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A Systematic Review of Monogenic Inflammatory Bowel Disease

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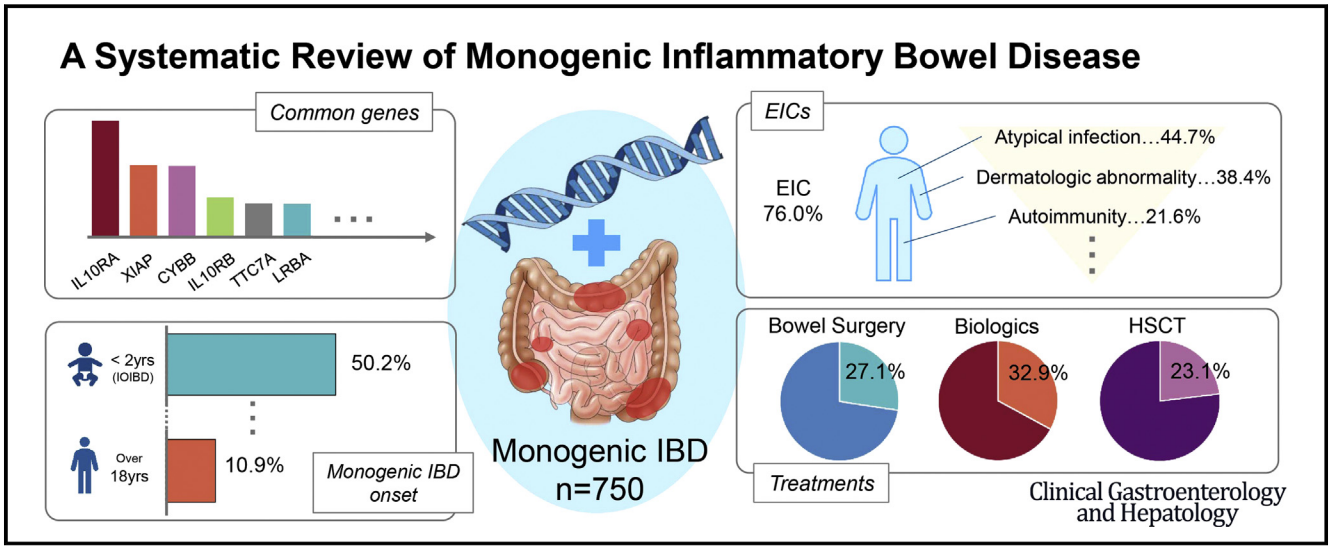

BACKGROUND & AIMS: **Advances in genomic technologies have led to increasing reports of monogenic inflammatory bowel disease (IBD). Here, we systematically review the literature to determine the clinical features, genetic profile, and previously used treatment strategies in monogenic IBD.**

METHODS: **A systematic review of MEDLINE articles published between January 2000 and December 2020 was conducted. A total of 750 individual monogenic IBD cases were identified from 303 eligible articles.**

RESULTS: **The most frequently reported monogenic IBD genes were *IL10RA/B*, *XIAP*, *CYBB*, *LRBA*, and *TTC7A*. In total, 63.4% of patients developed IBD before 6 years of age, 17.4% developed IBD between ages 10 and 17.9 years, and 10.9% developed IBD after age 18. There was a substantial difference between these age groups and the underlying monogenic disorders. Only 31.7% had**

Abbreviations used in this paper: AR, autosomal recessive; CGD, chronic granulomatous disease; CNV, copy number variant; EIC, extraintestinal comorbidity; GI, gastrointestinal; HSCT, hematopoietic stem cell transplantation; IBD, inflammatory bowel disease; IL, interleukin; NGS, next-generation DNA sequencing; TGPS, targeted gene-panel sequencing; TNF-α, tumor necrosis factor α; UC, ulcerative colitis; VEOIBD, very early onset inflammatory bowel disease; WES, whole-exome sequencing; WGS, whole-genome sequencing.

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any history of extraintestinal comorbidity (EIC) before IBD onset, but 76.0% developed at least 1 EIC during their clinical course. The most common EICs were atypical infection (44.7%), dermatologic abnormality (38.4%), and autoimmunity (21.9%). Bowel surgery, biologic therapy, and hematopoietic stem cell transplantation were performed in 27.1%, 32.9%, and 23.1% of patients, respectively.

CONCLUSIONS: **Monogenic IBD cases, although rare, have varied extraintestinal comorbidities and limited treatment options including surgery and transplant. Early identification and improved understanding of the characteristics of the genes and underlying disease processes in monogenic IBD is important for effective management.**

Keywords: IBD; VEOIBD; Monogenic Disorder; Whole-Exome Sequence; Pediatric.

Inflammatory bowel disease (IBD) is a disease of intractable chronic intestinal inflammation that is classified based on the clinical characteristics of Crohn's disease, ulcerative colitis (UC), and IBD-unclassified.[1] Genetic factors, abnormal immune responses associated with environmental predisposition, and microbial dysbiosis in the gut are thought to cause IBD.[2] Advances in next-generation DNA sequencing (NGS) technology have made it possible to genetically diagnose patients with IBD and IBD-like disease. These monogenic forms of IBD typically are rare, severe, and refractory to conventional therapies.[3,4] IBD and IBD-like diseases that are caused by monogenic variants with Mendelian inheritance patterns have been described as monogenic IBD in contrast to typical idiopathic IBD. Age of onset, family history, atypical endoscopic findings, severity, atypical infection history, and extraintestinal comorbidity (EIC) are factors that may help distinguish monogenic from polygenic IBD.[5] To date, between 80 and 90 causative genes associated with monogenic IBD have been reported. Recently, the Pediatric IBD Porto group of European Society for Paediatric Gastroenterology Hepatology and Nutrition agreed on a consensus list of 75 monogenic IBD genes.[6]

The number of reported cases of monogenic IBD has increased in recent years. There are several high-quality reviews of very early onset IBD (VEOIBD) that help guide clinical practice.[7–9] However, these reviews focused on an IBD diagnosis before 6 years of age, rather than on monogenic IBD cases. Although there is overlap, with a high frequency of monogenic IBD in this population, the monogenic IBD population is likely unique with separate clinical characteristics and management strategies. In addition, there are no detailed reports containing a comprehensive picture of monogenic IBD with specific numbers on age distribution, proportion of EICs, relationship of EICs to age at onset, or detailing the clinical course of monogenic IBD. Because each gene-specific cause of monogenic IBD is rare, it is difficult to collect cases in a single study even with international collaborative cohort studies such as COLitis of early Onset - Rare diseaseS, Care-for-Rare, NEOPICS.org, and VEOIBD.org. To this end, we conducted a systematic review of all published cases of monogenic IBD to review these clinical questions.

