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REVIEWS AND PERSPECTIVES

REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Robert F. Schwabe and John W. Wiley, Section Editors

The Diagnostic Approach to Monogenic Very Early Onset Inflammatory Bowel Disease

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Patients with a diverse spectrum of rare genetic disorders can present with inflammatory bowel disease (monogenic IBD). Patients with these disorders often develop symptoms during infancy or early childhood, along with endoscopic or histological features of Crohn's disease, ulcerative colitis, or IBD unclassified. Defects in interleukin-10 signaling have a Mendelian inheritance pattern with complete penetrance of intestinal inflammation. Several genetic defects that disturb intestinal epithelial barrier function or affect innate and adaptive immune function have incomplete penetrance of the IBD-like phenotype. Several of these monogenic conditions do not respond to conventional therapy and are associated with high morbidity and mortality. Due to the broad spectrum of these extremely rare diseases, a correct diagnosis is frequently a challenge and often delayed. In many cases, these diseases cannot be categorized based on standard histological and immunologic features of IBD. Genetic analysis is required to identify the cause of the disorder and offer the patient appropriate treatment options, which include medical therapy, surgery, or allogeneic hematopoietic stem cell transplantation. In addition, diagnosis based on genetic analysis can lead to genetic counseling for family members of patients. We describe key intestinal, extraintestinal, and laboratory features of 50 genetic variants associated with IBD-like intestinal inflammation. In addition, we provide approaches for identifying patients likely to have these disorders. We also discuss classic approaches to identify these variants in patients, starting with phenotypic and functional assessments that lead to analysis of candidate genes. As a complementary approach, we discuss parallel genetic screening using next-generation sequencing followed by functional confirmation of genetic defects.

Keywords: Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis; Unclassified Colitis; Indeterminate Colitis; Immunodeficiency; Pediatrics; IBD Unclassified; Genetics; Next-Generation Sequencing; Whole Exome Sequencing.

Inflammatory bowel diseases (IBDs) are a diverse group of complex and multifactorial disorders. The most common subtypes are Crohn's disease (CD) and ulcerative colitis (UC).[1,2] There is increasing evidence that IBD arises in genetically susceptible people, who develop a chronic and relapsing inflammatory intestinal immune response toward the intestinal microbiota. Disease development and progression are clearly influenced by environmental factors, which have contributed to the rapid global increase in the incidence of IBD in recent decades.[3]

Developmental, Genetic, and Biological Differences Among Age Groups

IBD location, progression, and response to therapy have age-dependent characteristics.[4–10] The onset of intestinal inflammation in children can affect their development and growth. Age of onset can also provide information about the

Abbreviations used in this paper: **CD, Crohn's disease; CGD, chronic granulomatous disease; CVID, combined variable immunodeficiency; EOIBD, early-onset inflammatory bowel disease; HSCT, hematopoietic stem cell transplantation; IBD, inflammatory bowel disease; Ig, immunoglobulin; IL, interleukin; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NEMO, nuclear factor κB essential modulator protein; NK, natural killer; PID, primary immunodeficiency; SCID, severe combined immunodeficiency; UC, ulcerative colitis; VEOIBD, very early onset inflammatory bowel disease; WAS, Wiskott–Aldrich syndrome; WES, whole-exome sequencing.**

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type of IBD and its associated genetic features. For example, patients with defects in interleukin (IL)-10 signaling have a particularly early onset of IBD, within the first few months of life. Our increasing understanding of age-specific characteristics has led to changes in the classification of pediatric IBD. Based on disease characteristics, several age subgroups have been proposed that correspond largely to the generally accepted age stages defined by National Institute of Child Health and Human Development pediatric terminology.[11]

Five major subgroups of pediatric IBD can be summarized according to age (Table 1). The Montreal classification[12] originally defined patients with age of onset younger than 17 years as a distinct group of patients with pediatric-onset IBD (A1). The Pediatric Paris modification[13] of the Montreal classification[12] later defined the pediatric-onset group of IBD as A1 but subdivided those with a diagnosis before 10 years of age as subgroup A1a and those with a diagnosis between 10 and <17 years of age as subgroup A1b.[13] This reclassification was based on several findings indicating that children with a diagnosis of IBD before 10 years of age develop a somewhat different disease phenotype compared with adolescents or adults. Particular differences that supported the modification were paucity of ileal inflammation and predominance of pancolonic inflammation as well as a low rate of anti–*Saccharomyces cerevisiae* antibodies in A1a patients with CD, with an increased risk of surgery (colectomy) and biological therapy in A1a patients with UC.[13]

In this review, we refer to the A1a group as having early-onset IBD (EOIBD). Very early onset IBD (VEOIBD), the subject of this review, represents children with a diagnosis before 6 years of age.[14] This age classification includes neonatal, infantile, toddler, and early childhood groups. Proposing an age group between infantile IBD and A1a EOIBD makes sense when taking account that the age of onset is often older than 2 years in multiple relevant subgroups of patients with monogenic IBD (such as those with *XIAP* deficiency, chronic granulomatous disease [CGD], or other neutrophil defects). On the other hand, from the age of 7 years, there is a substantial rise in the frequency of patients with a diagnosis of conventional polygenic IBD, particularly CD.[6,15] This leads to a relative enrichment of monogenic IBD in those with age of onset younger than 6 years. Approximately one-fifth of children with IBD younger than 6 years of age and one-third of children with IBD younger than 3 years of age are categorized as having IBD unclassified (or indeterminate colitis),[16] reflecting the lack of a refined phenotyping tool to categorize relevant subgroups of patients with VEOIBD and a potential bias due to incomplete diagnostic workup in very young children.[15] The enrichment of monogenic defects in EOIBD and VEOIBD becomes apparent when relating the approximately 1% of patients with IBD younger than 6 years of age and <0.2% younger than 1 year of age to reports that the majority of monogenic disorders can present at younger than 6 years of age and even younger than 1 year of age (Figure 1).

Table 1. Subgroups of Pediatric IBD According to Age

Group	Classification	Age range (*y*)
Pediatric-onset IBD	Montreal A1	Younger than 17
EOIBD	Paris A1a	Younger than 10
VEOIBD		Younger than 6
Infantile (and toddler) onset IBD		Younger than 2
Neonatal IBD		First 28 days of age

Although it is generally accepted that many patients with VEOIBD have low response rates to conventional anti-inflammatory and immunomodulatory therapy, there is a paucity of well-designed studies to support this hypothesis. Infantile (and toddler) onset of IBD was highlighted in the Pediatric Paris classification because of higher rates of affected first-degree family relatives, indicating an increased genetic component, severe disease course, and high rate of resistance to immunosuppressive treatment.[13] Features of autoimmunity with dominant lymphoid cell infiltration are frequently found in infants and toddlers.[17] Such patients are likely to have pancolitis; subgroups of patients develop severely ulcerating perianal disease, and there is a high rate of resistance to conventional therapy, a high rate of first-degree relatives with IBD, and increased lethality.[4–8] Recent guidelines and consensus approaches on the diagnosis and management of IBD[18,19] highlight that children with infantile onset of IBD have a particular high risk of an underlying primary immunodeficiency. An extreme early subgroup, neonatal IBD, has been described with manifestations during the first 27 days of life.[4,5,8]

Guidelines on the diagnosis and classification of IBD in pediatric patients[13,18–21] have addressed the need to recognize monogenic disorders and immunodeficiencies in particular, because these require a different treatment strategy than conventional IBD. Current guidelines do not, however, cover the spectrum of these rare subgroups of monogenic IBD. The identification of an underlying genetic defect is indeed challenging, owing to the orphan nature of these diseases, the wide phenotypic spectrum of disorders, and the limited information available on most genetic defects. This review and practice guide provides a comprehensive summary of the monogenic causes of IBD-like intestinal inflammation and a conceptual framework for the diagnostic evaluation of patients with suspected monogenic IBD. We categorize known genetic defects into functional subgroups and discuss key intestinal and extraintestinal findings. Based on the enrichment of known causative mutations as well as extreme phenotypes in very young children, we have focused on a practical approach to detect monogenic disorders in patients with VEOIBD and infantile IBD in particular. Because there is only modest biological evidence to support age-specific categorization of IBD above infantile IBD and within the EOIBD subgroup, we also discuss disease- and gene-specific ages of onset of intestinal inflammation (Figure 1).

