Invited Review

Turk J Immunol 2024;12(Suppl 1):17-36
DOI: 10.4274/tji.galenos.2023.09327

Immunologists' Perspectives on Monogenic Inflammatory Bowel Diseases

Maryiam Jama Ali Osman*[1,2], Emine Selva Aydoğdu*[3], Rafah Mackeh[2], Ahmet Özen[#4,5,6], Bernice Lo[#1,2]

[1]Hamad Bin Khalifa University Faculty of Medicine, College of Health and Life Sciences, Doha, Qatar
[2]Research Branch, Sidra Medicine, Doha, Qatar
[3]Marmara University Faculty of Medicine, İstanbul, Turkey
[4]Marmara University Faculty of Medicine, Department of Pediatrics, Division of Allergy and Immunology, İstanbul, Turkey
[5]İstanbul Jeffrey Modell Diagnostic Center for Primary Immunodeficiency Diseases, İstanbul, Turkey
[6]The Işıl Berat Barlan Center for Translational Medicine, İstanbul, Turkey
*These two authors contributed equally to this work
#Corresponding authors

Cite as: Osman MJA, Aydoğdu ES, Mackeh R, Özen A, Lo B. Immunologists' Perspectives on Monogenic Inflammatory Bowel Diseases. Turk J Immunol 2024;12(Suppl 1):17-36

Received: 24.10.2023 **Accepted:** 29.11.2023

Corresponding Author: Bernice Lo, Hamad Bin Khalifa University Faculty of Medicine, College of Health and Life Sciences; Research Branch, Sidra Medicine, Doha, Qatar
E-mail: blo@sidra.org **ORCID:** orcid.org/0000-0002-1087-6845

Abstract

Inflammatory bowel diseases (IBD) encompass a group of chronic inflammatory disorders primarily impacting the gastrointestinal system, and they may also affect other organ systems. While common forms of IBD typically arise from multifactorial causes, there exists a subset of patients with single gene defects known as monogenic IBD (mIBD). Over 100 genes have been associated with mIBD, spanning various biological pathways which affect various tissues; the immune system is the most commonly involved, but more rarely, the intestinal epithelium is the primarily affected compartment. Timely diagnosis hinges on awareness and the application of contemporary molecular techniques. Due to the diverse range of causes, managing mIBD requires a multidisciplinary approach. Conventional treatments often fall short, necessitating a personalized strategy that considers the multifaceted nature of mIBD presentations and the diverse etiologic factors. In recent times, novel therapies have emerged, targeting specific causative genes or affected pathways. This discussion delves into the fundamental aspects of mIBD, with particular emphasis on recent breakthroughs in the field, encompassing newly identified gene defects and innovative management strategies.

Keywords: Inflammatory bowel diseases, monogenic defects, immune system, multidisciplinary approach, personalized medicine

Introduction

Inflammatory Bowel Disorder

Inflammatory bowel diseases (IBD) are a heterogeneous group of chronic inflammatory conditions resulting from dysregulation of the mucosal immune system and the gut microbiota. This leads to chronic inflammation and damage to the gastrointestinal (GI) tract, which severely impacts an individual's quality of life (1,2). There are several factors that contribute, solely or combined, to IBD pathogenesis in susceptible individuals. This complex interaction makes IBD a multifactorial disorder. These factors include immune system disturbance, gut microbiome imbalance, environmental factors, intestinal barrier dysfunction, and genetic predisposition (3,4).

Traditionally, IBD is classified into two main categories: Crohn's disease (CD), characterized by a discontinuous pattern of inflammation that can affect any part of the GI tract, and ulcerative colitis (UC), characterized by a continuous inflammation extending from the rectum to the colon (5,6). In addition to UC and CD, IBD-undetermined (IBDU) has been used to describe the disease in patients who present with clinical similarities to UC and CD but do not clearly fit into either group (7,8). Interestingly, IBDU is more common in pediatric patients than adults (9). The clinical manifestations of IBD can occur at any age and vary depending on the

specific type of IBD. Moreover, the severity and frequency of these symptoms can fluctuate over time, with the episodes of flares and periods of remission (10,11).

Previous epidemiological studies showed increased IBD incidence and prevalence worldwide, affecting developed and developing nations (12-15). Studies from Asia explored the impact of IBD in different regions, including East Asia (16-20), Southeast Asia (21,22), South Asia (23,24), West Asia (25,26), and Central Asia (27). A modeling study has predicted that IBD prevalence will have increased in Asia and Iran by 2035 (28). Turkish studies have found that IBD incidence is less than in Northern and Western Europe but similar to that in the Middle East (29,30). Furthermore, studies from Europe have reported that around 0.2% of the population is affected by IBD (31). In the United States, about 1.3% of adults have been diagnosed with IBD during their lifetime (32), and up to 25% of patients were diagnosed before the age of 20 years (33). This pattern of increasing prevalence is not limited to the adult population but has also been observed in the pediatric population.

Classification of Pediatric Inflammatory Bowel Disorder

Childhood-onset of IBD is frequently associated with more severe disease symptoms, faster disease progression, and greater treatment resistance than adult-onset IBD (33,34). Therefore, there was a need to establish a revised classification system to account for pediatric IBD manifestations. The Paris classification is a pediatric IBD classification system that is derived from the Montreal classification, which was designed to categorize IBD in adults. The Paris classification categorized pediatric IBD based on age of onset, disease site or extent, behavior, and growth (35). Childhood-onset IBD has been categorized into five distinct groups. Pediatric-onset IBD refers to those patients who received an IBD diagnosis before their 17th birthday, whereas patients diagnosed before the age of ten years are classified as Early Onset-IBD (EO-IBD). Patients who are diagnosed before the age of six years are classified as Very Early Onset-IBD (VEO-IBD), and children who are diagnosed before the age of two years are classified as infantile-onset IBD (IO-IBD). However, patients who experience the disease within the first 27 days of life are referred to as neonatal-onset IBD (36). There is a growing literature suggesting that early onset IBD is more likely to be associated with a Mendelian disease.

Monogenic Inflammatory Bowel Disorder Pathogenesis

Genetic Overview of Monogenic Inflammatory Bowel Disorder

Various attempts have been made to analyze and comprehend the genetic component of IBD. Twin and family studies were the earliest types of studies that provided evidence to support the role of genetics in IBD pathogenesis (37-41). Subsequently, genome-wide association studies (GWAS) were employed to explore the genetic influence on adult-onset IBD. GWAS studies have revealed more than 200 genetic loci associated with IBD, many of which are shared by CD and UC (42-44).

As opposed to polygenic IBD, monogenic IBD (mIBD) is caused by rare single-gene mutations that can be inherited in a Mendelian manner. Patients with mIBD are more likely to have treatment-resistant disease that might not respond well to conventional therapies. Therefore, some mIBD patients might require different treatment options, such as other immunosuppressive or anti-inflammatory drugs, hematopoietic stem cell transplantation (HSCT), or surgical intervention (45-47).

Several approaches have been used throughout the years to discover rare genomic variations in IBD. Techniques such as targeted genetic sequencing and next-generation DNA sequencing have been critical in identifying these rare variants and improving our understanding of their clinical relevance to mIBD. This progress in the genetics of IBD has allowed for more accurate diagnoses, better-personalized treatment options, and improved management methods for individuals affected by monogenic forms of IBD (2).

The following sections will focus on selected genes recently discovered to be associated with monogenic forms of IBD, grouped as per their functional impact in the GI tract. A full updated list of mIBD genes is listed in Table 1.

Epithelial Barrier Dysfunction

The epithelial lining of the GI tract is formed by specialized epithelial cells, which play a crucial role in maintaining an intact mucosal barrier. This barrier protects the intestinal epithelium by preventing direct contact between the intestinal epithelium and luminal contents (48). Genetic studies in IBD revealed mutations in genes involved in maintaining a functional epithelial lining, especially in patients with VEO-IBD patients. Earlier studies revealed several gene mutations impacting epithelial barrier function, which were associated with mIBD and IBD-like manifestations, such as *IKBKG*, *ADAM17*, *COL7A1*, and *GUCY2C* (49). Here, we will discuss a few novel mutations reported recently.

Anterior gradient 2 (*AGR2*) gene mutations are an example of a genetic variation that leads to a potential disruption in intestinal barrier function. AGR2 is expressed in goblet cells and is important for the production of the mucus layer in the GI tract. It is involved in the processing of mucin (50) and in maintaining endoplasmic reticulum (ER) homeostasis (51,52). A recent study has

Table 1. Monogenic IBD gene list

Biological pathway	Gene	Disease	GI related clinical manifestations	Reference
Epithelial barrier dysfunction	*AGR2*	Enteropathy caused by AGR2 deficiency, Goblet cell Loss, and ER Stress (EAGLES)	Infantile-onset IBD	(53)
	TTC7A	TTC7A Deficiency	Enterocolitis, severe apoptotic	(55,166-169)
	IKBKG	NF-κB essential modulator (NEMO) deficiency	Enterocolitis	(170,171)
	COL7A1	Dystrophic epidermolysis bullosa	Enterocolitis	(171)
	FERMT1	Kindler syndrome	Ulcerative colitis	(107)
	ADAM17	ADAM-17 deficiency	Enterocolitis	(172)
	GUCY2C	Familial diarrhea	Enterocolitis	(173,174)
	SLC9A3	Congenital Diarrhea	Congenital sodium diarrhea osmotic or secretory	(175)
	IL37	IL-37 deficiency	Infantile ulcerative colitis	(61)
	P14KA	PI4KA deficiency	Multiple intestinal atresia and combined immunodeficiency	(56)
	ELF4	Deficiency in ELF4, X-linked (DEX)	Gastrointestinal inflammation with oral ulcerations	(70)
	WNT2B	WNT2B deficiency	Neonatal onset chronic diarrhea	(176)
Immunoregulation	*FOXP3*	IPEX	Enterocolitis	(118-121)
	IL2RA/ CD25	IPEX-like	Enterocolitis	(122,123)
	STAT1 GOF	IPEX-like	Enterocolitis	(124)
	MALT1	MALT1 deficiency (IPEX-like)	Enterocolitis	(177)
	STAT3 GOF	STAT3	Enterocolitis	(178)
	JAK1 GOF	JAK1	Enterocolitis	(179)
	PTPN2	PTPN2 deficiency	Severe autoimmune enteropathy, IPEX-like symptoms	(135)
	BACH2	BACH2-related immunodeficiency and autoimmunity (BRIDA)	Infancy-onset colitis	(180)
	IL2RB	IL-2RB deficiency	Infantile enteropathy	(131,132)
	IL10RA	IL-10Rb deficiency	Crohn's disease	(40,63,181-193)
	IL10RB	IL-10Rb deficiency		
	IL10	IL-10 deficiency		
T and B-cell defects	*LRBA*	LRBA deficiency	Crohn's like Enterocolitis	(128-130,194-197)
	CTLA4	CTLA4 deficiency	Crohn's disease	(125,127)
	IL21	IL-21 deficiency	Crohn's like Enterocolitis	(198-200)
	WAS	Wiskott Aldrich syndrome	Ulcerative colitis-like	(109,201)
	CD40LG	Hyperimmunoglobulinemia	Mouth and colitis	(115)
	AICDA	Hyperimmunoglobulinemia	Crohn's-like Mouth and enterocolitis	(116)
	BTK	Bruton's agammaglobulinemia	Crohn's-like colitis	(113,114)
	DCLRE1C \ ARTEMIS	Artemis-deficiency combined immunodeficiency	Crohn's like Enterocolitis	(202,203)
	PIK3R1	PI3K activation syndrome	Colitis	(204)
	PIK3CD	PI3K activation syndrome	Colitis	(205)
	ZAP70	SCID	Colitis	(102)
	RAG2	Leaky SCID	Colitis	(103,104)
	IL2RG	SCID/Omenn	Colitis	(105)
	LIG4	Leaky SCID	Colitis	(106,107)