Methods

Search Strategy

A comprehensive search of MEDLINE limited to English language articles was performed using PubMed (http://pubmed.ncbi.nlm.gov). The following search terms were used: gene names, protein names, protein abbreviations, disease names, or disease abbreviations from 75 genes, respectively, and the combination of "IBD," "inflammatory bowel disease," "colitis," "Crohn," or "enteropathy" (see Supplementary Table 1 for a full list of the search strings used).

Study Selection

The inclusion criteria were as follows: (1) peer-reviewed article, (2) articles including clinical information about a monogenic IBD case or cases, (3) articles published between January 2000 and December 2020, (4) cases in which genetic testing was definitively performed, and (5) cases in which gastrointestinal (GI) manifestations were marked directly as IBD or IBD-like by the investigators (including, "ulcerative colitis," "Crohn disease," "intestinal Bechet," and "granulomatous colitis"). The exclusion criteria were as follows: (1) articles not in English, (2) review articles with previously published cases, (3) articles not containing the details of individual cases (eg, a study showing only the number of patients with IBD in a large cohort of 1 monogenic disorder or intestinal disease was not described as IBD), and (4) interventional clinical trials. Monogenic IBD was defined as follows: (1) caused by a gene variant, (2) the gene variant was damaging and rare, (3) known to cause a monogenic disorder from previous reports, and/or (4) consistent with the patient's clinical phenotype. Articles initially were screened according to the title and abstract to exclude irrelevant studies. Full-text articles then were evaluated for the inclusion and exclusion criteria. Simultaneously, the reference lists of all full-text articles were reviewed manually for further eligible articles. This process was performed for each gene. Finally, we removed duplicate articles.

What You Need to Know

Background

Monogenic IBD has been studied extensively in very young children and infants, but there are limited data regarding older patients, clinical presentation, and treatment options.

Findings

Although monogenic IBD is more common in young children, nearly one third of all patients were diagnosed after 6 years of age and more than 10% as adults. The nongastrointestinal characteristics of monogenic IBD are diverse, with 76% developing at least 1 extraintestinal comorbidity during the clinical course. Treatments including bowel surgery and hematopoietic stem cell transplantation were performed in 27.1% and 23.1% of patients, respectively.

Implications for patient care

Monogenic IBD is rare but can be identified in adolescents and adults with IBD. Early identification and improved understanding of the characteristics of monogenic IBD is critical to caring for this patient group.

Data Extraction and Quality Assessment

Data were collected and organized in a spreadsheet. The following data were collected for each selected article: name of the first author, article year, country of the corresponding author, journal name, sex, family history of IBD (within first- or second-degree relatives), consanguinity, age at onset of first manifestation, age at IBD onset, IBD subtype (UC, Crohn's disease, or IBD-unclassified), if IBD or EICs developed first, GI complications, atypical infection history (including recurrent or severe infection), EICs during the clinical course (including atypical infection), modality that first identified the genetic mutation, genetic variant, inheritance pattern, identified variant type, and treatment history (including biologics, surgery, and hematopoietic stem cell transplantation [HSCT]). An atypical infection included recurrent infection, severe infection, and atypical infection type (such as fungal infection). Finally, cases that appeared in more than 1 article were excluded based on the genetic variant, age at IBD onset, and names of authors. Two authors evaluated this procedure independently.

Statistical Analysis

Descriptive data were calculated as percentages for discrete findings. Chi-square or Fisher exact tests were used for group comparisons. We considered *P* values less than .05 as statistically significant. Statistical analyses were performed using PRISM version 8.0 (GraphPad Software, San Diego, CA) and EZR (Jichi Medical University, Saitama, Japan).

Results

Article Selection Through Systematic Review

The initial electronic database search identified 11,702 articles, of which 10,930 were excluded after screening their titles and abstracts (Supplementary Figure 1). Subsequently, 772 articles were identified. In addition, 415 articles were selected from the reference list of the initial 772 studies. From those 1187 articles, 448 were excluded for not including or showing IBD, 87 for review not showing new cases, 74 for basic research not including clinical cases, 74 for not showing monogenic IBD, 63 for not performing genetic tests, and 53 for not containing sufficient individual clinical information after full-text screening. After screening, 388 articles remained. Of these, 85 articles were excluded because they summarized data from cases of 2 or more genes causative of monogenic IBD. Overall, 303 articles matched the inclusion criteria for this systematic review. These articles covered 68 of the 75 genes known to be associated with monogenic IBD. For the remaining 7 described monogenic genes, the articles did not meet the inclusion criteria. Regarding 6 of these genes (*ADA*, *IL2RA*, *IL2RB*, *ITCH*, *POLA1*, and *RAG2*), several articles described GI symptoms as enteropathy[10,11] or chronic diarrhea,[12] but the cases were not described definitively as IBD through explanations of endoscopy or pathology. In addition, there were no published full reports of *STXBP3* causing monogenic IBD during the review period, only a published abstract.[13]

There has been a dramatic increase in the number of articles reporting monogenic IBD cases since 2012 (Supplementary Figure 2). This is presumably because of increased awareness and widespread use of NGS. The use of whole-exome sequencing (WES) increased after approximately 2012, and the utilization of targeted gene-panel sequencing (TGPS) increased after approximately 2017. The use of whole-genome sequencing (WGS) in this population remains uncommon but appears to be increasing.

