also has an intermediate response to second line therapy. Both scores are useful tools to aid clinical decision making but do not replace timely multidisciplinary care for these patients.

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Disclosure of Interest None Declared.

OC-003 GENOME-WIDE EPIGENETIC ANALYSIS IN CHILDHOOD-ONSET CROHN'S DISEASE IMPLICATES MIR21

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Introduction DNA methylation influences transcriptional activity and marks sites of active transcription. Technological developments allow the rapid assessment of methylation state at 450,000 sites across the genome. The aim of this study was to identify genes with a possible role in Crohn's disease pathogenesis, and candidate genes for methylation based diagnostic biomarkers.

Methods Using the Illumina 450k platform we analysed genome-wide DNA methylation in symptomatic children who underwent diagnostic colonoscopy, half of whom were diagnosed with CD and half had no pathology. Replication was performed in children with established CD vs. symptomatic non-disease controls. Further targeted replication by pyrosequencing was performed in adults with CD vs. healthy controls, with qPCR and microarray data to analyse expression.

Results Meta-analysis of the combined paediatric datasets (n = 66) identified 165 individual CpGs with epigenome-wide significance (Bonferroni correction) and 138 differentially methylated regions (DMR). Methylation changes were significantly enriched ($p < 0.0001$) in proximity to loci implicated by genome-wide association studies (GWAS).

The strongest result by each approach was MicroRNA 21, within the autophagy gene VMP1 ($p = 1.2 \times 10^{-14}$), 48 kb from GWAS SNP rs1292053. In adults with CD we replicated MIR21 hypomethylation ($p = 6.6 \times 10^{-5}$, n = 172), and showed increased expression in blood ($p < 0.005$, n = 66). Intestinal expression increased with inflammation in CD ($p = 1.4 \times 10^{-6}$, n = 99) but not controls (n = 73).

Linear discriminant analysis of methylation in the paediatric discovery cohort accurately predicted disease state in the paediatric replication cohort (94% sensitivity, 100% specificity) based on methylation at two CpG sites.

Conclusion MIR21 emerges as a target for further investigation based on methylation and expression, further strengthened by other positive findings – notably dysregulation in dysplasia and colorectal cancer in IBD, an established role in T-cell differentiation, and protection from DSS-induced fatal colitis by MIR21 knockout. These data demonstrate a novel approach for identifying biological variations associated with germ-line variants identified by GWAS, and demonstrate translational potential for biomarker development and therapeutic target discovery.

Disclosure of Interest None Declared.

OC-004 THIOPURINE INDUCED PANCREATITIS IN INFLAMMATORY BOWEL DISEASE: CLINICAL FEATURES AND GENETIC DETERMINANTS

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Introduction Pancreatitis is a rare, but important complication of thiopurine treatment. The aims of this project were to a) characterise the clinical features of thiopurine-induced pancreatitis and b) identify clinical useful genetic markers that might predict development of this serious adverse drug reaction.

Methods Patients were identified and recruited from 172 sites (128 UK). Inclusion criteria included a) onset of acute severe abdominal pain within three months of starting thiopurine treatment b) ≥ two-fold rise in amylase or lipase c) medical opinion implicating thiopurine therapy and drug withdrawal.

Results We recruited 303 patients. Following adjudication 48 cases classified as definite (recurrent pancreatitis on rechallenge) and 195 cases classified as probable (temporal relationship and no other cause for pancreatitis) were taken forward for analyses. 46% of patients were smokers at the time of development of pancreatitis. Patients were treated with a thiopurine for a median of 19 days (95% CI: 17 – 21) before development of pancreatitis. Most cases were mild, with only 5 cases developing single organ dysfunction. 70% of patients were hospitalised with a median length of stay of 4 days (95% CI: 3.2 – 4.8). Neither age ($p = 0.08$), drug dose ($p = 0.11$), BMI ($p = 0.73$) nor smoking ($p = 0.59$) predicted length of hospital stay or severity of pancreatitis in multivariate analysis. Using a control cohort of 4,109 Crohn's disease and ulcerative colitis cases we conducted a genome wide association study with these 239 patients. A significant variant was identified in the Class II MHC region (Odds ratio 3.03, $p = 2.63 \times 10–20$). Dedicated HLA and 1000 genome project imputation refined the association within the MHC (R squared > 0.8 and MAF > 0.01). This association was robust to principle component correction. TPMT genotype was not associated with pancreatitis development ($p = 0.99$). A second cohort of 100 cases and 500 independent disease controls treated with thiopurines but screened for pancreatitis has been generated to confirm the association.

Conclusion We describe the largest clinical characterisation of thiopurine-induced pancreatitis to date and use this cohort to undertake a pharmacogenetics genome wide association study that has

identified a significant association within the Class II MHC region.

Disclosure of Interest None Declared.

OC-005 NOVEL PATHWAY-CENTRIC ANALYSIS REVEALS VARIANTS ASSOCIATED WITH TOXICITY AND RESPONSE TO THIOPURINES IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Introduction Thiopurines remain the first line immunosuppressants recommended in the management of inflammatory bowel disease (IBD). Unfortunately, 30–40% of patients prescribed these agents develop adverse drug reactions or fail to derive therapeutic benefit. Candidate gene studies have identified loci that explain some of these treatment failures; however a substantial fraction of the genetic contribution remains undefined. Using whole thiopurine pathway analysis the aim of this study was to identify novel loci associated with toxicity and response to azathioprine (AZA)/mercaptopurine (MP) in patients with IBD.

