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THE RISK OF AZATHIOPRINE-INDUCED PANCREATITIS DEPENDS ON GENETIC VARIANTS IN THE HLA GENE REGION

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Introduction Acute pancreatitis occurs in around 2% of inflammatory bowel disease patients exposed to azathioprine or 6-mercaptopurine and is an important limiting toxicity of these thiopurine antimetabolites. Factors determining the risk of pancreatitis are unknown: the risk is not related to dose, though it may occur more commonly in individuals with Crohn's disease than in other disorders. Recently genome-wide association studies (GWASs) identified common genetic variants conferring substantial effects on risk for other idiosyncratic drug reactions (*SCOL1B* variants in simvastatin-induced myopathy and *HLA-B5701* in flucloxacillin-induced liver injury). We hypothesised that the risk of pancreatitis was similarly determined by unknown common genetic variants of large effect size and that such variants might enable stratification of individuals for pancreatitis risk prior to commencing thiopurine therapy.

Methods We performed a genome-wide association study (GWAS, Stage 1) of thiopurine-induced pancreatitis, genotyping 55 UK and Dutch cases and comparing these with 5782 previously genotyped population controls. We genotyped cases using Illumina 670-Quad custom and 1M-Duo SNP arrays. In total, 535 753 SNPs passed quality controls in all Stage 1 samples with a further 384 513 SNPs available for 40 of the cases and 4936 of the controls from the UK. 43 SNPs from 32 independent genomic loci showing evidence of association with thiopurine-induced pancreatitis ($P_{\text{GWAS}} < 10^{-4}$) were included in the design of an autoimmune disease genotyping array (Illumina ImmunoChip) to facilitate follow-up genotyping. Follow-up (Stage 2) genotyping was performed in 13 New Zealand cases and 47 thiopurine-exposed IBD controls and 12 Spanish cases and 352 population controls.

Results Meta-analysis of all cases and controls from Stage 1 and 2, stratified by country, for 43 SNPs identified in the GWAS phase and a further 28 082 SNPs from autoimmune disease candidate regions present on the Illumina ImmunoChip (including 17 631 SNPs in the 20 Mb broad HLA region on chromosome 6) was performed. rs2647087, mapping 28 Kb from the closest gene *HLA-DQA2*, showed the strongest association ($p = 3.89 \times 10^{-6}$) with thiopurine-induced pancreatitis in our study (OR for risk allele = 2.69).

Conclusion Genetic association in the HLA gene region suggests an immune-mediated pathogenesis of thiopurine-induced pancreatitis possibly involving HLA-restricted T cell activation. Identification of the causal HLA alleles is the next priority and may enable clinically useful stratification of individuals for pancreatitis risk prior to starting thiopurine treatment.

Competing interests None.

Keywords azathioprine, genetics, human leucocyte antigen, mercaptopurine, pancreatitis.