Basic Case Characteristics

The 303 articles included a total of 955 cases of monogenic IBD, originating from 31 different countries (Supplementary Figure 3). However, 205 cases appeared in 2 or more articles. Thus, after removing repeated cases, 750 individual patients with monogenic IBD were analyzed (472 males, 259 females, and 19 with gender not reported). A total of 173 of 750 cases (23.1%) were shown to have a family history of IBD in first- or second-degree relatives, and 163 cases (21.7%) reported known consanguinity (Supplementary Table 2). Within each

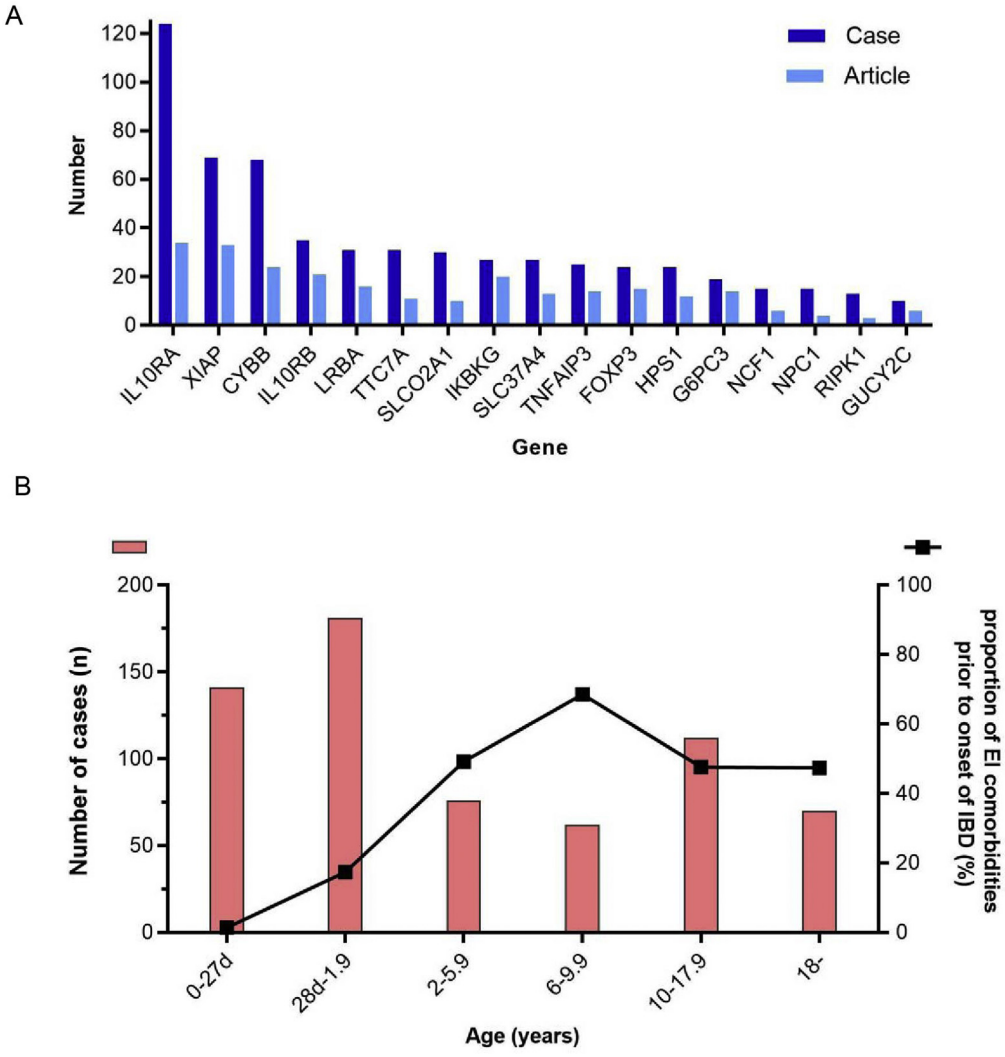

Figure 1. Common genes and age at onset of monogenic inflammatory bowel disease (IBD). (*A*) Number of reported monogenic IBD cases and articles stratified by gene. Only genes that have 10 or more cases are listed. *Dark blue bars*, number of cases; *light blue bars*, number of articles. (*B*) Distribution of IBD onset age. Orange bar (left y-axis) is the number of cases in each age group. The line graph (right y-axis) is the proportion of patients with extraintestinal (EI) manifestations before onset of IBD.

article, 34% were labeled as Crohn's disease, 6% as UC, and 49.5% as IBD (see Supplementary Table 3 for details on the clinical subtype frequency for each monogenic disorder).

Figure 1*A* shows the number of reported monogenic IBD cases and articles per causative gene for the 17 most frequently reported genes (see Supplementary Figure 4 for details on the number of all 68 genes reported). The most commonly reported gene was *IL10RA* (124 cases in 34 articles), followed by *XIAP* (69 cases in 33 articles), *CYBB* (68 cases in 24 articles), *IL10RB* (33 cases in 21 articles), *LRBA* (31 cases in 16 articles), and *TTC7A* (31 in 11 articles).

Figure 1*B* shows the distribution of age at IBD onset and the proportion with a history of EICs before the onset of IBD in each age group. Infantile-onset IBD (from 28 days to younger than 2 years of age) was the most common group (n = 181; 28.2%), and 431 of 679 cases (63.4%) developed IBD before the age of 6 years (for 71 cases, age at onset was not provided). On the other hand, 17.4% and 10.9% of patients developed IBD between 10 and 17.9 years and after 18 years of age, respectively. Of 606 cases, 192 (31.7%) had EICs before IBD onset (clear information about EIC onset was not provided for 144 cases). Almost all patients in the neonatal IBD group (98.6%) and in the infantile-onset IBD group (82.6%) had no EICs before the onset of IBD. However, more than half of the patients diagnosed with monogenic IBD at older than 2 years of age had EICs before the onset of IBD. There was no significant difference between primary EIC onset rate and any of the groups older than the age of 2 years.

