

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, extra-intestinal, 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.

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 κ B 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.

Keywords: Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis; Unclassified Colitis; Indeterminate Colitis;

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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 classification¹² 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 modification¹³ of the Montreal classification¹² 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).

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.

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

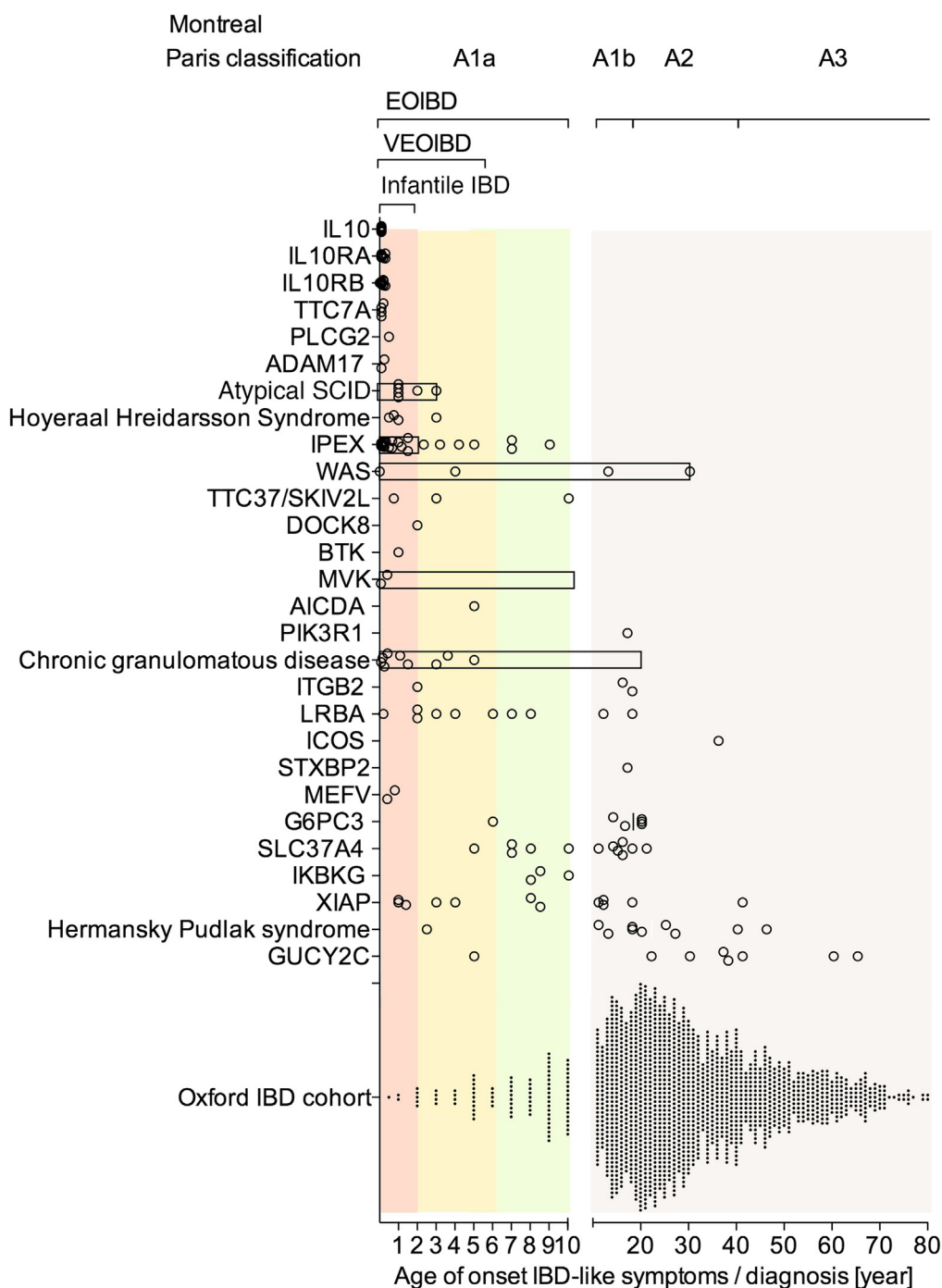


Figure 1. Age of onset of IBD-like symptoms in patients with monogenic diseases. Multiple genetic defects are summarized in the group of atypical SCID, Hoyeraal-Hreidarsson syndrome, CGD, and Hermansky-Pudlak syndrome. By comparison, an unselected IBD population is presented (Oxford IBD cohort study; 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 Uhlig²⁹). 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 κ B essential modulator protein [NEMO])³⁴ and *ADAM17* deficiency³⁵ 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

