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Inflammatory Bowel Disease

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INTRODUCTION

Inflammatory bowel disease (IBD) comprises two disorders: ulcerative colitis and Crohn's disease. The diagnosis of IBD is based on review of clinical, endoscopic, radiologic, and histologic data. Despite the chronic nature of these two diseases and the fact that their causes have not yet been defined, new and emerging targeted anti-inflammatory treatments hold great promise in helping to reduce morbidity and improve the quality of life of individuals with IBD.

DEFINITION AND EPIDEMIOLOGY

Ulcerative colitis (UC) is characterized by inflammatory changes that involve the colonic mucosa in a continuous superficial fashion, typically starting in the rectum and extending proximally. Depending on the extent of the disease, UC can be divided into proctitis (rectum only), proctosigmoiditis (rectum and sigmoid), left-sided colitis (extending to the splenic flexure), and pancolitis (inflammation extends proximal to the splenic flexure). This classification is significant for both prognosis and therapy. Unlike UC, Crohn's disease can involve any segment of the gastrointestinal tract from the mouth to the anus, often in a discontinuous fashion. It is characterized by transmural inflammation, which results in complications such as abscesses, fistulas, and strictures.

In the United States, about 1.4 million individuals have IBD, and the overall annual incidence is about 20 new cases per 100,000 persons years. Although the incidence of UC has remained stable for several decades, the incidence of Crohn's disease has been increasing; it now seems to have plateaued at levels approximately equivalent to those of UC. The prevalence of IBD in the United States is between 249 to 319 per 100,000 persons. A bimodal age at presentation exists, with an initial peak between the second and fourth decades of life and another peak in the sixth decade. The sexes are equally affected.

The incidence and prevalence of IBD reflects the interplay of complex genetic and environmental factors that contribute to these disorders. For example, both diseases are more common in northern climates and among whites, particularly populations with Northern European ancestry such as North Americans, South Africans, and Australians. Individuals of Ashkenazi Jewish descent also have a twofold to eightfold increased risk for these disorders compared with non-Jews. Although incidence rates of IBD are lowest among Hispanics and Asians, IBD can occur in any ethnic or racial group from anywhere in the world. The cause of IBD remains unknown, but it is believed that a combination of genetic, immunologic, infectious, and environmental factors plays a role. In addition, state-of-the-art research points toward a relationship between the human microbiome and dysfunction of the immune system in patients with IBD.

Approximately 5% to 20% of patients with IBD have a first-degree relative with the disease, and first-degree relatives of IBD patients have about a 10- to 15-fold increased risk for developing IBD, predominantly with the same disease as the proband. A positive family history is more frequently observed in patients with Crohn's disease compared with UC, suggesting that genetic factors contribute more significantly in the etiology of Crohn's disease.

Through advances in genome-wide association studies, several susceptibility loci on multiple chromosomes have been linked to IBD, supporting a polygenic cause for these disorders. Polymorphisms in the *NOD2* gene (previously known as *CARD15*), located on chromosome 16, were the first definitive genetic risk factors identified for Crohn's disease. Homozygous mutations of the *NOD2* gene are associated with a greater than 20-fold increase in susceptibility for Crohn's disease. Defects in the NOD2 protein appear to result in abnormal intestinal immune responses to bacterial cell wall components. These gene mutations are estimated to account for 15% to 25% of the cases of Crohn's disease and are linked predominantly to fibrostenotic terminal ileal disease. In addition to *NOD2*, other genes associated with Crohn's disease have been identified that regulate autophagy; they include *ATG16L1*, *IRGM*, and *LRRK*. Genes that regulate the interleukin-17 (IL-17) and IL-23 receptor pathways have been found to increase the risk for both UC and Crohn's disease; they include *IL23R*, *IL12B*, *STAT3*, *JAK2*, and *TYK2*. *IL27* and *TNFSF15* have been implicated only in Crohn's disease. Genes regulating epithelial barrier function have also been discovered for IBD, including members of the *OCTN/IBD5* susceptibility locus (*SLC22A4* and *SLC22A5*), *ECM1*, *CDH1*, *HNF4A*, *LAMB1*, and *GNA12*.

Currently, it is believed that IBD results from an inappropriate, overactive mucosal immune response to commensal intestinal bacteria or the microbiome in genetically susceptible individuals. Profound alterations in mucosal immunology have been demonstrated in patients with IBD. In the normal immunologic state of the intestine, recently activated lymphoid tissue is abundant within the mucosal compartment. This state has been described as controlled or *physiologic* inflammation, and it likely develops in response to constant encounters with antigenic substances (derived from host microbial flora or dietary and environmental sources) that have crossed the epithelial barrier from the luminal environment. Indeed, one of the main functions of the intestinal immune system is to discriminate noxious or harmful substances