Table 1. Continued

T and B-cell defects	*ADA*	SCID	Colitis	(108)
	CD3Ɣ	SCID	Enterocolitis; Perianal disease.	(101)
	ICOS	ICOS deficiency	Enterocolitis	(110-112)
	DKC1	Hoyeraal Hreidarsson syndrome	Enterocolitis with ulcerations and strictures	(206-208)
	RTEL1	Hoyeraal Hreidarsson syndrome	Colitis/enteropathy	(209,210)
	TGFBR1	Loeys-Dietz syndrome	Colitis	(211)
	TGFBR2	Loeys-Dietz syndrome	Colitis	(211)
	TGFB1	TGF-β1 deficiency	Chronic active pancolitis with encephalopathy	(212)
	ZBTB24	Immunodeficiency centromeric instability, facial anomalies (ICF) syndrome	Colitis	(213)
	RIPK1	RIPK1 deficiency	Pancolitis, Ulcers Oral lesions; Perianal disease	(214)
	CASP8	Caspase-8 deficiency	Crohn's like pancolitis; Strictures; Fistulas; Perianal disease	(215)
Phagocyte defects	*CYBB*	CGD	Crohn's-like colitis	(216-219)
	CYBA			
	NCF1			
	NCF2			
	NCF4			
	SLC37A4	Glycogen Storage Disease Type 1 b	Crohn's-like colitis with ulcerations; Strictures; Perianal fistula	(220-222)
	G6PC3	Congenital neutropenia	Crohn's-like colitis with Strictures; Oral and genital aphthous ulcerations	(223-226)
	ITGB2	Leukocyte adhesion deficiency 1	Crohn's like with stenosis\Stricturing phenotype; Lip ulcer	(227,228)
	NPC1	Niemann-Pick type C disease	Crohn's	(229-231)
	CYBC1	CYBC1 deficiency	Chronic granulomatous disease	(232)
	PRKCD	PRKCD deficiency	CGD Like symptoms	(75)
	TLR4	TLR4 deficiency	Crohn disease associated with complex perianal fistulizing disease	(78)
	MD2	human MD2 deficiency	Very early onset inflammatory bowel disease	(77)
	FMNL2	FMNL2 deficiency	Crohn's disease	(233)
Hyperinflammatory and autoinflammatory	*XIAP*	X-linked lymphoproliferative syndrome 2 (XLP2)	Crohn's like granulomatous colitis	(81,82,234-238)
	HPS1	Herman-sky-Pudlak syndrome	Crohn's like enterocolitis; Perianal fistula/ abscess	(89,91,92,239-242)
	HPS4	Herman-sky-Pudlak syndrome	Crohn's like enterocolitis; Perianal fistula/ abscess	(89,91,241)
	HPS6	Herman-sky-Pudlak syndrome	Enterocolitis	(90)
	MVK	Mevalonate kinase deficiency	Severe neonatal onset ulcerative colitis; enterocolitis; Strictures; Adhesions; Perforations; deep ulcers	(83-86,90,243,244)
	PLCG2	Phospholipase Cy2 defects	Infantile-onset ulcerative colitis and early onset enterolocitis	(245)
	MEFV	Familial Mediterranean fever	Infantile or toddler-onset patchy colitis with white; exudate; Nodularity; Anal fissures	(87,88)
	STXBP2	Familial hemophagoytic lymphohistiocytosis type 5	Enterocolitis	(93-95)

Table 1. Continued

Hyperinflammatory and autoinflammatory	*STXBP3*	STXBP3 deficiency	Refractory infantile-onset IBD	(96)
	TRIM22	TRIM22 defect	Granulomatous Crohn's colitis; Severe perianal disease	(246)
	SLCO2A1	Prostaglandin Transporter Deficiency	Chronic non-specific multiple ulcers of the small intestine (CNSU)	(247,248)
	CARD8	CARD8 deficiency	Crohn's disease	(99,100)
	CDC42	NOCARH syndrome	Intestinal bleeding, associated with persistent/chronic diarrhea; unremitting neonatal enterocolitis	(249)
	SYK GOF	GOF SYK systemic inflammation	Colitis	(97)
Other	*SKIV2L*	Trichohepatoenteric syndrome	Enterocolitis within weeks of life	(250-252)
	TTC37	Trichohepatoenteric syndrome	Infantile-onset diarrhea	(251,252)
	ARPC1B	ARPC1B deficiency	Colitis	(253)
	CD55	CHAPLE syndrome	Enterocolitis with ulcers in terminal ileum	(149-153)
	IPO8	IPO8 deficiency	Severe colitis	(254)
	IFIH1 (viral sensing)	MDA5 deficiency	VEOIBD	(255)

GOF: Gain of function. Adopted and updated from Ouahed et al. (256) with recently reported novel genes incorporated according to classification suggested by Azabdaftari et al. (47)

found a biallelic mutation in the *AGR2* gene in two siblings, resulting in infantile-onset IBD (53). Al-Shaibi and colleagues demonstrated that the mutation led to loss of AGR2 function, which resulted in elevated ER stress and inflammation and a reduction in mucin and goblet cells. As a result, the integrity of the intestinal barrier was compromised, contributing to IBD pathogenesis. Interestingly, the patient's clinical data are consistent with the phenotype observed in *AGR2* knockout mice, further supporting that the AGR2 mutation was the disease-causative variant (53).

Phosphatidylinositol 4-kinase IIIa, encoded by the *PI4KA* gene, has also recently been associated with mIBD. PI4KA forms a complex with Tetratricopeptide Repeat Domain 7 (TTC7) and FAM126 to synthesize the membrane phospholipid phosphatidylinositol 4-phosphate (PI4P). PI4P is crucial in many cellular functions, including membrane trafficking, vesicular transport, and intracellular signaling pathways (54,55). Additionally, it contributes to the adhesion, survival, and polarization of epithelial cells (55). Both PI4KA and TTC7A are expressed in enterocytes and play an important role in enterocyte survival and function. Mutations in either *PI4KA* or *TTC7A* disturb these cellular processes, contributing to the development of IBD and other disorders (55-57). Biallelic mutations in the *PI4KA* gene were noted in several patients who presented with complex phenotypes of neurological abnormalities, immunodeficiency, and intestinal disease within the first weeks or year of life (56,58). The finding of intestinal disease in human PI4KA deficiency is consistent with previous research on PI4KA mutant mice, which developed a severe intestinal phenotype characterized by extensive mucosal epithelial degeneration (59). TTC7A deficiency, caused by homozygous or compound heterozygous damaging variants, also results in a severe form of monogenic VEO-IBD. Disease from TTC7A deficiency may present as early as the neonatal period with severe apoptotic enterocolitis, intestinal atresia, and severe combined immunodeficiency (SCID) (55,57).

Interleukin (IL)-37, an IL-1 family cytokine, has anti-inflammatory properties and is expressed in various human tissues and cells (60). A recent study has found a homozygous loss-of-function IL-37 mutation in a 4-month-old Turkish male with infantile UC. Functional analysis demonstrated that the mutant allele expressed an unstable protein that could not inhibit proinflammatory signals resulting in activated hyperinflammatory macrophages. Furthermore, the patient responded well to immunosuppressive treatment, which resolved all GI symptoms (61). This differs from patients with IL-10 signaling defects, in which standard treatments are generally not effective, thus requiring allogeneic HSCT to induce remission (40,62-65).

ELF4 is an X-linked ETS (Erythroblast Transformation Specific) transcription factor gene that regulates both adaptive and innate immunity. It has a wide range of functions, including regulating the development of the natural killer cells (NK) (66) and the proliferation of $CD8^+$ T-cells to control their expansion (67). ELF4 is also a key transcription factor in the type 1 interferon (IFN) response to viral infection (68). Moreover, ELF4 is regarded as an anti-inflammatory regulator since it suppresses $CD4^+$ T-cell

differentiation to Th17 cells (69). Patients with mutations in the *ELF4* gene have been reported recently. Tyler and colleagues were the first to identify a loss-of-function variant in ELF4 in three unrelated patients with mucosal inflammation. For example, one patient developed fever, inflammation in the GI tract, and mouth ulcers at the age of 2 years (70). A colonoscopy showed inflamed mucosa with neutrophilic infiltration, as well as elevated expression of IL-17A and RORγT. Furthermore, the patient's cells showed a low number of NK cells, memory B-cells, and slightly increased numbers of naive $CD4^+$ and $CD8^+$ cells. Further *in vitro* functional investigation on patient cells and on animals demonstrated that the ELF4 deficiency resulted in increased inflammatory Th17 cell responses, which stimulated neutrophil recruitment and promoted mucosal and intestinal inflammation. In addition, it led to a hyperinflammatory state in macrophages (70).

Phagocytic Dysfunction

Innate immunity in the gut involves several phagocytic cells. The main function of these cells is to maintain intestinal homeostasis through eliminating microbes, triggering inflammatory cytokine release, and recruiting immune cells to the region (71). Multiple studies have discovered various disorders with impairments in phagocytic function caused by gene mutations, which can affect host defense against infections.

Chronic granulomatous disease (CGD) is characterized by defects in phagocytic activity. Approximately 50% of CGD patients develop intestinal inflammation that resembles the disease in IBD patients (72). Genetic mutations in *CYBA*, *CYBB*, *NCF1*, *NCF2*, *NCF4*, and *CYBC1* have been identified in CGD patients (73). These genes encode the NADPH oxidase complex's components, and loss of activity in any of these genes results in phagocyte NADPH oxidase deficiency and impaired reactive oxygen species (ROS) generation (74). This leads to an increased susceptibility to bacterial and fungal infections. A recent study has revealed that mutations in the *PRKCD* gene causes impaired activation of the NADPH oxidase complex (75). PRKCD encodes protein kinase C delta (PKCδ), and it regulates B-cell homeostasis as well as apoptosis, cell development, proliferation, and cell survival in a variety of cells, including lymphocytes and phagocytes (76). Neehus and colleagues reported that patients with the PRKCD mutation had childhood-onset autoimmunity and recurrent infection, particularly GI infections, similar to those with CGD. Functional investigations revealed that the patients' phagocytic cells had a substantial impairment in ROS production and neutrophil extracellular trap formation after being stimulated with phorbol 12-myristate 13-acetate (PMA). This suggests that protein kinase C (PKC) is essential in activating the NADPH oxidase complex, which may contribute to their CGD-like infectious manifestation (75).

Mutations in Myeloid differentiation protein 2 (*MD2*) and Toll-Like Receptor-4 (*TLR4*) were recently found in patients with IBD and shown to impair *TLR4* signaling (77,78). Under physiological conditions, *MD2* and CD14 serve as *TLR4* coreceptors and bind lipopolysaccharide (LPS). This causes Myeloid differentiation primary response-88 (MyD88) to be recruited to the Toll/IL-1 receptor (TIR) domain, which subsequently triggers the activation of the mitogen-activated protein kinases (MAPKs) and nuclear factor-kappa B (NFκB) pathways (77-79). In parallel, LPS-binding protein (LBP) mediates LPS transfer to CD14, and then CD14 presents LPS to the *MD2-TLR4* complex. This results in *MD2-TLR4* complex internalization and activation and promotes *TLR4* endocytosis and TBK1-IKKε-IRF3-IFN-β pathway activation (80). Dysfunction of the *TLR4* signaling pathway might result in a dysregulated inflammatory response in the intestine. A biallelic LOF mutation in *MD2* was discovered in a patient with infantile colitis since the age of 4 months, as well as a sibling with pneumonia and recurrent otitis media. *TLR4* endocytosis, NFκB and MAPK signaling, cytokine production, and bacterial handling were all found to be impaired in the patient (77). Another study investigated a biallelic *TLR4* mutation in a patient who presented with complex perianal CD and found that the *TLR4* deficiency caused impaired LPS-stimulated cytokine responses while maintaining antimicrobial activity towards salmonella (78). In both studies, the *MD2* or *TLR4* mutations were associated with incomplete penetrance and/or variable expressivity since not all carriers of the mutations experienced symptoms to the same degree (77,78).

Autoinflammation and Hyperinflammation

Patients with autoinflammatory and hyperinflammatory disorders present with IBD-like symptoms due to intestinal inflammation. Mutations in several genes such as the *XIAP* (81,82), *MVK* (83-86), *MEFV* (87,88), *HPS1,4,6* (89-92), or *STXBP2* (93-95) have been documented to lead to inflammatory disease. Recently Ouahed et al. (96) found novel heterozygous or biallelic variants in *STXBP3* (*Syntaxin-Binding Protein 3* gene) associated with VEO-IBD, sensorineural hearing impairment, and immune dysregulation. Functional analysis of the affected patients showed that STXBP3 expression was reduced in the blood. Knockdown of STXBP3 in an intestinal epithelial cell line resulted in delayed formation of a cellular monolayer and impaired polarization, which suggests that STXBP3 might have a role in maintaining the polarity and integrity of the epithelial barrier (96).

A new monogenic cause of IBD has recently been reported by Wang et al. (97), who identified patients with

monoallelic missense gain of function (GOF) mutations in *SYK* (Spleen tyrosine kinase). These patients presented with multiorgan inflammation. SYK is a cytosolic non-receptor protein tyrosine kinase (PTK) that serves as a downstream signaling molecule for various immune cell receptors. In addition, *SYK* is important for the activation, differentiation, proliferation, and survival of B-cells (98). The GOF mutations in *SYK* resulted in constitutive activation of SYK and its downstream signaling pathways, resulting in hyperinflammatory responses and immunodeficiency. Interestingly, the study showed that knock-in mice with a *SYK* gain-of-function mutation did not develop spontaneous intestinal inflammation, suggesting that SYK hypersensitivity requires other factors to initiate prominent intestinal inflammation. This could explain the variable manifestations that were seen among the cases with SYK gain-of-function variants since they exhibited mild and/or intermittent intestinal symptoms (97).

