Chapter 1
A Primer on IBD: Phenotypes, Diagnosis, Treatment, and Clinical Challenges

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Abstract The inflammatory bowel diseases are chronic, relapsing disorders characterized by inflammation and ulceration in part of or the entire gastrointestinal tract. IBD affects people worldwide but is most prevalent in northern Europe and North America. Etiologically, the current consensus is that the intestinal inflammation is largely caused by an aberrant and excessive immune response to environmental triggers (intestinal bacterial infection, medications, or other agents) in genetically susceptible individuals. IBD exerts a heavy toll on patients' quality of life and imposes a considerable economic burden on the healthcare system. Some forms of IBD lead to severe complications such as formation of fistulae and intestinal strictures, for which management options are very limited. Moreover, many IBD patients develop drug tolerance and toxic responses, which severely compromise the disease control. Over the past decade, modern genetics has led to a new era of IBD research. Up to 163 genes have been identified to be associated with IBD. A growing number of new diagnostic tools and therapeutic agents resulted from the IBD genetics have already been implemented in the management of IBD; however, unmet needs persist. By utilizing new experimental tools such as powerful next-generation DNA sequencing machines along with accessing large cohorts of IBD patients, genetic studies will lead to a better understanding of the causes of individual IBD, more diagnostic tools to aid in evaluating the disease course and responsiveness to treatment, more novel targets to be identified for new drug development, and ultimately the most desirable strategies for IBD prevention.

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Introduction

The inflammatory bowel diseases (IBD) are idiopathic, chronic, relapsing disorders of the small and/or large bowel, characterized pathologically by inflammation and ulceration of the mucosal and submucosal layers or mucosal layer only. The principal categories of IBD are ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis (IC) [1].

The incidence of both CD and UC has particular geographic patterns, with the highest prevalence in Western developed countries, including Europe and North America, and intermediate prevalence in countries such as Japan, Korea, Hong Kong, South Africa, and Israel. In less developed countries, the prevalence is low. The overall prevalences of UC and CD in North America are similar. It is estimated that the prevalence of UC is approximately 37–246 cases per 100,000 persons and for CD it is 26–199 cases per 100,000 persons [2]. In general, there are no gender differences in terms of the frequency of UC and CD. The onset of UC and CD occurs at any age, but the peak incidence is more likely to be around late adolescence and early adulthood. In female CD patients there is also a second peak during the sixth and seventh decades of life. Multiple studies suggest there is a tendency in early onset CD for upper GI involvement, including gastric, duodenal, and the proximal small bowel, whereas in late onset CD, colonic inflammation is more common [2].

The etiology of IBD remains unknown. The current consensus is that intestinal inflammation is largely caused by an aberrant and excessive immune response to environmental triggers (intestinal bacterial infection, medications, or other agents) in genetically susceptible individuals [3, 4]. IBD, particularly CD and to a lesser extent UC, tends to cluster in families, suggesting there is a strong genetic component to the pathology [5, 6]. Interestingly, environmental factors appear also to play an important role, as demonstrated by the fact that both CD and UC appeared to be more frequent in northern parts of the United States than in southern and in urban more than rural parts [7, 8]. Intestinal microflora may also be a contributing factor. In geographic areas of low IBD prevalence such as Asia, people tend to have the highest frequency of indigenous intestinal infections, including helminthic infestations. Recent studies have found that intestinal bacteria are altered in IBD [9]. The role of the microbiota in IBD is an interesting area worthy of intensive investigation. Other environmental factors have also been found to have an impact on IBD. For example, smoking increases the risk of CD, but intriguingly it lowers the risk of UC [10, 11]. Clinical and endoscopic recurrence in CD and disease activity after surgery were affected by active smoking, and transdermal nicotine patches have been shown to improve symptoms in UC patients [12]. The use of nonsteroidal anti-inflammatory drugs has been shown to increase disease flares in IBD patients [13]. In general, the interface between gut mucosa, luminal bacteria, environmental factors, and immune cells may determine the onset and course of disease in susceptible individuals.

