Genotypic and Phenotypic Correlations In Very Early Onset Inflammatory Bowel Disease

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Objectives:
Inflammatory Bowel Disease (IBD) affects 1 in 250 Canadians. Very Early Onset IBD, or VEO-IBD, is defined as patients diagnosed under age 6. The pathogenesis of VEO-IBD is expected to be greatly influenced by inherited factors due to: (a) the young age of onset, (b) increased prevalence of familial disease, and (c) a phenotype characterized by increased severity and extension of disease that is significantly different than adult onset IBD. Yet, recently published Genome Wide Association Studies (GWAS) have not focused on VEO-IBD patients. VEO-IBD is thought to have a very different genetic risk as shown by two recent examples of work carried out in our laboratory including a novel variant in the IL10RA gene and by a variant in the Chronic Granulomatous Disease (CGD) pathway. Our aim is to investigate the genotypic differences of selected Single Nucleotide Polymorphisms (SNPs) in the largest VEO-IBD cohort to date.

Method:
A large number of SNPs (769) were genotyped from Caucasian patients with IBD from SickKids Hospital and Mount Sinai Hospital. Patients were phenotyped according to the Paris Modification of the Montreal Classification. DNA samples collected from whole blood were genotyped using the Illumina GoldenGate Custom SNP assay on the Illumina BeadStation500G (San Diego, CA). Using two definitions for age of diagnosis, less than 6 years of age or greater than 6 years of age, logistic regression models were applied using an additive genetic model. Hardy-Weinberg Equilibrium (HWE) was tested by using Pearson's chi-square test for each SNP, and all analysis was done using SAS.

Results:
When comparing patients diagnosed under 6 with colonic involvement against patients with colonic involvement diagnosed over 6, regardless of diagnosis, 27 SNPs were found to have significance ($p<0.05$). Many of these SNP were not shown in recent GWAS. The functions of the genes associated with these SNPs include: extracellular signaling to the matrix, mesodermal cell immunoglobulin superfamily production, intracellular tubule synthesis, keratinocyte proliferation, autophagy, glucocorticoid receptor, NADPH oxidase/CGD pathways, the TNF alpha receptor, and calcineurin regulation. When directly examining the SNPs investigated in adult and older children GWAS, only one

gene was found to be associated in Crohn's Disease, while none were found to be significant in Ulcerative Colitis.

Conclusion:
VEO-IBD, defined as patients diagnosed under 6 years of age, appears to be a distinct subpopulation of patients with Inflammatory Bowel Disease with a distinct genetic risk profile. These findings may lead to pathway discovery in the pathogenesis of IBD leading to novel therapies as we have previously shown for patients with VEO-IBD.