Epidemiology of Pediatric IBD

Approximately 20% to 25% of patients with IBD develop intestinal inflammation during childhood and adolescence.

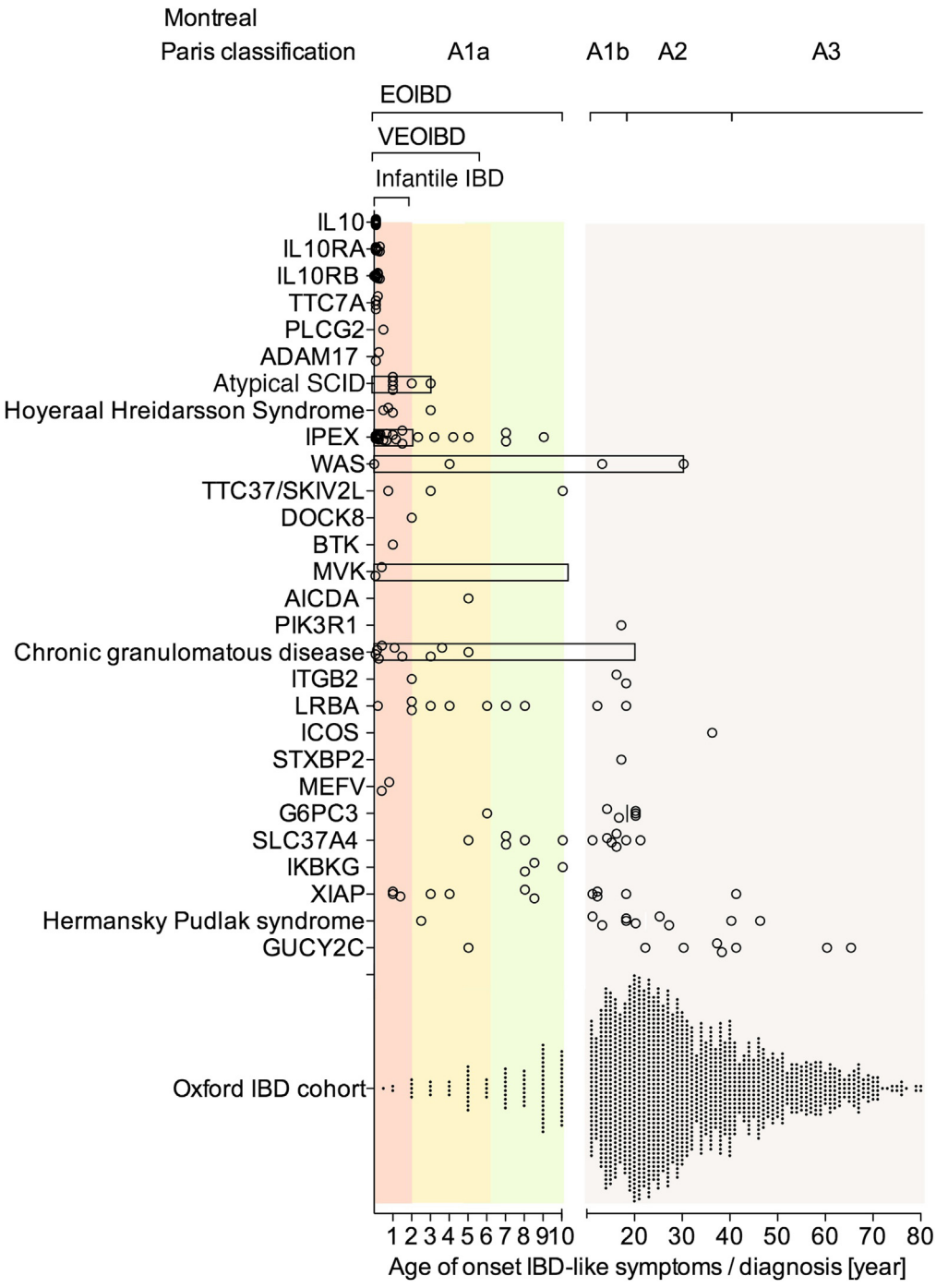

Figure 1. Age of onset of IBD-like symptoms in patients with monogenic diseases. Multiple genetic defects are summarized in the group of atypical SCID, Hoyeraal–Hreidarsson syndrome, CGD, and Hermansky–Pudlak syndrome. By comparison, an unselected IBD population is presented (Oxford IBD cohort study; pediatric and adult referral-based IBD cohort, n = 1605 patients comprising CD, UC, and IBD unclassified [IBDU]). *Symbols* represent individual patients. *Bars* represent the age range of case series if individual data were not available. The age ranges of infantile IBD, VEOIBD, EOIBD, and Montreal/Paris classification A1a, A1b, A2, and A3 are shown for reference. Age of onset data refer to references provided in Table 2. Additional references for disease subgroups are provided in Supplementary Information for Figure 1.

IBD in children younger than 1 year of age has been reported in approximately 1% and VEOIBD in approximately 15% of pediatric patients with IBD.[6] VEOIBD has an estimated incidence of 4.37 per 100,000 children and a prevalence of 14 per 100,000 children.[22] The incidence of pediatric IBD is increasing.[22,23] Some studies have reported that the incidence of IBD is increasing particularly rapidly in young children,[24,25] although not all studies have confirmed this observation.[9]

Polygenic and Monogenic Forms of IBD

Twin studies have provided the best evidence for a genetic predisposition to IBD, which is stronger for CD than UC. Conventional IBD is a group of polygenic disorders in which hundred(s) of susceptibility loci contribute to the overall risk of disease. Meta-analyses of (genome-wide) association studies of adolescent- and adult-onset IBD identified 163 IBD-associated genetic loci encompassing approximately 300 potential candidate genes. However, it is

important to consider that these 163 loci individually contribute only a small percentage of the expected heritability in IBD.[26] This suggests that IBD, including CD and UC, can be regarded as a classic polygenic disorder. Findings from initial genome-wide pediatric association studies focused on adolescents and confirm a polygenic model.[27,28] There are no well-powered genome-wide association studies of patients with EOIBD or VEOIBD.

Although most cases of IBD are caused by a polygenic contribution toward genetic susceptibility, there is a diverse spectrum of rare genetic disorders that produce IBD-like intestinal inflammation.[29] The genetic variants that cause these disorders have a large effect on gene function. However, these variants are so rare in allele frequency (many private mutations) that those genetic signals are not detected in genome-wide association studies of patients with IBD. With recent advances in genetic mapping and sequencing techniques and increasing awareness of the importance of those "orphan" disorders, approximately 50 genetic disorders have been identified and associated with IBD-like immunopathology (for a partial summary, see Uhlig[29]). For simplicity, we refer to these disorders in the following text as monogenic IBD, even if there is a spectrum of penetrance of the IBD phenotype. We will compare those monogenic forms of IBD with polygenic conventional IBD.

All data suggest that the fraction of monogenic disorders with IBD-like presentation among all patients with IBD correlates inversely with the age of onset. Despite a growing genotype spectrum, monogenic disorders still account for only a fraction of VEOIBD cases. The true fraction is unknown. In a study of 66 patients who developed IBD at ages younger than 5 years, 5 patients were found to carry mutations in *IL10RA*, 8 in *IL10RB*, and 3 in *IL10*.[30] All patients developed symptoms within the first 3 months of life.[30] A recent study detected 4 patients with presumed pathogenic *XIAP* mutations in a group of 275 patients with pediatric IBD (A1a/A1b Paris classification) and 1047 patients with adult-onset CD (A2 and A3 Montreal classification).[31] Because all patients with *XIAP* variants were infantile to adolescent male patients with CD, this could suggest an approximate prevalence of 4% among young male patients with IBD. However, studies like these focus on specific genes and may have strong selection bias toward an expected clinical subphenotype. They might therefore overestimate the frequency of specific variants. Analysis of large, multicenter, population-based cohorts is needed to determine the proportion of cases of VEOIBD caused by single gene defects and to estimate penetrance.