In another recent study, Mao et al. (99) have investigated a mutation in Caspase Recruitment Domain Family Member 8 (CARD8) and its involvement in the IBD pathogenesis. CARD8 is a negative regulator of NLRP3 inflammasome activation and IL-1β production (99,100). Mao et al. (99) reported that a patient with a dominant-negative mutation in CARD8 developed CD-like intestinal inflammation. The molecular investigation showed that mutant CARD8 failed to interact with NLRP3, resulting in increased inflammasome activation and enhanced IL-1β secretion, thus leading to intestinal inflammation (100).

Immune Dysregulation

The homeostasis of the immune system is maintained through a balance of activation and repression. Effector and memory immune cells activate the system, whereas regulatory T-cells suppress it. Dysregulation of the immune system contributes to the development of IBD.

Several gene mutations have been extensively studied as causative agents of T and B-cell defects which contribute to various manifestations of intestinal inflammation. Mutations in genes, including *CD3Ɣ* (101), *ZAP70* (102), *RAG2* (103,104), *IL2RG* (105), *LIG4* (106,107), *ADA* (108), can lead to SCID. Deleterious mutations in the *WAS* gene lead to Wiskott-Aldrich Syndrome (WAS), a rare X-linked Primary Immunodeficiency (PID), in which patients also frequently suffer from a wide range of autoimmune manifestations (109). In addition, mutations in the inducible T-cell co-stimulator (*ICOS*) gene result in Common Variable Immunodeficiency (CVID), characterized by a defect in generating class-switched memory B-cells and hypogammaglobulinemia. Patients with *ICOS* mutations often experience enteropathy, lymphoproliferative diseases, autoimmune disorders, and respiratory infections (110-112). Furthermore, previous studies have reported mutations causing primary humoral immune deficiencies and immunoglobulin deficiency in genes, such as *BTK* (113,114), *CD40LG* (115), and *AICDA* (116), which can also lead to enteropathy.

Regulatory T-cells (Treg cells) contribute to immune homeostasis by maintaining immune tolerance and preventing an exaggerated immune response (117). Dysfunction of these cells is seen in immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. The syndrome is characterized by severe enteropathy, lymphoproliferation, chronic dermatitis, autoimmune endocrinopathies including early onset type I diabetes mellitus, and other autoimmune manifestations (118). The classical IPEX is caused by deleterious mutations in the transcriptional factor Forkhead box protein P3 (FOXP3), which is crucial for Treg development (119-121). IPEX-like disorders are caused by a number of mutations that have an effect on Treg function and differentiation, and their manifestations resemble FOXP3 deficiency. IL2RA/CD25 deficiency (122,123) and STAT1 GOF (124) are examples of IPEX-like disorders. Mutations in the *CTLA4* (125-127) and *LRBA* genes (128-130) can also lead to IPEX-like disease due to immune system hyperactivation and Treg dysfunction.

Recently, mutations in *IL2RB*, which encodes for IL-2Rβ, have been identified to lead to an IPEX-like disorder (131,132). IL-2 is a cytokine produced mainly by T-cells, which has many functions, including promoting lymphocyte expansion, the development and survival of Treg cells and T helper cell subsets, as well as the activation of cytotoxic effector cells (133). IL-2RB is essential for the signaling of IL-2 and IL-15 and plays a critical role in peripheral tolerance (134). IL-2RB dysfunction leads to autoimmune and immunodeficiency disorders (131,132). Two independent studies found *IL2RB* mutations in patients presenting with enteropathy, allergies, skin abnormalities, and infection. Fernandez et al. (131) showed that this mutation led to IL-2Rβ expression reduction and dysregulated IL-2 and IL-15 signaling, as well as impaired NK cell responses, leading to an IPEX-like syndrome. The cohort study by Zhang et al. (132) consisted of patients with three different IL2Rβ mutations, each resulting in disease via a different biochemical mechanism. Patients with the p.L77P IL-2Rβ mutation showed impaired IL-2Rβ surface expression, reduced IL-2 signaling in T-cells, and increased cytolytic activity of NK cells. Patients with the p.S40L IL-2Rβ allele had decreased IL-2 binding, while patients with the p.Q96* IL-2Rβ stop-gain mutation had no IL-2Rβ expression and IL-2 signaling. Nonetheless, all these mutations resulted in IL-2Rβ deficiency and dysregulation of the immune system.

IPEX-like disease can also be caused by dysregulation of the JAK-STAT pathway. A recent study has reported

a mutation in tyrosine-protein phosphatase non-receptor type 2 (*PTPN2*) in a patient who has suffered from severe chronic secretory diarrhea and eczema since the age of three months (135). PTPN2 is a negative regulator of the JAK-STAT pathway, and its dysfunction has been implicated in various disorders, including IBD, inflammatory disorders, and tumor development (136). Through functional analysis, Parlato et al. (135) demonstrated that PTPN2 deficiency led to JAK/STAT pathway hyperactivation. These findings suggest that suppressing JAK/STAT activation may minimize intestinal inflammation and that JAK-STAT signaling dysregulation plays a role in IPEX-like pathogenesis.

Furthermore, genes of the NF-κB signaling pathway have been associated with the etiology of mIBD. NF-κB signaling is an important cellular signaling pathway that regulates innate and adaptive immune functions, as well as acts as a key regulator of inflammatory reactions. It also maintains epithelial integrity and intestinal immune homeostasis (137). CARMIL2 is a protein that plays a role in cytoskeletal organization and cell migration. It acts as a scaffold to mediate CD28 signaling and stimulate the NF-κB pathway in T-cells for activation and differentiation (138,139). Recent studies have shown that CARMIL2 loss of function contributes to the pathogenesis of primary immunodeficiency and VEO-IBD (138-141). Caspase activation and recruitment domain 11 (CARD11) is another scaffold protein involved in the activation of the NF-κB pathway and the activation and differentiation of immune cells. Mutations in CARD11 were also shown to be associated with a diverse spectrum of human disease manifestations, including VEO-IBD (142,143).

Complement Overactivation and mIBD

The complement system is a complex network of extracellular proteins, which regulates both the innate and the adaptive branches of the immune system. It functions to eliminate pathogens and clear immune complexes, apoptotic cells, and cellular debris (144,145). Activation of the complement system generates biologically active peptides known as anaphylatoxins, which modulate immune responses (146). Complement activation is carefully regulated by endogenous inhibitors, including cell surface glycoproteins like CD55 (also known as decay accelerating factor or DAF), CD46, and CD59, which shield normal hematopoietic, endothelial and epithelial cells from damage caused by complement (147).

Intestinal lymphangiectasia is an important cause of protein-losing enteropathy, a condition characterized by the loss of serum proteins through the GI tract (148). In 2017, the identification of "CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and PLE (CHAPLE disease, OMIM #226300)" unveiled that one of the causes of this disorder was an overactive complement system due to a deficiency in the *CD55* gene (149,150). The primary characteristics of this disease encompass severe protein-losing enteropathy arising from primary intestinal lymphangiectasia (PIL), accompanied by symptoms such as diarrhea, vomiting, abdominal pain, edema, recurrent infections due to low levels of gamma globulins, and severe, often life-threatening thromboembolic complications (148,149,151). The disease may present as early-onset IBD, with characteristic intestinal ulcers resembling CD. In a group of 16 CHAPLE patients, a complement inhibitor antibody, eculizumab, was used on an off-label basis and consistently reversed all manifestations of the disease, corrected abnormalities in the serum protein composition, and induced a positive shift in gut microbial composition towards a healthy state (152). Remarkably, a novel subcutaneously administered C5-blocking antibody called pozelimab has received approval from the U.S. Food and Drug Administration (FDA) for use in the CHAPLE disease (153).

Presenting Features of Monogenic Inflammatory Bowel Disease

Age at Onset Matters

IBD predominantly exhibits a polygenic nature, with monogenic causes representing a minority of all IBD cases. A recent study by Crowley et al. (154) in Canada focused on 1,000 children aged 0-18 years, who were diagnosed with IBD. Surprisingly, only 3% of these children were found to have a monogenic basis for their IBD. Even when examining the subset of Very Early Onset IBD patients, those under 6 years of age, only 7.8% were identified as having mIBD. These findings suggest a correlation between an earlier onset of symptoms and a heightened likelihood of monogenic etiologies being responsible for the condition (154).

The Interplay Between mIBD and Inborn Errors of Immunity

The bulk of genes implicated in the pathogenesis of mIBD primarily serve roles in host defense or immune regulation. Consequently, the majority of mIBDs are categorized as "Inborn Errors of Immunity", previously known as "Primary Immunodeficiencies". Conversely, in a smaller subset of mIBDs, the primary issue lies in epithelial dysfunction. In these instances, the heightened inflammation stems from the inherent malfunction of the intestinal epithelium (155).

When viewed from the perspective of Inborn Errors of Immunity (IEI), it becomes apparent that approximately one-third of these conditions impact the GI system (GIS) (156). These IEIs often result in inflammatory damage

within the GI tract, leading to a clinical presentation that is endoscopically indistinguishable from polygenic IBD (157).

Differential Diagnosis and Treatment in Monogenic Inflammatory Bowel Disorders

Roles of Different Disciplines in Managing mIBD

Pediatricians, gastroenterologists, immunologists, and medical geneticists all play pivotal roles in diagnosing and managing potential cases of mIBD. However, determining the appropriate referral pathway for these patients can be challenging, given the rarity of mIBD.

Given that mIBD typically presents early in life, pediatricians are often the initial point of contact for patients. The pediatrician's expertise in history-taking, physical examination, and clinical judgment significantly influences the timeliness of receiving appropriate care. However, due to the frequent diagnostic delays associated with IEI, individuals with mIBD may endure a considerable period of undiagnosed illness before obtaining an accurate diagnosis (158). Studies indicate that the average time from the onset of symptoms to diagnosis for IBD patients is approximately 4-8 months for polygenic IBD cases (159). However, for mIBD cases, patients may endure years without a correct or any diagnosis, leading to ineffective treatments. These delays can lead to inappropriate patient management and treatment failures.

For example, certain IEI conditions that manifest as mIBD may necessitate an allogeneic HSCT. Ideally, this procedure should be performed when the patient is in optimal overall health, typically during the early stages of the disease, before any organ deterioration has occurred. Diagnostic delays may result in a missed opportunity window, rendering HSCT impractical.

Efforts to raise awareness about mIBD manifestations among primary care physicians and pediatricians must be prioritized. Furthermore, it is crucial to provide comprehensive information about the subsequent diagnostic and management steps that a typical mIBD patient will undergo. Highlighting the multidisciplinary approach to managing this condition is of utmost importance, as every member of the healthcare team plays a pivotal role at various stages of the process, from planning initial clinical tests to coordinating consultations with specialists and facilitating connections with specialized centers capable of conducting advanced molecular investigations. After connecting the subject with the core specialists' team, future management plans can be meticulously organized, taking into account the prevailing conditions in the local environment.

Considering that polygenic IBD is notably more prevalent than mIBD (154), pediatricians and primary caregivers should initially contemplate the likelihood of polygenic IBD. Arguably the most significant distinguishing factor between mIBD and polygenic IBD is the age at which it presents, with the likelihood of mIBD rising in younger age groups (155).

A gastroenterologist can perform a GI tract endoscopy to identify lesions, inflammation, anatomical variations, and defects. Tissue examination provides vital information about the nature of inflammation and helps narrow the differential diagnosis. A definitive diagnosis often requires a tailored approach that considers the entire clinical picture and the results of prior investigations.

It is imperative to recognize that specific indicators may prompt a physician to give greater consideration to immunodeficiencies as a primary differential diagnosis. As up to one-third of all IEI cases present with GI symptoms (157), investigating the possibility of IEI becomes pivotal in identifying the underlying cause of the patient's GI issues. Warning signs of immunodeficiency should be carefully considered in this context (160). These signs include severe infections, delayed recovery from infections, recurrent thrush or yeast infections, persistent diarrhea, poor growth in children, persistent fatigue, susceptibility to unusual infections, autoimmune disorders, increased allergies, or oncologic manifestations (160).