Clinical Manifestations and Phenotypes of IBD

In UC, the symptoms tend to begin gradually, typically presenting with rectal bleeding, diarrhea, and abdominal cramping pain. The Mayo score system (ranging from 0 to 12) is commonly used to assess UC activity in clinical trials and is based on stool pattern, rectal bleeding, endoscopic findings, and overall assessment by a physician, with higher scores correlating with greater severity [14]. In contrast to UC, the clinical manifestations of CD are variable and sometimes insidious, featuring diarrhea and abdominal cramping pain associated with iron deficiency anemia, fatigue, weight loss, and fever [15]. Rectal bleeding is less severe in CD, except in CD affecting the colon only, also referred to as Crohn's colitis. Fistula and abscess formation preferentially occur in CD due to transmural bowel inflammation. Patients with CD affecting the upper GI tract are younger at onset, with clinical presentations of abdominal pain and cramps, nausea and vomiting, and general malaise and fatigue [16]. It can present with aphthous ulcers in the mouth and difficulty or pain in swallowing. CD is also characterized by malabsorption of bile acids, iron, calcium, water-soluble vitamins such as folic acid and vitamin B12, fat-soluble vitamins—such as vitamins A, D, E, and K—and trace minerals such as zinc, resulting in diarrhea, gallstones, iron deficiency anemia, vitamin B12 deficiency, vitamin D deficiency, hypocalcemia, and vague abdominal pain. In Crohn's ileitis, excessive oxalate is absorbed in the colon, leading to calcium oxalate kidney stone formation. Perianal complications include perirectal abscesses, anorectal fistulas, and anal fissures, all of which are accompanied by perianal pain and discomfort. Both CD and UC can have extraintestinal manifestations, and about 50–60 % of patients suffer from joint pain due to arthropathies and sacroiliitis [17], osteopenia or osteoporosis [18], skin lesions (such as erythema nodosum and pyoderma gangrenosum) [19], uveitis and iritis [20], which are often correlated with disease activity [21]. Mild abnormality in liver function tests may be present, and primary sclerosing cholangitis (PSC) occurs more frequently in UC than CD. PSC is known to be associated with an increased risk for colorectal cancer [1, 22, 23].

UC is characterized by diffuse mucosal inflammation restricted to the colon but varying in extent from the rectum to the cecum. Based on the affected anatomy, UC can be clinically divided into distal and more extensive forms. Distal UC is defined as colitis with features of inflammation confined to the rectum (proctitis) or rectum and sigmoid colon (proctosigmoiditis). The more extensive forms of UC include left-sided UC with inflammation extending up to the splenic flexure and pancolitis, with inflammation that extends proximal to the splenic flexure, affecting the entire colon. The Montreal consensus classified UC based on anatomic extent into three categories, ulcerative proctitis (E1), distal or left-sided UC (E2), and extensive UC involving the colon proximal to splenic flexure (E3) [1]. The severity of UC was also classified into mild, moderate, and severe based on daily frequency of bowel movements including bloody stool and the presence of systemic toxicity. In addition, age of onset is considered to be one of the important factors for classification of UC subtypes [1]. In contrast, CD can affect any part of the gastrointestinal (GI)

tract from mouth to anus, with a characteristic feature of patchy and transmural inflammation. It may be further defined based on the location of inflammation (terminal ileal (L1), colonic (L2), ileocolic (L3), isolated upper GI (L4)) or the pattern of clinical complications (non-stricturing and non-penetrating (B1), structuring (B2), penetrating (B3), or perianal disease (p)) [1, 24–27]. Both L4 and p can coexist with L1–L3 and B1–B3 disease. Additionally, by considering age at diagnosis as a risk factor for developing severe complications, CD is also classified into A1 (<16 years old), A2 (17–40 years old), and A3 (>40 years old) [1]. Although the majority of CD patients (approximately 80 %) have small bowel involvement, 20 % have inflammation limited to the colon only [24, 28]. In contrast to the invariable involvement of the rectum in patients with UC, the rectum is spared in 50 % of CD patients [24]. Further subdivision of CD is as follows: about 50 % of patients have ileocolitis, which refers to involvement of both the ileum and colon, and 14–30 % have disease only involving the distal ileum (ileitis). About 37 % of patients with Crohn's colitis have perianal inflammation, such as perianal CD and perianal fistula formation [29]. Less than 5 % of patients have involvement of the upper GI tract, including the mouth, esophagus, gastroduodenal area, and the proximal small bowel [24, 28]. It is worth noting that about 5–10 % of IBD patients are unclassifiable, referred to as IC, and they have pathological features of both UC and CD. IC occurs more often in children (12.7 %) than in adults (6.0 %) [30–33].

Other chronic, nonspecific colitides include microscopic colitis (either collagenous or lymphocytic), in which the colon appears normal, but lymphocyte infiltrations are present on biopsy [34]; diversion colitis, which occurs in the part of the colon that is excluded from the fecal stream [35]; diverticular colitis, which is limited to portions of the colon with diverticula present [36]; and pouchitis, which occurs in nearly half of patients with UC who have undergone ileal pouch-anal anastomosis [32].