Underlying Monogenic Disorders

The most often reported underlying monogenic disorder was interleukin (IL)10-signaling colitis (164 cases; involving the *IL10*, *IL10RA*, and *IL10RB* genes), followed by chronic granulomatous disease (CGD; 99 cases involving the *CYBA*, *CYBB*, *NCF1*, *NCF2*, and *NCF4* genes) and X-linked inhibitor of apoptosis (XIAP) deficiency (69 cases involving the *XIAP* gene) (Supplementary Figure 5). The age at onset of IBD for each monogenic disorder is shown in Figure 2. Some underlying monogenic disorders had a significant difference in the age at

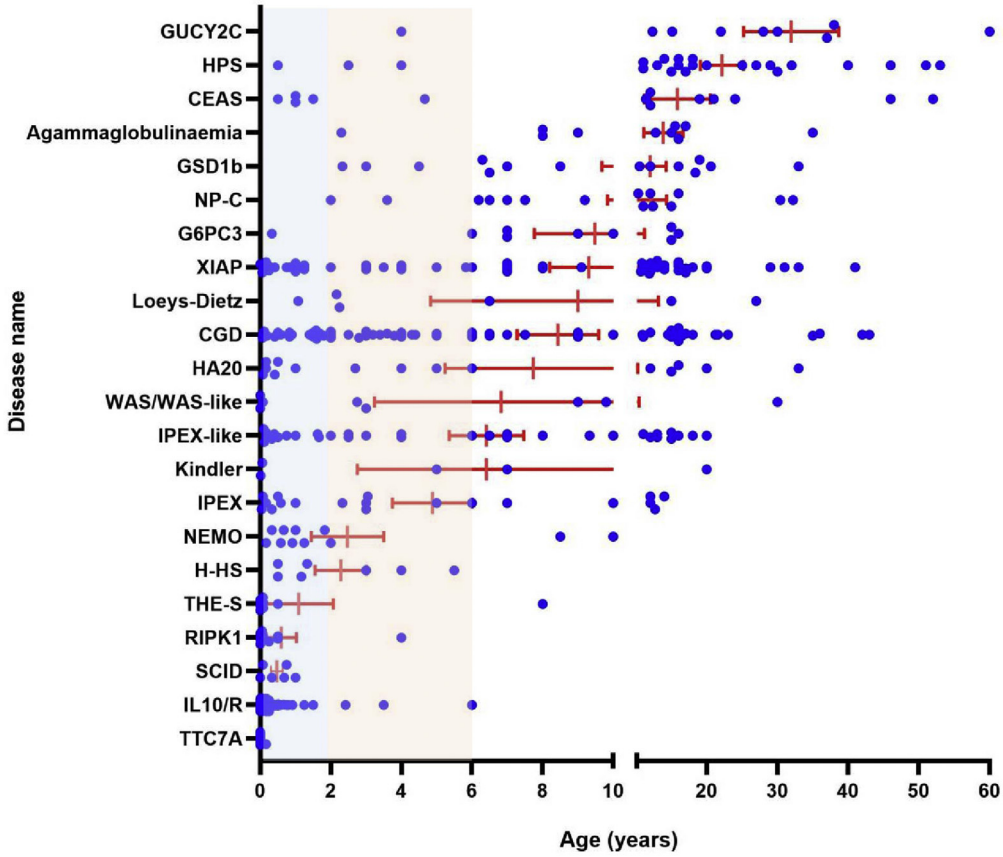

Figure 2. Distribution of age at inflammatory bowel disease (IBD) onset stratified by underlying monogenic disorder. *Blue shaded region*, 0 to 1.9 years; *red shaded region*, 2 to 5.9 years. Each *blue dot* is a separate patient, and the *vertical red lines* indicates the means, with the *horizontal line* showing the standard error. GUCY2C, familial GUCY2C diarrhea syndrome (*GUCY2C*); HPS, Hermansky–Pudlak syndrome (*HPS1*, *HPS4*, *HPS6*); CEAS, chronic enteropathy associated with SLCO2A1 gene (*SLCO2A1*); agammaglobulinemia (*BTK*, *PIK3CD*, *PIK3R1*); GSD1b, glycogen storage disease type 1B (*SLC37A4*); NP-C, Niemann–Pick disease type C (*NPC1*); G6PC3, G6PC3 deficiency (*G6PC3*); XIAP, XIAP deficiency (*XIAP*); Loeys–Dietz, Loeys–Dietz syndrome (*TGFBR1*, *TGFBR2*); CGD, chronic granulomatous disease (*CYBA*, *CYBB*, *NCF1*, *NCF2*, *NCF4*); HA20, haploinsufficiency of A20 (*TNFAIP3*); WAS/WAS-like, Wiskott–Aldrich syndrome/Wiskott–Aldrich–like syndrome (*WAS*, *ARPC1B*); IPEX-like immunodysregulation polyendocrinopathy enteropathy X-linked–like syndrome (*STAT1*, *STAT3*, *CTLA4*, *LRBA*, *IL21*, *MALT1*); Kindler, Kindler syndrome (*FERMT1*); IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (*FOXP3*); NEMO, nuclear factor-κB essential modulator deficiency (*IKBKG*); H-HS, Hoyeraal–Hreidarsson syndrome (*DKC1*, *RTEL1*); THE-S, trichohepatoenteric syndrome (*SKIV2L*, *TTC37*); RIPK1, RIPK1 deficiency (*RIPK1*); SCID, severe combined immunodeficiency (*CD3G*, *DCLRE1C*, *IL2RG*, *LIG4*, *RAG1*); IL10/R, IL10, and IL10-receptor associated colitis (*IL10*, *IL10RA*, *IL10RB*); TTC7A, TTC7A deficiency (*TTC7A*).

presentation (Supplementary Table 4). Most cases of IL10-signaling colitis, Tetratricopeptide repeat domain-7A (TTC7A) deficiency, and Receptor interacting serine/threonine kinase 1 (RIPK1) deficiency developed IBD within the first 6 months of life, whereas most cases of Hermansky–Pudlak syndrome and familial *GUCY2C* diarrhea syndrome developed IBD in adulthood. Patients with the XIAP, CGD, and haploinsufficiency of A20 subtypes developed IBD at varying ages, from infancy to their third decade of life.

The proportion of patients with a history of EICs before IBD onset varies widely depending on the underlying monogenic disorder (Supplementary Figure 5). In most cases with glycogen storage disease type 1B and Niemann–Pick disease type C, EICs specific to each monogenic disorder often were observed before the development of IBD. However, GI symptoms were the primary manifestation of disease in most cases with IL10-signaling colitis, TTC7A deficiency, and chronic enteropathy associated with the *SLCO2A1* gene. CGD and XIAP have lower rates of EICs before the onset of IBD (36.8% and 19.0%, respectively), despite the high frequency of these diseases among monogenic IBD.