														Extraintestinal findings			References
Group	Syndrome/disorder	Gene	Inheritance	Intestinal findings							Skin lesions	Autoimmunity, inflammation	HLH/ MAS	Neoplasia			
				CD- like	Granuloma	UC- like	Epithelial defect (apoptosis)	Disease location (1–5)	Perianal fistula/ abscess	Penetrating fistulas					Strictures		
1	Epithelial barrier	Dystrophic bullosa	<i>COL7A1</i>	AR				+	3			+	eb				32 (A. Martinez ^a) 32, 149 (A. Martinez ^a) 34, 150, 151
2		Kindler syndrome	<i>FERMT1</i>	AR			+	+	5			+	eb				
3		X-linked ectodermal immunodeficiency	<i>IKBKG</i>	X	+				+	3			+	A, Vasc			
4		<i>TTC7A</i> deficiency	<i>TTC7A</i>	AR				+	3			+					38
5		<i>ADAM17</i> deficiency	<i>ADAM17</i>	AR			(+)	+	3				n, h				35
6		Familial diarrhea	<i>GUCY2C</i>	AD	+				3			+					33 (A. Janecke ^a)
7	Phagocyte defects	CGD	<i>CYBB</i>	X	+	+			1, 3	+			e				39
8		CGD	<i>CYBA</i>	AR	+	+			3	+			e				41
9		CGD	<i>NCF1</i>	AR	+	+			1, 3	+			e				39
10		CGD	<i>NCF2</i>	AR	+	+			1, 3	+			e				39
11		CGD	<i>NCF4</i>	AR	+	+			1, 3				e				40
12		Glycogen storage disease type Ib	<i>SLC37A4</i>	AR	+	+			1, 3	+		+	f				
13		Congenital neutropenia	<i>G6PC3</i>	AR	+				1, 3	+	?	(+)	f				50, 138, 152
14		Leukocyte adhesion deficiency 1	<i>ITGB2</i>	AR	+				1, 3	+		+	f				51, 52
15	Hyperinflammatory and	Mevalonate kinase deficiency	<i>MVK</i>	AR					3			+	+	A, SJ	+		54, 55, 71
16	autoinflammatory	Phospholipase C-γ2 defects	<i>PLCG2</i>	AD			+		3				(eb), e	A, NSIP			56
17	disorders	Familial Mediterranean fever	<i>MEFV</i>	AR			+		5				+	S			57–59
18		Familial hemophagocytic lymphohistiocytosis type 5	<i>STXBP2</i>	AR					3						+		69
19		X-linked lymphoproliferative syndrome 2 (XLP2)	<i>XIAP</i>	X	+	+			3	+	+	(+)	+	?	+		31, 66–68, 72, 73, 127
20		X-linked lymphoproliferative syndrome 1 (XLP1)	<i>SH2D1A</i>	X					3						+	+	65
21		Hermansky–Pudlak syndrome (type 1)	<i>HPS1</i>	AR	+	+			3	+		(+)	+				60–63
22		Hermansky–Pudlak syndrome (type 4)	<i>HPS4</i>	AR	+	+			3	+		(+)	+				60, 62, 153
23		Hermansky–Pudlak syndrome (type 6)	<i>HPS6</i>	AR					3				+				64
24	T- and B-cell defects	CVID 1	<i>ICOS</i>	AR					5				p	A			86
25		CVID 8	<i>LRBA</i>	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)	<i>IL21</i>	AR	+	+											90
27	Agammaglobulinemia	<i>BTK</i>	X	+				5					AIHA			75, 76
28	Agammaglobulinemia	<i>PIK3R1</i>	AR					5				EN	+			77
29	Hyper IgM syndrome	<i>CD40LG</i>	X					1, 5	+				AIHA			78
30	Hyper IgM syndrome	<i>AICDA</i>	AR	+				1, 3					AIHA			79
31	WAS	<i>WAS</i>	X			+		5				e	AIHA, A			80
32	Omenn syndrome	<i>DCLRE1C</i>	AR	+				1, 3								81
33	SCiD	<i>ZAP70</i>	AR			+		5				e				154
34	SCiD/hyper IgM syndrome	<i>RAG2</i>	AR					5				+	AIHA			82, 155
35	SCiD	<i>IL2RG</i>	X					3								156, 157
36	SCiD	<i>LIG4</i>	AR				No further information					+	AN			82
37	SCiD	<i>ADA</i>	AR				No further information					+	AIHA			82
38	SCiD	<i>CD3γ</i>	AR	+				5	+			+				95
39	Hoyeraal–Hreidarsson syndrome	<i>DKC1</i>	X				(+)	1, 3			+	+, n, h			+	99–101
40	Hoyeraal–Hreidarsson syndrome	<i>RTEL1</i>	AR				+	5			+	+, n, h			+	97, 98
41	Hyper IgE syndrome	<i>DOCK8</i>	AR		+			1, 5				e	PSC			158
42	Immunoregulation IPEX	<i>FOXP3</i>	X					3				e, p	AIHA, HT, T1D...			111, 112
43	IPEX-like	<i>IL2RA</i>	AR					2				e	AIHA, HT, T1D...			114
44	IPEX-like	<i>STAT1</i>	AD					2								116
45	IL-10 signaling defects	<i>IL10RA</i>	AR	+	(+)			3	+	+		f, e	A		+	30, 102–105, 107
46	IL-10 signaling defects	<i>IL10RB</i>	AR	+	(+)			3	+	+		f	A, AIH		+	30, 102–105, 107
47	IL-10 signaling defects	<i>IL10</i>	AR	+	(+)			3	+	+						30, 102, 104, 105, 107
48	Others	<i>MASP</i> deficiency	<i>MASP2</i>	AR		+						+	A			159
49	Trichohepatoenteric syndrome	<i>SKIV2L</i>	AR					3				h, +				117, 160
50	Trichohepatoenteric syndrome	<i>TTC37</i>	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; T1D, type 1 diabetes mellitus; MAS, macrophage activation syndrome; NSIP, non-specific interstitial pneumonitis; S, serositis.