Methods Genomic DNA was extracted from EDTA blood samples of 472 well-characterised IBD patients treated with AZA/MP. We examined exome array data using the Illumina HumanExome Beadchip and restricted the analysis to variants associated with the thiopurine pathway as defined by the KEGG database (100 genes, 639 single nucleotide polymorphisms). Using a case-control design we firstly tested for genetic associations between patients with (n = 154) and without (n = 258) adverse drug reactions, and secondly for polymorphisms differentiating patients with (n = 188) and without (n = 141) response to thiopurines after 12 months of treatment. One year intervention-free clinical response was defined by 3 investigators (PB, PI, JS).

Results Following adjustment for principal components, the minor alleles at *ADK* rs946185 (p = 0.0078; OR 1.675), *SLC28A1* rs2242046 (p = 0.0168; OR 1.600) and *ABCA1* rs4149268 (p = 0.033; OR 1.487) were associated with the development of drug toxicity, whereas the minor alleles at *ABCB5* rs2301641 (p = 0.0170; OR 0.608), *ABCC4* rs4148549 (p = 0.027; OR 0.652) and *AOX1* rs55754655 (p = 0.038; OR 0.549) protected against it. The minor allele at *RRM2* rs1130609 ($p = 3.80 \times 10^{-5}$; OR 0.461), which codes a subunit of ribonucleotide reductase involved in the conversion of thioguanine nucleotide to deoxy-thioguanine nucleotide, and a higher normalised dose of AZA/MP were associated with protection from non-response. Conversely, the minor allele at *ABCA1* rs2230808 (p = 0.008; OR 2.585) and Crohn's disease (p = <0.001; OR 5.007) were associated with non-response to treatment at 12 months.

Conclusion High-throughput sequencing using exome array technology has revealed new loci, other than thiopurine-*S*-methyltransferase, explaining toxicity and response to thiopurines. Validation of these markers in separate cohorts will allow the development of biomarker panels to predict outcomes prior to the start of treatment.

Disclosure of Interest None Declared.

OC-006 SAFETY AND EFFICACY OF LOW DOSE AZATHIOPRINE AND ALLOPURINOL CO-THERAPY: A LARGE SINGLE CENTRE EXPERIENCE

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Introduction The effectiveness of full dose azathioprine (FDA) for inflammatory bowel disease (IBD) has been questioned in recent scientific literature. A popular strategy to improve its outcomes recommends the use of low dose azathioprine with allopurinol co-therapy (LDAA) for patients profiled as "hypermethylators" (30% of non-responders). The aim of this study was to determine the safety and efficacy of LDAA without using thiopurine metabolite (TM) profiling.

Methods Records of IBD patients treated with LDAA were retrospectively analysed.

Patients who had poor response and/or side-effects to FDA were offered LDAA by all Consultants whilst a single IBD physician also offered LDAA to thiopurine-naïve patients. Azathioprine dose was reduced to 25% of the thiopurine methyl transferase (TPMT) adjusted dose (0.5 mg/kg for wild type and 0.25 mg/kg for heterozygotes) followed by conventional haematological monitoring. Non-adherence was assessed by TM measurements. Full response (FR) was defined as steroid free remission (Harvey Bradshaw index ≤3, Truelove-Witts normal) for greater than 3 months after a 3 month induction period for LDAA.

Results Of 300 LDAA patients, adequate data was available for 295 cases. Group 1 (G1) were treated 1st line (n,105) and Group 2 (G2) were switched from FDA to LDAA (n,190). Overall, for both groups, there were 207 (70%) full responders (FR), 20 partial responders (PR) and 68 non-responders (NR). Full response rate was 78% in G1 and 66% in G2. The commonest indication for switching to LDAA was non-response to FDA (n,118).

Analysis of haematological indices revealed significant changes (p < 0.05) in erythrocyte sedimentation rate, white cell count and platelet count after therapy induction.

Myelotoxicity occurred in 5 patients (all NR, WCC >2 and <3.5) and 12 patients had asymptomatic hepatotoxicity (ALT range: 100–700) which resolved by increasing allopurinol to 200 mg in 9 patients (all FR).

Time on treatment: 208 patients took LDAA for more than twelve months with a median length of therapy of 24 months.

Conclusion Appropriately dosed LDAA therapy delivers a therapeutically effective dose of azathioprine without the

Abstract OC-006 Table 1

	Clinical response (n)			
Indication	**FR**	**PR**	**NR**	**Total**
AZA/6MP Naive (LDAA without FDA exposure)	82	7	16	105
Switched from FDA to LDAA	125	13	52	190
Poor response	81	10	27	
GI intolerance	16	n/a	11	
Hepatotoxicity	7	1	3	
Myelotoxicity	13	2	1	
"Flu-like" symptoms	3	n/a	1	
Other	5	n/a	9	