Extraintestinal Comorbidity and Gastrointestinal Complications

In total, 76.0% (570 of 750) of all patients had EICs. A total of 62.7% (470 of 750) had at least 1 EIC besides atypical infection. The number of reported individual EICs and the proportion seen before IBD diagnosis is listed in Figure 3*A* (also see Supplementary Table 5 and Supplementary Figure 6 for further subset data**)**. The

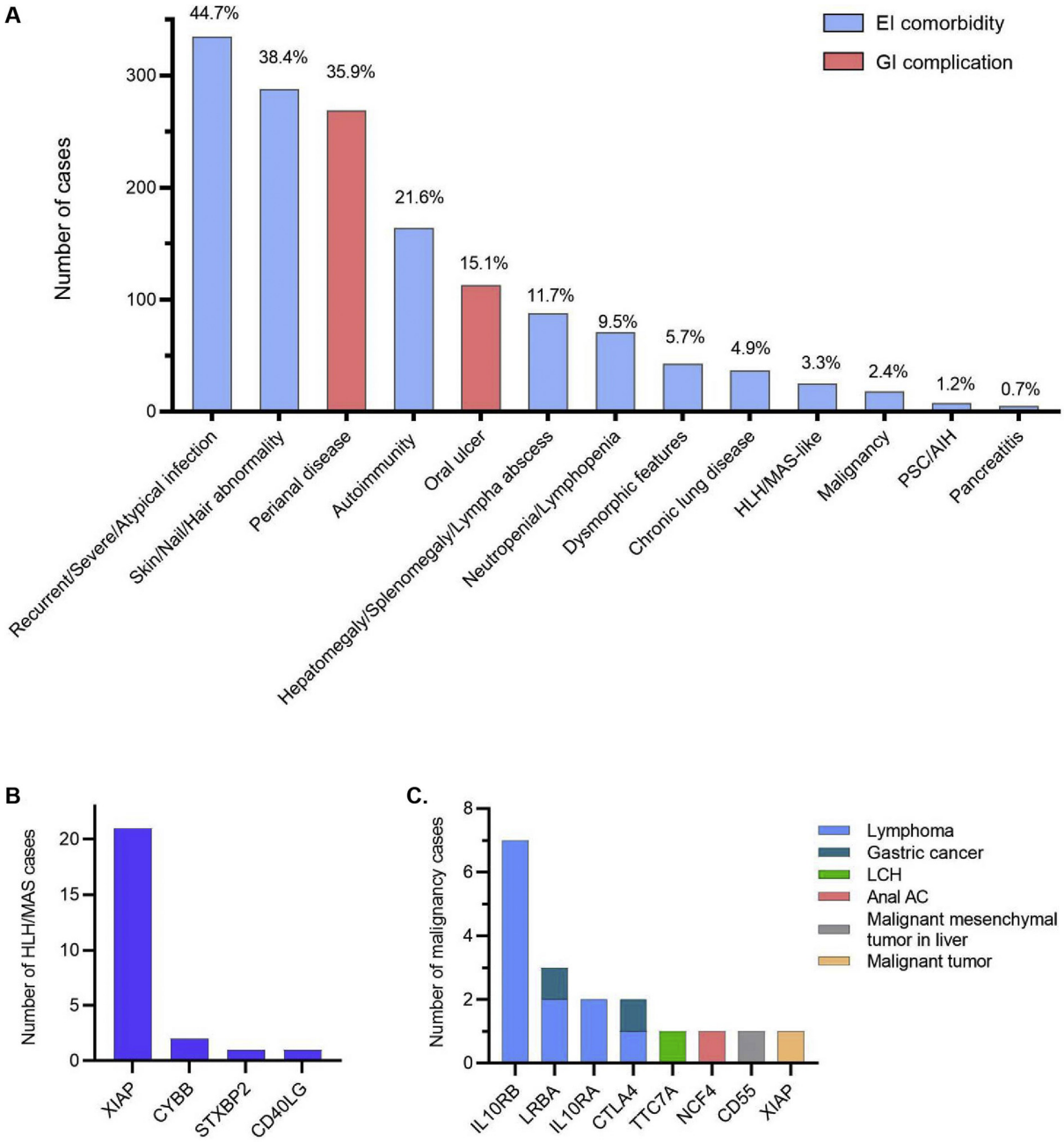

Figure 3. Number of extraintestinal comorbidities (EICs) across monogenic inflammatory bowel disease (IBD) cases. (*A*) Number of EICs in all monogenic IBD cases, where reported (*red bars* show gastrointestinal [GI] complications of perianal disease and oral ulcers). Autoimmunity includes autoimmune hepatitis, arthritis, arthralgia, type 1 diabetes mellitus, hypothyroiditis, psoriasis, autoimmune hemolytic anemia, autoimmune neutropenia, immune thrombocytopenic purpura, uveitis, primary sclerosing cholangitis, vasculitis, autoimmune pancreatitis, autoimmune growth hormone deficiency, glomerular nephropathy, nephrotic syndrome, and autoimmune lymphoproliferative syndrome. Chronic lung disease includes interstitial lung disease, bronchiectasis, and pulmonary fibrosis. Perianal disease includes fistula, abscess, rectovaginal fistula, and ulcer (not including fissure or skin tags). (*B*) Number of monogenic IBD cases with HLH/MAS by causative genes. (*C*) Number of monogenic IBD cases associated with malignancy by causative genes. AC, adenocarcinoma; HLH, hemophagocytic lymphohistiocytosis; LCH, Langerhans cell histiocytosis; MAS, macrophage activation syndrome.

most common EICs were atypical infection (n = 335; 44.7%), skin lesion/nail dystrophy/hair abnormality (n = 288; 38.4%), and autoimmunity (eg, arthritis, type 1 diabetes mellitus, thyroiditis, and autoimmune hemolytic anemia; n = 162; 21.6%) (see Supplementary Table 6 for further subset data). Hemophagocytic lymphohistiocytosis/macrophage activation syndrome–like symptoms were seen in 25 cases across 4 genes (*XIAP*, *STXBP2*, *CD40LG*, and *CYBB*), most of which were in *XIAP* cases (Figure 3*B*). Malignancies were seen in 18 cases involving 8 genes in this review (Figure 3*C*). The frequencies of oral ulcer and perianal disease, which