Diagnosis and Management of UC and CD

The diagnosis of IBD can be made by clinical history and physical examination in combination with radiologic, endoscopic, and histologic findings [21]. Endoscopy and histology are considered the gold standard for diagnosing IBD, monitoring the effectiveness of treatment and relapses of disease, and IBD-related cancer surveillance [37]. The severity of UC can be determined by colonoscopy as mild (duller, redder mucosa with a "granular" or fine sandpaper-like texture, and decreased vascular pattern), moderate (gross pitting mucosa with friability), and severe (diffuse ulceration with mucopurulent exudate and spontaneous hemorrhage) (see Fig. 1.1a–c) [1]. The histology of UC includes crypt distortion, crypt atrophy, distorted or branched glands, and neutrophilic microabscesses inside the lumen of crypts. UC also displays diffuse lamina propria inflammation, caused by increased acute and chronic inflammatory cells. Basal plasmacytosis and basal lymphoid hyperplasia are apparently unique to UC [37–39].

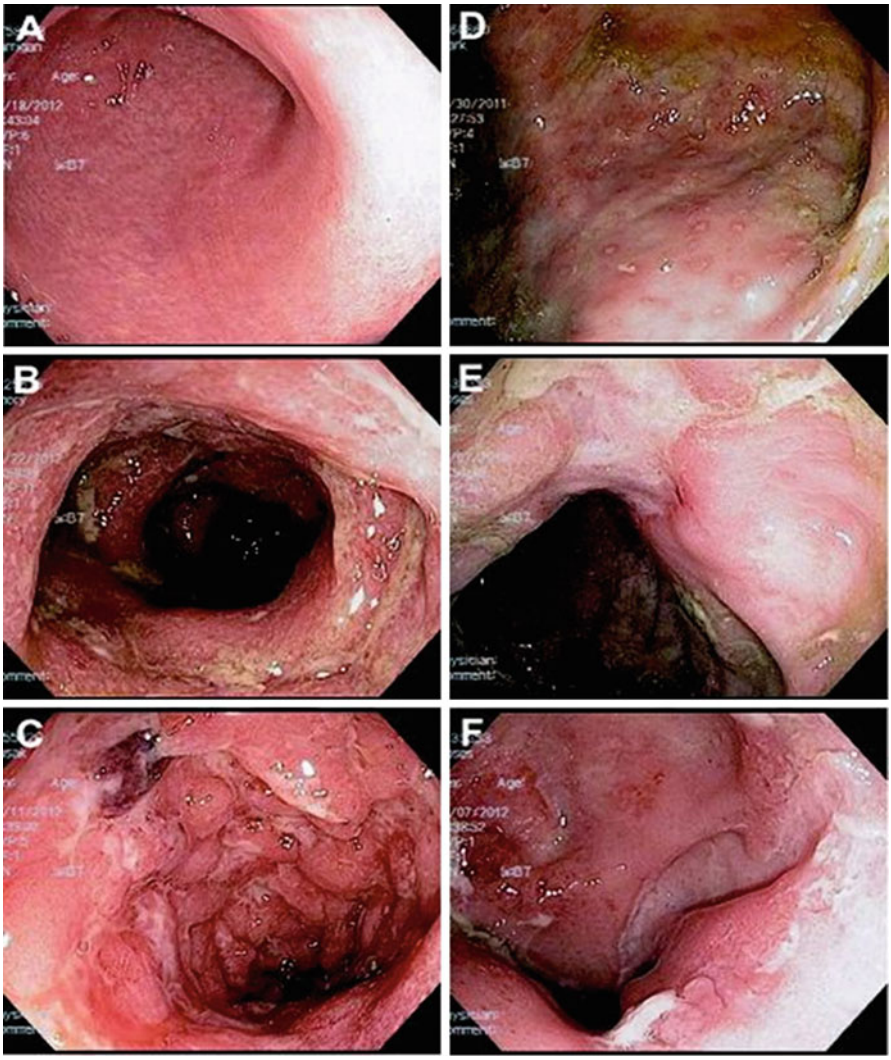

Fig. 1.1 Endoscopic features of UC and CD. Colonoscopic examination determines the severity of UC and CD. (**a**–**c**) UC can be graded as mild (duller, redder mucosa with granular texture) (**a**), moderate (mucosa with ulceration, friability, and loss of normal vascular pattern) (**b**), and severe (diffuse ulceration with mucopurulent exudates and spontaneous hemorrhage) (**c**). (**d**–**f**) CD can be graded as mild (discrete pouched-out aphthous ulcers) (**d**), moderate (stellate ulcers and longitudinal ulcers) (**e**), and severe (macroulcerations and pseudopolyps) (**f**)

Pathological changes in the inflammatory intestine of CD depend on disease severity, ranging from discrete pouched-out aphthae, irregular stellate ulcers, and longitudinal ulcers to macroulcerations and pseudopolyps (see Fig. 1.1d–f). Endoscopic indices, such as Rutgeerts' score, have been used for grading disease severity following ileocolonic resection. Histologically, CD is characterized by patchy, segmental,

and transmural inflammation, consisting of small collections of polymorphonuclear cells and chronic inflammatory cells. The hallmark of CD is the presence of epithelioid granuloma. In addition, serum markers of inflammation, such as ESR, CRP, and platelet count, are also used for monitoring disease activity [40].

