Variants in Nicotinamide Adenine Dinucleotide Phosphate Oxidase Complex Components Determine Susceptibility to Very Early Onset Inflammatory Bowel Disease

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BACKGROUND & AIMS: The colitis observed in patients with very early onset inflammatory bowel disease (VEOIBD; defined as onset of disease at younger than 6 years of age) often resembles that of chronic granulomatous disease (CGD) in extent and features of colonic inflammation observed by endoscopy and histology. CGD is a severe immunodeficiency caused by defects in the genes that encode components of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex. We investigated whether variants in genes that encode NADPH oxidase components affect susceptibility to VEOIBD using independent approaches. METHODS: We performed targeted exome sequencing of genes that encode components of NADPH oxidases (cytochrome b light chain and encodes p22 phox protein; cytochrome b-245 or NADPH oxidase 2, and encodes Nox2 or gp91 phox; neutrophil cytosol factor 2 and encodes p67 phox protein; NCF4, neutrophil cytosol factor 4 and encodes p40 phox protein; and Ras-related C3 botulinum toxin substrate 1 and 2) in 122 patients with VEOIBD diagnosed at The Hospital for Sick Children, University of Toronto, from 1994 through 2012. Gene variants were validated in an independent International Early Onset Pediatric IBD Cohort Study cohort of patients with VEOIBD. In a second approach, we examined Tag single nucleotide polymorphisms in a subset of patients with VEOIBD in which the NOX2 NADPH oxidase gene in CGD patients mostly result in the complete loss of phagocytes’ ability to mount the sufficient respiratory burst required to kill invading pathogens, leading to a severe immunodeficiency with

CONCLUSIONS: We found that VEOIBD patients carry heterozygous functional hypomorphic variants in components of the NOX2 NADPH oxidase complex. These do not cause overt immunodeficiency, but instead determine susceptibility to VEOIBD. Specific approaches might be developed to treat individual patients based on their genetic variant.

Keywords: VEOIBD; CGD; Genetics; Phagocytes.