A set of initial laboratory assessments, including a complete blood count, inflammatory markers, lymphocyte subsets, and immunoglobulin levels, should be conducted at baseline for patients with suspected IBD. Any hints of IEI should be meticulously assessed. Additionally, more advanced immune investigations, such as neutrophil oxidative burst or deeper immune phenotyping, can be performed with a high index of suspicion. Family history is a vital component of the medical history, especially if a relative has exhibited similar symptoms. Physicians should inquire about sibling deaths and any history of undiagnosed IBD within the family. Given that most mIBDs are inherited in an autosomal recessive manner, a thorough family history can lead to a correct diagnosis (155).

Monogenic IBD in Adults

While mIBD typically manifests early in life, certain mIBD types may present later. Examples include Hermansky-Pudlak syndrome (HPS) and familial GUCY2C diarrhea syndrome, which may not develop IBD until adulthood. Additionally, patients with the XIAP, CGD, and haploinsufficiency of A20 (HA20) subtypes can experience the onset of IBD at various ages, ranging from infancy to their third decade of life (161).

Refractory IBD Cases

Cases of refractory IBD, which do not respond to conventional therapies, should raise suspicion of mIBD. In such instances, considering a referral to an immunologist

is advisable. The decision to proceed with an extensive diagnostic evaluation hinges on the patient's comprehensive clinical profile and the results of laboratory investigations. If the clinical judgment of an immunologist suggests a substantial probability of an Inborn Error of Immunity or an epithelial barrier dysfunction, genetic testing may be warranted.

Extraintestinal Manifestations

Extraintestinal manifestations can occur in both monogenic and polygenic IBD patients. In cases of polygenic IBD, these manifestations are often typical and familiar to physicians and include joint issues, skin problems, eye inflammation, mouth sores, and occasionally neurological symptoms (162). However, in mIBD, a broader range of multisystem involvement may occur. IEI are characterized by autoimmunity, increased susceptibility to infections, an elevated risk of cancer, and allergies. Additionally, hematological disorders can be observed in IEI (160). Consequently, patients may initially present in medical specialties other than pediatrics, gastroenterology, and immunology, such as hematology, dermatology, pulmonology, and infectious diseases.

Autoimmunity in mIBD encompasses a wide spectrum of conditions, including autoimmune hepatitis, arthritis, type 1 diabetes mellitus, hypothyroidism, 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 (161). As patients usually present with overlapping signs and symptoms, understanding the phenotypic correlation with molecular etiology is crucial. Thorough evaluation, including immunological assessment, is warranted in such cases.

Given that mIBD primarily affects the immune system, it is advisable to consider an immunology referral when there is suspicion of a monogenic etiology. The multifaceted nature of this condition necessitates the involvement of immunologists in managing its intricate clinical course and associated complications.

In addition to the intrinsic immune abnormalities associated with mIBD, a subset of mIBDs can result in GI protein leakage, leading to a secondary immune deficiency state (163). Such conditions are also categorized as protein-losing enteropathy (PLE). It is important to note that PLE is not a single disease but rather a syndrome encompassing various intestinal and extraintestinal disorders. When a patient presents with PLE, etiological investigations should encompass the broad spectrum of potential causes (151).

The malabsorption triggered by PLE or other forms of mIBD can lead to nutritional deficiencies and exacerbate immune dysfunction. This combination can result in a severe immune deficiency, making patients highly susceptible to severe multisystemic infections. The specific infectious agents involved may vary depending on the type of immunity affected and the pathways involved in the disease's progression. This knowledge guides immunologists in prescribing appropriate antimicrobial prophylaxis targeted at the expected infectious agents.

Immunologists also play a pivotal role in devising treatment strategies for disease modification. Nowadays, there are numerous therapeutic options available that specifically target the immune pathways primarily responsible for driving the disease process. These treatments can include immune-modifying pharmacotherapeutics or curative therapies such as HSCT or gene therapy (160). Such interventions not only reverse the intestinal pathology but also provide a cure for extraintestinal manifestations.

Collaboration between immunologists and gastroenterologists is crucial for providing comprehensive care to patients. Immunologists should consider referring IBD patients to gastroenterology for endoscopy and further evaluation. Even when the GI system is not the primary focus in cases of IEI, it is important for the managing immunologist to recognize the high likelihood of future GI involvement. Any GI complaints, even if mild, should prompt consideration of a gastroenterology referral. The threshold for referring to gastroenterology can be lowered to include cases of simple acute diarrhea or mild failure to thrive. Given the likelihood of eventual GI involvement in IEI, this should remain on the immunologist's radar.

Gastroenterologists possess expertise in nutrition, particularly when it comes to managing cases of failure to thrive. While this is a common issue in various childhood chronic illnesses, in mIBD, nutritional deficiencies can be severe enough to result in stunted growth and significant failure to thrive. Gastroenterologists can effectively manage the patient's diet and provide essential nutritional support. Therefore, prompt referral to gastroenterology is crucial for minimizing growth delays. Early referral to gastroenterology offers the patient a better chance to catch up with their peers in terms of growth and development.

In some cases, immune suppression treatment may be suitable for mIBD patients, especially when inflammation is severe. Gastroenterologists play a key role in making decisions about immune suppression and selecting the appropriate immunosuppressant, dosage, and duration of therapy.

Genetic and Immunological Testing Guidelines

Immunological and genetic testing is necessary for accurate diagnosis of monogenic IBD's since they often involve inherited mutations in immunological pathways.

Genetic testing in the context of IBD is becoming the routine clinical practice, whereas in the past, it was merely a tool for research. However, for most of the world, genome-wide analysis is either very expensive to put in routine clinical practice or not available at all (47).

The approach to diagnosis varies from center to center and from country to country in the case of mIBD. Sometimes, it is the immunologist who takes the lead, while other times, it is the gastroenterologist who manages the patient primarily. Immunologists focus on various aspects, including the immunology profile and identification of affected immune compartments. Geneticists play a crucial role in determining the diagnostic tests needed for identifying the genetic basis of the condition.

Recent guidelines published by the British Society of Gastroenterology and Pediatric Gastroenterology recommend genetic testing for all patients with IBD under the age of 2 years. For patients aged 2-6 years, genomic testing should be considered if any of the genomic testing criteria are met. These criteria encompass infection susceptibility with abnormal laboratory tests indicative of primary immunodeficiency, inflammatory features such as autoimmune manifestations or hemophagocytic lymphohistiocytosis, congenital multiple intestinal atresias or diarrhea, early-onset malignancy, family history of suspected mIBD, and interventions with irreversible consequences. Supportive features include a family history suggestive of a genetic disorder, failure to thrive or growth delay, severe perianal disease and impaired wound healing, and IBD refractory to multiple therapies (155).

Immunological testing can be a valuable diagnostic tool for mIBD, and it should be left to the discretion of immunologists to determine which patients should undergo specific immunologic investigations. In certain disorders, immunologic studies can effectively establish the molecular diagnosis, with genetic studies serving as confirmatory measures. Notable examples include SCID, CGD where phagocyte oxidative burst testing is pivotal, and CHAPLE disease, where CD55 staining is diagnostic. Additionally, antibody deficiency disorders like CVID can often be diagnosed through immunologic studies (160).

Furthermore, the presence of certain syndromic features may suggest complex immune disorders, leading to focused diagnostic testing using relevant assays. Examples of this include Hermansky Pudlak syndrome, characterized by oculocutaneous albinism and a bleeding diathesis, and NEMO deficiency, marked by ectodermal dysplasia and susceptibility to infections.

Unfortunately, for most mIBDs, functional immunological assays are unavailable, and diagnosis primarily relies on genetic testing (47). The number of genes associated with mIBD is over 100 and the numbers are still growing. To address the wide range of potential diagnoses, high-throughput tests, such as those employing Next Generation Sequencing, are increasingly being utilized.

Panel sequencing, whole exome sequencing (WES), and whole genome sequencing (WGS) are widely employed in genetic analysis at numerous research and clinical centers. These techniques serve distinct purposes: panel sequencing concentrates on a predefined set of genes, WES delves into the protein-coding regions of an individual's genome, and WGS scrutinizes the complete genome, encompassing both coding and non-coding regions.

While these powerful diagnostic tools are becoming more accessible, significant challenges persist in the realm of molecular diagnosis. Typically, bioinformatic analyses unveil a set of genetic variants, which are nucleotide changes rarely encountered in the general population. Frequently, the observed variants in the patient are novel, with no previous record, and *in silico* tools may provide conflicting interpretations regarding their pathogenicity. In such instances, determining a definitive diagnosis becomes an immensely difficult and time-consuming process. It is possible that the efforts required to validate candidate gene variants identified in the clinical setting may surpass the available resources, including both human expertise and funding, particularly in research settings. We should actively seek comprehensive solutions to address these challenges, with collective efforts aimed at effectively tackling the complexities of molecular diagnosis. Key components for advancing our capacity to diagnose and comprehend mIBDs include collaboration, standardization, leveraging advanced technology, and a steadfast commitment to enhancing genetic knowledge.

Precision Medicine for Monogenic IBD

The treatment landscape for IBD is complex and multidimensional. Differentiating between polygenic and mIBD is essential for selecting appropriate treatment strategies. Standard treatments for IBD are not often effective in mIBD cases. For some forms of mIBD, certain standard IBD therapies may even be considered contraindicated. For instance, infliximab treatment was found to predispose CGD patients to more severe infections, although it was effective in controlling intestinal inflammation (164).

Monogenic IBD patients may require tailored approaches, including immune-suppressive therapies or targeted immunological treatments. Collaborative decision-making involving gastroenterologists, immunologists, and geneticists is crucial in determining the most suitable treatment plans for each patient's unique situation.

Thanks to advances in genomics, there are now more

precise treatments for mIBD. By identifying the specific genetic causes, we can tailor therapies to each patient, using medications that target particular pathways, NSCT, or gene therapy. There are various treatment options available because mIBD results from a range of underlying factors that cause inflammation. One particularly promising treatment is allogeneic HSCT. Some examples of precision medicine treatments include HSCT for IL-10 signaling defects, recombinant human IL-18 binding protein for XIAP deficiency, CTLA4 fusion protein for CTLA4 insufficiency, empagliflozin for G6P metabolism defects, and gene therapy for CGD (165). A C5-blocking antibody, pozelimab, which was recently approved by the U.S. Food and Drug Administration (FDA), can effectively cure the complement-mediated protein-losing enteropathy called CHAPLE disease (153).

Conclusion

The management of IBD patients requires a multidisciplinary approach involving pediatricians, gastroenterologists, and immunologists. Early identification and proper referral are crucial, especially when considering the possibility of mIBD. By following these recommendations alongside their clinical judgment, healthcare professionals can collaborate to provide optimal care and enhance outcomes for patients with IBD.

Authorship Contributions

Concept: M.J.A.O., E.S.A., R.M., A.O., B.L., Design: M.J.A.O., E.S.A., R.M., A.O., B.L., Data Collection or Processing: M.J.A.O., E.S.A., R.M., A.O., B.L., Literature Search: M.J.A.O., E.S.A., R.M., A.O., B.L., Writing: M.J.A.O., E.S.A., R.M., A.O., B.L.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This work was supported by a precision medicine grant (PPM 05-0419-210008) from the Qatar National Research Fund (QNRF) and a grant by the Marmara University, Scientific Research Projects Committee (BAPKO project ID: 10788).