^aPersonal 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- γ 2 defects,⁵⁶ familial Mediterranean fever,^{57–59} Heman-sky-Pudlak syndrome (type 1, 4, and 6),^{60–64} X-linked lymphoproliferative syndrome type 1⁶⁵ 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-1 β .⁷⁰ Inhibiting IL-1 β signaling with antibodies that block IL-1 β 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 syndrome⁸⁰ (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 trichiohepatoenteric 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-1 β , so treatment with IL-1 β 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 deficiency¹⁰⁹ or skin and hematopoietic malignancies in Hoyerdal-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

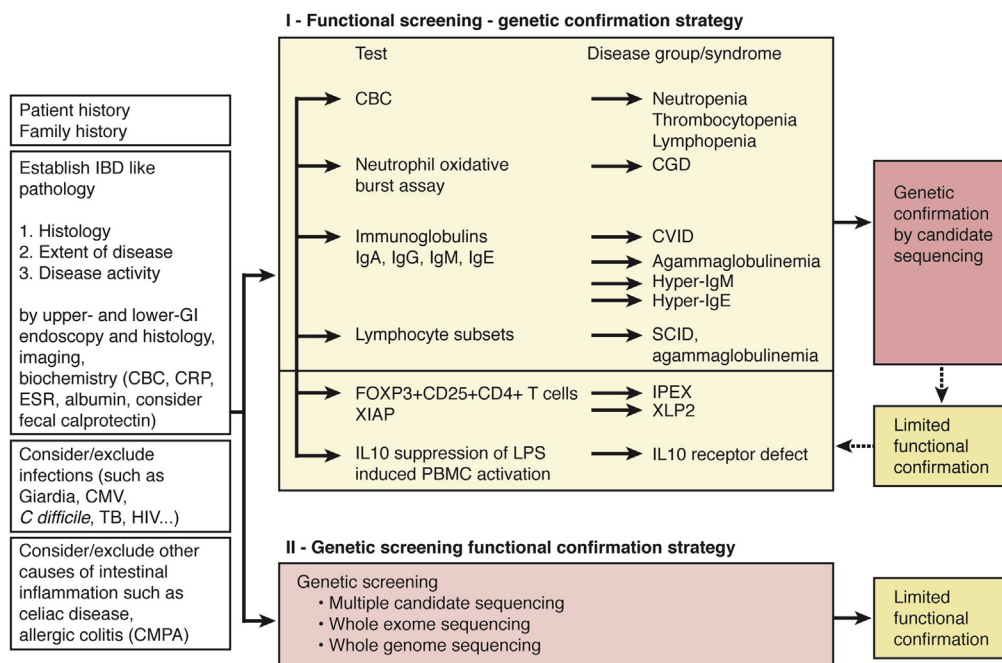


Figure 2. Diagnosis of VEOIBD. Patient and family history, physical examination, endoscopic investigations, imaging, and limited biochemistry and microbiology/virology tests are required to establish the diagnosis of IBD, assess disease localization and behavior, and determine inflammatory activity. 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 variants⁶⁷ 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 data¹⁴⁷ 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>.

References

- Maloy KJ, Powrie F. Intestinal homeostasis and its breakdown in inflammatory bowel disease. *Nature* 2011;474:298–306.
- Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. *Nature* 2011;474:307–317.
- Cosnes J, Gower-Rousseau C, Seksik P, et al. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011;140:1785–1794.
- Thapar N, Shah N, Ramsay AD, et al. Long-term outcome of intractable ulcerating enterocolitis of infancy. *J Pediatr Gastroenterol Nutr* 2005;40:582–588.
- Ruemmele FM, El Khoury MG, Talbotec C, et al. Characteristics of inflammatory bowel disease with onset during the first year of life. *J Pediatr Gastroenterol Nutr* 2006;43:603–609.
- Heyman MB, Kirschner BS, Gold BD, et al. Children with early-onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry. *J Pediatr* 2005;146:35–40.
- Paul T, Birnbaum A, Pal DK, et al. Distinct phenotype of early childhood inflammatory bowel disease. *J Clin Gastroenterol* 2006;40:583–586.
- Cannioto Z, Berti I, Martelossi S, et al. IBD and IBD mimicking enterocolitis in children younger than 2 years of age. *Eur J Pediatr* 2009;168:149–155.
- Ruel J, Ruane D, Mehandru S, et al. IBD across the age spectrum—is it the same disease? *Nat Rev Gastroenterol Hepatol* 2014;11:88–98.
- Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology* 2008;135:1114–1122.
- Williams K, Thomson D, Seto I, et al. Standard 6: age groups for pediatric trials. *Pediatrics* 2012;129(suppl 3):S153–S160.
- Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;19(suppl A):5A–36A.
- Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis* 2011;17:1314–1321.
- Muise AM, Snapper SB, Kugathasan S. The age of gene discovery in very early onset inflammatory bowel disease. *Gastroenterology* 2012;143:285–288.
- de Bie CI, Buderus S, Sandhu BK, et al. Diagnostic workup of paediatric patients with inflammatory bowel disease in Europe: results of a 5-year audit of the EUROKIDS registry. *J Pediatr Gastroenterol Nutr* 2012;54:374–380.
- Prenzel F, Uhlig HH. Frequency of indeterminate colitis in children and adults with IBD - a metaanalysis. *J Crohns Colitis* 2009;3:277–281.
- Ojuawo A, St Louis D, Lindley KJ, et al. Non-infective colitis in infancy: evidence in favour of minor immunodeficiency in its pathogenesis. *Arch Dis Child* 1997;76:345–348.
- Levine A, Koletzko S, Turner D, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr* 2014;58:795–806.
- Turner D, Levine A, Escher JC, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr* 2012;55:340–361.
- Turner D, Travis SP, Griffiths AM, et al. Consensus for managing acute severe ulcerative colitis in children: a systematic review and joint statement from ECCO, ESPGHAN, and the Porto IBD Working Group of ESPGHAN. *Am J Gastroenterol* 2011;106:574–588.
- Van Assche G, Dignass A, Reinisch W, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: special situations. *J Crohns Colitis* 2010;4:63–101.
- Benchimol EI, Fortinsky KJ, Gozdyra P, et al. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis* 2011;17:423–439.
- Henderson P, Hansen R, Cameron FL, et al. Rising incidence of pediatric inflammatory bowel disease in Scotland. *Inflamm Bowel Dis* 2012;18:999–1005.
- Benchimol EI, Guttman A, Griffiths AM, et al. Increasing incidence of paediatric inflammatory bowel disease in Ontario, Canada: evidence from health administrative data. *Gut* 2009;58:1490–1497.
- Benchimol EI, Mack DR, Nguyen GC, et al. Incidence, outcomes, and health services burden of children with very early onset inflammatory bowel disease. *Gastroenterology* 2014 Jun 18 [Epub ahead of print].
- Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 2012;491:119–124.
- Kugathasan S, Baldassano RN, Bradfield JP, et al. Loci on 20q13 and 21q22 are associated with pediatric-onset inflammatory bowel disease. *Nat Genet* 2008;40:1211–1215.
- Imielinski M, Baldassano RN, Griffiths A, et al. Common variants at five new loci associated with early-onset inflammatory bowel disease. *Nat Genet* 2009;41:1335–1340.
- Uhlig HH. Monogenic diseases associated with intestinal inflammation: implications for the understanding of inflammatory bowel disease. *Gut* 2013;62:1795–1805.
- Kotlarz D, Beier R, Murugan D, et al. Loss of interleukin-10 signaling and infantile inflammatory bowel disease: implications for diagnosis and therapy. *Gastroenterology* 2012;143:347–355.