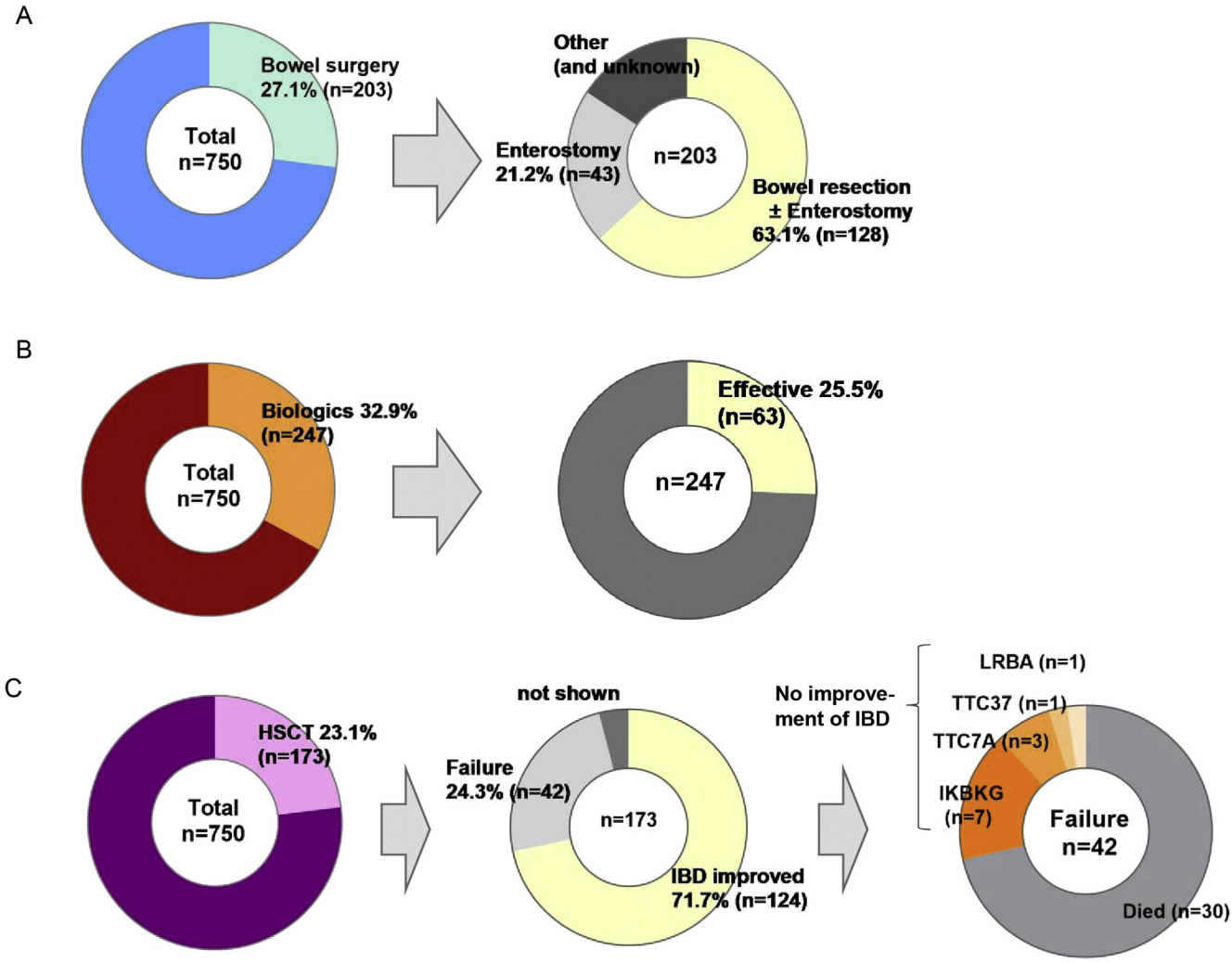

Figure 4. Therapeutic management across monogenic inflammatory bowel disease (IBD) cases. (*A*) Proportion of monogenic IBD cases shown requiring bowel surgery, and for those cases requiring surgery the proportions of the types of surgery are shown. (*B*) Proportion of monogenic IBD cases receiving biologic therapies (including infliximab, adalimumab, golimumab, ustekinumab and vedolizumab, abatacept, anakinra, basiliximab, canakinumab, cerotilizumab, etanercept, natalizumab, rituximab, tocilizumab, tofacitinib, and ruxolitinib), and efficacy. Tofacitinib and ruxolitinib are small-molecule drugs. (*C*) Proportion of monogenic IBD cases that underwent hematopoietic stem cell transplant (HSCT), and, of those, the response rate. The right-most image illustrates the details of the cases that HSCT did not improve.

are GI complications commonly associated with non-monogenic IBD, were identified as 15.1% and 35.9%, respectively.

Inheritance Pattern and Variant Type

Table 1 shows the inheritance pattern and variant types for the monogenic IBD cases. Autosomal recessive (AR) was the most common inheritance pattern (62.0%). Fifteen cases were described as a monoallelic inheritance pattern including 9 cases of heterozygous female carriers, while 8 cases had only single-allele mutations despite the fact that they were in genes usually described with AR inheritance (Supplementary Table 7). Regarding variant type, there were 534 unique variants across 694 patients (no detailed variant description was provided for the remaining 56 cases). Missense was the most common variant type (45.7%), followed by frameshift (20.4%), and stop-gain (16.5%). Deletions and intronic variants (which are sometimes challenging to identify with WES or TGPS) were found in some cases (4.1% and 1.7%, respectively), and only 7 (1.0%) cases showed copy number variants (CNVs).

Therapeutic Management of Monogenic Inflammatory Bowel Disease

We collected information on previously attempted treatment options for severe monogenic IBD cases including surgery, biologic therapy, and HSCT. Bowel surgery was noted in 203 cases (27.1%), of which bowel resection was performed in 63.1% (Figure 4*A*). The number and rate of bowel surgeries and bowel