Monogenic defects have been found to alter intestinal immune homeostasis via several mechanisms (Table 2). These include disruption of the epithelial barrier and the epithelial response as well as reduced clearance of bacteria by neutrophil granulocytes and other phagocytes. Other single-gene defects induce hyperinflammation or autoinflammation or disrupt T- and B-cell selection and activation. Hyperactivation of the immune response can result from defects in immune inhibitory mechanisms, such as defects in IL-10 signaling or dysfunctional regulatory T-cell activity.

Epithelial Barrier and Response Defects

Genetic disorders that affect intestinal epithelial barrier function include dystrophic epidermolysis bullosa,[32] Kindler syndrome,[32] familial diarrhea caused by dominant activating mutations in guanylate cyclase C,[33] X-linked ectodermal dysplasia and immunodeficiency,[34] and ADAM17 deficiency.[35]

X-linked ectodermal dysplasia and immunodeficiency, caused by hypomorphic mutations in *IKBKG* (encodes nuclear factor κB essential modulator protein [NEMO])[34] and *ADAM17* deficiency[35] cause epithelial and immune dysfunction. Recently, *TTC7A* deficiency was described in patients with multiple intestinal atresia, with and without severe combined immunodeficiency (SCID) immunodeficiency.[36,37] Hypomorphic mutations in *TTC7A* have been found to cause VEOIBD without intestinal stricturing or severe immunodeficiency, most likely due to a defect in epithelial signaling.[38]

Dysfunction of Neutrophil Granulocytes

Variants in genes that affect neutrophil granulocytes (and other phagocytes) predispose people to IBD-like intestinal inflammation. Chronic granulomatous disease is characterized by genetic defects in components of the phagocyte reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (phox) complex. Genetic mutations in all 5 components of the phagocyte NADPH oxidase (phox)—gp91-phox (*CYBB*), p22-phox (*CYBA*), p47-phox (*NCF1*), p67-phox (*NCF2*), and p40-phox (*NCF4*)—are associated with immunodeficiency and can cause IBD-like intestinal inflammation.

As high as 40% of patients with CGD develop CD-like intestinal inflammation.[39–41] Multiple granulomas and the presence of pigmented macrophages can indicate the group of defects histologically. Missense variants in *NCF2* that affect RAC2 binding sites have recently been reported in patients with VEOIBD.[42] Recently, several heterozygous functional hypomorphic variants in multiple components of the NOX2 NADPH oxidase complex were detected in patients with VEOIBD that do not cause CGD-like immunodeficiency but have a moderate effect on reactive oxygen species production and confer susceptibility to VEOIBD.[43] Tumor necrosis factor α inhibitors can resolve intestinal inflammation in patients with CGD but could increase the risk of severe infections in patients with CGD.[44] Allogeneic hematopoietic stem cell transplantation (HSCT) can cure CGD and resolve intestinal inflammation.[44–46] Monocytes produce high levels of IL-1 in patients with CGD, and an IL-1 receptor antagonist (anakinra) has been used to treat noninfectious colitis in those patients.[47]

In addition to CGD, a number of other neutrophil defects are associated with intestinal inflammation. Defects in glucose-6-phosphate translocase (*SLC37A4*)[48,49] and glucose-6-phosphatase catalytic subunit 3 (*G6PC3*)[50] are associated with congenital neutropenia (and other distinctive features) but also predispose people to IBD. Leukocyte adhesion deficiency type 1 is caused by mutations in the gene encoding CD18 (*ITGB2*) and is associated with

Table 2. Genetic Defects and Phenotype of Monogenic IBD

					Intestinal findings								Extraintestinal findings				
	Group	Syndrome/disorder	Gene	Inheritance	CD-like	Granuloma	UC-like	Epithelial defect (apoptosis)	Disease location (1–5)	Perianal fistula/ abscess	Penetrating fistulas	Strictures	Skin lesions	Autoimmunity, inflammation	HLH/ MAS	Neoplasia	References
1	Epithelial barrier	Dystrophic bullosa	*COL7A1*	AR				+	3			+	eb				32 (A. Martinez[a])
2		Kindler syndrome	*FERMT1*	AR			+	+	5			+	eb				32, 149 (A. Martinez[a])
3		X-linked ectodermal immunodeficiency	*IKBKG*	X	+			+	3				+	A, Vasc			34, 150, 151
4		*TTC7A* deficiency	*TTC7A*	AR				+	3			+					38
5		*ADAM17* deficiency	*ADAM17*	AR			(+)	+	3				n, h				35
6		Familial diarrhea	*GUCY2C*	AD	+				3			+					33 (A. Janecke[a])
7	Phagocyte defects	CGD	*CYBB*	X	+	+			1, 3	+			e				39
8		CGD	*CYBA*	AR	+	+			3	+			e				41
9		CGD	*NCF1*	AR	+	+			1, 3	+			e				39
10		CGD	*NCF2*	AR	+	+			1, 3	+			e				39
11		CGD	*NCF4*	AR	+	+			1, 3				e				40
12		Glycogen storage disease type Ib	*SLC37A4*	AR	+	+			1, 3	+		+	f				48, 49, 53
13		Congenital neutropenia	*G6PC3*	AR	+				1, 3	+	?	(+)	f				50, 138, 152
14		Leukocyte adhesion deficiency 1	*ITGB2*	AR	+				1, 3	+		+	f				51, 52
15	Hyperinflammatory and	Mevalonate kinase deficiency	*MVK*	AR					3			+	+	A, SJ	+		54, 55, 71
16	autoinflammatory disorders	Phospholipase C-γ2 defects	*PLCG2*	AD			+		3				(eb), e	A, NSIP			56
17		Familial Mediterranean fever	*MEFV*	AR			+		5				+	S			57–59
18		Familial hemophagocytic lymphohistiocytosis type 5	*STXBP2*	AR					3						+		69
19		X-linked lymphoproliferative syndrome 2 (XLP2)	*XIAP*	X	+	+			3	+	+	(+)	+	?	+		31, 66–68, 72, 73, 127
20		X-linked lymphoproliferative syndrome 1 (XLP1)	*SH2D1A*	X					3						+	+	65
21		Hermansky–Pudlak 1	*HPS1*	AR	+	+			3	+		(+)	+				60–63
22		Hermansky–Pudlak 4	*HPS4*	AR	+	+			3	+		(+)	+				60, 62, 153
23		Hermansky–Pudlak 6	*HPS6*	AR					3				+				64
24	T- and B-cell defects	CVID 1	*ICOS*	AR					5				p	A			86
25		CVID 8	*LRBA*	AR	+				3				EN	AIHA			87–89

Table 2. Continued

	Group	Syndrome/disorder	Gene	Inheritance	Intestinal findings							Extraintestinal findings				References
					CD-like	Granuloma	UC-like	Epithelial defect (apoptosis)	Disease location (1–5)	Perianal fistula/ abscess	Penetrating fistulas	Strictures	Skin lesions	Autoimmunity, inflammation	HLH/ MAS	Neoplasia	
26		IL-21 deficiency (CVID-like)	*IL21*	AR	+	+											90
27		Agammaglobulinemia	*BTK*	X	+				5					AIHA			75, 76
28		Agammaglobulinemia	*PIK3R1*	AR					5				EN	+			77
29		Hyper IgM syndrome	*CD40LG*	X					1, 5	+				AIHA			78
30		Hyper IgM syndrome	*AICDA*	AR	+				1, 3					AIHA			79
31		WAS	*WAS*	X			+		5				e	AIHA, A			80
32		Omenn syndrome	*DCLRE1C*	AR	+				1, 3								81
33		SCID	*ZAP70*	AR			+		5				e				154
34		SCID/hyper IgM syndrome	*RAG2*	AR					5				+	AIHA			82, 155
35		SCID	*IL2RG*	X					3								156, 157
36		SCID	*LIG4*	AR		No further information							+	AN			82
37		SCID	*ADA*	AR		No further information							+	AIHA			82
38		SCID	*CD3γ*	AR	+				5	+			+				95
39		Hoyeraal–Hreidarsson S.	*DKC1*	X				(+)	1, 3			+	+, n, h			+	99–101
40		Hoyeraal–Hreidarsson S.	*RTEL1*	AR				+	5			+	+, n, h			+	97, 98
41		Hyper IgE syndrome	*DOCK8*	AR		+			1, 5				e	PSC			158
42	Immunoregulation	IPEX	*FOXP3*	X					3				e, p	AIHA, HT, T1D…			111, 112
43		IPEX-like	*IL2RA*	AR					2				e	AIHA, HT, T1D…			114
44		IPEX-like	*STAT1*	AD					2								116
45		IL-10 signaling defects	*IL10RA*	AR	+	(+)			3	+	+		f, e	A		+	30, 102–105, 107
46		IL-10 signaling defects	*IL10RB*	AR	+	(+)			3	+	+		f	A, AIH		+	30, 102–105, 107
47		IL-10 signaling defects	*IL10*	AR	+				3	+	+						30, 102, 104, 105, 107
48	Others	*MASP* deficiency	*MASP2*	AR			+						+	A			159
49		Trichohepatoenteric S.	*SKIV2L*	AR					3				h, +				117, 160
50		Trichohepatoenteric S.	*TTC37*	AR					3				h, +				117