References

1. Graham DB, Xavier RJ. Pathway paradigms revealed from the genetics of inflammatory bowel disease. Nature. 2020;578:527-39.
2. Nambu R, Muise AM. Advanced understanding of monogenic inflammatory bowel disease. Front Pediatr. 2021;8:618918.
3. Jans D, Cleynen I. The genetics of non-monogenic IBD. Hum Genet. 2023;142:669-82.
4. Kim DH, Cheon JH. Pathogenesis of inflammatory bowel disease and recent advances in biologic therapies. Immune Netw. 2017;17:25-40.
5. Leong RWL. The significance of granulomas in Crohn's disease and inflammatory bowel disease epidemiology in Asia. J Gastroenterol Hepatol. 2020;35:523-4.
6. Molnár T, Tiszlavicz L, Gyulai C, Nagy F, Lonovics J. Clinical significance of granuloma in Crohn's disease. World J Gastroenterol. 2005;11:3118-21.
7. Thurgate LE, Lemberg DA, Day AS, Leach ST. An overview of inflammatory bowel disease unclassified in children. Inflamm Intest Dis. 2019;4:97-103.
8. Mossotto E, Ashton JJ, Coelho T, Beattie RM, MacArthur BD, Ennis S. Classification of paediatric inflammatory bowel disease using machine learning. Sci Rep. 2017;7:2427.
9. Prenzel F, Uhlig HH. Frequency of indeterminate colitis in children and adults with IBD - a metaanalysis. J Crohns Colitis. 2009;3:277-81.
10. Fakhoury M, Negrulj R, Mooranian A, Al-Salami H. Inflammatory bowel disease: clinical aspects and treatments. J Inflamm Res. 2014;7:113-20.
11. Su HJ, Chiu YT, Chiu CT, Lin YC, Wang CY, Hsieh JY, et al. Inflammatory bowel disease and its treatment in 2018: Global and Taiwanese status updates. J Formos Med Assoc. 2019;118:1083-92.
12. Ramos GP, Papadakis KA. Mechanisms of disease: Inflammatory bowel diseases. Mayo Clin Proc. 2019;94:155-65.
13. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017;390:2769-78.
14. Okobi OE, Udoete IO, Fasehun OO, Okobi T, Evbayekha EO, Ekabua JJ, et al. A review of four practice guidelines of inflammatory bowel disease. Cureus. 2021;13:e16859.
15. Ponder A, Long MD. A clinical review of recent findings in the epidemiology of inflammatory bowel disease. Clin Epidemiol. 2013;5:237-47.
16. Park SH, Kim YJ, Rhee KH, Kim YH, Hong SN, Kim KH, et al. A 30-year trend analysis in the epidemiology of inflammatory bowel disease in the Songpa-Kangdong district of Seoul, Korea in 1986-2015. J Crohns Colitis. 2019;13:1410-7.
17. Okabayashi S, Kobayashi T, Hibi T. Inflammatory bowel Disease in Japan-is it similar to or different from Westerns? J Anus Rectum Colon. 2020;4:1-13.
18. Zheng JJ, Zhu XS, Huangfu Z, Shi XH, Guo ZR. Prevalence and incidence rates of Crohn's disease in mainland China: a meta-analysis of 55 years of research. J Dig Dis. 2010;11:161-6.
19. Ng SC, Leung WK, Shi HY, Li MK, Leung CM, Ng CK, et al. Epidemiology of inflammatory bowel disease from 1981 to 2014: Results from a Territory-Wide population-based registry in Hong Kong. Inflamm Bowel Dis. 2016;22:1954-60.
20. Yen HH, Weng MT, Tung CC, Wang YT, Chang YT, Chang CH, et al. Epidemiological trend in inflammatory bowel disease in Taiwan from 2001 to 2015: a nationwide populationbased study. Intest Res 2019;17:54-62.
21. Hilmi I, Jaya F, Chua A, Heng WC, Singh H, Goh KL. A first study on the incidence and prevalence of IBD in Malaysia--results from the Kinta Valley IBD Epidemiology Study. J Crohns Colitis. 2015;9:404-9.
22. Mokhtar NM, Nawawi KNM, Verasingam J, Zhiqin W, Sagap I, Azman ZAM, et al. A four-decade analysis of the incidence trends, sociodemographic and clinical characteristics of inflammatory

bowel disease patients at single tertiary centre, Kuala Lumpur, Malaysia. BMC Public Health. 2019;19(Suppl 4):550.

23. Niriella MA, De Silva AP, Dayaratne AH, Ariyasinghe MH, Navarathne MM, Peiris RS, et al. Prevalence of inflammatory bowel disease in two districts of Sri Lanka: a hospital based survey. BMC Gastroenterol. 2010;10:32.

24. Sood A, Midha V, Sood N, Bhatia AS, Avasthi G. Incidence and prevalence of ulcerative colitis in Punjab, North India. Gut. 2003;52:1587-90.

25. Malekzadeh MM, Vahedi H, Gohari K, Mehdipour P, Sepanlou SG, Ebrahimi Daryani N, et al. Emerging epidemic of inflammatory bowel disease in a middle income country: A Nation-wide study from Iran. Arch Iran Med. 2016;19:2-15.

26. Mosli M, Alawadhi S, Hasan F, Abou Rached A, Sanai F, Danese S. Incidence, prevalence, and clinical epidemiology of inflammatory bowel disease in the Arab World: A systematic review and meta-analysis. Inflamm Intest Dis. 2021;6:123-31.

27. Kaibullayeva J, Ualiyeva A, Oshibayeva A, Dushpanova A, Marshall JK. Prevalence and patient awareness of inflammatory bowel disease in Kazakhstan: a cross-sectional study. Intest Res. 2020;18:430-7.

28. Olfatifar M, Zali MR, Pourhoseingholi MA, Balaii H, Ghavami SB, Ivanchuk M, et al. The emerging epidemic of inflammatory bowel disease in Asia and Iran by 2035: A modeling study. BMC Gastroenterol 2021;21:204.

29. Can G, Poşul E, Yılmaz B, Can H, Korkmaz U, Ermiş F, et al. Epidemiologic features of ınflammatory bowel disease in Western Blacksea region of Turkey for the last 10 years: retrospective cohort study. Korean J Intern Med. 2019;34:519-29.

30. Tozun N, Atug O, Imeryuz N, Hamzaoglu HO, Tiftikci A, Parlak E, et al. Clinical characteristics of inflammatory bowel disease in Turkey: A multicenter epidemiologic survey. J Clin Gastroenterol. 2009;43:51-7.

31. Zhao M, Gönczi L, Lakatos PL, Burisch J. The Burden of inflammatory bowel disease in Europe in 2020. J Crohns Colitis. 2021;15:1573-87.

32. Dahlhamer JM, Zammitti EP, Ward BW, Wheaton AG, Croft JB. Prevalence of inflammatory bowel disease among adults aged ≥18 years - United States, 2015. MMWR Morb Mortal Wkly Rep. 2016;65:1166-9.

33. Jakobsen C, Bartek J Jr, Wewer V, Vind I, Munkholm P, Groen R, Paerregaard A. Differences in phenotype and disease course in adult and paediatric inflammatory bowel disease--a population-based study. Aliment Pharmacol Ther. 2011;34:1217-24.

34. Jezernik G, Mičetić-Turk D, Potočnik U. Molecular genetic architecture of monogenic pediatric IBD differs from complex pediatric and adult IBD. J Pers Med. 2020;10:243.

35. Levine A, Griffiths A, Markowitz J, Wilson DC, Turner D, Russell RK, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis. 2011;17:1314-21.

36. Uhlig HH, Schwerd T, Koletzko S, Shah N, Kammermeier J, Elkadri A, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology, 2014;147:990-1007.e3.

37. Tysk C, Lindberg E, Järnerot G, Flodérus-Myrhed B. Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and the influence of smoking. Gut. 1988;29:990-6.

38. Halfvarson J, Bodin L, Tysk C, Lindberg E, Järnerot G. Inflammatory bowel disease in a Swedish twin cohort: a long-term follow-up of concordance and clinical characteristics. Gastroenterology. 2003;124:1767-73.

39. Ng SC, Woodrow S, Patel N, Subhani J, Harbord M. Role of genetic and environmental factors in British twins with inflammatory bowel disease. Inflamm Bowel Dis. 2012;18:725-36.

40. Glocker EO, Kotlarz D, Boztug K, Gertz EM, Schäffer AA, Noyan F, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. N Engl J Med. 2009;361:2033-45.

41. Halme L, Turunen U, Heliö T, Paavola P, Walle T, Miettinen A, et al. Familial and sporadic inflammatory bowel disease: comparison of clinical features and serological markers in a genetically homogeneous population. Scand J Gastroenterol. 2002;37:692-8.

42. Garcia-Etxebarria K, Merino O, Gaite-Reguero A, Rodrigues PM, Herrarte A, Etxart A, et al. Local genetic variation of inflammatory bowel disease in Basque population and its effect in risk prediction. Sci Rep. 2022;12:3386.

43. Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature. 2012;491:119-24.

44. Liu JZ, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. Nat Genet. 2015;47:979-86.

45. Uhlig HH. Monogenic diseases associated with intestinal inflammation: implications for the understanding of inflammatory bowel disease. Gut. 2013;62:1795-805.

46. Pazmandi J, Kalinichenko A, Ardy RC, Boztug K. Early-onset inflammatory bowel disease as a model disease to identify key regulators of immune homeostasis mechanisms. Immunol Rev. 2019;287:162-85.

47. Azabdaftari A, Jones KDJ, Kammermeier J, Uhlig HH. Monogenic inflammatory bowel disease-genetic variants, functional mechanisms and personalised medicine in clinical practice. Hum Genet. 2023;142:599-611.

48. Ali A, Tan H, Kaiko GE. Role of the intestinal epithelium and its interaction with the microbiota in food allergy. Front Immunol. 2020;11:604054.

49. Leung G, Muise AM. Monogenic intestinal epithelium defects and the development of inflammatory bowel disease. Physiology (Bethesda). 2018;33:360-9.

50. Park SW, Zhen G, Verhaeghe C, Nakagami Y, Nguyenvu LT, Barczak AJ, et al. The protein disulfide isomerase AGR2 is essential for production of intestinal mucus. Proc Natl Acad Sci U S A. 2009;106:6950-5.

51 Higa A, Mulot A, Delom F, Bouchecareilh M, Nguyên DT, Boismenu D, et al. Role of pro-oncogenic protein disulfide isomerase (PDI) family member anterior gradient 2 (AGR2) in the control of endoplasmic reticulum homeostasis. J Biol Chem. 2011;286:44855-68.

52. Maloy KJ, Powrie F. Intestinal homeostasis and its breakdown in inflammatory bowel disease. Nature. 2011;474:298-306.

53. Al-Shaibi AA, Abdel-Motal UM, Hubrack SZ, Bullock AN, Al-Marri AA, Agrebi N, et al. Human AGR2 deficiency causes mucus barrier dysfunction and infantile inflammatory bowel disease. Cell Mol Gastroenterol Hepatol. 2021;12:1809-30.

54. Batrouni AG, Baskin JM. The chemistry and biology of phosphatidylinositol 4-phosphate at the plasma membrane. Bioorg Med Chem. 2021;40:116190.

55. Avitzur Y, Guo C, Mastropaolo LA, Bahrami E, Chen H, Zhao Z, et al. Mutations in tetratricopeptide repeat domain 7A result in a severe form of very early onset inflammatory bowel disease. Gastroenterology. 2014;146:1028-39.

56. Salter CG, Cai Y, Lo B, Helman G, Taylor H, McCartney A, et al. Biallelic PI4KA variants cause neurological, intestinal and immunological disease. Brain. 2021;144:3597-610.

57. Neves JF, Afonso I, Borrego L, Martins C, Cordeiro AI, Neves C, et al. Missense mutation of TTC7A mimicking tricho-hepato-enteric (SD/THE) syndrome in a patient with very-early onset inflammatory bowel disease. Eur J Med Genet. 2018;61:185-8.

58. Verdura E, Rodríguez-Palmero A, Vélez-Santamaria V, Planas-Serra L, de la Calle I, Raspall-Chaure M, et al. Biallelic PI4KA variants cause a novel neurodevelopmental syndrome with hypomyelinating leukodystrophy. Brain. 2021;144:2659-69.

59. Vaillancourt FH, Brault M, Pilote L, Uyttersprot N, Gaillard ET, Stoltz JH, et al. Evaluation of phosphatidylinositol-4-kinase IIIα as a hepatitis C virus drug target. J Virol. 2012;86:11595-607.

60. Su Z, Tao X. Current Understanding of IL-37 in human health and disease. Front Immunol. 2021;12:696605.

61. Zhang ZZ, Zhang Y, He T, Sweeney CL, Baris S, Karakoc-Aydiner E, et al. Homozygous IL37 mutation associated with infantile inflammatory bowel disease. Proc Natl Acad Sci U S A. 2021;118:e2009217118.

62. Gassas A, Courtney S, Armstrong C, Kapllani E, Muise AM, Schechter T. Unrelated donor hematopoietic stem cell transplantation for infantile enteropathy due to IL-10/IL-10 receptor defect. Pediatr Transplant. 2015;19:E101-3.

63. Kotlarz D, Beier R, Murugan D, Diestelhorst J, Jensen O, Boztug K, et al. Loss of interleukin-10 signaling and infantile inflammatory bowel disease: implications for diagnosis and therapy. Gastroenterology. 2012;143:347-55.

64. Murugan D, Albert MH, Langemeier J, Bohne J, Puchalka J, Järvinen PM, 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;34:331-9.

65. Pigneur B, Escher J, Elawad M, Lima R, Buderus S, Kierkus J, et al. Phenotypic characterization of very early-onset IBD due to mutations in the IL10, IL10 receptor alpha or beta gene: a survey of the Genius Working Group. Inflamm Bowel Dis. 2013;19:2820-8.

66. Lacorazza HD, Miyazaki Y, Di Cristofano A, Deblasio A, Hedvat C, Zhang J, et al. The ETS protein MEF plays a critical role in perforin gene expression and the development of natural killer and NK-T cells. Immunity. 2002;17:437-49.

