Novel Genetic Susceptibility Candidates in Granulomatous and Non-Granulomatous Pediatric Crohn’s Disease

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Background

Non-steroidal granulomas are a hallmark histopathological finding of Crohn’s disease (CD), but found only in ~50% cases. Previous studies have suggested that the presence of granulomas may indicate a more aggressive CD phenotype associated with a complicated clinical course, including stricturing and/or penetrating disease, need for biologic therapy, and need for surgery.

As such, identification of genetic associations of granulomatous CD (GCD) may help elucidate disease pathogenesis, which in turn may optimize treatments and guide novel therapeutics to combat CD complications. Genome-wide association studies have identified more than 20 loci associated with inflammatory bowel disease. However, there is relatively sparse genetic knowledge about CD subtypes, especially GCD.

Objectives

The aim of this study was to determine the extent of genetic variation between pediatric CD patients with and without a pathologic sub-mucosal granuloma detected at the time of diagnosis.

Methods

Whole-exome next-generation sequencing (WES) was performed on peripheral blood derived DNA from 36 patients with GCD and non-GCD (NGCD) groups.

PLINK analysis was used to identify single nucleotide polymorphisms (SNPs) that were significantly (p<0.01) enriched between GCD and NGCD groups.

PLINK-identified SNP allele frequencies were compared to publicly available, large population-based genomic data in gnomAD (p<0.05). Additionally, subgroup HLA haplotypes were compared to those of a large database from the Houston area population.

The potential deleteriousness of single nucleotide variants was determined by the CADD scoring tool (CADD>20 indicates the disruptive nature of a SNP to be among the top 1% most deleterious changes in the human genome).

Table 1. Baseline characteristics and clinical outcomes by histopathologic group. Number of subjects for whom data were present for each variable is shown in parentheses, with the numerator representing the number of subjects meeting that subgroup. The denominator is the total number of subjects with available data in that subgroup. Mean values are shown for continuous variables.

Table 2. Top candidate SNPs (a) shared by PLINK-based GCD and NGCD analysis, and also enriched in both cohorts compared to gnomAD; (b) shared in GCD group only between PLINK and gnomAD; and (c) shared in NGCD group only between PLINK and gnomAD dbSNP = Single Nucleotide Polymorphism Database

Table 3. HLA haplotype frequency in CD patient sample and local control population. Frequency of HLA haplotypes compared amongst the CD group and the granuloma-based subsets, and a large control population with HLA data from local database. HLA-DQA1*05:01 and HLA-DQB1*03:01 haplotypes were enriched in GCD compared to NGCD and a non-CD population.

Results

WES was completed for 17 patients with GCD and 19 with NGCD. There were no significant differences in baseline clinical characteristics, treatments, nor 1-year outcomes between the groups.

Overlap analyses between PLINK- and gnomAD-generated SNPs revealed significant enrichment in those associated with HLA-DQA1, LIPA, KAZ, FCOR, HLA-A, and HLA-B shared by GCD and NGCD groups.

GCD-specific (top candidates linked with HLA-B and MUC4) and NGCD-specific (top candidate linked with ACOT7) SNPs were sparse.

H LA-DQA1*05:01 and HLA-DQB1*03:01 haplotypes were more frequently present in the GCD group as compared to NGCD group and the general population.

Conclusions

This is the first WES-based genetic variation analysis between treatment-naïve pediatric CD patients purely separated by the presence of a sub-mucosal epithelioid granuloma. GCD-associated genetic variation was subtle, but HLA-DQA1 and HLA-DQB1 haplotypes may be important in predicting granulomatous inflammation in pediatric CD patients.

Our findings will require subsequent confirmation in larger, but similarly scrutinized cohorts of patients.

References and Acknowledgements

7. Owen M, Kelleher D, Green J, et al. Identification of novel Crohn's disease susceptibility loci using a network of the Crohn's and Colitis Foundation. This work was supported by the Wellcome Trust/Investigator Award (no. 099153/Z/12/Z) and the Gastroenteritis Collaborative Research Network (GACRN), National Institute for Health Research, England.

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