NOTE. Genetic defects are grouped according to functional subgroups. Gene names refer to HUGO gene nomenclature. CD-like and UC-like were marked only when patient characteristics in the original reports were described as typical CD or UC pathologies. Unclassified or indeterminate colitis is the not specified default option. Disease location is classified as follows: 1, mouth; 2, enteropathy; 3, enterocolitis; 4, isolated ileitis; 5, colitis; 6, perianal disease. Epithelial defects refer in particular to finding of epithelial lining nonadherent at the basal membrane or increased epithelial apoptosis and epithelial tufting. Key laboratory findings are provided in Supplementary Table 1, and examples of additional defects of possible or unclear relevance are listed in the Supplementary Information for Table 1.

HLH, hemophagocytic lymphohistiocytosis; AR, autosomal recessive; eb, epidermolysis bullosa; X, X-linked; A, arthritis; vasc, vasculitis; n, nail; h, hair; AD, autosomal dominant; e, eczema; f, folliculitis/pyoderma; SJ, Sjögren syndrome; p, psoriasis; AIHA, autoimmune hemolytic anemia; AN, autoimmune neutropenia; PSC, primary sclerosing cholangitis; HT, Hashimoto thyroiditis; AIH, autoimmune hepatitis; TID, type 1 diabetes mellitus; MAS, macrophage activation syndrome; NSIP, non-specific interstitial pneumonitis; S, serositis.

[a]Personal information and communication.

defective transendothelial migration of neutrophil granulocytes. Patients typically present with high peripheral granulocyte counts and bacterial infections, and some present with IBD-like features.[51,52]

CD-like disease is a typical manifestation of glycogen storage disease type Ib, characterized by neutropenia and neutrophil granulocyte dysfunction.[48,49,53] Granulocyte colony-stimulating factor has been used to treat neutropenia and colitis in some patients with glycogen storage disease type Ib.[53]

In addition to neutrophil defects, defects in several other genes, including *WAS*, *LRBA*, *BTK*, *CD40LG*, and *FOXP3*, can lead to autoantibody-induced or hemophagocytosis-induced neutropenia. These multidimensional mechanisms of secondary immune dysregulation indicate the functional complexity of some seemingly unrelated genetic immune defects and the broad effects they might have on the innate immune system.

Hyperinflammatory and Autoinflammatory Disorders

VEOIBD has been described in a number of hyperinflammatory and autoinflammatory disorders such as mevalonate kinase deficiency,[54,55] phospholipase C-γ2 defects,[56] familial Mediterranean fever,[57–59] Hermansky–Pudlak syndrome (type 1, 4, and 6),[60–64] X-linked lymphoproliferative syndrome type 1[65] and type 2,[66–68] or familial hemophagocytic lymphohistiocytosis type 5.[69] Among these, mevalonate kinase deficiency is a prototypic autoinflammatory disorder, characterized by increased activation of caspase-1 and subsequent activation of IL-1β.[70] Inhibiting IL-1β signaling with antibodies that block IL-1β or IL-1 receptor antagonists can induce complete or partial remission in patients, including those with VEOIBD.[54,55,71]

X-linked lymphoproliferative syndrome 2 is caused by defects in the *XIAP* gene. At least 20% of patients with *XIAP* defects develop a CD-like immunopathology with severe fistulizing perianal phenotype.[66–68,72,73] In these patients, Epstein–Barr virus infections can lead to life-threatening hemophagocytic lymphohistiocytosis. Originally associated with a poor outcome after HSCT,[74] less toxic induction regimens could improve the prognosis and cure this form of IBD.[67,73]

Complex Defects in T- and B-Cell Function

IBD-like immunopathology is a common finding in patients with defects in the adaptive immune system. Multiple genetic defects that disturb T- and/or B-cell selection and activation can cause complex immune dysfunction, including immunodeficiency and autoimmunity as well as intestinal inflammation. Disorders associated with IBD-like immunopathology include B-cell defects such as common variable immunodeficiency (CVID), hyper-immunoglobulin (Ig) M syndrome, and agammaglobulinemia.[75–79] Several other primary immune deficiencies, such as Wiskott–Aldrich syndrome[80] (WAS) and atypical SCID or Omenn syndrome[81,82] can also cause IBD-like intestinal inflammation.

CVID, Agammaglobulinemia, and Hyper IgM Syndrome

Patients with CVID have clinical features of different types of IBD, spanning CD, UC, and ulcerative proctitis–like findings.[83,84] Although CVID is largely polygenic, a small proportion of cases of CVID have been associated with specific genetic defects. CVID type 1 is caused by variants in the gene encoding the inducible T-cell costimulator (*ICOS*),[85,86] whereas CVID type 8 is caused by variants in *LRBA*.[87–89] Patients with these mutations can present with IBD-like pathology. Recently, IBD and CVID-like disease was described in a family with IL-21 deficiency.[90]

Patients with agammaglobulinemia, caused by defects in *BTK* or *PIK3R1*, as well as patients with subtypes of hyper IgM syndrome caused by defects in *CD40LG*, *AICDA*, or *IKBKG* can develop IBD-like immunopathology.[75–79] It is worth considering that several other immunodeficiencies, not regarded as primary B-cell defects, are similarly associated with low numbers of B cells and/or Igs (such as those caused by variants in *SKIV2L* and *TTC37*; see Table 2 and Supplementary Table 1).

WAS

WAS is a primary immunodeficiency. Many patients with WAS present with UC-like noninfectious colitis during early infancy.[80] The syndrome is caused by the absence or abnormal expression of the cytoskeletal regulator WASP and is associated with defects in most immune subsets (effector and regulatory T cells, natural killer [NK] T cells, B cells, dendritic cells, macrophages, NK cells, and neutrophils).[91] In addition to features of UC, patients develop many other autoimmune complications. Allogeneic bone marrow transplantation is the standard of care for those patients.[80] Patients who are not candidates for bone marrow transplantation have been successfully treated with experimental gene therapy approaches.[92,93]

Atypical SCID Defects

Patients with atypical SCID defects have residual B- and T-cell development and oligoclonal T-cell expansion.[94] VEOIBD is commonly observed in patients with atypical SCID due to hypomorphic defects in multiple genes such as *DCLRE1C*, *ZAP70*, *RAG2*, *IL2RG*, *LIG4*, *ADA*, and *CD3G*.[81,82,95] This list of genes is likely not complete, and it seems reasonable to assume that most genetic defects that cause T-cell atypical SCID also cause IBD.

A subset of patients with SCID present with severe eczematous rash (Omenn syndrome).[81] It is not clear whether residual lymphocyte function in patients with hypomorphic *TTC7A* mutations is a precondition for IBD or contributes to VEOIBD.[38] Intestinal and skin lesions also develop in patients with SCID due to graft-versus-host disease in response to maternal cells.[96]

Hoyeraal–Hreidarsson Syndrome

Hoyeraal–Hreidarsson syndrome is a severe form of dyskeratosis congenita characterized by dysplastic nails, lacy reticular skin pigmentation, and oral leukoplakia. It is a multiorgan disorder. Patients with mutations in *RTEL1*[97,98] or *DKC1*[99–101] can develop SCID and intestinal inflammation.