67. Yamada T, Park CS, Mamonkin M, Lacorazza HD. Transcription factor ELF4 controls the proliferation and homing of CD8+ T cells via the Krüppel-like factors KLF4 and KLF2. Nat Immunol. 2009;10:618-26.

68. You F, Wang P, Yang L, Yang G, Zhao YO, Qian F, et al. ELF4 is critical for induction of type I interferon and the host antiviral response. Nat Immunol. 2013;14:1237-46.

69. Lee PH, Puppi M, Schluns KS, Yu-Lee LY, Dong C, Lacorazza HD. The transcription factor E74-like factor 4 suppresses differentiation of proliferating CD4+ T cells to the Th17 lineage. J Immunol. 2014;192:178-88.

70. Tyler PM, Bucklin ML, Zhao M, Maher TJ, Rice AJ, Ji W, et al. Human autoinflammatory disease reveals ELF4 as a transcriptional regulator of inflammation. Nat Immunol. 2021;22:1118-26.

71. Marshall JS, Warrington R, Watson W, Kim HL. An introduction to immunology and immunopathology. Allergy Asthma Clin Immunol 2018;14(Suppl 2):49.

72. Bolton C, Smillie CS, Pandey S, Elmentaite R, Wei G, Argmann C, et al. An Integrated Taxonomy for Monogenic Inflammatory Bowel Disease. Gastroenterology. 2022;162:859-76.

73. Matute JD, Arias AA, Wright NA, Wrobel I, Waterhouse CC, Li XJ, 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: 3309-15.

74. LaBere B, Gutierrez MJ, Wright H, Garabedian E, Ochs HD, Fuleihan RL, et al. Chronic granulomatous disease with inflammatory bowel disease: Clinical presentation, treatment, and outcomes from the USIDNET registry. J Allergy Clin Immunol Pract. 2022;10:1325-33.e5.

75. Neehus AL, Moriya K, Nieto-Patlán A, Le Voyer T, Lévy R, Özen A, et al. Impaired respiratory burst contributes to infections in PKCδ-deficient patients. J Exp Med. 2021;218:e20210501.

76. Belot A, Kasher PR, Trotter EW, Foray AP, Debaud AL, Rice GI, et al. Protein kinase cδ deficiency causes mendelian systemic lupus erythematosus with B cell-defective apoptosis and hyperproliferation. Arthritis Rheum. 2013;65:2161-71.

77. Li Y, Yu Z, Schenk M, Lagovsky I, Illig D, Walz C, et al. Human MD2 deficiency-an inborn error of immunity with pleiotropic features. J Allergy Clin Immunol. 2023;151:791-6.e7.

78. Capitani M, Al-Shaibi AA, Pandey S, Gartner L, Taylor H, Hubrack SZ, et al. Biallelic TLR4 deficiency in humans. J Allergy Clin Immunol. 2023;151:783-90.e5.

79. Lu Y, Li X, Liu S, Zhang Y, Zhang D. Toll-like receptors and inflammatory bowel disease. Front Immunol. 2018;9:72.

80. Tsukamoto H, Takeuchi S, Kubota K, Kobayashi Y, Kozakai S, Ukai I, et al. Lipopolysaccharide (LPS)-binding protein stimulates CD14-dependent Toll-like receptor 4 internalization and LPS-induced TBK1-IKKε-IRF3 axis activation. J Biol Chem. 2018;293:10186-201.

81. Latour S, Aguilar C. XIAP deficiency syndrome in humans. Semin Cell Dev Biol. 2015;39:115-23.

82. Xu T, Zhao Q, Li W, Chen X, Xue X, Chen Z, et al. X-linked lymphoproliferative syndrome in mainland China: review of clinical, genetic, and immunological characteristic. European Journal of Pediatrics. 2020;179:327-38.

83. Favier LA, Schulert GS. Mevalonate kinase deficiency: current perspectives. Appl Clin Genet. 2016;9:101-10.

84. Levy M, Arion A, Berrebi D, Cuisset L, Jeanne-Pasquier C, Bader-Meunier B, et al. Severe early-onset colitis revealing mevalonate kinase deficiency. Pediatrics. 2013;132:e779-83.

85. Bader-Meunier B, Florkin B, Sibilia J, Acquaviva C, Hachulla E, Grateau G, et al. Mevalonate kinase deficiency: a survey of 50 patients. Pediatrics. 2011;128:e152-9.

86. Nimubona L, Laloum D, Rolland MO, Read MH, Guillois B, Duhamel JF. An intestinal obstruction in an eight-month-old child suffering from mevalonic aciduria. Acta Paediatr. 2002;91:714-6.

87. 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;167:391-3.

88. Egritas O, Dalgic B. Infantile colitis as a novel presentation of familial Mediterranean fever responding to colchicine therapy. J Pediatr Gastroenterol Nutr. 2011;53:102-5.

89. Anderson PD, Huizing M, Claassen DA, White J, Gahl WA. Hermansky-Pudlak syndrome type 4 (HPS-4): clinical and molecular characteristics. Hum Genet. 2003;113:10-7.

90. Mora AJ, Wolfsohn DM. The management of gastrointestinal disease in Hermansky-Pudlak syndrome. J Clin Gastroenterol. 2011;45:700-2.

91. Hazzan D, Seward S, Stock H, Zisman S, Gabriel K, Harpaz N, et al. Crohn's-like colitis, enterocolitis and perianal disease in Hermansky-Pudlak syndrome. Colorectal Dis. 2006;8:539-43.

92. Ishihara J, Mizuochi T, Uchida T, Takaki Y, Konishi KI, Joo M, et al. Infantile-onset inflammatory bowel disease in a patient with Hermansky-Pudlak syndrome: a case report. BMC Gastroenterol. 2019;19:9.

93. Fujikawa H, Shimizu H, Nambu R, Takeuchi I, Matsui T, Sakamoto K, et al. Monogenic inflammatory bowel disease with STXBP2 mutations is not resolved by hematopoietic stem cell transplantation but can be alleviated via immunosuppressive drug therapy. Clin Immunol. 2023;246:109203.

94. Meeths M, Entesarian M, Al-Herz W, Chiang SC, Wood SM, Al-Ateeqi W, et al. Spectrum of clinical presentations in familial hemophagocytic lymphohistiocytosis type 5 patients with mutations in STXBP2. Blood. 2010;116:2635-43.

95. Pagel J, Beutel K, Lehmberg K, Koch F, Maul-Pavicic A, Rohlfs AK, et al. Distinct mutations in STXBP2 are associated with variable clinical presentations in patients with familial hemophagocytic lymphohistiocytosis type 5 (FHL5). Blood. 2012;119:6016-24.

96. Ouahed J, Kelsen JR, Spessott WA, Kooshesh K, Sanmillan ML, Dawany N, et al. Variants in STXBP3 are Associated with Very Early Onset Inflammatory Bowel Disease, Bilateral Sensorineural Hearing Loss and Immune Dysregulation. J Crohns Colitis. 2021;15:1908-19.

97. Wang L, Aschenbrenner D, Zeng Z, Cao X, Mayr D, Mehta M, et al. Gain-of-function variants in SYK cause immune dysregulation and systemic inflammation in humans and mice. Nat Genet. 2021;53:500-10.

98. Liu D, Mamorska-Dyga A. Syk inhibitors in clinical development for hematological malignancies. J Hematol Oncol. 2017;10:145.

99. Mao L, Kitani A, Similuk M, Oler AJ, Albenberg L, Kelsen J, et al. Loss-of-function CARD8 mutation causes NLRP3 inflammasome activation and Crohn's disease. J Clin Invest. 2018;128:1793-806.

100. Ito S, Hara Y, Kubota T. CARD8 is a negative regulator for NLRP3 inflammasome, but mutant NLRP3 in cryopyrin-associated periodic syndromes escapes the restriction. Arthritis Res Ther. 2014;16:R52.

101. Ozgür TT, Asal GT, Cetinkaya D, Orhan D, Kiliç SS, Usta Y, et al. Hematopoietic stem cell transplantation in a CD3 gamma-deficient infant with inflammatory bowel disease. Pediatr Transplant. 2008;12:910-3.

102. Chan AY, Punwani D, Kadlecek TA, Cowan MJ, Olson JL, Mathes EF, et al. A novel human autoimmune syndrome caused by combined hypomorphic and activating mutations in ZAP-70. J Exp Med. 2016;213:155-65.

103. Felgentreff K, Perez-Becker R, Speckmann C, Schwarz K, Kalwak K, Markelj G, et al. Clinical and immunological manifestations of patients with atypical severe combined immunodeficiency. Clin Immunol. 2011;141:73-82.

104. Chou J, Hanna-Wakim R, Tirosh I, Kane J, Fraulino D, Lee YN, 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;130:1414-6.

105. DiSanto JP, Rieux-Laucat F, Dautry-Varsat A, Fischer A, de Saint Basile G. 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;91:9466-70.

106. Grunebaum E, Bates A, Roifman CM. Omenn syndrome is associated with mutations in DNA ligase IV. J Allergy Clin Immunol. 2008;122:1219-20.

107. Ashton JJ, Andreoletti G, Coelho T, Haggarty R, Batra A, Afzal NA, et al. Identification of variants in genes associated with single-gene inflammatory bowel disease by whole-exome sequencing. Inflamm Bowel Dis. 2016;22:2317-27.

108. Roifman CM, Zhang J, Atkinson A, Grunebaum E, Mandel K. Adenosine deaminase deficiency can present with features of Omenn syndrome. J Allergy Clin Immunol. 2008;121:1056-8.

109. Catucci M, Castiello MC, Pala F, Bosticardo M, Villa A. Autoimmunity in wiskott-Aldrich syndrome: an unsolved enigma. Front Immunol. 2012;3:209.

110. Takahashi N, Matsumoto K, Saito H, Nanki T, Miyasaka N, Kobata T, et al. Impaired CD4 and CD8 effector function and decreased memory T cell populations in ICOS-deficient patients. J Immunol. 2009;182:5515-27.

111. Robertson N, Engelhardt KR, Morgan NV, Barge D, Cant AJ, Hughes SM, et al. Astute clinician report: A novel 10 bp frameshift deletion in exon 2 of ICOS causes a combined immunodeficiency associated with an enteritis and hepatitis. J Clin Immunol. 2015;35:598-603.

112. Chou J, Massaad MJ, Cangemi B, Bainter W, Platt C, Badran YR, et al. A novel mutation in ICOS presenting as hypogammaglobulinemia with susceptibility to opportunistic pathogens. J Allergy Clin Immunol. 2015;136:794-7.e1.

113. Agarwal S, Mayer L. Pathogenesis and treatment of gastrointestinal disease in antibody deficiency syndromes. J Allergy Clin Immunol. 2009;124:658-64.

114. Maekawa K, Yamada M, Okura Y, Sato Y, Yamada Y, Kawamura N, 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;44:300-4.

115. Levy J, Espanol-Boren T, Thomas C, Fischer A, Tovo P, Bordigoni P, et al, Clinical spectrum of X-linked hyper-IgM syndrome. J Pediatr. 1997;131:47-54.

116. Quartier P, Bustamante J, Sanal O, Plebani A, Debré M, Deville A, 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;110:22-9.

117. Rocamora-Reverte L, Melzer FL, Würzner R, Weinberger B. The complex role of regulatory T cells in immunity and aging. Front Immunol. 2020;11:616949.

118. Gambineri E, Ciullini Mannurita S, Hagin D, Vignoli M, Anover-Sombke S, DeBoer S, et al. Clinical, immunological, and molecular heterogeneity of 173 patients with the phenotype of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. Front Immunol. 2018;9:2411.

119. Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet. 2001;27:20-1.

120. Barzaghi F, Passerini L, Bacchetta R. Immune dysregulation, polyendocrinopathy, enteropathy, x-linked syndrome: a paradigm of immunodeficiency with autoimmunity. Front Immunol. 2012;3:211.

121. Narula M, Lakshmanan U, Borna S, Schulze JJ, Holmes TH, Harre N, et al. Epigenetic and immunological indicators of IPEX disease in subjects with FOXP3 gene mutation. J Allergy Clin Immunol. 2023;151:233-46.e10.

122. Caudy AA, Reddy ST, Chatila T, Atkinson JP, Verbsky JW. 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;119:482-7.

123. Vignoli M, Ciullini Mannurita S, Fioravanti A, Tumino M, Grassi A, Guariso G, et al. CD25 deficiency: A new conformational mutation prevents the receptor expression on cell surface. Clin Immunol. 2019;201:15-9.

124. Uzel G, Sampaio EP, Lawrence MG, Hsu AP, Hackett M, Dorsey MJ, 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;131:1611-23.

