

Media release from the Wellcome Trust and the National Association for Colitis and Crohn's Disease

Powerful genetic studies reveal secrets of adult and childhood inflammatory bowel disease

- *Three new genetic associations linked to ulcerative colitis highlight role of 'leaky gut'*
- *Five new genetic associations linked to childhood inflammatory bowel disease*

Two of the largest ever studies of the genetics of inflammatory bowel disease – one looking at ulcerative colitis, the other at childhood-onset inflammatory bowel disease – have identified key genetic regions which increase susceptibility to these conditions. The ulcerative colitis study shows the first conclusive evidence of the role played by genetic defects in the epithelium, the layer of cells which line the gut.

There are two main types of inflammatory bowel disease (IBD): ulcerative colitis and Crohn's disease. Together, these conditions affect around one in 250 people. Both are chronic and debilitating conditions which produce symptoms of diarrhoea, rectal bleeding and abdominal pain. Crohn's disease can also cause malnutrition and growth failure in children. Both often require expensive and potentially toxic drug treatments or surgery. Childhood-onset IBD may be particularly devastating – it is often more aggressive than later-onset disease, extensively affecting the intestinal tract. Over the long term, IBD can also lead to increased risk of colorectal cancer.

Both diseases are known to have a genetic component. Researchers have previously identified around seven genes which affect susceptibility to ulcerative colitis and two genetic regions relating to childhood IBD.

Now, two studies with funding from the Wellcome Trust and support from the National Association for Colitis and Crohn's Disease (NACC) have identified a further three genetic regions which affect susceptibility to ulcerative colitis and five which relate to childhood IBD. Both studies are published today in the journal *Nature Genetics*.

UK group identifies three new genetic associations linked to ulcerative colitis highlighting role of 'leaky gut'¹

Researchers from the UK IBD Genetics Consortium and the Wellcome Trust Case Control Consortium scanned the genomes and followed up promising signals in a total of almost 4,700 patients affected by ulcerative colitis and compared the results with over 8,000 controls (people unaffected by the disease). All were UK residents of European ancestry. This is over twice as large as previous scans, allowing far greater robustness.

The scans highlighted genetic variants in three regions of the genome which appeared to increase the risk of ulcerative colitis. These were found on chromosomes seven, sixteen and twenty and each contains at least one biologically-relevant candidate gene. All of the candidate genes - *LAMB1*, *CDH1*, *CDH3* and *HNF4A* – are known to play a role in creating, repairing and managing the function of the epithelium, which lines the intestine and acts as a barrier between gut bacteria and the immune system. In particular these genes affect the seals at the junctions between the cells of the epithelium.

The gut contains myriad bacteria known as 'flora', which perform a host of useful functions, such as preventing growth of harmful bacteria and regulating the development of the gut. Defects in the epithelial lining of the gut, and the seals between the cells, can allow the bacterial flora to leak into the wall of the intestine, where they can trigger an immune

reaction leading to prolonged inflammation – one of the main characteristics of ulcerative colitis.

Dr Miles Parkes, Consultant Gastroenterologist at Addenbrooke's Hospital and the University of Cambridge, who worked on the study, comments: "We have long suspected that genetic defects in the epithelial barrier are important in ulcerative colitis. This large scale genetic study provides the first robust genetic evidence that this is the case."

Co-author Professor Chris Mathew from King's College London adds: "This is very significant as most treatments to date are based on damping down immune response. In fact, our data suggests there may be mileage in trying to tighten up the mucosal barrier as well."

Of particular interest to the researchers was the discovery that *CDH1* may be involved in ulcerative colitis. *CDH1* encodes the protein E-cadherin, which is involved in building and repairing the epithelium. The gene is known to be less active in areas affected by ulcerative colitis; the loss of this protein has also been implicated in the spread of colon cancer. This provides the first genetic link between the two conditions.

Five new genome regions linked to childhood inflammatory bowel disease²

In a second Nature Genetics paper, an international team of researchers, including the International IBD Genetics Consortium, scanned the genomes of over 3,400 patients – including around 500 from Scotland – with childhood IBD and almost 12,000 controls. This is by far the largest genetic study to date of childhood-onset disease.

The researchers found five new genetic regions associated with susceptibility to childhood IBD. One of these was close to the gene *IL27*. This gene is part of a pathway already heavily implicated in adult-onset IBD, which triggers inappropriate activation of the immune cells in the gut.

The genome scans also highlighted the close relationship between how disease occurs in both childhood and adult-onset IBD: multiple regions previously implicated in adult-onset IBD were also detected in this new study.

