

Dr J C Mansfield – Royal Victoria Infirmary, Newcastle-upon-Tyne

Grant awarded: £38,000 (12 Months)

Application to NACC in respect of the “Newcastle Legacy”

Lay summary of the project:

Title: Histological Correlation with Genetic Variation in Crohn’s Disease

Applicants: Newcastle IBD Consortium – lead investigator Dr J C Mansfield, in collaboration with Professor C G Mathew and Professor A D Burt

For many years the cause of Crohn’s disease has been unknown and the best explanation has been that a number of factors combine to produce the disease. Smoking is well recognised as an important environmental factor and the increased incidence of Crohn’s within families, and especially in identical twins, is good evidence for a genetic contribution. In 1996 genetic studies identified a number of areas in the human genome where some of the susceptibility genes were likely to be located, but it was not until 2001 that individual genes and specific mutations within them were finally identified. This represents a major advance as further research, based on these genetic discoveries, will define new aspects of disease causation.

Not all patients share the same genetic factors. The first gene to be identified with a major impact into Crohn’s disease susceptibility was called NOD2, now re-named CARD15. A second susceptibility gene has been located on chromosome 5 (5q31). The interaction of recently discovered susceptibility genes is an area of active research.

The project aims to identify the relationship between the histology, that is the microscopic appearance, of Crohn’s disease and the genetic variations which predispose to the disease. It is possible that despite genetic differences the histological features will be indistinguishable. Alternatively, there may be subtle quantitative or qualitative differences which may allow the histological analysis of a resected specimen to predict the genetic mutations carried by that individual. This would represent an important re-classification of the disease, with implications for prediction of clinical course and responsiveness to various treatments.

The question this study seeks to answer can only be answered by a large and meticulous study. Crohn’s disease can affect any part of the intestine and histological features differ between locations. This variability is overcome in this study by focusing exclusively on ileal resections, and by including a large sample size of ileal resections from more than 250 patients.

The nature of this study is multidisciplinary and will involve collaboration between medical and surgical clinicians from a number of hospitals in North East England. Professor A D Burt and Dr J Henry will lead the team from the pathology department, and Professor C G Mathew, Professor of Medical and Molecular Genetics at Guy’s Hospital London, who is a recognised leader in the field of inflammatory bowel disease genetics will assist with the genotyping.

The search for correlations between the genetic and histologic variation in Crohn’s disease is timely, in view of the exciting new genetic discoveries, and achievable within the one year project duration.