125. Schwab C, Gabrysch A, Olbrich P, Patiño V, Warnatz K, Wolff D, et al. Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4-insufficient subjects. J Allergy Clin Immunol. 2018;142:1932-46.

126. Miyazaki H, Hoshi N, Kohashi M, Tokunaga E, Ku Y, Takenaka H, et al. A case of autoimmune enteropathy with CTLA4 haploinsufficiency. Intest Res. 2022;20:144-9.

127. Zeissig S, Petersen BS, Tomczak M, Melum E, Huc-Claustre E, Dougan SK, et al. Early-onset Crohn's disease and autoimmunity associated with a variant in CTLA-4. Gut. 2015;64:1889-97.

128. Lo B, Zhang K, Lu W, Zheng L, Zhang Q, Kanellopoulou C, et al. AUTOIMMUNE DISEASE. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. Science 2015;349:436-40.

129. Lopez-Herrera G, Tampella G, Pan-Hammarström Q, Herholz P, Trujillo-Vargas CM, Phadwal K, et al. Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. Am J Hum Genet. 2012;90:986-1001.

130. Alroqi FJ, Charbonnier LM, Baris S, Kiykim A, Chou J, Platt CD, et al. Exaggerated follicular helper T-cell responses in patients with LRBA deficiency caused by failure of CTLA4-mediated regulation. J Allergy Clin Immunol. 2018;141:1050-9.e10.

131. Fernandez IZ, Baxter RM, Garcia-Perez JE, Vendrame E, Ranganath T, Kong DS, et al. A novel human *IL2RB* mutation results in T and NK cell-driven immune dysregulation. J Exp Med. 2019;216:1255-67.

132. Zhang Z, Gothe F, Pennamen P, James JR, McDonald D, Mata CP, et al. Human interleukin-2 receptor β mutations associated with defects in immunity and peripheral tolerance. J Exp Med. 2019;216:1311-27.

133. Liao W, Lin JX, Leonard WJ. IL-2 family cytokines: new insights into the complex roles of IL-2 as a broad regulator of T helper cell differentiation. Curr Opin Immunol. 2011;23:598-604.

134. Waldmann TA. The shared and contrasting roles of IL2 and IL15 in the life and death of normal and neoplastic lymphocytes: implications for cancer therapy. Cancer Immunol Res. 2015;3:219-27.

135. Parlato M, Nian Q, Charbit-Henrion F, Ruemmele FM, Rodrigues-Lima F, Cerf-Bensussan N; et al. Loss-of-function mutation in PTPN2 causes aberrant activation of JAK signaling via STAT and very early onset intestinal inflammation. Gastroenterology. 2020;159:1968-71.e4.

136. Song J, Lan J, Tang J, Luo N. PTPN2 in the immunity and tumor immunotherapy: A concise review. Int J Mol Sci. 2022;23:10025.

137. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. Signal Transduct Target Ther. 2017;2:17023-.

138. Bosa L, Batura V, Colavito D, Fiedler K, Gaio P, Guo C, et al. Novel CARMIL2 loss-of-function variants are associated with pediatric inflammatory bowel disease. Scientific Reports. 2021;11:5945.

139. Schober T, Magg T, Laschinger M, Rohlfs M, Linhares ND, Puchalka J, et al. A human immunodeficiency syndrome caused by mutations in CARMIL2. Nat Commun. 2017;8:14209.

140. Sorte HS, Osnes LT, Fevang B, Aukrust P, Erichsen HC, Backe PH, et al. A potential founder variant in *CARMIL2/RLTPR* in three Norwegian families with warts, molluscum contagiosum, and T-cell dysfunction. Mol Genet Genomic Med. 2016;4:604-16.

141. Magg T, Shcherbina A, Arslan D, Desai MM, Wall S, Mitsialis V, et al. CARMIL2 deficiency presenting as very early onset inflammatory bowel disease. Inflamm Bowel Dis. 2019;25:1788-95.

142. Dorjbal B, Stinson JR, Ma CA, Weinreich MA, Miraghazadeh B, Hartberger JM, et al. Hypomorphic caspase activation and recruitment domain 11 (CARD11) mutations associated with diverse immunologic phenotypes with or without atopic disease. J Allergy Clin Immunol. 2019;143:1482-95.

143. Hu W, Ye Z, Li P, Wang Y, Huang Y. Very early onset inflammatory bowel disease caused by a novel dominant negative mutation of caspase recruitment domain 11 (CARD11). J Clin Immunol. 2023;43:528-31.

144. Mevorach D. Clearance of dying cells and systemic lupus erythematosus: the role of C1q and the complement system. Apoptosis. 2010;15:1114-23.

145. Holers VM. Complement and its receptors: new insights into human disease. Annu Rev Immunol. 2014;32:433-59.

146. Kwan WH, van der Touw W, Heeger PS. Complement regulation of T cell immunity. Immunol Res. 2012;54:247-53.

147. Elvington M, Liszewski MK, Atkinson JP. Evolution of the complement system: from defense of the single cell to guardian of the intravascular space. Immunol Rev. 2016;274:9-15.

148. Waldmann TA, Steinfeld JL, Dutcher TF, Davidson JD, Gordon RS. The role of the gastrointestinal system in "idiopathic hypoproteinemia". Gastroenterology. 1961;41:197-207.

149. Ozen A, Comrie WA, Ardy RC, Domínguez Conde C, Dalgic B, Beser ÖF, et al. CD55 deficiency, early-onset protein-losing enteropathy, and thrombosis. N Engl J Med. 2017;377:52-61.

150. Kurolap A, Eshach-Adiv O, Hershkovitz T, Paperna T, Mory A, Oz-Levi D, et al, Loss of CD55 in eculizumab-responsive protein-losing enteropathy. N Engl J Med. 2017;377: 87-9.

151. Ozen A. CHAPLE syndrome uncovers the primary role of complement in a familial form of Waldmann's disease. Immunol Rev. 2019;287:20-32.

152. Ozen A, Kasap N, Vujkovic-Cvijin I, Apps R, Cheung F, Karakoc-Aydiner E, et al. Broadly effective metabolic and immune recovery with C5 inhibition in CHAPLE disease. Nat Immunol. 2021;22:128-39.

153. Ozen A, Chongsrisawat V, Sefer AP, Kolukisa B, Jalbert JJ, Meagher KA, et al. Evaluating the efficacy and safety of pozelimab in patients with CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy disease: an open-label phase 2 and 3 study. Lancet. 2024;403:645-56.

154. Crowley E, Warner N, Pan J, Khalouei S, Elkadri A, Fiedler K, et al. Prevalence and clinical features of inflammatory bowel diseases associated with monogenic variants, identified by whole-exome sequencing in 1000 children at a single center. Gastroenterology. 2020;158:2208-20.

155. Kammermeier J, Lamb CA, Jones KDJ, Anderson CA, Baple EL, Bolton C, et al. Genomic diagnosis and care co-ordination for monogenic inflammatory bowel disease in children and adults: consensus guideline on behalf of the British Society of Gastroenterology and British Society of Paediatric Gastroenterology, Hepatology and Nutrition. Lancet Gastroenterol Hepatol. 2023;8:271-86.

156. Ouahed JD. Understanding inborn errors of immunity: A lens into the pathophysiology of monogenic inflammatory bowel disease. Front Immunol. 2022;13:1026511.

157. Hartono S, Ippoliti MR, Mastroianni M, Torres R, Rider NL. Gastrointestinal disorders associated with primary immunodeficiency diseases. Clin Rev Allergy Immunol. 2019;57:145-65.

158. Ozen A, Baris S, Karakoc-Aydiner E, Ozdemir C, Bahceciler NN, Barlan IB. Outcome of hypogammaglobulinemia in children: immunoglobulin levels as predictors. Clin Immunol. 2010;137:374-83.

159. Jayasooriya N, Baillie S, Blackwell J, Bottle A, Petersen I, Creese H, et al. Systematic review with meta-analysis: Time to diagnosis and the impact of delayed diagnosis on clinical outcomes in inflammatory bowel disease. Aliment Pharmacol Ther. 2023;57:635-52.

160. Demir DD, Asnaashari K, Rezaei N, Özen A. Management of inborn errors of immunity in the genomic era. Turk Arch Pediatr. 2022;57:132-45.

161. Nambu R, Warner N, Mulder DJ, Kotlarz D, McGovern DPB, Cho J, et al. A systematic review of monogenic inflammatory bowel disease. Clin Gastroenterol Hepatol. 2022;20:e653-e63.

162. Jansen FM, Vavricka SR, den Broeder AA, de Jong EM, Hoentjen F, van Dop WA. Clinical management of the most common extra-intestinal manifestations in patients with inflammatory bowel disease focused on the joints, skin and eyes. United European Gastroenterol J. 2020;8:1031-44.

163. Ozen A, Lenardo MJ. Protein-losing enteropathy. N Engl J Med. 2023;389:733-48.

164. Uzel G, Orange JS, Poliak N, Marciano BE, Heller T, Holland SM. Complications of tumor necrosis factor-α blockade in chronic granulomatous disease-related colitis. Clin Infect Dis. 2010;51:1429-34.

165. Uhlig HH, Booth C, Cho J, Dubinsky M, Griffiths AM, Grimbacher B, et al. Precision medicine in monogenic inflammatory bowel disease: proposed mIBD REPORT standards. Nat Rev Gastroenterol Hepatol. 2023;20:810-28.

166. Bigorgne AE, Farin HF, Lemoine R, Mahlaoui N, Lambert N, Gil M, et al. TTC7A mutations disrupt intestinal epithelial apicobasal polarity. J Clin Invest. 2014;124:328-37.

167. Chen YE, Chen J, Guo W, Zhang Y, Li J, Xie H, et al. Clinical characteristics, *in silico* analysis, and intervention of neonatal-onset inflammatory bowel disease with combined immunodeficiency caused by novel *TTC7A* variants. Front Genet. 2022;13:921808.

168. Lien R, Lin YF, Lai MW, Weng HY, Wu RC, Jaing TH, et al. Novel mutations of the *Tetratricopeptide Repeat Domain* 7A gene and phenotype/genotype comparison. Front Immunol. 2017;8:1066.

169. Dhingani N, Guo C, Pan J, Li Q, Warner N, Jardine S, et al. The E3 ubiquitin ligase UBR5 interacts with TTC7A and may be associated with very early onset inflammatory bowel disease. Sci Rep. 2020;10:18648.

170. 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;113:725-33.

171. Cheng LE, Kanwar B, Tcheurekdjian H, Grenert JP, Muskat M, Heyman MB, et al. Persistent systemic inflammation and atypical enterocolitis in patients with NEMO syndrome. Clin Immunol. 2009;132:124-31.

172. Blaydon DC, Biancheri P, Di WL, Plagnol V, Cabral RM, Brooke MA, et al. Inflammatory skin and bowel disease linked to ADAM17 deletion. N Engl J Med. 2011;365:1502-8.

173. Fiskerstrand T, Arshad N, Haukanes BI, Tronstad RR, Pham KD, Johansson S, et al. Familial diarrhea syndrome caused by an activating GUCY2C mutation. N Engl J Med. 2012;366:1586-95.

174. Müller T, Rasool I, Heinz-Erian P, Mildenberger E, Hülstrunk C, Müller A, et al. Congenital secretory diarrhoea caused by activating germline mutations in GUCY2C. Gut. 2016;65:1306-13.

175. Janecke AR, Heinz-Erian P, Yin J, Petersen BS, Franke A, Lechner S, et al. Reduced sodium/proton exchanger NHE3 activity causes congenital sodium diarrhea. Hum Mol Genet. 2015;24:6614-23.

176. O'Connell AE, Zhou F, Shah MS, Murphy Q, Rickner H, Kelsen J, et al. Neonatal-onset chronic diarrhea caused by homozygous nonsense WNT2B mutations. Am J Hum Genet. 2018;103:131-7.

177. Charbit-Henrion F, Jeverica AK, Bègue B, Markelj G, Parlato M, Avčin SL, et al. Deficiency in mucosa-associated lymphoid tissue lymphoma translocation 1: A novel cause of IPEX-like syndrome. J Pediatr Gastroenterol Nutr. 2017;64:378-84.

178. Haapaniemi EM, Kaustio M, Rajala HL, van Adrichem AJ, Kainulainen L, Glumoff V, et al. Autoimmunity, hypogammaglobulinemia, lymphoproliferation, and mycobacterial disease in patients with activating mutations in STAT3. Blood. 2015;125:639-48.

179. Gruber CN, Calis JJA, Buta S, Evrony G, Martin JC, Uhl SA, et al. Complex autoinflammatory syndrome unveils fundamental principles of JAK1 kinase transcriptional and biochemical function. Immunity. 2020;53:672-84.e11.