Regulatory T Cells and IL-10 Signaling

Loss-of-function defects in IL-10 and its receptor (encoded by *IL10RA* and *IL10RB*)[102–106] cause VEOIBD with perianal disease and folliculitis within the first months of life. All patients with loss-of-function mutations that prevent IL-10 signaling develop IBD-like immunopathology, indicating that these defects are a monogenic form of IBD with 100% penetrance.[106,107] The anti-inflammatory cytokine IL-10 is secreted by natural and induced regulatory T cells (in particular, intestinal $CD4^{+}FOXP3^{+}$ and Tr1 cells), macrophages, and B cells. Many intestinal and extraintestinal cell types express the IL-10 receptor and respond to IL-10. Defects in IL-10 receptor signaling affect the differentiation of macrophage M1/M2, shifting them toward an inflammatory phenotype.[108] Defects in IL-10 signaling are associated with extraintestinal inflammation such as folliculitis or arthritis and predispose to B-cell lymphoma.[102,103,109] Conventional therapy options are largely not effective in patients with IL-10 signaling defects, but allogeneic matched or mismatched HSCT can induce sustained remission of intestinal inflammation.[30,102,103,107,110]

X-linked immune dysregulation, polyendocrinopathy, enteropathy syndrome (IPEX) is caused by mutations in the transcription factor FOXP3. Those mutations affect natural and induced regulatory T cells, causing autoimmunity and immunodeficiency but also enteropathy in a large percentage of patients with colitis.[111,112] The intestinal lesions that develop in patients with IPEX can be classified as graft-versus-host disease–like changes with small bowel involvement and colitis, celiac disease–like lesions, or enteropathy with goblet cell depletion.[113]

Antibodies against enterocytes and/or antibodies against goblet cells can be detected in the serum of patients with IPEX.[113] IPEX-like immune dysregulation with enteropathy can also be caused by defects in IL-2 signaling in patients with defects in the IL-2 receptor α chain (IL2RA, encoding CD25)[114,115] or a dominant gain of function in STAT1 signaling.[116]

Other Disorders and Genes

IBD or IBD-like disorders have been described in patients with several other disorders. In some disorders, there is no well-defined plausible functional mechanism. For example, patients with trichohepatoenteric syndrome have presumed defects in epithelial cells that lead to intractable diarrhea.[117,118] However, an adaptive immune defect might also cause this disorder, because the patients have Ig deficiencies that require Ig substitution.

Several genes, described in the Supplementary Information for Table 1, are associated with a single or less well-defined case report of patients who developed IBD-like features. Some of these patients might happen to have intestinal inflammation by coincidence, and even several case reports cannot exclude a publication bias.

Heterozygous defects in the *PTEN* phosphatase are associated not only with multiple tumors but also immune dysregulation and autoimmunity.[119] Inflammatory polyps are common among patients with PTEN hamartoma tumor syndrome and indeterminate colitis, and ileitis is a rare complication.[119] The functional mechanism involved in intestinal inflammatory polyps and intestinal inflammation is not clear because heterozygous mutations in *PTEN* are not associated with conventional immunodeficiency and affect multiple cell types.

Very early onset enteropathies and intestinal infections are described in several monogenic immunodeficiency and/or autoinflammation disorders, including defects in the itchy E3 ubiquitin protein ligase activity encoded by the *ITCH* gene, defects in E3 ubiquitin ligase HOIL-1 encoded by *HOIL1*, and gain of function defects in *IKBA* encoded by *NFKBIA* (see Supplementary Information for Table 1). It is not clear what activates the inflammatory events in those patients; it could be pathogenic microbes in the intestine, food, or IBD-like intestinal inflammation induced by the commensal microbiota.

Additional disorders are associated with intestinal inflammation without immunodeficiency or without known epithelial mechanisms. For example, some patients with Hirschsprung disease, an intestinal innervation and dysmotility disorder, develop enterocolitis associated with dominant germline mutations in *RET*.[120,121] One possible pathomechanism could be increased bacterial translocation due to bacterial stasis leading to subsequent inflammation.

Despite multiple reports of complement system deficiencies and IBD, this group of disorders is not clearly defined. *MASP2* deficiency has been reported in a patient with pediatric-onset IBD. However, reports of intestinal inflammation in several other complement defects are much harder to interpret because those patients present with inconsistent disease phenotypes; some are less well documented and could be simple chance findings (see Supplementary Information for Table 1).

Why Should We Care About Monogenic Defects?

It is a challenge to diagnose the rare patients with monogenic IBD, but differences in the prognosis and medical management argue that a genetic diagnosis should not be missed. As a group, these diseases have high morbidity and subgroups have high mortality if untreated. Based on their causes, some require different treatment strategies than most cases of IBD.

Allogeneic HSCT has been used to treat several monogenic disorders. It is the standard treatment for patients with disorders that do not respond to conventional treatment, those with high mortality, or those that increase susceptibility to hematopoietic cancers (eg IL-10 signaling defects, IPEX, WAS, or increasingly *XIAP* deficiency). Introduction of HSCT as a potentially curative treatment option

for intestinal and extraintestinal manifestations of these disorders has changed clinical practice.[30,73,74,107,111]

However, there is evidence from mouse models and clinical studies that patients with epithelial barrier defects are less amenable to HSCT, because this does not correct the defect that causes the disease (eg, *NEMO* deficiency or possibly *TTC7A* deficiency). For example, severe recurrence of multiple intestinal atresia after HSCT in patients with TTC7A deficiency[36,37] indicates a contribution of the enterocyte defect to pathogenesis. Due to the significant risk associated with HSCT, including graft-versus-host disease and severe infections, it is important to determine the genetic basis of each patient's VEOIBD before selecting HSCT as a treatment approach.

Understanding the pathophysiology of a disorder caused by a genetic defect can identify unconventional biological treatment options that interfere with specific pathogenic pathways. Patients with mevalonate kinase deficiency or CGD produce excess amounts of IL-1β, so treatment with IL-1β receptor antagonists has been successful.[54,55] This treatment is not part of the standard therapeutic repertoire for patients with conventional IBD. Access to individualized genotype-specific therapies is particularly important, because it might avoid both surgery (including colectomy) and the adverse effects of medical therapy in patients who are unlikely to benefit from conventional IBD therapies in the long term.

A further incentive to establish a specific genetic diagnosis is the ability to anticipate complications. Some patients should be screened for infections (such as for Epstein–Barr virus infection status in *XIAP* defects) or cancer (including B-cell lymphomas in patients with IL-10 receptor deficiency[109] or skin and hematopoietic malignancies in Hoyeraal–Hreidarsson syndrome). Genetic information can also identify patients who should be screened for extraintestinal manifestations such as idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, autoimmune neutropenia, or autoimmune hepatitis (Table 2). Knowledge of the genetic predisposition can reduce the time to detect associated complications.

Families who are aware of the genetic basis of their disease can receive genetic counseling.

When Should We Suspect Monogenic IBD?