31. Zeissig Y, Petersen BS, Milutinovic S, et al. XIAP variants in male Crohn's disease. *Gut* 2014 Feb 26 [Epub ahead of print].
32. Freeman EB, Koglmeyer J, Martinez AE, et al. Gastrointestinal complications of epidermolysis bullosa in children. *Br J Dermatol* 2008;158:1308–1314.
33. Fiskerstrand T, Arshad N, Haukanes BI, et al. Familial diarrhea syndrome caused by an activating GUCY2C mutation. *N Engl J Med* 2012;366:1586–1595.
34. Cheng LE, Kanwar B, Tcheurekdjian H, et al. Persistent systemic inflammation and atypical enterocolitis in patients with NEMO syndrome. *Clin Immunol* 2009;132:124–131.
35. Blaydon DC, Biancheri P, Di WL, et al. Inflammatory skin and bowel disease linked to ADAM17 deletion. *N Engl J Med* 2011;365:1502–1508.
36. Chen R, Giliani S, Lanzi G, et al. Whole-exome sequencing identifies tetratricopeptide repeat domain 7A (TTC7A) mutations for combined immunodeficiency with intestinal atresias. *J Allergy Clin Immunol* 2013;132:656–664.e17.
37. Samuels ME, Majewski J, Alirezaie N, et al. Exome sequencing identifies mutations in the gene TTC7A in French-Canadian cases with hereditary multiple intestinal atresia. *J Med Genet* 2013;50:324–329.
38. Avitzur Y, Guo C, Mastropaolo LA, et al. Mutations in tetratricopeptide repeat domain 7A result in a severe form of very early onset inflammatory bowel disease. *Gastroenterology* 2014;146:1028–1039.
39. Schappi MG, Smith VV, Goldblatt D, et al. Colitis in chronic granulomatous disease. *Arch Dis Child* 2001;84:147–151.
40. **Matute JD, Arias AA**, Wright NA, et al. A new genetic subgroup of chronic granulomatous disease with autosomal recessive mutations in p40 phox and selective defects in neutrophil NADPH oxidase activity. *Blood* 2009;114:3309–3315.
41. Al-Bousafy A, Al-Tubuly A, Dawi E, et al. Libyan boy with autosomal recessive trait (P22-phox defect) of chronic granulomatous disease. *Libyan J Med* 2006;1:162–171.
42. Muise AM, Xu W, Guo CH, et al. NADPH oxidase complex and IBD candidate gene studies: identification of a rare variant in NCF2 that results in reduced binding to RAC2. *Gut* 2012;61:1028–1035.
43. Dhillon SS, Fattouh R, Elkadri A, et al. Variants in nicotinamide adenine dinucleotide phosphate oxidase complex components determine susceptibility to very early onset inflammatory bowel disease. *Gastroenterology* 2014;147:680–689.
44. Uzel G, Orange JS, Poliak N, et al. Complications of tumor necrosis factor- α blockade in chronic granulomatous disease-related colitis. *Clin Infect Dis* 2010;51:1429–1434.
45. **Kato K, Kojima Y**, Kobayashi C, et al. Successful allogeneic hematopoietic stem cell transplantation for chronic granulomatous disease with inflammatory complications and severe infection. *Int J Hematol* 2011;94:479–482.
46. Freudenberg F, Wintergerst U, Roesen-Wolff A, et al. Therapeutic strategy in p47-phox deficient chronic granulomatous disease presenting as inflammatory bowel disease. *J Allergy Clin Immunol* 2010;125:943–946.e1.
47. Meissner F, Seger RA, Moshous D, et al. Inflammasome activation in NADPH oxidase defective mononuclear phagocytes from patients with chronic granulomatous disease. *Blood* 2010;116:1570–1573.
48. Visser G, Rake JP, Fernandes J, et al. Neutropenia, neutrophil dysfunction, and inflammatory bowel disease in glycogen storage disease type Ib: results of the European Study on Glycogen Storage Disease type I. *J Pediatr* 2000;137:187–191.
49. Yamaguchi T, Ihara K, Matsumoto T, et al. Inflammatory bowel disease-like colitis in glycogen storage disease type 1b. *Inflamm Bowel Dis* 2001;7:128–132.
50. Begin P, Patey N, Mueller P, et al. Inflammatory bowel disease and T cell lymphopenia in G6PC3 deficiency. *J Clin Immunol* 2013;33:520–525.
51. D'Agata ID, Paradis K, Chad Z, et al. Leucocyte adhesion deficiency presenting as a chronic ileocolitis. *Gut* 1996;39:605–608.
52. Uzel G, Kleiner DE, Kuhns DB, et al. Dysfunctional LAD-1 neutrophils and colitis. *Gastroenterology* 2001;121:958–964.
53. Davis MK, Rufo PA, Polyak SF, et al. Adalimumab for the treatment of Crohn-like colitis and enteritis in glycogen storage disease type Ib. *J Inher Metab Dis* 2008 Jan 5 [Epub ahead of print].
54. **Bader-Meunier B, Florkin B**, et al. Mevalonate kinase deficiency: a survey of 50 patients. *Pediatrics* 2011;128:e152–e159.
55. Galeotti C, Meinzer U, Quartier P, et al. Efficacy of interleukin-1-targeting drugs in mevalonate kinase deficiency. *Rheumatology* 2012;51:1855–1859.
56. **Zhou Q, Lee GS**, Brady J, et al. A hypermorphic missense mutation in PLCG2, encoding phospholipase Cgamma2, causes a dominantly inherited auto-inflammatory disease with immunodeficiency. *Am J Hum Genet* 2012;91:713–720.
57. Egritas O, Dalgic B. Infantile colitis as a novel presentation of familial Mediterranean fever responding to colchicine therapy. *J Pediatr Gastroenterol Nutr* 2011;53:102–105.
58. Sari S, Egritas O, Dalgic B. The familial Mediterranean fever (MEFV) gene may be a modifier factor of inflammatory bowel disease in infancy. *Eur J Pediatr* 2008;167:391–393.
59. Cardinale CJ, Kelsen JR, Baldassano RN, et al. Impact of exome sequencing in inflammatory bowel disease. *World J Gastroenterol* 2013;19:6721–6729.
60. Hazzan D, Seward S, Stock H, et al. Crohn's-like colitis, enterocolitis and perianal disease in Hermansky-Pudlak syndrome. *Colorectal Dis* 2006;8:539–543.
61. Erzin Y, Cosgun S, Dobrucali A, et al. Complicated granulomatous colitis in a patient with Hermansky-Pudlak syndrome, successfully treated with infliximab. *Acta Gastroenterol Belg* 2006;69:213–216.
62. Anderson PD, Huizing M, Claassen DA, et al. Hermansky-Pudlak syndrome type 4 (HPS-4): clinical and molecular characteristics. *Hum Genet* 2003;113:10–17.