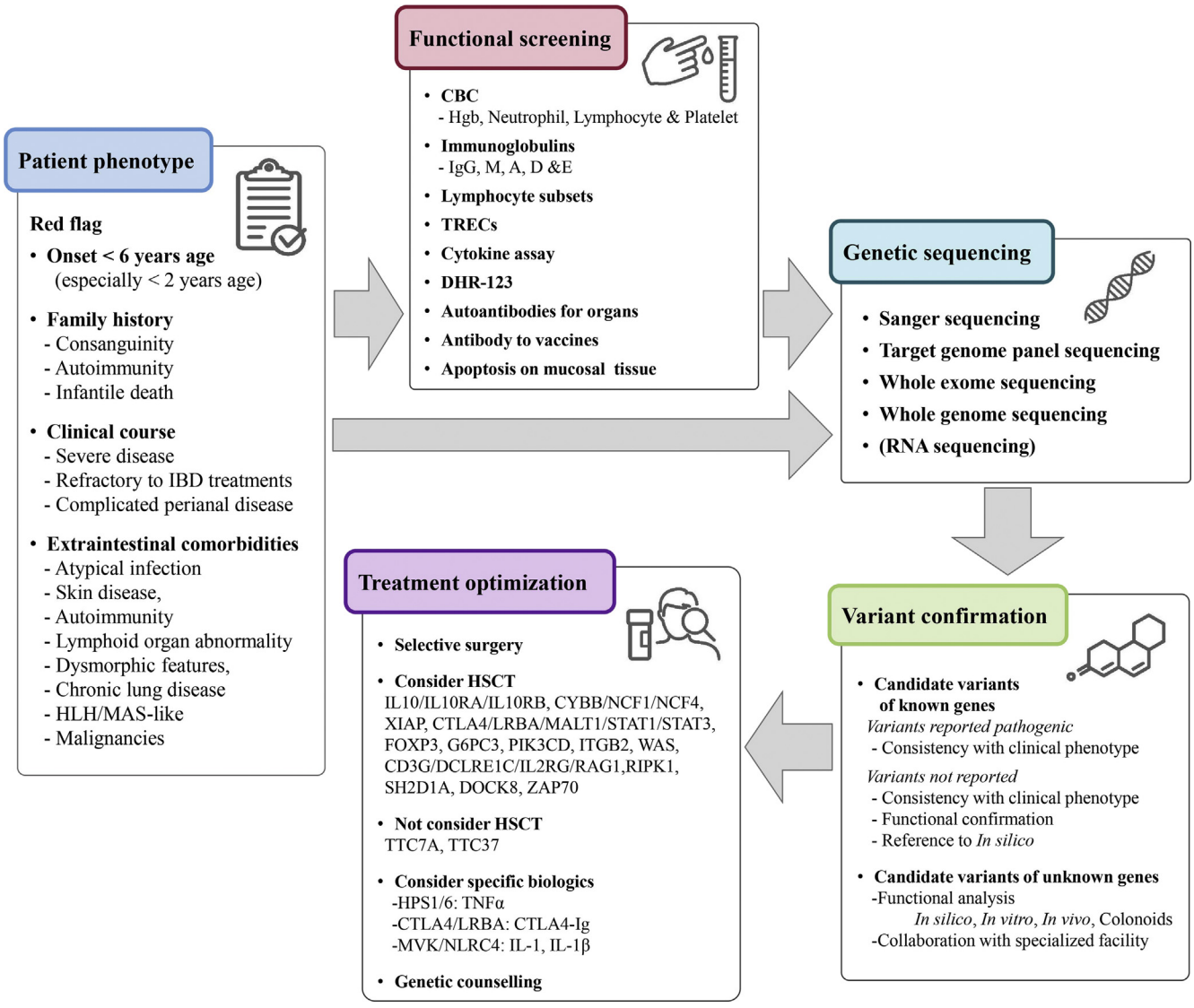

Figure 5. Executive flowchart for the management of monogenic inflammatory bowel disease (IBD). CBC, complete blood count; DHR-123, dihydrorhodamine 123; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation; MAS, macrophage activation syndrome; TREC, T-cell–receptor excision circle.

resections per gene are shown in Supplementary Table 8*A*. In IL10-signaling colitis and TTC7A deficiency, surgery was required early in the disease course (Supplementary Figure 7*A*). The rates of surgery were similar between the groups with an age at onset of younger than 6 years and those with an age at onset of older than 6 years (29.9% vs 30.7%, respectively) (Supplementary Figure 7*B*).

Biologic therapy was used in 247 cases (32.9%) (Figure 4*B*, the number and rate of biologics used per gene are shown in Supplementary Table 8*B* and Supplementary Figure 8). In addition to conventional biologics used for pediatric IBD (infliximab, adalimumab, golimumab, ustekinumab, and vedolizumab), other specific therapies have been used, including abatacept, anakinra, basiliximab, canakinumab, cerotilizumab, etanercept, natalizumab, rituximab, tocilizumab, tofacitinib, and ruxolitinib (small-molecule drugs) also were used (Supplementary Table 9). Biologics were shown to be effective in 25.5% of 247 cases (not including partial effectiveness). Notably, the efficacy of anti–tumor necrosis factor α (TNF-α) agents for monogenic IBD with Hermansky–Pudlak syndrome was 100% in the 7 reported cases. However, anti–TNF-α agents were not shown to be effective for IL10-signaling colitis and LPS Responsive Beige-Like Anchor Protein (LRBA) defects. Overall, there were insufficient data regarding biologic use in monogenic IBD.

HSCT was performed in 173 cases (23.1%) (Figure 4*C*), with resolution of intestinal inflammation in 124 cases and no improvement in 42 cases, including death in 30 cases. The number of HSCTs and the rate of IBD improvement per gene are shown in Supplementary Table 8*C* and Supplementary Figure 8). In this systematic review, HSCT in patients with CGD, LRBA deficiency, XIAP deficiency, and IL10-signaling colitis had a high

Table 1. Inheritance Pattern and Variant Types Identified in This Study

Inheritance pattern	n	%	Variant types identified	n	%
Autosomal recessive	465	62.0	Missense	244	45.7
X-linked recessive	204	27.2	Frameshift	109	20.4
Autosomal dominant	64	8.5	Stop gained	88	16.5
Heterozygous-like form	17	2.3	Splice site	42	7.9
			Deletion	22	4.1
			Intronic	9	1.7
			Inframe	7	1.3
			Insertion	4	0.7
			Start/stop loss	4	0.7
			Inversion	2	0.4
			Synonymous	2	0.4
			Duplication	1	0.2
Total	750	100.0		534	100

success rate (96.2%, 90.0%, 81.8%, and 78.8%, respectively). In contrast, the success rates were low for cases with TTC7A deficiency or nuclear factor-κB essential modulator deficiency. Three of the 5 TTC7A deficiency cases did not improve and 2 died after transplant. Four of the 18 cases with nuclear factor-κB essential modulator deficiency did not improve, 5 died, and 3 cases developed IBD after HSCT, which was performed for severe immunodeficiency and/or autoimmune skin disease.