The timely diagnosis of monogenic IBD requires assessments of intestinal and extraintestinal disease phenotypes in conjunction with the histopathology and appropriate laboratory tests to exclude allergies or infections.[18,19] Classification of clinical, endoscopic, histological, and imaging findings into CD-like and UC-like phenotypes can be helpful but is not sufficient to differentiate patients with a monogenic disorder from conventional idiopathic CD (such as discontinuous, transmural inflammation affecting the entire gastrointestinal tract, fistulizing disease, or granuloma formation) or UC (a continuous, colonic disorder with crypt abscess formation and increases in chronic inflammatory cells, typically restricted to the lamina propria). Histopathologists use nonspecific terms such as IBD unclassified in a relevant proportion of patients with VEOIBD, including monogenic forms of IBD. In the absence of highly specific and sensitive intestinal histological markers of monogenic forms of IBD, extraintestinal findings and laboratory test results are important factors to focus the search for monogenic forms of IBD (Table 3 and Figure 2). A phenotypic aide-mémoire summarizing the key findings to ensure that a careful clinical history for VEOIBD and examination to narrow the search for an underlying monogenetic defect is YOUNG AGE MATTERS MOST (YOUNG AGE onset, Multiple family members and consanguinity, Autoimmunity, Thriving failure, Treatment with conventional medication fails, Endocrine concerns, Recurrent infections or unexplained fever, Severe perianal disease, Macrophage activation syndrome and hemophagocytic lymphohistiocytosis, Obstruction and atresia of intestine,

Table 3. Pivotal Prompts for Suspecting Monogenic IBD

Key points	Comments
Very early age of onset of IBD-like immunopathology	Likelihood increases with very early onset, particularly in those younger than 2 years of age at diagnosis
Family history	In particular consanguinity, predominance of affected males in families, or multiple family members affected
Atypical endoscopic or histological findings	For example, extreme epithelial apoptosis or loss of germinal centers
Resistance to conventional therapies	Such as exclusive enteral nutrition, corticosteroids, and/or biological therapy
Skin lesions, nail dystrophy, or hair abnormalities	For example, epidermolysis bullosa, eczema, folliculitis, pyoderma or abscesses, woolen hair, or trichorrhexis nodosa
Severe or very early onset perianal disease	Fistulas and abscesses
Lymphoid organ abnormalities	For example, lymph node abscesses, splenomegaly
Recurrent or atypical infections	Intestinal and nonintestinal
Hemophagocytic lymphohistiocytosis	Induced by viral infections such as Epstein–Barr virus or cytomegalovirus or macrophage activation syndrome
Associated autoimmunity	For example, arthritis, serositis, sclerosing cholangitis, anemia, and endocrine dysfunction such as thyroiditis, type 1 diabetes mellitus
Early development of tumors	For example, non-Hodgkin lymphoma, skin tumors, hamartoma, thyroid tumors

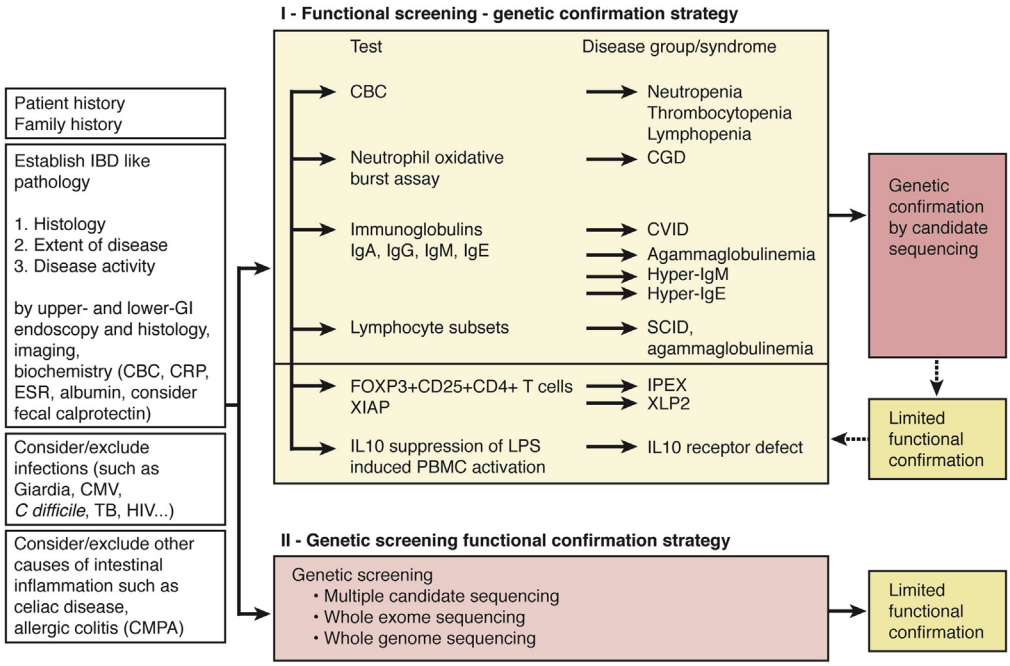

Figure 2. Diagnosis of VEOIBD. Patient and family history, physical examination, endoscopic investigations, imaging, and limited biochemistry and microbiology/virology tests are required to establish the diagnosis of IBD, assess disease localization and behavior, and determine inflammatory activity. If there is doubt, those tests can contribute to exclude the much more frequent gastrointestinal infections and non-IBD immune responses toward dietary antigens. Cow's milk protein allergy can present with enteropathy and colitis, and celiac disease can mimic autoimmune enteropathies. Fecal calprotectin can be helpful but may be increased even in healthy infants. The current diagnostic strategy to investigate a monogenic cause of IBD-like intestinal inflammation is largely based on restricted functional screening followed by genetic confirmation. A restricted set of laboratory tests is needed to propose candidate genes of the most common genetic defects for subsequent limited sequencing. As a complementary approach, genetic screening for IBD-causative rare variants using next-generation sequencing might be followed by limited functional confirmatory studies. The complexity of problems in these children requires interdisciplinary support, including pediatric gastroenterologists, immunologists, geneticists, and infectious disease specialists. CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CMV, cytomegalovirus; TB, tuberculosis; HIV, human immunodeficiency virus; CMPA, cow's milk protein allergy.

Skin lesions and dental and hair abnormalities, and Tumors). An important component of management is to solicit advice from a specialist in VEOIBD.

Very early age of onset of intestinal symptoms and IBD-like endoscopic and histological changes are strong indicators of monogenic IBD as a group (Figure 1). However, there are clear gene-specific differences in the age of onset. The reported time of onset of IBD-like immunopathology in subgroups with, for example, IL-10 signaling defects, WAS, or IPEX, is infancy and early childhood. However, atypical late onset of IBD has been reported in patients with WAS[122,123] as well as IPEX.[124–126] The age is variable in neutrophil defects, B-cell defects, and *XIAP* deficiency. Indeed, *XIAP* deficiency caused by identical genetic defects within families can be associated with VEOIBD or adult-onset IBD.[68,73,127] Other diseases, such as *GUCY2C* deficiency, typically develop during adulthood (Figure 1). Phenotypes of many monogenic forms of IBD change over time; gastrointestinal problems can present as an initial or a later finding.

Some candidate disorders will be recognized by their pathognomonic symptom combinations. Because there are no specific and fully reliable endoscopic and histological features of monogenic VEOIBD, patients with VEOIBD and multiple other features (listed in Table 3) should be considered to have increased likelihood to carry disease-causing mutations. The degree of suspicion should dictate the extent of functional and genetic exploration for an underlying cause. It is important to emphasize that in the majority of patients with infantile IBD or VEOIBD, no genetic defect has currently been discovered that would explain the immunopathology. This fraction of causative defects will increase as our knowledge expands and with a growing number of patients undergoing whole-exome sequencing (WES). Although young age of IBD onset is a strong indicator, a strong suspicion for a monogenic cause should lead to limited functional or genetics screening irrespective of age.

Laboratory Tests and Functional Screens

Laboratory tests, upper and lower gastrointestinal endoscopy with histological analysis of multiple biopsy specimens, and imaging should be performed for every patient with VEOIBD according to guidelines.[13,18–21,128] Histological investigation is paramount not only to differentiate IBD-like features but also to exclude other established pathologies such as eosinophilic or allergic gastrointestinal disease and infection.

Cow's milk protein allergy is common and can cause severe colitis that resembles UC and even requires hospitalization. It manifests typically within the first 2 to 3 months of exposure to cow's milk protein. This may be apparent with breast-feeding or only after introducing formula feeding. Colitis resolves after cow's milk is removed from the diet, so a trial of exclusive feeding with an amino acid–based infant formula is a customary treatment strategy for all VEOIBD diagnosed when the patient is younger than 1 year of age. However, improvement of symptoms or inflammation does not exclude the possibility that a patient could have a monogenetic IBD disorder, because food intolerance and allergy can be secondary to the disorder and allergen avoidance by exclusive enteral nutrition with elemental formula could also alleviate the inflammation of classic IBD.

