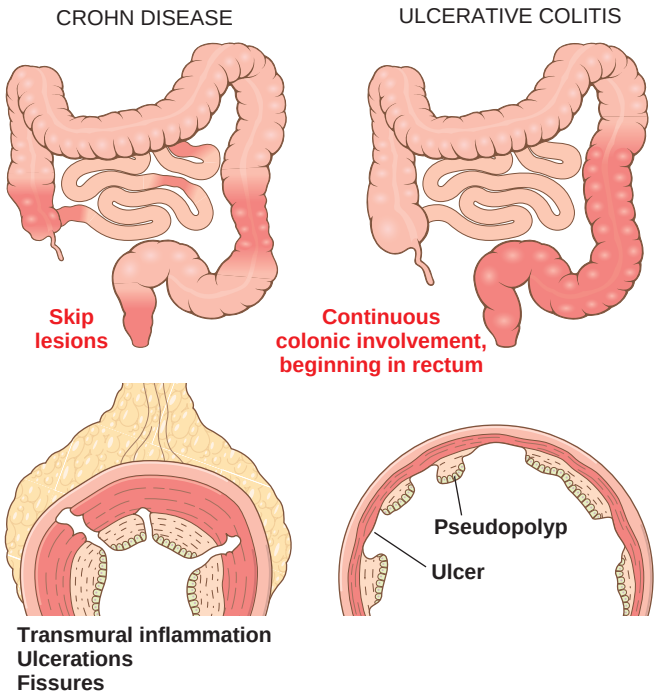

Figure 17-32 Distribution of lesions in inflammatory bowel disease. The distinction between Crohn disease and ulcerative colitis is primarily based on morphology.

gut microbiome composition. Apparently this results in inadequate development of regulatory processes that limit mucosal immune responses. This in turn allows some mucosa-associated microbial organisms to trigger persistent and chronic inflammation in susceptible hosts. Although many details to support this hypothesis are lacking, the observation that helminth infections, which are endemic in regions where IBD incidence is low, can prevent IBD development in animal models and even reduce disease in some patients, lends support to this idea.

Pathogenesis. Although precise causes are not yet defined **most investigators believe that IBD results from the combined effects of alterations in host interactions with intestinal microbiota, intestinal epithelial dysfunction, aberrant mucosal immune responses, and altered composition of the gut microbiome.** This view is supported by epidemiologic, genetic, and clinical studies as well as data from laboratory models of IBD (Fig. 17-33).

- **Genetics.** There is compelling evidence that genetic factors contribute to IBD. Risk of disease is increased when there is an affected family member and, in Crohn disease, the concordance rate for monozygotic twins approaches 50%. Genetic factors may also contribute to phenotypic expression of the disease, because twins affected by Crohn disease tend to present within a few years of each other and develop disease in similar regions of the GI tract. The concordance of monozygotic twins for ulcerative colitis is only about 15%, suggesting that genetic factors are less dominant than in Crohn disease. Concordance for dizygotic twins is less than 10% for both forms of IBD.

Population based genome wide association studies have identified over 160 IBD-associated genes. Most of these are shared between Crohn disease and ulcerative colitis, as well as other complex immune-mediated diseases. Interestingly, several IBD associated genes overlap with genes involved in responses to mycobacteria, including *Mycobacterium tuberculosis* and *Mycobacterium leprae*. This supports the idea that host-microbial interactions are critical to the pathogenesis of IBD and may explain some overlap in the histopathology of Crohn disease and mycobacterial infection. One of genes most strongly associated with Crohn disease is *NOD2* (nucleotide oligomerization binding domain 2), which encodes an intracellular protein that binds to bacterial peptidoglycans and activates signaling events, including the NF-κB pathway. Despite the increase in risk attributable to *NOD2* polymorphisms, it should be remembered that fewer than 10% of individuals carrying risk associated *NOD2* variants develop disease. Thus, as is the case with all IBD-associated genes, any one gene confers only a small increase in the risk of developing these diseases.

In addition to *NOD2*, two Crohn disease–related genes of particular interest are *ATG16L1* (autophagy-related 16-like), and *IRGM* (immunity-related GTPase M). Both are part of the autophagy pathways that are critical for cellular responses to intracellular bacteria; *ATG16L1* may also regulate epithelial homeostasis.

NOD2, ATG16L1, and *IRGM* are expressed in multiple cell types, and their precise roles in the pathogenesis of Crohn disease have yet to be defined. However, all

Table 17-9 Features That Differ between Crohn Disease and Ulcerative Colitis

Feature	Crohn Disease	Ulcerative Colitis
Macroscopic		
Bowel region	Ileum ± colon	Colon only
Distribution	Skip lesions	Diffuse
Stricture	Yes	Rare
Wall appearance	Thick	Thin
Microscopic		
Inflammation	Transmural	Limited to mucosa
Pseudopolyps	Moderate	Marked
Ulcers	Deep, knife-like	Superficial, broad-based
Lymphoid reaction	Marked	Moderate
Fibrosis	Marked	Mild to none
Serositis	Marked	Mild to none
Granulomas	Yes (~35%)	No
Fistulae/sinuses	Yes	No
Clinical		
Perianal fistula	Yes (in colonic disease)	No
Fat/vitamin malabsorption	Yes	No
Malignant potential	With colonic involvement	Yes
Recurrence after surgery	Common	No
Toxic megacolon	No	Yes

All features may not be present in a single case.