Discussion

Monogenic forms of IBD are rare, making it challenging to collect and analyze large patient cohorts. This study aimed to improve the understanding of monogenic IBD through a systematic review of the monogenic IBD literature. We reviewed published cases of monogenic IBD genes described in patients from across 6 continents (31 countries) representing a diverse ethnic background. This study provides a comprehensive picture of the heterogeneity of the genetic mechanisms underlying these diseases, clinical presentation, and response to therapy. Another strength of this systematic review is that we focused not only on children with VEOIBD (defined as those with disease onset before 6 years of age) but also on monogenic IBD occurring in adolescence and adulthood, although the majority of studies thus far on monogenic IBD focused on those diagnosed before 6 years of age.[14–16]

Diseases such as IL10-associated colitis, CGD, XIAP, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome–like disease, and TTC7A deficiency, which have been widely reported, should be considered based on clinical presentation enabling early diagnosis using targeted sequencing (such as Sanger sequencing or TGPS). On the other hand, more than half of all monogenic IBD genes that met the criteria for inclusion in this review had fewer than 5 cases reported.

In terms of the utility of age at diagnosis of monogenic IBD, patients presenting before 6 years of age (labeled VEOIBD), account for the majority of cases (63.4%), and adolescent- and adult-onset monogenic IBD cases comprised more than one third of the cases. This finding differs from previous reports that estimated the prevalence of monogenic IBD in children younger than 6 years of age with IBD as an even larger majority of cases.[17–19] On the other hand, there are no reports showing the proportion of monogenic IBD in adult-onset IBD. Charbit-Henrion et al[17] performed genetic testing on severe, treatment-resistant cases of IBD between the ages of 6 and 18 years and found that 18.2% (4 of 22) were monogenic IBD, while Uchida et al[18] similarly found monogenic IBD in 25.9% (7 of 27) of cases in the same age category. In addition, in our local Toronto-based cohort we previously showed that 2.3% (20 of 863) of 6- to 18-year-old IBD patients have monogenic IBD.[19] Given that genetic testing is generally pursued less aggressively for adult-onset and older pediatric cases than for those younger than 6 years of age, clinicians should suspect monogenic IBD more than previously thought, especially if a patient has EIC or shows refractory responses to conventional therapy, even if the patient is not younger than 6 years of age.

Many of the reported monogenic IBD disorders including CGD, XIAP, chronic enteropathy associated with the *SLCO2A1* gene, and haploinsufficiency A20 are difficult to differentiate from typical IBD. These disorders present across a wide range of ages and there is infrequently a history of disease-specific EICs before IBD onset. Early diagnosis is particularly beneficial for CGD and XIAP patients because HSCT can be performed before the development of hemophagocytic lymphohistiocytosis for XIAP deficiency,[20] while the use of anti-TNF drugs can lead to severe infections and even death in CGD.[21] These findings further highlight the importance of obtaining timely genetic testing in patients in whom there is a high suspicion for monogenic disorders (Figure 5).

Further variant types, such as CNVs, intronic variants, synonymous variants, and inversions, often are missed by WES,[22,23] and poor coverage of some regions of known monogenic IBD genes by WES has been well described.[14,19] It is likely that 8 cases with heterozygous-like inheritance in AR monogenic disorder had these variants (Supplementary Table 7). The advantages and disadvantages for each genetic detection method should be considered when investigating a patient for monogenic IBD. Given that there are not yet many reports of monogenic IBD diagnosis using WGS (Supplementary

Figure 1), we expect that the number of reports using WGS will increase as the use of WGS becomes more widespread. It also is likely that monogenic IBD variants that are more amenable to discovery by WGS, such as CNVs and intronic variants, will increase similarly over time. The method of detection is also evolving as the cost of NGS technology in general continues to decrease, as does the time to reporting.

In terms of therapy, of the 46 genes responsible for monogenic IBD for which biologics were used, many genes had only a few reported cases, and monogenic cases linked to 15 genes showed 0% efficacy from biologic therapy (Supplementary Table 8B). Some treatments, such as CTLA4-Ig, have been reported to be effective therapies in *LRBA* and *CTLA4* deficiency,[24] and anti-IL1β biologics for *MVK* and *NLRC4*[25]; however, the use of specific biologics in most monogenic IBDs has not been established and should be used with caution. In our study, HSCT improved IBD in approximately 70% of cases. This number is likely an overestimate as a result of reporting bias, in which successful HSCT likely is reported more often than unsuccessful HSCT. These results particularly emphasize the poor transplant outcomes in nonhematopoietic forms of monogenic IBD in which the gene expression is known to be present in the intestinal epithelium, such as *IKBKG*, *TTC7A*, and *TTC37*.[26,27] Interestingly, a preclinical study identified leflunomide as a potential therapy for TTC7A deficiency,[28] leading to the discovery of new therapeutic agents and the establishment of treatment modalities, although bedside to bench research are required.

This systematic review had some limitations. First, the reason why genetic testing was pursued was not clearly reported for many cases. It is probable that the study population included a selection bias in which severe cases with treatment resistance or extraintestinal comorbidity were tested preferentially. Second, outcomes regarding complications and treatment might have been underestimated because the actual events were not described sufficiently or occurred after publication. Third, we excluded cases in which genetic testing was not performed. As such, monogenic IBD with CGD, glycogen storage disease type 1B, Wiskott-Aldrich syndrome (which can be diagnosed by molecular testing), and dystrophic epidermolysis bullosa (which can be diagnosed with physical examination findings) are likely to be more common in clinical practice than in the present study.

Overall, monogenic IBD diagnosis and management is a challenging clinical problem across many age groups. The EICs of monogenic IBD are highly diverse, and the management of monogenic IBD is difficult. Many monogenic IBD genes have only a few reported cases and therefore generalizations about the clinical course are limited. However, we now have an improved understanding of the underlying genetic basis of these diseases, especially those with relatively high frequencies. In recent years, the number of novel genes causing monogenic IBD has been increasing, but in parallel with these discoveries there is an urgent need to better understand this group of diseases to enable prompt diagnosis, improve prognosis, predict the clinical course, and to establish new treatment strategies. From this systematic review, we now have an improved understanding of the underlying genetic basis of these diseases, especially those with relatively high frequencies, paving the way for prognostication and effective management.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2021.03.021.

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