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Background: Several large genome wide association studies have identified an increasing number of IBD risk loci with currently more than 240 established loci and generated robust data on disease association. However, knowledge remains limited on distinctive associations to specific clinical characteristics. The Swiss IBD Cohort Study (SIBDCS) represents a large prospective cohort study with clinically and phenotypically sound data collection since 2006 including genotyping. In this study, we aimed to determine individual associations of known risk loci with clinical features of patients in the SIBDCS, as well as their combined effect on clinical outcomes.

Methods: Based on 158 analysed SNPs, we investigated the numerical distribution of risk alleles and determined an individual SNP risk score (defined as percentage of risk alleles; i.e. number of risk alleles divided by twice the number of given SNPs multiplied with 100). We then performed linear regression modelling to investigate, whether relevant clinical disease characteristics associate with this SNP risk score. Further, for each given clinical outcome, a model was run with all SNPs as potential predictors, and the number of significant associations per SNP counted.

Results: In a total of 2304 genotyped patients, we observed a median number of risk alleles of 167, 168 and 167 for IBD overall, CD and UC/IC, respectively with a narrow inter quartile range [11 (q25 = 162, q75 = 173) for IBD and CD; 12 (q25 = 161, q75 = 173) for UC/IC]. A higher SNP risk score was significantly associated with any complications (defined as a composite of any or more of colorectal cancer, colon dysplasia, intestinal lymphoma, osteopenia/-porosis, anaemia, deep venous thrombosis, pulmonary embolism, nephro- or cholelithiasis, malabsorption syndrome, massive haemorrhage, perforation/peritonitis, pouchitis), stenosis in CD patients; pancolitis, conversion to CD, female sex in UC patients; higher clinical disease activity in both CD & UC.

Regarding individual SNPs, we identified substantial differences in terms of the frequency of associations to disease-related outcomes with up to 11 for rs4899554 in CD and 7 for rs9557195 in UC, respectively.

Conclusion: In our large population of IBD patients there is high per patient frequency of hetero- and homozygous SNP risk alleles. The association of higher SNP risk score with several disease-related outcomes indicates a potential interplay of per patient given SNP risk alleles.

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A predictive molecular classification developed in UC patients with active disease is observed consistently in a heterogeneous group of IBD patients

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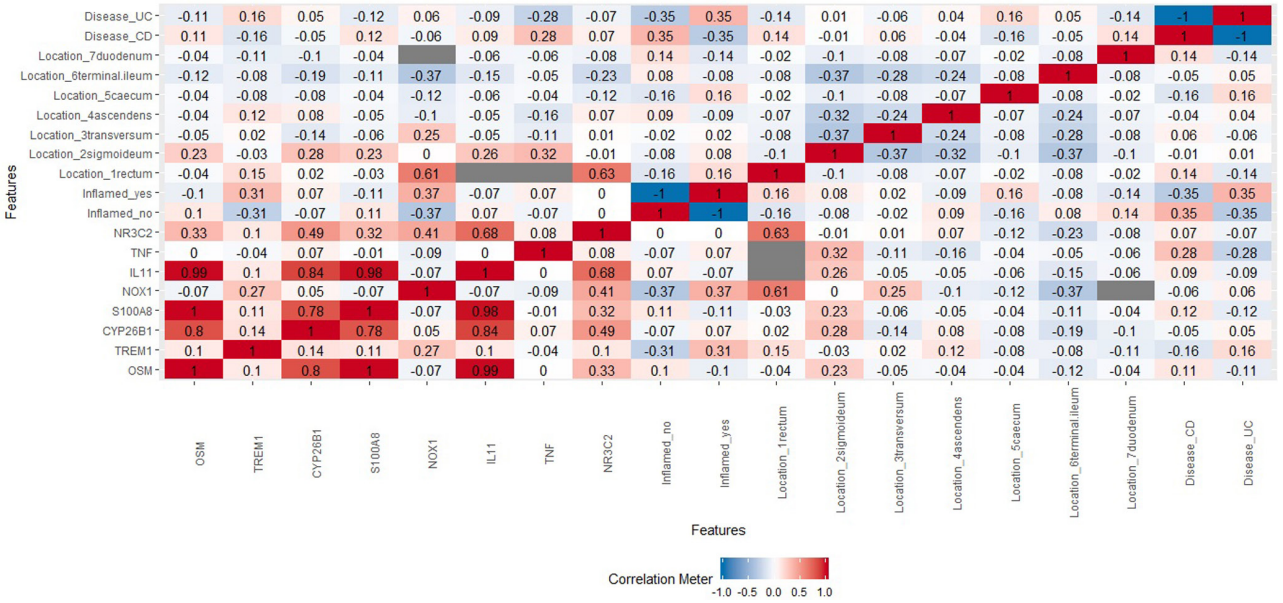
Background: We have previously identified an unsupervised molecular classification of ulcerative colitis (UC) into two groups, UC1 and UC2, predictive of response to biologic therapy[1]. In that study, gene expression data in inflamed colonic biopsies from several published UC cohorts were used. UC1 is characterised by, for example, high expression of Cytochrome P450 26B1 (CYP26B1), calprotectin (S100A8) and interleukin 11 (IL11) and poor response to infliximab, which is also predicted by high expression of oncostatin M (OSM)[2]. In the current study the consistency of this classification