High levels of IgE and/or eosinophilia are also found in patients with monogenic disorders caused by defects in *FOXP3*, *IL2RA*, *IKBKG*, *WAS*, or *DOCK8* (Table 2 and Supplementary Table 1). It should also be standard practice to exclude infectious causes such as bacteria (*Yersinia* spp, *Salmonella* spp, *Shigella* spp, *Campylobacter* spp, *Mycobacterium tuberculosis*, *Clostridium difficile*), parasites (*Entamoeba histolytica*, *Giardia lamblia*), and viral infections (cytomegalovirus or human immunodeficiency virus), remembering that some infections can mimic IBD. However, most of these pathogens do not cause bloody diarrhea for more than 2 to 3 weeks. In addition, monogenic disorders (such as B- or T-cell defect immunodeficiencies or familial HLH type 5, caused by *STXBP2* deficiency) predispose patients to intestinal infections.[69] Celiac disease should be considered as a differential diagnosis for patients with suspected autoimmune enteropathy presenting with villous atrophy (such as IPEX or IPEX-like patients).

To detect possible causes of monogenic IBD-like immunopathology, we propose additional laboratory screening for all children diagnosed before 6 years of age. The limited set of laboratory tests includes measurements of IgA, IgE, IgG, and IgM; flow cytometry analysis of lymphocyte subsets (CD3, CD4, CD8, CD19/CD20, NK cells); and analysis of oxidative burst by neutrophils (using the nitro blue tetrazolium test or flow cytometry–based assays such as the dihydrorhodamine fluorescence assay).

When placed in the context of clinical, histopathologic, and radiological data, these tests can guide the diagnosis toward the more prevalent defects of neutrophil, B-cell, or T-cell dysfunction. Further tests are necessary to characterize particular subgroups, such as those who develop the disease when they are younger than 2 years of age, those with excessive autoimmunity, or those with severe perianal disease. Those tests include flow cytometry analysis of XIAP expression by lymphocytes and NK cells[129,130] or FOXP3 expression in $CD4^+$ T cells, which can diagnose a significant proportion of patients with XLP2 and IPEX. Flow cytometry can detect functional defects in MDP signaling in patients with *XIAP* deficiency.[131] IL10RA and IL10RB defects can be detected by assays that determine whether exogenous IL-10 will suppress lipopolysaccharide-induced peripheral blood mononuclear cell cytokine secretion or IL-10–induced STAT3 phosphorylation.[30,103,107] Increased levels of antibodies against enterocytes can indicate autoimmune enteropathy, in particular in patients with IPEX.

In contrast to measurements of Igs, flow cytometry, and oxidative burst assays (which are largely standardized), other tests such as IL-10–mediated suppression of LPS-induced peripheral blood mononuclear cell activation and detection of antibodies against enterocytes are nonroutine assays. Similarly, additional tests for extremely rare genetic defects might be appropriate but are only available at specialized laboratories, often as part of research projects. The clinical utility of the algorithm to use a limited set of laboratory tests to differentiate between conventional and monogenic VEOIBD, as suggested in Figure 2, is based on experience, case reports, and case series of individual disorders. It has not been validated in prospective studies of patients with all forms of VEOIBD.

Diagnosis via Sequencing of Candidate Genes Versus Parallel Next-Generation Sequencing

The classic approach to detect monogenic forms of IBD, as described in the preceding text and summarized in Figure 2, is based on careful phenotypic analysis and candidate sequencing to confirm a suspected genetic diagnosis. Due to the increasing number of candidate genes, sequential candidate sequencing can be costly and time consuming. It is therefore not surprising to propose that this strategy of functional screening followed by genetic confirmation will increasingly be complemented by early parallel genetic screening using next-generation sequencing followed by functional confirmation. The US Food and Drug Administration has recently granted marketing authorization for the first next-generation genomic sequencer, which will further pave the way for genome, exome, or other targeted parallel genetic tests in routine practice.[132,133] WES or even whole-genome sequencing will increasingly become part of the routine analysis of patients with suspected genetic disorders including subtypes of IBD.[59,134,135] This has several important implications for selecting candidate gene lists, identification of disease-causing variants, and dealing with a large number of genetic variants of unknown relevance. In research and clinical settings, WES has been shown to reliably detect genetic variants that cause VEOIBD in genes such as *XIAP*,[67] *IL10RA*,[136,137] *G6PC3*,[138] *MEFV*,[59] *LRBA*,[88] *FOXP3*,[126] and *TTC7A*.[38]

There are several reasons to propose extended parallel candidate sequencing for patients with suspected monogenic IBD. Immune and gastrointestinal phenotypes of patients evolve over time, whereas the diagnosis needs to be made at the initial presentation to avoid unnecessary tests and treatment. IBD-like immunopathology can be linked to nonclassic phenotypes of known immunodeficiencies, such as hypomorphic genetic defects in SCID patients (in genes such as *ZAP70*, *RAG2*, *IL2RG*, *LIG4*, *ADA*, *DCLRE1C*, *CD3G*, or *TTC7A*; see Table 2) with residual B- and T-cell development,[38,81,82] glucose-6-phosphatase 3 deficiency with lymphopenia,[50] or *FOXP3* defects without the classic IPEX phenotype.[126] WES has revealed unexpected known causative variants[67] even after workup in centers with specialized

immunologic and genetic clinical and research facilities. This all demonstrates that current knowledge about the disease phenotype spectrum is incomplete, which means that a pure candidate approach is not reliable and genetic screening may have advantages. The 50 monogenic defects associated with IBD provide an initial filter to identify patients with monogenic disorders.

Because of the greatly reduced costs of next-generation sequencing, it is probably cost effective in many cases to perform multiplex gene sequencing, WES, or whole-genome sequencing rather than sequential Sanger sequencing of multiple genes. A big advantage of WES is the potential to identify novel causal genetic variants once the initial candidate filter list of known disease-causing candidates has been analyzed. The number of gene variants associated with VEOIBD is indeed constantly increasing, largely due to the new sequencing technologies, so data sets derived from WES allow updated analysis of candidates as well as novel genes. Because multiple genetic defects can lead to spontaneous or induced colitis in mice,[1,139] assuming homology, it is likely that many additional human gene variants will be associated with IBD.

Targeted sequencing of genes of interest is an alternative approach to exome-targeted sequencing. Initial studies to perform targeted next-generation parallel sequencing showed the potential power of this approach.[140] Targeted next-generation sequencing of the 170 primary immunodeficiency (PID)-related genes accurately detected point mutations and exonic deletions.[140] Only 9 of 170 PID-related genes analyzed showed inadequate coverage. Four of 26 patients with PID without an established prescreening genetic diagnosis, despite routine functional and genetic testing, were diagnosed, indicating the advantage of parallel genetic screening. Because a major group of VEOIBD-causing variants is associated with PID-related genes, it is obvious how this approach can be adapted and extended to monogenic IBD genes.

Genetic approaches also offer practical advantages. Specialized functional immune assays are often only available in research laboratories and are not necessarily validated; functional tests often require rapid processing of peripheral blood mononuclear cells or biopsy specimens in specialized laboratories. This means that handling of DNA and sequencing seems far less prone to error or variation.

However, relying solely on genetic screening can be misleading, because computational mutation prediction can fail to detect functional damaging variants. For example, variants in the protein-coding region of the *IL10RA* gene were misclassified as "tolerated" by certain prediction tools, whereas other prediction tools and functional analysis reported defects in IL-10 signaling.[30] Although most studies report variants in protein-coding regions in monogenic diseases, there could be selection bias. It is indeed far more difficult to establish the biological effects of variants that affect processes such as splicing, gene expression, or messenger RNA stability. It should go without saying that novel genetic variants require appropriate functional validation.