Therapy for IBD is a fast-evolving field and new agents are continuously emerging. The primary aims of medical treatment for UC and CD are to control inflammation and reduce symptoms, achieve steroid-free clinical remission, and if possible achieve mucosal healing. The choices of therapy for UC and the mode of delivery of medications depend largely on clinical severity and anatomic extent of the disease (Table 1.1). Mildly to moderately active UC can be treated with 5-aminosalicylic acid (5-ASA) derivatives. Oral and topical mesalamine are effective in inducing and maintaining remission in distal UC [41]. An additive benefit is achieved in patients with distal UC who received the combination of topical rectal mesalamine (4 g rectal enema once nightly) and oral mesalamine (2.4 g/day), which produced results similar to those achieved with a higher dose of oral mesalamine (4.8 g/day) [42]. Corticosteroids are only used for controlling flare of UC in patients with more severe symptoms, but are not recommended for long-term use [43]. Moderate to severe UC can be treated with steroid-free regimens such as immunomodulatory agents (AZA or 6-MP) or biologics (such as anti-TNF monoclonal antibodies) or both. AZA and 6-MP have slow onset of action (3–6 months) and are associated with severe adverse events which limit their use, including bone marrow suppression, infection, hepatotoxicity, pancreatitis, and malignancies, particularly hepatosplenic T-cell lymphoma. Two FDA-approved anti-TNF monoclonal antibodies, infliximab and adalimumab, are currently used for the treatment of moderately to severely active UC in adults [44, 45]. Cyclosporine can be used as a salvage therapy for severe and refractory UC for less than 3–6 months and as a bridge for thiopurine therapy [46]. Additional new drugs, such as Tofacitinib, an anti-JAK antibody [47], are currently under development (Table 1.1).

The choice of CD therapy also depends on the anatomic location and severity of the disease [48]. The Crohn's Disease Activity Index (CDAI) is mostly used to evaluate disease severity in clinical trials as follows: asymptomatic remission (CDAI <150), mild to moderate (CDAI 150–220), moderate to severe (CDAI 220–450), and severe-fulminant disease (CDAI >450). A drop in the CDAI of 70 points is considered to be responsiveness. Current medications include oral 5-ASA derivatives, antibiotics, glucocorticoids, nonsystemic glucocorticoids, immunomodulators, and biologic therapies.

The use of 5-ASA medications for CD is not as effective as in UC patients. Generally 5-ASA drugs are used to treat mild ileitis, ileocolitis, or Crohn's colitis. Antibiotics such as metronidazole, ciprofloxacin, and rifaximin are recommended as an adjuvant therapy for active luminal Crohn's colitis, perianal fistulizing CD (especially when requiring draining of abscess), postoperative recurrence of ileocolitis, UC, and pouchitis [49, 50]. Short-course use of oral or intravenous glucocorticoids with tapering is often used to treat patients with moderate to severe disease at the initial presentation or during flares [51]. A steroid-sparing regimen should be used concomitantly with the steroid and continued as maintenance therapy once

Table 1.1 Drugs used in the treatment of IBD

Medications	Clinical applications	References
5-ASA	First line therapy for remission and maintenance in mild UC	[41]
Mesalazine	High dose 4.8 g/day, the faster resolution of symptoms of UC	[41]
Sulfasalazine	May reduce the risk of colorectal cancer by up 75 %	[42]
Topical 5-ASA	Combination with oral 5-ASA has been shown to be more effective in UC	
Metronidazole	Following ileocecal resection, 20 mg/kg/day for 3 months reduces risk of recurrence of CD	[49]
	Treat perianal disease and pouchitis	[50]
Ciprofloxacin	Greater benefit than metronidazole in perianal disease and pouchitis	
Corticosteroids	Potent reagent for inducing remission in moderate to severe UC and CD	[51]
	Rectal steroids are effective adjuvants but less effective than topical 5-ASA	[52]
Budesonide	Therapeutic benefit in ileocecal CD or UC	[53]
Thiopurines	Moderate to severe UC with clinical and endoscopic remission in 53 % patients in UC	[55]
	Effective for both induction and maintenance of remission in moderate and severe CD	[56]
	Modestly prevent postoperative recurrence of CD (at 1 year 8–13 % and 15 % for clinical and endoscopic remission, respectively)	[46]
Methotrexate	Effective for the induction and maintenance of remission in CD in RCT	
Cyclosporine	Rapid effective as a salvage therapy for severe and refractory UC for less than 3–6 months and as a bridge for thiopurine therapy	
Infliximab	Moderate to severe refractory CD with 81 % response rate at 4 weeks and 48 % at week 12	[44]
	Efficacy for fistula closure is 36 %	[45]
	Effective in severe UC, corticosteroid-refractory UC	[59]
Adalimumab	Moderate to severe refractory CD in TNF naïve patients and those who failed infliximab	[57]
	Efficacy for fistula closure is 33 % at week 56 compared with 13 % given placebo	
	Effective to moderate to severe UC and intolerance to infliximab	
Certolizumab	Effective in induction and maintenance of response and remission in complicated CD	[57]
Natalizumab	Moderate to severe refractory CD who failed IFX therapy	[62]

