GENETIC CONSIDERATIONS

The genetic underpinning of IBD is known from its occurrence in the context of several genetic syndromes and the development of severe, refractory IBD in early life in the setting of single gene defects that affect the immune system (Table 351-2). In addition, IBD has a familial origin in at least 10% of afflicted individuals (Fig. 351-2). In the majority of patients, IBD is considered to be a polygenic disorder that gives rise to multiple clinical subgroups within UC and CD. A variety of genetic approaches including candidate gene studies, linkage analysis, and genome-wide association studies (GWASs) that focus on the identification of disease-associated, single-nucleotide polymorphisms (SNPs) within the human genome and, more recently, whole-genome sequencing have elucidated many of the genetic factors that affect risk for these diseases. GWASs have, to date, identified 163 genetic loci with 100 of these loci observed to be associated with both disease phenotypes (Table 351-3). The remainder are specific for either CD (30 loci) or UC (20 loci). These genetic similarities account for the overlapping immunopathogenesis and consequently epidemiologic observations of both diseases in the same families and similarities in response to therapies. Because the specific causal variants for each identified gene or locus are largely unknown, it is not clear whether the similarities in the genetic risk factors associated with CD and UC that are observed are shared at structural or functional levels. The risk conferred by each identified gene or locus is unequal and generally small, such that only ~20% of the genetic variance is considered to be explained by the current genetic information. Further, many of the genetic risk factors identified are also observed to be associated with risk for other immune-mediated diseases, suggesting that related immunogenetic pathways are involved in the pathogenesis of multiple different disorders accounting for the common responsiveness to similar types of biologic therapies (e.g., anti–tumor necrosis factor therapies) and possibly the simultaneous occurrence of these disorders. The diseases and the genetic risk factors that are shared with IBD include rheumatoid arthritis (*TNFAIP3*), psoriasis (*IL23R*, *IL12B*), ankylosing spondylitis (*IL23R*), type 1 diabetes mellitus (*IL10*, *PTPN2*), asthma (*ORMDL3*), and systemic lupus erythematosus (*TNFAIP3*, *IL10*) among others.

The genetic factors defined to date that are recognized to mediate risk for IBD have highlighted the importance of several common mechanisms of disease (Table 351-3). These include the following: those genes that are associated with fundamental cell biologic processes such as endoplasmic reticulum (ER) and metabolic stress (e.g., *XBP1*, *ORMDL3*, *OCTN*), which serve to regulate the secretory activity of cells involved in responses to the commensal microbiota such as Paneth and goblet cells and the manner in which intestinal cells respond to the metabolic products of bacteria; those associated with innate immunity and autophagy (e.g., *NOD2*, *ATG16L1*, *IRGM, JAK2, STAT3*) that function in innate immune cells (both parenchymal and hematopoietic) to respond to and effectively clear bacteria, mycobacteria, and viruses; those that are associated with the regulation of adaptive immunity (e.g., *IL23R, IL12B, IL10, PTPN2*), which regulate the balance between inflammatory and anti-inflammatory (regulatory) cytokines; and, finally, those that are involved in the development and resolution of inflammation (e.g., *MST1, CCR6, TNFAIP3, PTGER4*) and ultimately leukocyte recruitment and inflammatory mediator production. Some of these loci are associated with specific subtypes of disease such as the association between *NOD2* polymorphisms and fibrostenosing CD or *ATG16L1* and fistulizing disease, especially within the ileum. However, the clinical utility of these genetic risk factors for the diagnosis or determination of prognosis and therapeutic responses remains to be defined.

TABLE 351-2 PRIMARY GENETIC DISORDERS ASSOCIATED WITH IBD

Name	Genetic Association	Phenotype
Turner's syndrome	Loss of part or all of X chromosome	Associated with UC and colonic CD
Hermansky-Pudlak	Autosomal recessive chromosome 10q23	Granulomatous colitis, oculocutaneous albinism, platelet dysfunction, pulmonary fibrosis
Wiskott-Aldrich syndrome (WAS)	X-linked recessive disorder, loss of WAS protein function	Colitis, immunodeficiency, severely dysfunctional platelets, and thrombocytopenia
Glycogen storage disease	Deficiency of the glucose-6-phosphate transport protein type B1	Granulomatous colitis, presents in infancy with hypoglycemia, growth failure, hepatomegaly, and neutropenia
Immune dysregulation polyendocrinopathy, enteropathy X-linked (IPEX)	Loss of FoxP3 transcription factor and T regulatory cell function	UC-like autoimmune enteropathy, with endocrinopathy (neonatal type 1 diabetes or thyroiditis), dermatitis
Early-onset IBD	Deficient IL-10 and IL-10 receptor function	Severe, refractory IBD in early life

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; IL, interleukin; UC, ulcerative colitis.

COMMENSAL MICROBIOTA AND IBD

The endogenous commensal microbiota within the intestines plays a central role in the pathogenesis of IBD. Humans are born sterile and acquire their commensal microbiota initially from the mother during egress through the birth canal and subsequently from environmental sources. A stable configuration of up to 1000 species of bacteria that achieves a biomass of approximately 10^{12} colony-forming units per gram of feces is achieved by 3 years of age, which likely persists into adult life, with each individual human possessing a unique combination of species. In addition, the intestines contain other microbial life forms including archae, viruses, and protists. The microbiota is thus considered as a critical and sustaining component of the organism. The establishment and maintenance of the intestinal microbiota composition and function is under the control of host (e.g., immune and epithelial responses), environmental (e.g., diet and antibiotics), and likely genetic (e.g., *NOD2*) factors (Fig. 351-1). In turn, the microbiota, through its structural components and metabolic activity, has major influences on the epithelial and immune function of the host, which, through epigenetic effects, may have durable consequences. During early life when the commensal microbiota is being established, these microbial effects on the host may be particularly important in determining later life risk for IBD. Specific components of the microbiota can promote or protect from disease. The commensal microbiota in patients with both UC and CD is demonstrably different from nonafflicted individuals, a state of dysbiosis, suggesting the presence of microorganisms that drive disease (e.g., Proteobacteria such as enteroinvasive and adherent *Escherichia coli*) and to which the immune response is directed and/or the loss of microorganisms that hinder inflammation (e.g., Firmicutes such as *Faecalibacterium prausnitzii*). Many of the changes in the commensal microbiota occur as a consequence of the inflammation. In addition, agents that alter the intestinal microbiota such as metronidazole, ciprofloxacin, and elemental diets, may improve CD. CD may also respond to fecal diversion, demonstrating the ability of luminal contents to exacerbate disease.

DEFECTIVE IMMUNE REGULATION IN IBD

The mucosal immune system is normally unreactive to luminal contents due to oral (mucosal) tolerance. When soluble antigens are administered orally rather than subcutaneously or intramuscularly, antigen-specific nonresponsiveness is induced. Multiple mechanisms are involved in the induction of oral tolerance and include deletion or anergy of antigen-reactive T cells or induction of CD4+ T cells that suppress gut inflammation (e.g., T regulatory cells expressing the FoxP3 transcription factor) that secrete anti-inflammatory cytokines such as interleukin (IL) 10, IL-35, and transforming growth factor β (TGF-β). Oral tolerance may be responsible for the lack of immune responsiveness to dietary antigens and the commensal microbiota