Abstract P826 Figure 1. Data normalised to housekeeping Beta-2 microglobulin (B2M). Similar data was generated with housekeeping Hypoxanthine Phosphoribosyltransferase (HPRT), data not shown.

was investigated in a heterogeneous group of inflammatory bowel disease (IBD) patients. Also, we sought to validate a quantitative polymerase chain reaction (qPCR) primer set as an alternative, more convenient methodology instead of microarray.

Methods: PCR primers for 7 differentially expressed genes that distinguished UC1 from UC2 in our microarray study were validated. OSM was also included. Separate gut biopsy samples (n = 44) from 15 patients, (8 Crohn's disease, 7 UC), from different locations and at different time points, were analysed with qPCR.

Results: A heatmap of Pearson correlation coefficients (r) between gene expression levels and clinical factors for the pooled data was generated, Figure 1. Strong correlations, defined as $0.7 \leq r \leq 1.0$, were found between OSM, CYP26B1, S100A8 and IL-11 (pairwise correlations were statistically significant, $p < 0.00001$). Similar inter-gene correlations were also observed within individual samples, (data not shown). Gene expression levels were not associated with inflammation, Figure 1.

Conclusion: These data demonstrate that the group genes we have previously identified as predictive of response to biologic therapy in UC, (CYP26B1, S100A8 and IL-11) plus OSM are also concordantly up-regulated in biopsy material from heterogeneous patients. Thus not only patients with active UC, but also other forms of IBD may be sub-grouped according to this gene expression pattern. The capacity of this gene expression profile to predict therapeutic response should therefore be tested in a broader range of IBD patients. The fact that the concordance of the up-regulation of these genes was independent of inflammation per se, supports the clinical significance of this molecular clustering. Establishment of qPCR-based characterisation into UC1 and UC2 presents a more convenient methodology for clinical stratification.

References

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The clinical phenotype of collagenous colitis is associated with T-cell-related genetic variants

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Background: Collagenous colitis (CC) is a common cause of chronic diarrhoea and highly associated with immune-mediated diseases. The aetiology of CC may involve a dysregulated immune response in genetically predisposed individuals. Our preliminary data identified ancestral HLA haplotype 8.1 and non-HLA CC risk loci being associated with CC. We here carried out the first genotype/clinical phenotype association study in a large cohort of CC patients.

Methods: This study combined Immunochip data from 300 patients with centrally read histologically confirmed CC with retrospectively collected clinical data in a quarternary care centre. We tested 21 SNPs previously associated with CC (Roda et al. submitted) for their genetic association with selected phenotypic variables (histology, autoimmune diseases, relapse rate, concomitant medications, number of bowel movements at diagnosis, sex and response to therapy). We performed univariable linear, logistic and Poisson regression analyses for associations with the outcome variables.

Results: 300 CC patients [median age 63 (IQR: 54–63); 80% female] were included after quality control. The genetic variants associated with clinical phenotypes can be found in Table 1. We identified a link of several genes involved in T cell function with CC phenotypes. IL2A was associated with risk of additional autoimmune disorders reinforcing the possible role of T cells in both diseases. RUNX3 involved in Th17 cells and TGF-beta pathways was a risk factor for IEL infiltrates. Notably, we identified two protective factors: one near C5orf30, previously implicated in rheumatoid arthritis and collagen-induced arthritis, was linked with a reduced rate of flares; ZNF365, involved in uric acid excretion and associated with ileal Crohn's disease, was found protective in relation to collagen band thickness. When assessing non-genetic variables, number of bowel movements correlated with collagen band thickness ($p < 0.01$); concomitant use of sertraline was protective for relapse rates ($p = 0.021$), and current smoking ($p = 0.022$) was linked with relapse rates.

Conclusion: We found a significant association of T-cell-related genes and CC clinical phenotypes. Additionally, our study identified current smoking and increased collagen band thickness as risk factors for disease severity.

Table 1.

Chr	Rs	*p*-value	Gene	Function	Univariable
2	rs35230759	0.012	ZNF804A	uric acid excretion	Autoimmunity
3	rs671046	0.034	IL2A	immune tolerance	
1	rs11249221	0.025	RUNX3	Th17 cell/TGF-beta	IELs infiltrate
2	rs1444543	0.018	CTNNA2	-	
5	rs2600825	0.026	SLCO4C1	-	
2	rs35230759	<0.001	ZNF804A	-	Relapse rates
5	rs115530159	0.026	C5orf30	rheumatoid arthritis and collagen-induced arthritis	
6	rs3129716	0.036	HLA	Immune responses	
10	rs871985	0.017	ZNF365	-	Collagen band thickness