63. Mahadeo R, Markowitz J, Fisher S, et al. Hermansky-Pudlak syndrome with granulomatous colitis in children. *J Pediatr* 1991;118:904–906.
64. Mora AJ, Wolfsohn DM. The management of gastrointestinal disease in Hermansky-Pudlak syndrome. *J Clin Gastroenterol* 2011;45:700–702.
65. Booth C, Gilmour KC, Veys P, et al. X-linked lymphoproliferative disease due to SAP/SH2D1A deficiency: a multicenter study on the manifestations, management and outcome of the disease. *Blood* 2011;117:53–62.
66. Rigaud S, Fondaneche MC, Lambert N, et al. XIAP deficiency in humans causes an X-linked lymphoproliferative syndrome. *Nature* 2006;444:110–114.
67. Worthey EA, Mayer AN, Syverson GD, et al. Making a definitive diagnosis: successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease. *Genet Med* 2011;13:255–262.
68. Pachlopnik Schmid J, Canioni D, Moshous D, et al. Clinical similarities and differences of patients with X-linked lymphoproliferative syndrome type 1 (XLP-1/SAP deficiency) versus type 2 (XLP-2/XIAP deficiency). *Blood* 2011;117:1522–1529.
69. Meeths M, Entesarian M, Al-Herz W, et al. Spectrum of clinical presentations in familial hemophagocytic lymphohistiocytosis type 5 patients with mutations in STXBP2. *Blood* 2010;116:2635–2643.
70. van der Burgh R, Ter Haar NM, Boes ML, et al. Mevalonate kinase deficiency, a metabolic autoinflammatory disease. *Clin Immunol* 2013;147:197–206.
71. Levy M, Arion A, Berrebi D, et al. Severe early-onset colitis revealing mevalonate kinase deficiency. *Pediatrics* 2013;132:e779–e783.
72. Yang X, Kanegane H, Nishida N, et al. Clinical and genetic characteristics of XIAP deficiency in Japan. *J Clin Immunol* 2012;32:411–420.
73. Speckmann C, Ehl S. XIAP deficiency is a mendelian cause of late-onset IBD. *Gut* 2014;63:1031–1032.
74. Marsh RA, Rao K, Satwani P, et al. Allogeneic hematopoietic cell transplantation for XIAP deficiency: an international survey reveals poor outcomes. *Blood* 2013;121:877–883.
75. Agarwal S, Mayer L. Pathogenesis and treatment of gastrointestinal disease in antibody deficiency syndromes. *J Allergy Clin Immunol* 2009;124:658–664.
76. Maekawa K, Yamada M, Okura Y, et al. X-linked agammaglobulinemia in a 10-year-old boy with a novel non-invariant splice-site mutation in Btk gene. *Blood Cells Mol Dis* 2010;44:300–304.
77. Conley ME, Dobbs AK, Quintana AM, et al. Agammaglobulinemia and absent B lineage cells in a patient lacking the p85alpha subunit of PI3K. *J Exp Med* 2012;209:463–470.
78. Levy J, Espanol-Boren T, Thomas C, et al. Clinical spectrum of X-linked hyper-IgM syndrome. *J Pediatr* 1997;131:47–54.
79. Quartier P, Bustamante J, Sanal O, et al. Clinical, immunologic and genetic analysis of 29 patients with autosomal recessive hyper-IgM syndrome due to Activation-Induced Cytidine Deaminase deficiency. *Clin Immunol* 2004;110:22–29.
80. Catucci M, Castiello MC, Pala F, et al. Autoimmunity in wiskott-Aldrich syndrome: an unsolved enigma. *Front Immunol* 2012;3:209.
81. Rohr J, Pannicke U, Doring M, et al. Chronic inflammatory bowel disease as key manifestation of atypical ARTEMIS deficiency. *J Clin Immunol* 2010;30:314–320.
82. Felgentreff K, Perez-Becker R, Speckmann C, et al. Clinical and immunological manifestations of patients with atypical severe combined immunodeficiency. *Clin Immunol* 2011;141:73–82.
83. Agarwal S, Smereka P, Harpaz N, et al. Characterization of immunologic defects in patients with common variable immunodeficiency (CVID) with intestinal disease. *Inflamm Bowel Dis* 2011;17:251–259.
84. Resnick ES, Moshier EL, Godbold JH, et al. Morbidity and mortality in common variable immune deficiency over 4 decades. *Blood* 2012;119:1650–1657.
85. Warnatz K, Voll RE. Pathogenesis of autoimmunity in common variable immunodeficiency. *Front Immunol* 2012;3:210.
86. Takahashi N, Matsumoto K, Saito H, et al. Impaired CD4 and CD8 effector function and decreased memory T cell populations in ICOS-deficient patients. *J Immunol* 2009;182:5515–5527.
87. Burns SO, Zenner HL, Plagnol V, et al. LRBA gene deletion in a patient presenting with autoimmunity without hypogammaglobulinemia. *J Allergy Clin Immunol* 2012;130:1428–1432.
88. Alangari A, Alsultan A, Adly N, et al. LPS-responsive beige-like anchor (LRBA) gene mutation in a family with inflammatory bowel disease and combined immunodeficiency. *J Allergy Clin Immunol* 2012;130:481–488.e2.
89. Lopez-Herrera G, Tampella G, Pan-Hammarstrom Q, et al. Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. *Am J Hum Genet* 2012;90:986–1001.
90. Salzer E, Kansu A, Sic H, et al. Early-onset inflammatory bowel disease and common variable immunodeficiency-like disease caused by IL-21 deficiency. *J Allergy Clin Immunol* 2014;133:1651–1659.e12.
91. Thrasher AJ, Burns SO. WASP: a key immunological multitasker. *Nat Rev Immunol* 2010;10:182–192.
92. Boztug K, Schmidt M, Schwarzer A, et al. Stem-cell gene therapy for the Wiskott-Aldrich syndrome. *N Engl J Med* 2010;363:1918–1927.
93. Aiuti A, Biasco L, Scaramuzza S, et al. Lentiviral hematopoietic stem cell gene therapy in patients with Wiskott-Aldrich syndrome. *Science* 2013;341:1233151.
94. Notarangelo LD. Functional T cell immunodeficiencies (with T cells present). *Annu Rev Immunol* 2013;31:195–225.
95. Ozgur TT, Asal GT, Cetinkaya D, et al. Hematopoietic stem cell transplantation in a CD3 gamma-deficient infant with inflammatory bowel disease. *Pediatr Transplant* 2008;12:910–913.
96. Cole TS, Cant AJ. Clinical experience in T cell deficient patients. *Allergy Asthma Clin Immunol* 2010;6:9.
97. Ballev BJ, Joseph V, De S, et al. A recessive founder mutation in regulator of telomere elongation helicase 1, RTEL1, underlies severe immunodeficiency and features