One of the lead researchers in the study, Professor Jack Satsangi from the University of Edinburgh, studies the genetics of both Crohn's disease and ulcerative colitis in Scotland, where the incidence of the disease in children is higher than elsewhere in the UK.

"Both studies further our understanding of the mechanisms involved in the development of these illnesses, and hold the promise of leading to real progress in the care of patients with Crohn's disease and ulcerative colitis," says Professor Satsangi. "Childhood IBD is a particularly devastating disease, which inevitably impacting seriously on all aspects of a child's life and indeed on all members of the child's family.

"Our findings suggest that certain susceptibility genes are more important in children than in adults. There are now a series of important questions to address, arising from this work. In high-incidence areas such as Scotland, it is especially important now for us to explore the interactions between genes and the environment and understand what triggers this disease in susceptible individuals."

Sir Mark Walport, Director of the Wellcome Trust, comments: "This is an excellent example of how genetic studies can point towards causative mechanisms of disease. The ulcerative colitis study strongly suggests that there is inherited variation in the strength of the barrier provided by the cellular lining of the gut to the contents of the intestine. This genetic variation

is associated with differences in the risk of developing inflammatory bowel disease. Although it is a long way from this discovery to developing new treatments for inflammatory bowel disease, new approaches to the treatment and prevention of chronic diseases require new insights into their causes."

The findings have been welcomed by Richard Driscoll, Director of the National Association for Colitis and Crohn's Disease, whose members provided patient samples.

Mr Driscoll says: "NACC is proud to have supported the work of the UK IBD Genetics Consortium which has significantly increased our knowledge of the genes that are predisposing people to develop Ulcerative Colitis. We also welcome the significant findings of the childhood early onset genetics study. Both new papers offer important insights for future research directions and underline the increasing role of genetics in understanding the causes of Inflammatory Bowel Disease.

"Currently, Colitis and Crohn's disease are incurable, life-long conditions. Every increase in knowledge moves us closer to the time when identifying a person's genes may enable them and their doctor to make decisions on treatment with a more certain understanding of how their disease is likely to develop over time."

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Notes for editors

1. The UK IBD Genetics Consortium and the Wellcome Trust Case Control Consortium 2. Genome-wide association study of ulcerative colitis identifies three new susceptibility loci, including the HNF4A region. Nature Genetics online in advance, 15 Nov 2009.

Principal funding for this study was provided by the Wellcome Trust.

2. Imielinski, M et al. Common variants at five new loci associated with early-onset inflammatory bowel disease. Nature Genetics online in advance, 15 Nov 2009.

Funding for the UK study was provided by the Action Medical Research, the Gay-Ramsay-Steel-Maitland or Stafford Trust, the Hazel M Wood Charitable Trust, the Medical Research Council, the Wellcome Trust Programme Grant, the Chief Scientist Office of the Scottish Government Health Department, a University of Edinburgh Medical Faculty Fellowship, and the GI/Nutrition Research Fund, Child Life and Health, University of Edinburgh.

About the Wellcome Trust

The Wellcome Trust is the largest charity in the UK. It funds innovative biomedical research, in the UK and internationally, spending over £600 million each year to support the brightest scientists with the best ideas. The Wellcome Trust supports public debate about biomedical research and its impact on health and wellbeing. <http://www.wellcome.ac.uk>

About the National Association for Colitis and Crohn's Disease

NACC provides a valuable support network and information resource for people and families affected by Colitis and Crohn's disease as well as raising significant funds for research. Since 1984, NACC members have raised over £4.5 million and more than 100 research awards have been made to hospitals and universities throughout the United Kingdom. The 70 local NACC Groups across the UK enable members to meet other people who have these illnesses and share information and experiences.

NACC also campaigns for better healthcare services and seeks to raise awareness of these illnesses and their impact on people's lives. NACC is a partner in the UK national IBD Audit Project and has been leading the IBD Standards Group developing national standards for NHS IBD Services.

The NACC Information Line (daytime) 0845 130 2233 is available to members and non-members alike who have queries about all aspects of their disease. The NACC-in-Contact Line (afternoons and evenings) offers people a chance to speak to a trained volunteer who has Colitis or Crohn's Disease.

Membership of NACC is open to anyone who has Colitis or Crohn's Disease, their friends and families, health professionals and anyone who wishes to support the charity. Membership costs £12 per year and NACC offers free membership to 16-18 year olds.
<http://www.nacc.org.uk>