Methods: We investigated 77 SNPs with moderate to strong association in five previously published genome-wide association studies of CD or UC, respectively. Our replication study comprised 447 Lithuanian and Latvian UC patients and 1,154 healthy controls. Single-marker case-control, genotype-phenotype association, SNP-SNP epistasis analyses and meta-analysis were performed.

Results: After correcting for multiple testing, we confirmed associations at 21q21.1 (rs1736135, \( P = 8.01 \times 10^{-6} \)), 6q21 (rs7746082, \( P = 6.61 \times 10^{-5} \)), JAK2 (rs10758669, \( P = 8.08 \times 10^{-4} \)), RNF186 (rs3806308, \( P = 2.40 \times 10^{-6} \)), and ORMDL3 (rs2872507, \( P = 1.24 \times 10^{-6} \)). Pooling our data with the original UC dataset substantiated four of the associations and revealed additional six loci to be associated with UC at genome-wide level (\( P < 5 \times 10^{-8} \)). No association with any disease subphenotype was found. SNP-SNP interaction analysis showed significant epistasis between SNPs in the PTPN22 (rs2476601) and C10orf31 (rs3764147) genes and increased risk for UC (\( P = 1.64 \times 10^{-6} \), OR = 2.44). In silico prediction of the interactive network of these genes further validated a possible interaction.

Conclusions: We confirmed the association of five loci (21q21.1, 6q21, JAK2, RNF186, and ORMDL3) with UC in the Lithuanian-Latvian population. SNP-SNP interaction analysis showed that the combination of SNPs in the PTPN22 (rs2476601) and C10orf31 (rs3764147) genes increase the risk for UC.

P686
Thiopurine methyltransferase polymorphism in Lithuanian inflammatory bowel disease patients
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Background: Inter-individual drug metabolism variability can influence treatment outcome. Genetic polymorphisms in thiopurine methyltransferase gene (TPMT) are known to correlate with the toxicity of azathioprine (AZA). Patients with low TPMT activity (poor metabolizers) are at high risk of developing severe haematopoietic toxicity. TPMT genetic polymorphisms were not investigated in Lithuanian IBD patients previously. The aim of this study was to investigate frequencies of TPMT polymorphisms and their association with adverse events during AZA therapy in the Lithuanian IBD patients.

Methods: The genotyping of TPMT*2 (rs1800462), TPMT*3B (rs1800460) and TPMT*3C (rs142345) was performed using allele-specific PCR or restriction fragment length polymorphism analysis methods. In total 460 consecutive IBD patients, referred to two university hospitals in Lithuania, were genotyped for TPMT*2 (G238C), TPMT*3A (G460A and A719G), TPMT*3B (G460A) and TPMT*3C (A719G) mutations. The use of AZA and its’ side effect was assessed retrospectively according to the data of hospital medical records during six year period before genetic testing.

Results: Among 460 IBD patients the frequency for the TPMT*1 (wild-type), TPMT*3A and TPMT*3B alleles were 96.6%, 3.0% and 0.3%, respectively. The frequency of the TPMT genotypes was 93.48% for TPMT*1/*1, 5.87% for TPMT*1/3A, 0.43% for TPMT*1/3B, and 0.22% for TPMT*3A/*3B. No significant differences between experimental and expected genotypic frequencies were observed by Hardy-Weinberg equilibrium. Prescription of AZA provoked neutropenia, which required adjustment of the dose or discontinuation of the drug, in 15.4% of cases bearing heterozygous (TPMT*1/3A or TPMT*1/3B) genotype, whereas patients with wild-type (TPMT*1/*1) genotype experienced this side effect only in 2% of cases (p=0.05). Only one patient had high-risk compound heterozygous genotype (TPMT*3A/*3B) and alarming experience of severe neutropenia after prescription of AZA.

Conclusions: TPMT*3A is the most prevalent variant allele in the Lithuanian IBD patients. The estimated frequency of variant alleles in the study group is similar to that observed in the Caucasian populations of Northern and Eastern Europe. Our work supports the strong evidence that patients with TPMT genotype TPMT*3A/*3B are at high risk of severe myelosuppression at standard doses of AZA. TPMT heterozygotes also experienced risk of neutropenia in comparison to controls.

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Genetic associations with high-grade dysplasia and colorectal cancer in patients with colonic inflammatory bowel disease: preliminary results from ImmunoChip using a targeted analytic approach
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Background: Colon IBD is a significant risk factor for colorectal cancer (CRC) and high-grade dysplasia (HGD). Extensive involvement of the colon, the co-existence of primary sclerosing cholangitis (PSC), disease activity, family history of CRC and disease duration have been shown to increase the risk for CRC. However, no specific genetic association has been repeatedly shown to be associated with CRC in patients with colonic IBD. We aimed to identify genetic associations with CRC/HGD in patients with colonic IBD using data from the ImmunoChip in a large multi-national cohort of patients with colonic IBD.

Methods: Members of the International IBD Genetic Consortium (IIBDGC) were asked to identify patients with colonic IBD who developed CRC or HGD, verified by pathology. Demographic and clinical data were also collected. For each HGD/CRC case 1-2 controls were matched (by IBD subtype, disease duration, endoscopic extent (Montreal Classification), ethnicity, co-existence of PSC and gender). Phenotypic variables were compared between CRC/HGD cases and controls using chi square for categorical variables and student’s t-test for continuous variables. Preliminary analysis of genotypes generated from available iChip data was undertaken using logistic regression in PLINK looking specifically at recently-reported IBD associations, PSC associations and SNPs in CRC-associated genes. p-value < 5×10^{-4} was considered significant.

Results: Overall, 585 colonic IBD cases (390 UC, 171 CD, 19 IBDU) were reported, 274 had either HGD or CRC and 311 were matched controls. There were 58% males, 95% Caucasian, and 12% current smokers. The mean age at diagnosis was 33. Disease duration to CRC/HGD diagnosis was significantly longer than length of F/U in controls (230 months vs. 180 months, respectively, p=0.005). There was no significant difference in proportions of patients with extensive disease between the groups. However, PSC was more common in cases vs. controls.