- of Hoyeraal Hreidarsson syndrome. *PLoS Genet* 2013; 9:e1003695.
98. Ballew BJ, Yeager M, Jacobs K, et al. Germline mutations of regulator of telomere elongation helicase 1, RTEL1, in dyskeratosis congenita. *Hum Genet* 2013;132: 473–480.
 99. Knight SW, Heiss NS, Vulliamy TJ, et al. Unexplained aplastic anaemia, immunodeficiency, and cerebellar hypoplasia (Hoyeraal-Hreidarsson syndrome) due to mutations in the dyskeratosis congenita gene, DKC1. *Br J Haematol* 1999;107:335–339.
 100. Sznajder Y, Baumann C, David A, et al. Further delineation of the congenital form of X-linked dyskeratosis congenita (Hoyeraal-Hreidarsson syndrome). *Eur J Pediatr* 2003; 162:863–867.
 101. Borggraefe I, Koletzko S, Arenz T, et al. Severe variant of x-linked dyskeratosis congenita (Hoyeraal-Hreidarsson syndrome) causes significant enterocolitis in early infancy. *J Pediatr Gastroenterol Nutr* 2009;49:359–363.
 102. Glocker EO, Frede N, Perro M, et al. Infant colitis—it's in the genes. *Lancet* 2010;376:1272.
 103. Glocker EO, Kotlarz D, Boztug K, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *N Engl J Med* 2009;361:2033–2045.
 104. Begue B, Verdier J, Rieux-Laucat F, et al. Defective IL10 signaling defining a subgroup of patients with inflammatory bowel disease. *Am J Gastroenterol* 2011;106: 1544–1555.
 105. Moran CJ, Walters TD, Guo CH, et al. IL-10R polymorphisms are associated with very-early-onset ulcerative colitis. *Inflamm Bowel Dis* 2013;19:115–123.
 106. Shouval DS, Ouahed J, Biswas A, et al. Interleukin 10 receptor signaling: master regulator of intestinal mucosal homeostasis in mice and humans. *Adv Immunol* 2014; 122:177–210.
 107. Engelhardt KR, Shah N, Faizura-Yeop I, et al. Clinical outcome in IL-10- and IL-10 receptor-deficient patients with or without hematopoietic stem cell transplantation. *J Allergy Clin Immunol* 2013;131:825–830.e9.
 108. Shouval DS, Biswas A, Goettel JA, et al. Interleukin-10 receptor signaling in innate immune cells regulates mucosal immune tolerance and anti-inflammatory macrophage function. *Immunity* 2014;40:706–719.
 109. Neven B, Mamessier E, Bruneau J, et al. A Mendelian predisposition to B-cell lymphoma caused by IL-10R deficiency. *Blood* 2013;122:3713–3722.
 110. Murugan D, Albert MH, Langemeier J, et al. Very early onset inflammatory bowel disease associated with aberrant trafficking of IL-10R1 and cure by T cell replete haploidentical bone marrow transplantation. *J Clin Immunol* 2014;34:331–339.
 111. Barzaghi F, Passerini L, Bacchetta R. Immune dysregulation, polyendocrinopathy, enteropathy, x-linked syndrome: a paradigm of immunodeficiency with autoimmunity. *Front Immunol* 2012;3:211.
 112. Bennett CL, Christie J, Ramsdell F, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. *Nat Genet* 2001;27:20–21.
 113. Patey-Mariaud de Serre N, Canioni D, Ganousse S, et al. Digestive histopathological presentation of IPEX syndrome. *Mod Pathol* 2009;22:95–102.
 114. Caudy AA, Reddy ST, Chatila T, et al. CD25 deficiency causes an immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like syndrome, and defective IL-10 expression from CD4 lymphocytes. *J Allergy Clin Immunol* 2007;119:482–487.
 115. Bezrodnik L, Caldirola MS, Seminario AG, et al. Follicular bronchiolitis as phenotype associated with Cd25 deficiency. *Clin Exp Immunol* 2014;175:227–234.
 116. Uzel G, Sampaio EP, Lawrence MG, et al. Dominant gain-of-function STAT1 mutations in FOXP3 wild-type immune dysregulation-polyendocrinopathy-enteropathy-X-linked-like syndrome. *J Allergy Clin Immunol* 2013; 131:1611–1623.
 117. Fabre A, Charroux B, Martinez-Vinson C, et al. SKIV2L mutations cause syndromic diarrhea, or trichohepatoenteric syndrome. *Am J Hum Genet* 2012;90:689–692.
 118. Hartley JL, Zachos NC, Dawood B, et al. Mutations in TTC37 cause trichohepatoenteric syndrome (phenotypic diarrhea of infancy). *Gastroenterology* 2010;138: 2388–2398, 2398 e1–2.
 119. Heindl M, Handel N, Ngeow J, et al. Autoimmunity, intestinal lymphoid hyperplasia, and defects in mucosal b-cell homeostasis in patients with PTEN hamartoma tumor syndrome. *Gastroenterology* 2012; 142:1093–1096.e6.
 120. Austin KM. The pathogenesis of Hirschsprung's disease-associated enterocolitis. *Semin Pediatr Surg* 2012;21: 319–327.
 121. Lacher M, Fitze G, Helmbrecht J, et al. Hirschsprung-associated enterocolitis develops independently of NOD2 variants. *J Pediatr Surg* 2010;45:1826–1831.
 122. Dupuis-Girod S, Medioni J, Haddad E, et al. Autoimmunity in Wiskott-Aldrich syndrome: risk factors, clinical features, and outcome in a single-center cohort of 55 patients. *Pediatrics* 2003;111:e622–e627.
 123. Folwaczny C, Ruelfs C, Walther J, et al. Ulcerative colitis in a patient with Wiskott-Aldrich syndrome. *Endoscopy* 2002;34:840–841.
 124. Bindl L, Torgerson T, Perroni L, et al. Successful use of the new immune-suppressor sirolimus in IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome). *J Pediatr* 2005;147:256–259.
 125. De Benedetti F, Insalaco A, Diamanti A, et al. Mechanistic associations of a mild phenotype of immunodysregulation, polyendocrinopathy, enteropathy, x-linked syndrome. *Clin Gastroenterol Hepatol* 2006;4:653–659.
 126. Okou DT, Mondal K, Faubion WA, et al. Exome sequencing identifies a novel FOXP3 mutation in a 2-generation family with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2014;58:561–568.
 127. Aguilar C, Lenoir C, Lambert N, et al. Characterization of Crohn disease in X-linked inhibitor of apoptosis-deficient male patients and female symptomatic carriers. *J Allergy Clin Immunol* 2014 Jun 15 [Epub ahead of print].
 128. Ruemmele FM, Veres G, Kolho KL, et al. Consensus guidelines of ECCO/ESPGHAN on the medical