remission is achieved. The nonsystemic glucocorticoid budesonide may be effective for short-term (up to 6 months to 1 year) maintenance of remission in mild to moderate ileitis or ileocolitis [52, 53]. Patients with severe forms of CD at initial presentation, who relapse or fail to respond, or who exhibit steroid dependency usually require a top-down therapy starting with immunomodulators (6MP, AZA, or methotrexate) or biologics (infliximab, adalimumab, certolizumab). 6MP and AZA are

effective in inducing remission and maintenance [54, 55] but require 4–6 weeks due to their long half-life. Methotrexate (25 mg/week intramuscularly) is effective for induction and maintenance of remission in CD [57]. All anti-TNF agents are efficacious in induction and maintenance of remission in patients with active luminal CD and penetrating diseases. For perianal diseases, including abscess and fistula formation, combination therapy should be recommended including metronidazole and ciprofloxacin [49, 50] and infliximab, adalimumab, and certolizumab [57, 58, 59], in addition to surgical intervention. To confirm loss of response, patients should undergo endoscopic or radiologic imaging to confirm the presence of active inflammation and to rule out other causes of symptoms such as infection. There are increasing percentage of *Clostridium difficile* infections and hospitalizations among IBD patients [60].

Severe forms of both CD and UC are managed medically using similar combinatorial therapies, including immunomodulators, biologics, or both. Disease relapse in both conditions is fairly common. It is recommended to measure infliximab and human anti-chimeric antibody (HACA) concentrations in patients with disease relapse for therapy stratification. When detectable HACA is present, patients should be switched to another anti-TNF medication. When a subtherapeutic anti-TNF level is detected, the drug dose should be escalated to achieve clinical response. For active CD patients with nonresponse, loss of response, or intolerance to infliximab, switching to adalimumab has shown some efficacy [61]. Natalizumab, an anti-α4 integrin antibody, has shown to be effective in treating moderate to severe refractory CD who failed anti-TNF therapy [62].

If patients develop toxic megacolon with uncontrolled active inflammation, demyelinating disease, congestive heart failure, drug-induced lupus, drug-induced psoriasis, vasculitis, or various infections, including hepatitis, viral infection, and granulomatous infections (tuberculosis, histoplasmosis), it is recommended to change to a drug of a different category or discontinue medical management.

Total colectomy can be considered particularly in patients with moderately to severely active disease who are refractory or intolerant to available medical therapies. However, disease recurrence postoperatively is common in CD and in UC with pouchitis. Anti-TNF medications have been shown to prevent postoperative recurrence of CD, as evidenced by less clinical and endoscopic relapse [63].

Progression of IBD to complications is common. Such complications are stricture, fistula, abscess, malnutrition, surgical resection-related complications, infection, and depression. Therefore, IBD management requires a coordinated effort involving specialists from multiple disciplines, including, but not limited to, surgeon, internist, nutritionist, and psychiatrist.

Management of IBD remains a formidable challenge. Although mild CD can be controlled by conventional medical therapy, most cases of IBD inevitably progress to more severe forms with complications or become tolerant to current treatment regimens and require aggressive therapy such as biologics. However, about 50–60 % of patients respond to aggressive therapies at the beginning and only 30–40 % of patients remain in remission.

Understanding Genetics in IBD Facilitates Coping with Clinical Challenges

Despite much progress in IBD over the past decade, various challenges are still encountered in managing IBD patients to achieve accurate diagnosis, effective control of inflammation, and prevention of severe complications. The goals of understanding the genetics of IBD are to identify those at risk for IBD, to provide tools for diagnosis, to evaluate disease course and responsiveness of treatment, to develop new therapeutics, and to prevent disease from developing.

