Methods The protein coding exons and promoters of 500 genes either located in GWAS hit regions, or that interact with genes in GWAS regions (as identified by protein network-based analysis) are being sequenced in 500 CD patients and 500 controls from the 1958 Birth Cohort. The 500 CD cases selected have early-onset disease and/or a strong family history of disease to enrich for mutations of higher penetrance. Sequencing is carried out in pools of 24 cases or controls, and the frequencies of rare variants are compared in the two groups. We are also screening affected relatives from IBD families with four or more affected members for more highly penetrant mutations by sequencing the entire set of known protein coding exons for all ~20 000 genes in the human genome.

Results Thus far, DNA pool size has been optimised using known individual genotypes at 150 target loci. Sequencing the first 140 CD patients has detected 1047 novel variants in candidate genes that occur in multiple individuals, including potential functional variants in *IRF8* and *JAK2*. Whole-exome sequencing in three families has identified multiple genes containing novel potential disease-causing mutations that are shared between affected relatives, including 5 nonsense mutations, 3 amino acid deletions and 25 splice-site mutations.

Conclusion Second generation sequencing is a powerful tool to identify novel disease-causing DNA sequence variants in patients and families with IBD. Careful analysis of the many variants detected and follow-up studies will be required to validate their role in pathogenesis. If confirmed, rare disease-causing variants are likely to have larger effects on disease risk and therefore be more useful in predicting disease risk in individuals with a family history of IBD as well as help indentify new CD susceptibility genes.

Competing interests None.

Keywords CD, genetics, IBD, UC.

OC-124

SCREENING FOR RARE PATHOGENIC SEQUENCE VARIANTS IN INFLAMMATORY BOWEL DISEASE

doi:10.1136/gut.2011.239301.124

N J Prescott,[1*] B Lehne,[1] K Harrison,[1] J Knight,[1] M Weale,[1] M Simpson,[1] P Green,[1] C Lewis,[1] A Hart,[2] J Sanderson,[3] J Mansfield,[4] T Schlitt,[1] C Mathew[1] *[1]Medical and Molecular Genetics, Kings College London, London, UK; [2]Inflammatory Bowel Disease Unit, St Mark's Hospital Academic Institute, Harrow, UK; [3]Department of Gastroenterology, Guy's and St Thomas' NHS Foundation Trust, London, UK; [4]Department of Gastroenterology and Hepatology, University of Newcastle upon Tyne, Newcastle, UK*

Introduction Genome-wide association studies (GWAS) have delivered significant discoveries of common genetic variants that increase susceptibility to IBD. However, a substantial portion of the genetic heritability remains unaccounted for. A possible source for this is disease causing variants that are too rare to be detected by GWAS, but may have stronger genetic effects.

We have adopted two strategies to identify rare disease causing variants in IBD utilising new sequencing technologies and our large London/Newcastle IBD biobank of over 4000 patient samples and 108 extended families. We aim to identify rare functional variants in IBD in order to: (1) help to explain some of the hidden heritability of IBD and (2) develop biomarkers for prediction of disease risk in relatives.

Gut: first published as 10.1136/gut.2011.239301.124 on 13 March 2011. Downloaded from http://gut.bmj.com/ on April 19, 2024 by guest. Protected by copyright.