

# FOCUS ON RESEARCH

## AN INVESTIGATION OF THE GENETIC DETERMINANTS OF SUSCEPTIBILITY TO CROHN'S DISEASE IN THE SCOTTISH POPULATION

### Researchers

Prof Jack Satsangi, Dr Elaine Nimmo, Prof David Porteous, Prof Malcolm Dunlop, Dr David Wilson, Dr Niall Anderson

### Aim

Inflammatory bowel disease (IBD) is thought to be caused by a combination of environmental factors, such as diet and smoking, and mutations in genes.

Only one of the genes, NOD2, which contributes to Crohn's disease, had been identified when we started this work. Our aim was to find other disease genes by detecting which proteins interacted with NOD2. Once these proteins were identified, we could look for mutations in their genes and see if any of these mutations were more common in patients than in healthy control subjects. If so then this could indicate that these genes were involved in the development of Crohn's disease.

We looked at how much of these proteins is made in cells when they are growing normally and how much is made in the gut of people with IBD.

### Project Outline/Methodology

We put the NOD2 protein into yeast cells and tested which proteins from human gut cells it could bind to. If NOD2 binds to another protein then the yeast can grow in experimental conditions, if NOD2 does not bind to another protein then the yeast will not grow. Those yeast that grew were picked and the protein that interacted with NOD2 was identified. Although the initial experiments were done in yeast cells, after we identified the proteins we checked that the same interaction took place in human gut cells.

Once the proteins were identified, we looked for mutations present in the corresponding genes. We compared the frequency of these mutations in patients and in healthy controls, and statistical analysis using specially developed programs identified those genes which may cause susceptibility to IBD.

### Key Results

We have identified 16 genes which were not previously known to be involved in the development of IBD. We were able to confirm that they interacted with NOD2 in cells from the intestine and not just in the yeast cell in which the experiment was done.

In some of these genes, patients had mutations more frequently than healthy controls, indicating that defects in these may cause Crohn's disease. Some of the mutations in genes also may cause ulcerative colitis, a related disease.

As well as identifying new genes for IBD we were also able to identify common functions of some of the genes. Some genes controlled cell death, some controlled expression of other genes and some were involved in cell signalling, all important processes in normal gut tissue. We also identified some genes which were involved in control of gene expression, in a process whereby genes can be switched off or on in response to environmental signals such as smoking. This is a new finding in IBD and one which we will follow up in further research.

### Conclusions

New IBD susceptibility genes have been identified. Mutations in these genes may lead to Crohn's disease or the related condition ulcerative colitis.

### What does this study add to the field?

Recently several new IBD susceptibility genes have been identified by large studies in Britain, Europe and America. Using a different method we have identified genes not previously known to be involved in IBD susceptibility. These genes may be specifically involved in disease in the Scottish population, further studies will address this.

### Implications for Practice or Policy

Testing patients for these new genes may eventually allow better prediction of the course of their disease.

### Where to next?

Two genes are being followed up in a further CSO grant. Another gene is the subject of a PhD project and one of the pathways identified will be the focus of a new grant proposal.

### Further details from:

Prof Jack Satsangi,  
Gastrointestinal Unit,  
Molecular Medicine Centre,  
University of Edinburgh,  
Western General Hospital,  
Edinburgh, EH4 2XU.