First of all, there is a need for additional diagnostic tools to assist separation of IBD subtypes. Classification within IBD is required for aiding patient counseling, prediction of disease progression, and ultimately delivery of optimal therapy to the individual patient. Though UC and CD have relatively distinct pathological and clinical characteristics and perhaps unique etiologies, making an accurate diagnosis is sometimes still difficult in IC cases. Moreover, IBD can be further categorized into subtypes based on the location of inflammation, onset of age, and the pattern of clinical complications. Therefore, understanding the genetic determinants underlying the predisposition to clinical phenotypes would also be extremely desirable for guiding treatment and prognosis.

Advances in medical genetics and human genetics, particularly over the past decade, have been truly phenomenal. Genetic epidemiological studies have revealed significantly higher risk among relatives in both UC and CD, suggesting that genetic factors play an important role in the pathogenesis of IBD. This is further exemplified by the fact that Ashkenazi Jews tend to have an overall increased risk for IBD, and there is concordance for IBD between monozygotic twins. In addition, more than 100 loci have been found to be significantly associated with IBD from genome-wide association [64]. These genes are involved in a diverse array of functions, including microbial recognition, lymphocyte activation, survival and proliferation, T-cell activation, IL-7 receptor, cytokine signaling, autophagy, and intestinal epithelial defense [65, 66].

Many IBD susceptibility genes discovered from GWAS are associated with both UC and CD. Interestingly, genetic studies have also uncovered that some of these genes are selectively associated with subtypes of IBD [67, 68]. It is conceivable that these genes could be used as diagnostic markers to aid clinicians in differentiating IBD subtypes from each other.

About 50 % of patients with IC will be eventually diagnosed with either CD or UC. The remaining cases are still undetermined. Therefore it is of great importance to develop a diagnostic test using genetic tools to be able to categorize phenotypic IC as it occurs more frequently among children who tend to develop a much more severe course with a greater chance of requiring colectomy and with pouch failure. In a recent study, several variants in genes, including *ICAM1*, *BTNL2*, and *SH2B1*, were found to be closely associated with IC at a young age [69]. Further study is needed to determine if this finding can be extended to a larger population of IC patients.

Second, it is of importance to stratify risk factors with a goal of appropriate care of patients with IBD to prevent severe complications and delay the time period for requiring surgery. These risk factors include age of onset, involvement of ileum, and

Table 1.2 Gene variants and clinical phenotypes of early-onset IBD

Genes variants	Characteristics	Mechanisms of action	References
OCTN SLC22A4 1672T, *SLC22A5-207*	Pediatric onset CD; mean 12 years old	Transport organic cations, e.g., carnitine	[71]
IBD5 risk allele	Pediatric onset CD	A region containing immunoregulatory genes	[72]
(*IRF1*, *OCTN1*, *OCTN2*, *PDLIM 4*, *P4HA2*)	Extensive inflammation	(*IL4*, *Il 13*, *IL5* and *IRF1*)	[73]
IL 10 RA rs2228054 and rs2228055	Infantile UC and severe arthritis	Cytokine signaling	[74]
IL 10 RB SNPs	Infantile CD	Cytokine signaling	[74]
IL 10 and IL 10R deficiency	Infantile CD	Cytokine signaling	[75]
NCF2 c.113 G/A R38Q	Infantile CD (L2, L3 and p)	A component of NADPH oxidase complex	[76]
XIAP p.C203Y	Infantile CD; fistulizing CD	Activation of NFκB	[77]
IRGM rs1000113 and rs4958847	Childhood CD	Autophagy pathway	[78]
NOD2/*CARD15*	Colonic CD, a higher male/female ratio	Microbial recognition	[70]
DLG5 rs2165047	Pediatric CD (<19 years old)	Intestinal epithelial permeability	[79]

disease behaviors. Up to a quarter of patients develop IBD prior to 18 years of age. Despite many similarities of IBD features between adult onset and early onset, early-onset IBD tends to be much more severe with more rapid progression and a higher risk of complications. Pediatric IBD has less involvement of the rectum but more frequent inflammation in the upper GI tract such as the stomach and duodenum. Very-early-onset CD occurs at ages younger than 8 years, featuring less perianal disease, a higher male-to-female ratio, higher anti-*Saccharomyces cerevisiae* antibodies, and seropositivity rates, and preferentially in Jewish individuals [70]. The exact genetic factors that contribute to early susceptibility to IBD remain unknown. Several variants of genes appear to be uniquely associated with early-onset IBD by GWAS and candidate-gene analysis (Table 1.2) [70–79]. These genes govern various biological functions including cytokine signaling, neutrophil and macrophage phagocytosis, involvement of the proinflammatory response and activation of NFκB, autophagy, microbial recognition, and intestinal epithelial permeability. Among these gene candidates, several research groups have repeatedly demonstrated that IL-10 and IL-10 receptor deficiency are associated with early onset of severe forms of IBD [74, 75]. Thus, IL-10 and IL-10R can potentially serve as important genetic indicators for initiation of aggressive treatment.

