

Lay Summary – Professor Christopher Mathew

There has been great progress in understanding the genetic contribution to inflammatory bowel disease (IBD) in the past 2-3 years. This has been made possible by the development of the “genome-wide scan” approach, in which the frequency of several hundred thousand variations of DNA sequence is compared in IBD patients and in healthy controls. Regions of the genome where differences in variant frequency occur indicate genes influencing susceptibility to IBD. This approach has led to the discovery of about 40 genes or regions that are telling us new things about how IBD develops. However, each of the new genes has a modest effect on disease risk, and together they explain only about 20% of the genetic contribution to Crohn’s disease. A popular theory about the “missing” genetics is that the genome scans are good at finding common genetic variants that increase disease risk in the general population but are not good at finding rare genetic variants that might produce a much greater increase in risk.

Whereas recent genetic research has, understandably, focused on IBD in the general population, this proposal is aimed at studying Crohn’s patients with a very strong family history of the disease. Our hypothesis is that families in which as many as 6-8 family members are affected with Crohn’s disease may carry a small number of genetic mutations which result in a large increase in disease risk. Very recently, a new class of DNA sequencing machines has been developed that sequence hundreds of thousands of small pieces of DNA simultaneously. Techniques have also been developed that allow scientists to select or “capture” a portion of the genome which they wish to sequence rather than sequencing all 3000 million bases of an individual’s DNA. During the past few months it has been shown that these methods can be used to capture and sequence almost all the coding regions (the parts of a gene that contain the code for making proteins) of nearly all the approximately 20,000 genes in the human genome and to screen them for mutations.

Our proposal is to use these very exciting technical developments to test our hypothesis by sequencing almost all of the coding regions of all genes in 20 individuals who are affected with Crohn’s disease and who are members of families with 4-8 affected family members. Using this comprehensive genome-wide approach, we hope to find gene mutations that are contributing to the very high risk of Crohn’s disease in these families. If we are successful, it may be possible in the future to identify unaffected family members who are at high risk of disease and to offer them regular screening. In the longer term such families could be offered participation in clinical trials of treatment and lifestyle options that may delay or even prevent the onset of disease. The discovery of new genes which increase disease risk will also reveal targets for the development of new therapies for IBD.