to devise new treatments to help our patients."

Some of the most likely candidates for so-called "druggable" targets include the CCR6 gene, which is thought to be part of the signalling machinery that causes white blood cells in the gut to become over-active, leading to inflammation. These particular white blood cells, known as Th17 cells, are also present in inflamed joints, implying that CCR6 may also be relevant to rheumatoid arthritis, and therefore of added interest to the pharmaceutical industry.

"Genetics, and particularly the large scale approach of genome wide association studies, offers much hope for understanding the biological causes of complex diseases," says Dr Mark Walport, Director of the Wellcome Trust. "Studies such as this also highlight the important relationships between different diseases and, as such, may offer valuable insights into the pathways that lead to common symptoms such as inflammation."

Source: Wellcome Trust