CD affecting the ileum typically displays a unique clinical phenotype associated with developing severe complications such as formation of fistulae and intestinal stricture. There are very limited options available for effective management of these pathologies. In most cases, surgery becomes inevitable to attenuate disease

progression after an average of 7–15 years from diagnosis. It is therefore beneficial to initiate aggressive treatment during the early course of disease or postoperatively, if severe complications are anticipated. Genetics has been shown to play a role in the susceptibility to ileal CD and development of severe complications. Several gene variants have been discovered to be closely associated with ileal CD (Table 1.3), including *NOD2* 1007fs, *ATG16L1* rs2241879 and rs2241880, *IRGM* rs4958847, calcium-activated potassium channel 4 (*KCNN4*) rs2306801, *AK097548* gene rs1363670 G, *IL-10* promoter 627 CA, and *TCF-4* rs3814570 [67, 80–85]. Other gene variants have been linked to structuring disease, such as *NOD2* 1007fs, *ATG16L1* rs2241879 and rs2241880, *AK097548* gene rs1363670 G, *TCF-4* rs3814570, *IL-10* promoter 627 CA, *CXCL16* p.Ala181Val, and *TGFB1* codon 25 [80, 81, 83–90]. Perianal diseases including fistulae formation have distinct gene variants such as *NCF4*, *XIAP*, *IRGM* rs4958847, *NOD2* 1007fs, *DLG5* rs2165047, the carnitine/organic cation transporter (*OCTN*) on 5q31 (*IBD5*), and *CDKAL1* rs6908425 [76–79, 83, 91–94]. Interestingly, some of these gene variants associated with ileal CD were found to overlap with those linked to either stricturing or perianal diseases, suggesting that these genes perhaps reflect severe clinical phenotypes, a connection which might be exploited for clinical application. These gene variants associated with structuring or penetrating disease are fairly distinctive. However, it requires verification in a larger population of IBD patients.

Genetic testing has begun to provide a new approach to better determine the subtypes in IBD patients. For example, mutation of the *NOD2* gene is closely associated with CD, and genetic testing for *NOD2* mutations (or variants) is already available. However, the challenge is how to best utilize these tests for the benefit of patient care in general. Apparently, monitoring the *NOD2* gene alone is not sufficient as a diagnostic test because 70 % of CD patients have no *NOD2* major variants. Moreover, around 10 % of the healthy population carries *NOD2* major variants. Therefore use of a panel of genes in genetic testing may be the better molecular methods for IBD diagnosis. In addition to providing tools for assisting in diagnosis, clinicians may eventually utilize genetic information to guide decision-making in IBD therapy, especially to manage IBD and to avoid severe complications. For example, as noted above, *NOD2* and *IL-10*/*IL-10R* mutations tend to be associated with severe early onset of IBD with severe complications. These gene variants could be used to guide early aggressive therapy (using biologics and immunomodulators) so that severe complications such as irreversible fibrostenotic disease could be prevented.

It is worth mentioning that extraintestinal manifestations are common in patients with IBD, suggesting that IBD may represent an intestinal manifestation of syndromes with multiorgan involvement due to immunological disorders. GWAS results revealed that some genes appear to be associated with IBD along with other chronic inflammatory diseases. These gene variants are *STAT41* rs11889341, *HLA-B**27, *B**58, *HLA-DRB1*0103*, *1031 TNFA*, and *GPR35* rs3749171(Thr/Met) (Table 1.4) [95–98], which could potentially be used as genetic markers to further refine those IBD subgroups with extraintestinal symptoms and to further assist decision-making in treatment choice.

