

UK researchers make landmark discoveries in the genetics of inflammatory bowel diseases

27 April 2008. St Alban's, Herts, UK. A UK multi-centre study published in the journal *Nature Genetics* today identifies a new gene for ulcerative colitis – one of the first to be confirmed for this condition – and in a decisive breakthrough establishes a series of genetic links between the inflammatory bowel diseases (IBD), ulcerative colitis and Crohn's disease. Since these are diseases of young people involving debilitating pain, embarrassing symptoms, a high risk of surgery and an increased risk of cancer, the researchers hope that these findings will translate directly to safe effective therapeutic strategies.

The multi-centre UK IBD Genetics team led jointly by Professor Jack Satsangi of Western General Hospital, University of Edinburgh; Professor Chris Mathew of King's College London, and Dr Miles Parkes of Addenbrooke's Hospital, Cambridge found the new ulcerative colitis gene, ECM1, and further showed that five other genes, which were previously shown to be involved in Crohn's disease, also predispose to ulcerative colitis.

Professor Satsangi explains, "This new study sheds more light on the underlying inherited factors that place people at risk of developing ulcerative colitis, and with the discovery of the ECM1 gene involvement highlights the role of gut barrier function."

Funded by the National Association for Colitis and Crohn's disease (NACC), the study involved over 3,000 UK patients with ulcerative colitis and applied new technologies for human genome scanning. As such it is the most detailed investigation of ulcerative colitis genetics in the world literature.

Three of the findings will be of great impact on the direction of inflammatory bowel research. Firstly, the new UC gene identified in this study, ECM1 encodes a protein which is implicated in maintaining the barrier function of the gut wall, and the finding suggests that an inherited defect in the gut wall - a leaky gut - may predispose to ulcerative colitis. Secondly, the five genes which the investigators show to predispose to either ulcerative colitis or Crohn's disease are involved in aspects of regulation of the immune system. Finally, several genes which this team have previously shown to be important determinants in Crohn's disease are not implicated in ulcerative

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colitis – of these Crohn's disease-specific determinants, NOD2/CARD15, ATG16L1 and IRGM all affect the body's ability to identify and deal with gut bacteria.

“This study represents another major step forward in understanding the processes involved in the development of the inflammatory bowel diseases, and extends last year's success in Crohn's disease genetics,” explains Professor Jack Satsangi .

Professor Satsangi continues, “The results are of real importance to patients, physicians as well as scientists. The insights gained from these genetic discoveries may lead to new treatment strategies, for individual patients. Moreover, for the first time, we are finding scientific evidence for the relationship between Crohn's disease and ulcerative colitis, sharing some but not all susceptibility genes. These findings provide a springboard for further studies of IBD genetics, and for the mechanisms whereby environmental factors interact with these genetic determinants. We hope these findings will translate directly to safe effective therapeutic strategies, by identifying new drug targets.”

Director of NACC, Richard Driscoll explains, “Ulcerative colitis is a painful, distressing and sometimes life-threatening inflammatory bowel disease which affects up to 120,000 people in the UK. It is often diagnosed in young people who will require medication and medical care for the rest of their lives. These findings will offer further encouragement to everyone that real progress is being made into how ulcerative colitis develops. NACC supports numerous medical research projects into IBD throughout the UK every year and we are delighted that this study, our largest medical grant to date, has yielded such clear and positive results.”

***Nature Genetics* Publication Study Authors – UK IBD Genetics Group Members:**

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The UK IBD Genetics Group has been researching the genetics of inflammatory bowel disease since 1992. Having published numerous papers in this specialist area, this new study represents the latest progress in work spanning over 16 years, and involving more than 8,000 IBD patients.

The group gratefully acknowledges the technical expertise of Dr Panos Deloukas's team at the Wellcome Trust Sanger Institute. The Wellcome Trust Case Control Consortium kindly assisted the study through design of the genotyping array and the supply of control genotype data, and NACC wishes to acknowledge the generous donation towards this project from the Rosetrees Trust.

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Editor's Notes

1. Background Information on NACC

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. 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. The 70 local NACC Groups across the UK enable members to meet other people who have these illnesses and share information and experiences.

The NACC Information Line (daytime) 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 in the first year, £10 thereafter. NACC is now offering free membership to 16-18 year olds.

2. Background on Ulcerative colitis

Who is affected?

There is no national database of people who have ulcerative colitis. The following estimates are taken from the Inflammatory Bowel Disease Guidelines published by the British Society of Gastroenterology in September 2004. Between **60,000 and 120,000 people** in the United Kingdom live with this life-long and potentially life-threatening condition. (Over 14,000 of these are members of NACC.)

Between **6,000 and 12,000 new cases** are diagnosed each year. The most common age for diagnosis is between 15 and 35. This can have a huge impact on a young person's life and may result in childhood and adolescence being severely disrupted. In some cases this can delay pubertal and physical growth. The number of new cases each year has not risen recently, but the incidence is not decreasing. Ulcerative colitis affects men and women equally.

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What are the symptoms?

Ulcerative colitis affects the colon (large intestine) or rectum and can cause a variety of distressing and sometimes embarrassing symptoms. Inflammation and ulcers develop on the inside lining of the colon resulting in pain, urgent and bloody diarrhoea, continual tiredness, weight loss and loss of appetite. A good analogy is to imagine the worst bout of gastric flu that you have ever suffered recurring unexpectedly for the rest of your life.

The condition varies as to how much of the colon is affected and the severity of the symptoms also fluctuates unpredictably over time. Patients are likely to experience flare-ups in between intervals of reduced symptoms or remission. Unfortunately, to date there is no cure for ulcerative colitis.

How is it treated?

Most patients will be treated with drugs, including steroids, to control or reduce the inflammation. In severe cases some people need surgery to remove the affected part of the colon, if their symptoms do not respond to treatment with drugs.

What causes ulcerative colitis?

The cause has not yet been fully identified although the new study findings indicate a genetic predisposition. Ulcerative colitis is not a form of cancer and is neither contagious nor infectious. An overview of research into IBD is available on www.nacc.org.uk/content/research

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