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Inflammatory Bowel Disease—Environmental Modification and Genetic Determinants

Subra Kugathasan, MD[a,*],
Devendra Amre, MBBS, PhD[b]

[a]*Department of Pediatrics, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA*
[b]*Department of Pediatrics, University of Montreal, Research Center, Saint-Justine Hospital, 3175, Cote-Ste-Catherine, Montreal, PQ H3T 1C5, Canada*

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel disease (IBD), are increasing in incidence among children and negatively impact their growth, education, and social well-being. The currently proposed genetic model for IBD phenotypes emphasizes complex interactions between environmental factors and promoting and modifying genetic determinants, resulting in the clinical expression of the disease in the gastrointestinal (GI) tract of genetically predisposed individuals. Complex disease such as IBD is controlled by multiple risk factors that interact and evolve together. A major breakthrough in understanding the pathogenesis of CD occurred with the identification of the first IBD susceptibility gene, *CARD15*. More recently, many more single nucleotide polymorphisms (SNPs) in at least eight susceptibility loci from several chromosomes have been associated with IBD. The most consistent environmental factors believed to be associated in the etiology of CD are smoking, perinatal events, childhood infections, microbial agents, diet, and domestic hygiene. Complex diseases such as IBD cannot be understood in terms of a simple disease model; instead, they inherently and intrinsically are characterized by complex networks of interacting genetic and environmental causal agents that are embedded in pathways connecting the genome with disease-related phenotypes. Clarification of these genes and environmental interactions will require well-designed clinical studies in carefully phenotyped

* Corresponding author.
E-mail address: skuga@mcw.edu (S. Kugathasan).

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population-based cohorts to identify the lifetime gene–gene and gene–environmental interactions that determine the susceptibility and eventual outcome of IBD (Fig. 1). Studies such as International HapMap Project and the promise of whole genome association scans likely will lead to major advances during the next decade.

Introduction: interaction of environmental and genetics in pediatric inflammatory bowel disease

Is there an environmental cause for pediatric IBD when there is a strong link between genetics and IBD? This is perhaps the key question that has been dominating research in the pathogenesis of IBD for the past 20 years. Numerous reviews on the topic emphasize the importance of this research and highlight the complexity of defining the specific risk factors [1–3]. Various lines of evidence suggest that the environment could play an important role. The most convincing evidence is based on observations from twin studies. Monozygotic twins (MZ) show concordance rates ranging from 36% to 58% for CD and 8% to 16% for UC. Dizygotic twins (DZ) show average concordance rates of 4% for CD and UC [4]. Although the higher concordance observed among MZ twins compared with DZ twins suggests contributions from genetic risk factors, the high concordance is confounded by shared environmental risk factors and shared genetic risk factors. In addition, the approximately 50% lack of concordance for CD and nearly 80% lack of concordance for UC among monozygotic twins strongly suggests that a large proportion of CD and UC cases are linked to environmental exposures. In general, about 30% to 40% of adults who have IBD have a family history of IBD, whereas about 20% to 30% of children who have IBD have a family member affected with IBD [4]. These proportions

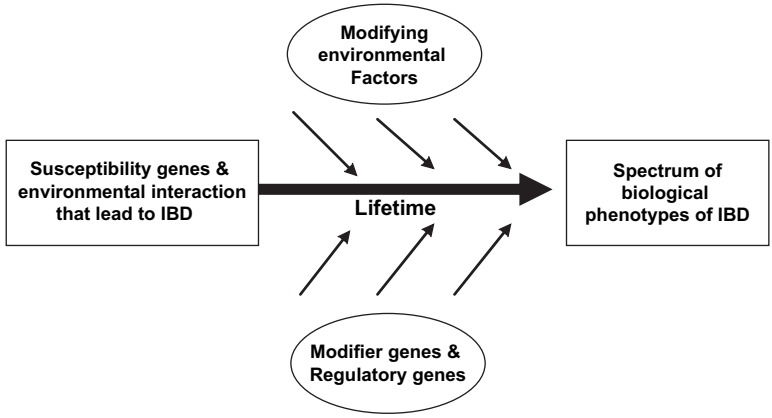

Fig. 1. Lifetime interactions between genetic and environmental interactions continue to play roles in IBD susceptibility and different phenotypes.