Table 1.3 Association of gene variants with different phenotypes of CD

NOD2	Ileal CD	Microbe recognition	[86]
(1007fs and other variants)			[80]
ATG16L1	Ileal CD	Autophagy	[81]
(rs2241879 and rs2241880)			[88]
AK097548 (rs1363670G)	Ileal CD	Encoding for hypothetical protein near the *IL12B gene*	[83]
TCF-4 rs3814570	Ileal CD	Wnt signaling pathway transcription factor	[85]
IL10 promoter 627 CA	Ileal CD	Cytokine	[84]
CXCL16 p.Ala181Val	Stricturing behavior	A chemokine for defense against bacteria	[89]
TGF beta1 codon 25	Stricturing behavior	Growth factor	[90]
Penetrating (B3)			
NCF4	Perianal CD	A component of NADPH oxidase complex	[91]
NCF2 c.113 G/A R38Q	Infantile CD with penetrating and perianal Disease	A component of NADPH oxidase complex	[76]
XIAP p.C203Y	Infantile CD with fistulizing CD	Activation of NFκB	[77]
IRGM rs4958847	Ileocolonic CD, frequent surgery and perianal fistula	Autophagy	[92]
OCTN, 5q31 (IBD5)	Perianal and penetrating CD	The carnitine/organic cation transporter	[93]
TNF2 allele	Penetrating disease	Cytokine signaling	[94]
CDKAL1 rs6908425	Development of perianal fistula	A methylthiotransferase modifying tRNA-Lysine	[83]
Perianal (p)			
DLG5 rs2165047	Pediatric-onset CD and perianal disease	Intestinal epithelial permeability	[79]
OCTN on 5q31 (IBD5)	Perianal and penetrating CD	The carnitine/organic cation transporter	[93]
NCF2 c.113 G/A R38Q	Infantile CD with penetrating and perianal disease	A component of NADPH oxidase complex	[76]
NCF4	Fistula formation	A component of NADPH oxidase complex	[91]
IRGM rs4958847	Ileocolonic CD and frequent surgery; perianal fistula	Autophagy	[78]
OCTN, 5q31 (IBD5)	Perianal and penetrating CD	The carnitine/organic cation transporter	[93]
CDKAL1 rs6908425	Perianal fistula	A methylthiotransferase modifying tRNA-Lysine	[83]

Table 1.4 Association of related genes and extrainstestinal manifestations in IBD

Genes involved	Characteristics	Mechanisms of action	References
STAT41 rs11889341	Joint pain	Signal transduction and activation of transcription	[95]
*HLA-B*27*, *B*58*	Uveitis	Autoimmunity	[96]
*HLA-DRB1*0103*	Uveitis	Autoimmunity	[96]
–1031 TNF-alpha	Erythema nodosum	Cytokine	[96]
GPR35 rs3749171 (Thr/Met)	UC and PSC	G-protein coupled receptor signaling	[97]

Thirdly, as managing IBD requires long-term medical therapy, drug tolerance and toxicity clearly become a major issue that severely compromise inflammation control. Knowledge of the genetics of IBD has been increasingly translated into clinical applications (pharmacogenetics). Recent studies revealed that genetic determinants play a role in unresponsiveness to drugs [79, 99, 100]. For example, variants in genes such as *HLA-DR8*, *ILRA*, *and NALP1* (*L155H*) are linked to treatment failure of budesonide and intravenous use of steroid. In contrast, *IL23R* genotype status along with disease activity and antineutrophil cytoplasmic antibody (ANCA) positivity are good indicators closely correlating with infliximab response in UC. It is hoped that genetic studies in the near future will pinpoint the genetic determinants underlying drug responsiveness and toxicity in individuals to enable choice of the most appropriate medical regimen or prompt switching to another class of medications.

Lastly, genetic studies have identified many genes associated with IBD, which potentially provide many new therapeutic targets. Physicians continue to face many challenges in managing severe IBD because of a lack of effective therapeutics and patients developing tolerance to conventional therapeutic regimens. Some severe forms of IBD require aggressive treatment, for example, biologics. However, only a portion of patients display a positive response to currently available medications and remain in remission. There is a pressing need for new effective therapeutics. By characterizing the altered intracellular pathways caused by candidate genes identified from genetic studies, new drugs could be developed to target specific subtypes of IBD.

Discovery of a large array of candidate genes associated with IBD from genetic studies will help to interpret the diverse clinical phenotype of IBD, including severity, and drug responsiveness, which will lead to many utilitarian improvements such as diagnostic tools, prognostic indicators, and more refined therapeutic regimens. However, challenges remain, for example, how to sort out the long list of IBD susceptibility genes and translate the genetic discoveries into real clinical applications. Of particular note, loss-of-function mutations in many IBD susceptibility genes do not seem to be sufficient to cause IBD. This supports the notion that IBD disorders are multifactorial, triggered in susceptible individuals when environmental factors become unfavorable. For example, the gut microbiome is now recognized as an important factor and could contribute to the observed familial clustering or geographic prevalence of IBD. It has become increasingly clear that specific genetic variations are associated with increased susceptibility to IBD and that environmental factors such as intestinal bacteria may serve as cofactors or triggers to the

development of IBD. It is therefore of interest to understand how interactions between genetics (mutations in IBD susceptibility genes) and environmental factors create a perfect storm that leads to intestinal inflammation. Studying these interactions may lead to discovery of an effective preventive strategy.

In summary, results from genetic studies could provide enormous benefits in guiding overall patient management. The more we know of the genetics of IBD, the environmental factors and triggers, and the genetics of drug responsiveness, the closer we will be to delivering truly personalized medicine that effectively treats IBD.

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