The increased availability of sequencing data sets highlights the role of mutation-specific IBD-causing variants that illustrate the functional balance of gene products affected by gain or loss of function variants as well as gene dosage effects. Inherited gain-of-function mutations in guanylyl cyclase cause diarrhea and increase susceptibility to IBD, whereas loss-of-function mutations lead to intestinal obstruction and meconium ileus.[141] Gain-of-function mutations in STAT1 cause an IPEX-like syndrome with enteropathy,[116] whereas loss-of-function mutations are found in patients with autosomal dominant chronic mucocutaneous candidiasis.[142] Loss of TTC7A activity results in multiple intestinal atresia and SCID,[36,37,143] whereas hypomorphic mutations cause VEOIBD.[38] Similarly, loss-of-function variants cause classic SCID defects, whereas hypomorphic variants in the same genes allow residual oligoclonal T-cell activation and are associated with immunopathology, including colitis.

Performing next-generation sequencing exome-wide or genome-wide will identify (in each patient) genetic variants of unknown relevance and, in some patients, known variants that are associated with incomplete penetrance or variable phenotype severity. Increasing use of DNA sequencing technologies will lead to detection of hypomorphic variants that cause milder phenotypes and/or later onset of IBD. The increased availability of genotype-phenotype data sets in databases such as ClinVar (http://www.ncbi.nlm.nih.gov/clinvar)[144] or commercial databases will increase our ability to differentiate variants that cause IBD from those without biological effects. WES analysis of patients with pediatric onset of IBD, including VEOIBD, has revealed multiple rare genetic variants in those IBD susceptibility genes that were discovered by association studies.[145] Similarly, WES analysis of patients with genetically confirmed mevalonate kinase deficiency identified multiple variants in IBD-related genes outside of the *MVK* gene.[146] It is currently not clear how strongly these rare variants influence the genetic susceptibility to IBD as additive or synergistic factors. In particular, in patients with nonconventional forms of IBD, the identification of variants of unknown relevance can lead to the therapeutic dilemma of whether to wait for the disease to progress or start early treatment. Because some of the disease-specific treatment options have potentially severe adverse effects, careful evaluation of genetic variants is required not only to validate sequence data[147] and statistical association but to provide functional evidence that those variants cause disease.[133,148]

Conclusion

Rare monogenic disorders that affect intestinal immune and epithelial function can lead to VEOIBD and severe phenotypes. These disorders are diagnosed based on clinical and genetic information. Accurate genetic diagnosis is required for assessing prognosis and proper treatment of patients. We summarized phenotypes and laboratory findings for more than 50 monogenic disorders and suggest a diagnostic strategy to identify these extremely rare diseases, which have large effects on patients and their families.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org and at http://dx.doi.org/10.1053/j.gastro.2014.07.023.

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Conflicts of interest
The authors disclose the following: H.H.U. has participated in industrial project collaboration with Eli Lilly, UCB Pharma, and Vertex Pharmaceuticals and received travel support from GlaxoSmithKline Foundation, Essex Pharma, Actelion, and MSD. T.S. has received speaker's fees from MSD and travel support from Nestlé Nutrition. S.K. has received consulting or speaker's fees from AbbVie, Danone, Janssen Pharmaceutical Research & Development, Merck, MSD, Nestlé Nutrition, Vifor, and Wyeth and has participated in industrial project collaboration with Euroimmun, Eurospital, Inova, Mead Johnson, Phadia/Thermo Fisher Scientific, and Nestlé Nutrition. N.S. has served as an advisory board member for Mead Johnson and received a unrestricted educational grant from MSD. D.C.W. has received consulting fees, speaker's fees, meeting attendance support, or research support from MSD, Ferring Pharmaceuticals, Falk, Pfizer, and Nestlé. S.P.T. has received consulting fees from AbbVie, Cosmo Technologies, Ferring Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutical Research & Development, Merck, Novartis, Novo Nordisk, Pfizer, Santarus, Schering-Plough, Shire Pharmaceuticals, Sigmoid Pharma, Tillotts Pharma AG, UCB Pharma, Vifor, and Warner Chilcott UK; research grants from AbbVie, Janssen Pharmaceutical Research & Development, Novartis, Pfizer, and UCB Pharma; and payments for lectures from AbbVie, Ferring Pharmaceuticals, Merck, Sanofi, and Tillotts Pharma AG. D.T. has received consulting fees, research grants, royalties, or honorarium from MSD, Janssen, Shire, Bristol-Myers Squibb, Hospital for Sick Children, and Abbott. S.B.S. has received consulting fees from AbbVie, Janssen Pharmaceutical Research & Development, Talecris, Cubist, Ironwoods, and Pfizer; speaking fees from UCB; and research grants from Pfizer. The remaining authors disclose no conflicts.

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Supplementary Information for Table 1

Examples of genetic variants with potential association with IBD and syndromes associated with IBD are shown. A systematic review of the literature was performed, focusing on IBD-like immunopathology in monogenic disorders largely through PubMed and OMIM databases. In addition to an iterated literature search focused on pediatric onset or monogenic IBD, an extensive list of primary immunodeficiencies[1,2] was searched for occurrence of the PID-associated gene symbols (partially gene or protein name) with reports of "colitis" or "Crohn" or "IBD" or "inflammatory bowel disease." A list of likely causative gene defects with association with IBD-like immunopathology was created. We selected intestinal and extraintestinal clinical features as well as laboratory findings that define key subgroups of patients with prototypic monogenic defects.

For each genetic defect, relevant reports were retrieved and selected clinical features and laboratory parameters were recorded. Data extraction was performed independently by 4 clinicians using a structured approach. Disagreements in data interpretation were resolved by several rounds of discussion until consensus was reached. All authors discussed key phenotype criteria that suggest monogenic IBD-like immunopathology as well as the core diagnostic approach to VEOIBD.

Because there are a number of hypomorphic variants with nonconventional phenotype, the key findings were extracted from the patients with IBD-like immunopathology and are therefore often but not necessarily representative of the classic disease phenotype. Activation mutations (gain of function) in *IKBA* are associated with diarrhea due to enteropathy, early intestinal infections, and possibly colitis.[3–6] *ITCH* deficiency can lead to autoimmune enteropathy with lymphocytic inflammation of the small bowel lamina propria, associated with antienterocyte antibodies, perinuclear antineutrophil cytoplasmic antibodies, or anti–smooth muscle antibodies.[7]

A very early onset of colitis was reported in a girl with severe congenital hypertriglyceridemia. WES identified compound heterozygous mutations in the *GPIHBP1* gene.[8]

Patients who developed IBD have been reported in other disorders. These include *SIRT1* defects,[9] Wolfram syndrome (*WFS1*),[10] Niemann–Pick type C disease (*NPC1*),[11–13] Charcot–Marie–Tooth disease (*CMT4C*),[14] Gorlin syndrome (*PTCH1*),[15] and Brooke–Spiegler syndrome (*CYLD*).[16]

No genetic diagnosis was provided in a patient with Chediak–Higashi syndrome[17] and patients with autoimmune lymphoproliferative syndrome[18] (personal communication, David Teachey, October 2013). Clear syndromal features without genetic diagnosis are seen in other patients, such as in pigmentary disorder, reticulate, with systemic manifestation (PDR syndrome)[19] or leukoencephalopathy, arthritis, colitis, and hypogammaglobulinemia (LACH syndrome).[20] Inflammation of the small and large bowel was found in patients with tufting enteropathy confirmed by negative epithelial cell adhesion molecule immunohistochemical staining.[21] Interestingly, the inflammatory infiltrates in those patients with tufting enteropathy resolved spontaneously over time.

A group of complement defects can present with intestinal inflammation. Despite a range of possible candidate genes, for the majority there is either no genetic diagnosis provided, no histological proof of IBD-like intestinal inflammation, or single patient adult-onset IBD that could present a chance finding or publication bias (reviewed by Marks et al[22,23]). This includes C2 deficiency and C1-esterase deficiency (reviewed by Marks et al[22,23]), C6 deficiency,[24] or H-ficolin deficiency (*FCN3*).[25]

Supplementary Information for Figure 1

Additional information is provided regarding age of intestinal inflammation in patients with CGD,[26,27] IPEX,[28–47] WAS,[48–51] ITGB2,[52] IL10RA,[53] and LRBA defects.

Supplementary References

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