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Grant awarded £41,455 (1 year)

Cambridge and eastern region IBD genetics

Of all the common diseases which have been subject to genetic analysis in the last 10 years studies of Crohn's disease (CD) and ulcerative Colitis (UC) have arguably progressed the furthest. One gene (called NOD2/CARD15) has been identified as playing a major part in Crohn's disease, and several other genes and chromosomal regions have been implicated. Much work remains to be done in clarifying the unconfirmed associations and pinpointing the remaining susceptibility genes. However, there is now the realistic prospect of a major leap forward in understanding the molecular basis of CD and UC and the heterogeneity within these conditions. Over the next 10 years this should enable the more rational use of existing treatments and the long term the development of new therapies.

To capitalise on the progress made in recent years and to take the developments to the next stage – identifying more genes including those relevant to specific sub-types of CD and UC, and ascertaining any genetically-determined variations in treatment response within these sub-groups – will require larger datasets than are currently available. It is clear from work already done that the genetic associations found are seen most strongly not with IBD overall or even with CD or UC alone but with sub-groups of CD and UC as defined by for example the location or pattern of intestinal inflammation. To prevent true associations being over-looked in genetic analysis there is thus a need to analyse large panels where even the disease subgroups (for example CD affecting the ileum only, or UC where inflammation extends to involve the whole colon – each comprising 20-35% of CD or UC overall) are sufficiently large to be independently statistically powerful.

It will also require the application, in due course, of low cost high throughput genotyping methods and appropriate levels of bioinformatic and statistical support. Cambridge is a world leading centre for the investigation of complex diseases like IBD and, having established collaborative agreements with several key players based locally, we are well positioned both to develop the necessary DNA / phenotype (=clinical pattern) databank and to carry out the large scale genotyping. However, with an IBD genetics program in its relative infancy we require a seed-corn grant to secure the opportunity and establish a major resource for IBD gene discovery and characterisation. With the current application we aim to initiate the genotyping program with a definitive re-evaluation of previously reported but unconfirmed 'hits' in this large dataset (i.e. genes showing modest association but where this has not been tested in independent panels, or where replication has been inconsistent – possibly due to heterogeneity and small sample sizes): given the size of our panel this will clarify whether these genes are involved in IBD or not.

The current application is for 12 months support from April 2004 for a part-time research nurse, a part-time research assistant with some consumables expenses, and funds to develop an Eastern region IBD database. The primary role of the nurse will be to expand the current dataset of 1200 patients (DNA and clinical data) recruited in Cambridge to a region-wide collection from 11 hospitals across Eastern England. The aim is to recruit a further 2000 'reagent grade' IBD-affected individuals which will represent IBD at the severe end of the spectrum. This tends to be less heterogeneous and have a stronger genetic contribution – for example IBD that has required surgery or developed in childhood. Much work has already been done in

securing ethics committee approval from MREC and LRECs and the region's consultants are enthusiastically supportive of the project but funds are now required for its implementation. The research assistant will process the DNA samples and perform genotyping for sub-phenotype specific re-evaluation of previously reported 'hits'. In due course this large resource will be used for a major fine mapping effort (identifying the IBD gene within) the IBD2 locus on chromosome 12, which is to be the subject of a future grant application.