- management of pediatric Crohn's disease. *J Crohns Colitis* 2014 Jun 5 [Epub ahead of print].
129. Marsh RA, Bleesing JJ, Filipovich AH. Using flow cytometry to screen patients for X-linked lymphoproliferative disease due to SAP deficiency and XIAP deficiency. *J Immunol Methods* 2010;362:1–9.
 130. Gifford CE, Weingartner E, Villanueva J, et al. Clinical flow cytometric screening of SAP and XIAP expression accurately identifies patients with SH2D1A and XIAP/BIRC4 mutations. *Cytometry B Clin Cytom* 2014;86:263–271.
 131. Ammann S, Elling R, Gyrd-Hansen M, et al. A new functional assay for the diagnosis of X-linked inhibitor of apoptosis (XIAP) deficiency. *Clin Exp Immunol* 2014;176:394–400.
 132. Collins FS, Hamburg MA. First FDA authorization for next-generation sequencer. *N Engl J Med* 2013;369:2369–2371.
 133. Biesecker LG, Green RC. Diagnostic clinical genome and exome sequencing. *N Engl J Med* 2014;370:2418–2425.
 134. Jacob HJ, Abrams K, Bick DP, et al. Genomics in clinical practice: lessons from the front lines. *Sci Transl Med* 2013;5:194–195.
 135. Yang Y, Muzny DM, Reid JG, et al. Clinical whole-exome sequencing for the diagnosis of mendelian disorders. *N Engl J Med* 2013;369:1502–1511.
 136. Mao H, Yang W, Lee PP, et al. Exome sequencing identifies novel compound heterozygous mutations of IL-10 receptor 1 in neonatal-onset Crohn's disease. *Genes Immun* 2012;13:437–442.
 137. Dinwiddie DL, Bracken JM, Bass JA, et al. Molecular diagnosis of infantile onset inflammatory bowel disease by exome sequencing. *Genomics* 2013;102:442–447.
 138. Cullinane AR, Vilboux T, O'Brien K, et al. Homozygosity mapping and whole-exome sequencing to detect SLC45A2 and G6PC3 mutations in a single patient with oculocutaneous albinism and neutropenia. *J Invest Dermatol* 2011;131:2017–2025.
 139. Kaser A, Zeissig S, Blumberg RS. Inflammatory bowel disease. *Ann Rev Immunol* 2010;28:573–621.
 140. Nijman IJ, van Montfrans JM, Hoogstraal M, et al. Targeted next-generation sequencing: A novel diagnostic tool for primary immunodeficiencies. *J Allergy Clin Immunol* 2014;133:529–534.
 141. Romi H, Cohen I, Landau D, et al. Meconium ileus caused by mutations in GUCY2C, encoding the CFTR-activating guanylate cyclase 2C. *Am J Hum Genet* 2012;90:893–899.
 142. van de Veerdonk FL, Plantinga TS, Hoischen A, et al. STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. *N Engl J Med* 2011;365:54–61.
 143. Bigorgne AE, Farin HF, Lemoine R, et al. TTC7A mutations disrupt intestinal epithelial apicobasal polarity. *J Clin Invest* 2014;124:328–337.
 144. Landrum MJ, Lee JM, Riley GR, et al. ClinVar: public archive of relationships among sequence variation and human phenotype. *Nucleic Acids Res* 2014;42:D980–D985.
 145. Christodoulou K, Wiskin AE, Gibson J, et al. Next generation exome sequencing of paediatric inflammatory bowel disease patients identifies rare and novel variants in candidate genes. *Gut* 2013;62:977–984.
 146. Bianco AM, Girardelli M, Vozzi D, et al. Mevalonate kinase deficiency and IBD: shared genetic background. *Gut* 2014;63:1367–1368.
 147. Strom SP, Lee H, Das K, et al. Assessing the necessity of confirmatory testing for exome-sequencing results in a clinical molecular diagnostic laboratory. *Genet Med* 2014;16:510–515.
 148. MacArthur DG, Manolio TA, Dimmock DP, et al. Guidelines for investigating causality of sequence variants in human disease. *Nature* 2014;508:469–476.
 149. Kern JS, Herz C, Haan E, et al. Chronic colitis due to an epithelial barrier defect: the role of kindlin-1 isoforms. *J Pathol* 2007;213:462–470.
 150. Mizukami T, Obara M, Nishikomori R, et al. Successful treatment with infliximab for inflammatory colitis in a patient with X-linked anhidrotic ectodermal dysplasia with immunodeficiency. *J Clin Immunol* 2012;32:39–49.
 151. Orange JS, Jain A, Ballas ZK, Schneider LC, Geha RS, Bonilla FA. The presentation and natural history of immunodeficiency caused by nuclear factor kappaB essential modulator mutation. *J Allergy Clin Immunol* 2004;113:725–733.
 152. Fernandez BA, Green JS, Bursey F, et al. Adult siblings with homozygous G6PC3 mutations expand our understanding of the severe congenital neutropenia type 4 (SCN4) phenotype. *BMC Med Genet* 2012;13:111.
 153. Hussain N, Quezado M, Huizing M, et al. Intestinal disease in Hermansky-Pudlak syndrome: occurrence of colitis and relation to genotype. *Clin Gastroenterol Hepatol* 2006;4:73–80.
 154. Parry DE, Blumenthal J, Tomar RH, et al. A 3-year-old boy with ZAP-70 deficiency, thrombocytopenia and ulcerative colitis. *J Allergy Clin Immunol* 1996;97:390.
 155. Chou J, Hanna-Wakim R, Tirosch I, et al. A novel homozygous mutation in recombination activating gene 2 in 2 relatives with different clinical phenotypes: Omenn syndrome and hyper-IgM syndrome. *J Allergy Clin Immunol* 2012;130:1414–1416.
 156. de Saint-Basile G, Le Deist F, Caniglia M, et al. Genetic study of a new X-linked recessive immunodeficiency syndrome. *J Clin Invest* 1992;89:861–866.
 157. DiSanto JP, Rieux-Laucat F, Dautry-Varsat A, et al. Defective human interleukin 2 receptor gamma chain in an atypical X chromosome-linked severe combined immunodeficiency with peripheral T cells. *Proc Natl Acad Sci U S A* 1994;91:9466–9470.
 158. Sanal O, Jing H, Ozgur T, et al. Additional diverse findings expand the clinical presentation of DOCK8 deficiency. *J Clin Immunol* 2012;32:698–708.
 159. Stengaard-Pedersen K, Thiel S, Gadjeva M, et al. Inherited deficiency of mannan-binding lectin-associated serine protease 2. *N Engl J Med* 2003;349:554–560.
 160. Egritas O, Dalgic B, Onder M. Tricho-hepato-enteric syndrome presenting with mild colitis. *Eur J Pediatr* 2009;168:933–935.

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Reprint requests

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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

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