180. Afzali B, Grönholm J, Vandrovcova J, O'Brien C, Sun HW, Vanderleyden I, et al. BACH2 immunodeficiency illustrates an association between super-enhancers and haploinsufficiency. Nat Immunol. 2017;18:813-23.

181. Engelhardt KR, Shah N, Faizura-Yeop I, Kocacik Uygun DF, Frede N, Muise AM, 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;131:825-30.

182. Glocker EO, Kotlarz D, Klein C, Shah N, Grimbacher B. IL-10 and IL-10 receptor defects in humans. Ann N Y Acad Sci. 2011;1246:102-7.

183. Glocker EO, Frede N, Perro M, Sebire N, Elawad M, Shah N, Grimbacher B. Infant colitis--it's in the genes. Lancet. 2010;376:1272.

184. Begue B, Verdier J, Rieux-Laucat F, Goulet O, Morali A, Canioni D, et al. Defective IL10 signaling defining a subgroup of patients with inflammatory bowel disease. Am J Gastroenterol. 2011;106:1544-55.

185. Moran CJ, Walters TD, Guo CH, Kugathasan S, Klein C, Turner D, et al. IL-10R polymorphisms are associated with very-early-onset ulcerative colitis. Inflamm Bowel Dis. 2013;19:115-23.

186. Neven B, Mamessier E, Bruneau J, Kaltenbach S, Kotlarz D, Suarez F, et al. A Mendelian predisposition to B-cell lymphoma caused by IL-10R deficiency. Blood. 2013;122:3713-22.

187. Yanagi T, Mizuochi T, Takaki Y, Eda K, Mitsuyama K, Ishimura M, et al. Novel exonic mutation inducing aberrant splicing in the IL10RA gene and resulting in infantile-onset inflammatory bowel disease: a case report. BMC Gastroenterology. 2016;16:10.

188. Oh SH, Baek J, Liany H, Foo JN, Kim KM, Yang SC, et al. A synonymous variant in IL10RA affects RNA splicing in paediatric patients with refractory inflammatory bowel disease. J Crohns Colitis. 2016;10:1366-71.

189. Kelsen JR, Dawany N, Moran CJ, Petersen BS, Sarmady M, Sasson A, et al. Exome sequencing analysis reveals variants in primary immunodeficiency genes in patients with very early onset inflammatory bowel disease. Gastroenterology. 2015;149:1415-24.

190. Lu D, Xu Y, Chen Y, Zeng P, Chen H, Zeng H. [Interleukin-10 receptor mutations in children with neonatal onset inflammatory bowel disease: genetic diagnosis and pathogenesis]. Zhonghua Er Ke Za Zhi. 2015;53:348-54.

191. Beser OF, Conde CD, Serwas NK, Cokugras FC, Kutlu T, Boztug K, et al. Clinical features of interleukin 10 receptor gene mutations in children with very early-onset inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2015;60:332-8.

192. Lee CH, Hsu P, Nanan B, Nanan R, Wong M, Gaskin KJ, et al. Novel de novo mutations of the interleukin-10 receptor gene lead to infantile onset inflammatory bowel disease. J Crohns Colitis. 2014;8:1551-6.

193. Charbit-Henrion F, Parlato M, Hanein S, Duclaux-Loras R, Nowak J, Begue B, et al. Diagnostic yield of next-generation sequencing in very early-onset inflammatory bowel diseases: A multicentre study. J Crohns Colitis. 2018;12:1104-12.

194. Burns SO, Zenner HL, Plagnol V, Curtis J, Mok K, Eisenhut M, et al. LRBA gene deletion in a patient presenting with autoimmunity without hypogammaglobulinemia. J Allergy Clin Immunol. 2012;130:1428-32.

195. Alangari A, Alsultan A, Adly N, Massaad MJ, Kiani IS, Aljebreen A, 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;130:481-8.e2.

196. Charbonnier LM, Janssen E, Chou J, Ohsumi TK, Keles S, Hsu JT, et al. Regulatory T-cell deficiency and immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like disorder caused by loss-of-function mutations in LRBA. J Allergy Clin Immunol. 2015;135:217-27.

197. Serwas NK, Kansu A, Santos-Valente E, Kuloğlu Z, Demir A, Yaman A, et al. Atypical manifestation of LRBA deficiency with predominant IBD-like phenotype. Inflamm Bowel Dis. 2015;21:40-7.

198. Kotlarz D, Ziętara N, Milner JD, Klein C. Human IL-21 and IL-21R deficiencies: two novel entities of primary immunodeficiency. Curr Opin Pediatr. 2014;26:704-12.

199. Kotlarz D, Ziętara N, Uzel G, Weidemann T, Braun CJ, Diestelhorst J, et al. Loss-of-function mutations in the IL-21 receptor gene cause a primary immunodeficiency syndrome. J Exp Med. 2013;210:433-43.

200. Salzer E, Kansu A, Sic H, Májek P, Ikincioğullari A, Dogu FE, et al. Early-onset inflammatory bowel disease and common variable immunodeficiency-like disease caused by IL-21 deficiency. J Allergy Clin Immunol. 2014;133:1651-9.e12.

201. Folwaczny C, Ruelfs C, Walther J, König A, Emmerich B. Ulcerative colitis in a patient with Wiskott-Aldrich syndrome. Endoscopy. 2002;34:840-1.

202. Rohr J, Pannicke U, Döring M, Schmitt-Graeff A, Wiech E, Busch A, et al. Chronic inflammatory bowel disease as key manifestation of atypical ARTEMIS deficiency. J Clin Immunol. 2010;30:314-20.

203. Ege M, Ma Y, Manfras B, Kalwak K, Lu H, Lieber MR, et al. Omenn syndrome due to ARTEMIS mutations. Blood. 2005;105:4179-86.

204. Conley ME, Dobbs AK, Quintana AM, Bosompem A, Wang YD, Coustan-Smith E, et al. Agammaglobulinemia and absent B lineage cells in a patient lacking the p85α subunit of PI3K. J Exp Med. 2012;209:463-70.

205. Cohen SB, Bainter W, Johnson JL, Lin TY, Wong JCY, Wallace JG, et al. Human primary immunodeficiency caused by expression of a kinase-dead p110δ mutant. J Allergy Clin Immunol. 2019;143:797-9.e2.

206. Knight SW, Heiss NS, Vulliamy TJ, Aalfs CM, McMahon C, Richmond P, 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;107:335-9.

207. Sznajer Y, Baumann C, David A, Journel H, Lacombe D, Perel Y, et al. Further delineation of the congenital form of X-linked dyskeratosis congenita (Hoyeraal-Hreidarsson syndrome). Eur J Pediatr. 2003;162:863-7.

208. Borggraefe I, Koletzko S, Arenz T, Fuehrer M, Hoffmann F, Dokal I, et al. Severe variant of x-linked dyskeratosis congenita (Hoyeraal-Hreidarsson Syndrome) causes significant enterocolitis in early infancy. J Pediatr Gastroenterol Nutr. 2009;49:359-63.

209. Ballew BJ, Joseph V, De S, Sarek G, Vannier JB, Stracker T, 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.

210. Ballew BJ, Yeager M, Jacobs K, Giri N, Boland J, Burdett L, et al. Germline mutations of regulator of telomere elongation helicase 1, RTEL1, in Dyskeratosis congenita. Hum Genet. 2013;132:473-80.

211. Naviglio S, Arrigo S, Martelossi S, Villanacci V, Tommasini A, Loganes C, et al. Severe inflammatory bowel disease associated with congenital alteration of transforming growth factor beta signaling. J Crohns Colitis. 2014;8:770-4.

212. Kotlarz D, Marquardt B, Barøy T, Lee WS, Konnikova L, Hollizeck S, et al. Human TGF-β1 deficiency causes severe inflammatory bowel disease and encephalopathy. Nat Genet. 2018;50:344-8.

213. Conrad MA, Dawany N, Sullivan KE, Devoto M, Kelsen JR. Novel ZBTB24 mutation associated with immunodeficiency, centromere instability, and facial anomalies type-2 syndrome identified in a patient with very early onset inflammatory bowel disease. Inflamm Bowel Dis. 2017;23:2252-5.

314. Li Y, Führer M, Bahrami E, Socha P, Klaudel-Dreszler M, Bouzidi A, et al. Human RIPK1 deficiency causes combined immunodeficiency and inflammatory bowel diseases. Proc Natl Acad Sci U S A. 2019;116:970-5.

215. Lehle AS, Farin HF, Marquardt B, Michels BE, Magg T, Li Y, et al. Intestinal inflammation and dysregulated immunity in patients with inherited caspase-8 deficiency. Gastroenterology. 2019;156:275-8.

216. Muise AM, Xu W, Guo CH, Walters TD, Wolters VM, Fattouh R, 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;61:1028-35.

217. Schäppi MG, Smith VV, Goldblatt D, Lindley KJ, Milla PJ. Colitis in chronic granulomatous disease. Arch Dis Child. 2001;84:147-51.

218. Marks DJ, Miyagi K, Rahman FZ, Novelli M, Bloom SL, Segal AW. Inflammatory bowel disease in CGD reproduces the clinicopathological features of Crohn's disease. Am J Gastroenterol. 2009;104:117-24.

219. Li Z, Chen H, Feng X, Ruan Y, Yang M. Hematopoietic stem cell transplantation for CYBB heterozygous mutation resulting in very early onset inflammatory bowel disease in children: a case report. BMC Pediatrics. 2023;23:348.

220. Saltik-Temizel IN, Koçak N, Ozen H, Yüce A, Gürakan F, Demir H. Inflammatory bowel disease-like colitis in a young Turkish child with glycogen storage disease type 1b and elevated platelet count. Turk J Pediatr. 2005;47:180-2.

221. Yamaguchi T, Ihara K, Matsumoto T, Tsutsumi Y, Nomura A, Ohga S, et al. Inflammatory bowel disease-like colitis in glycogen storage disease type 1b. Inflamm Bowel Dis. 2001;7:128-32.

222. Rake JP, Visser G, Labrune P, Leonard JV, Ullrich K, Smit GP. Glycogen storage disease type I: diagnosis, management, clinical course and outcome. Results of the European Study on Glycogen Storage Disease Type I (ESGSD I). Eur J Pediatr. 2002;161(Suppl 1):S20-34.

223. Bégin P, Patey N, Mueller P, Rasquin A, Sirard A, Klein C, et al. Inflammatory bowel disease and T cell lymphopenia in G6PC3 deficiency. J Clin Immunol. 2013;33:520-5.

224. Kaya Z, Eğritaş O, Albayrak M, Göçün PU, Koçak U, Dalgiç B, et al. Resolution of inflammatory colitis with pegfilgrastim treatment in a case of severe congenital neutropenia due to glucose 6 phosphatase catalytic subunit-3 deficiency. J Pediatr Hematol Oncol. 2014;36:e316-8.

225. Kiykim A, Baris S, Karakoc-Aydiner E, Ozen AO, Ogulur I, Bozkurt S, et al. G6PC3 deficiency: Primary immune deficiency beyond just neutropenia. J Pediatr Hematol Oncol. 2015;37:616-22.

226. Cullinane AR, Vilboux T, O'Brien K, Curry JA, Maynard DM, Carlson-Donohoe H, 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;131:2017-25.

227. D'Agata ID, Paradis K, Chad Z, Bonny Y, Seidman E. Leucocyte adhesion deficiency presenting as a chronic ileocolitis. Gut. 1996;39:605-8.

228. Uzel G, Kleiner DE, Kuhns DB, Holland SM. Dysfunctional LAD-1 neutrophils and colitis. Gastroenterology. 2001;121:958-64.

229. Schwerd T, Pandey S, Yang HT, Bagola K, Jameson E, Jung J, et al. Impaired antibacterial autophagy links granulomatous intestinal inflammation in Niemann-Pick disease type C1 and XIAP deficiency with NOD2 variants in Crohn's disease. Gut. 2017;66:1060-73.

230. Héron B, Valayannopoulos V, Baruteau J, Chabrol B, Ogier H, Latour P, et al. Miglustat therapy in the French cohort of paediatric patients with Niemann-Pick disease type C. Orphanet J Rare Dis. 2012,7:36.

231. Jolliffe DS, Sarkany I. Niemann-Pick type III and Crohn's disease. J R Soc Med. 1983;76:307-8.

232. Arnadottir GA, Norddahl GL, Gudmundsdottir S, Agustsdottir AB, Sigurdsson S, Jensson BO, et al. A homozygous loss-of-function mutation leading to CYBC1 deficiency causes chronic granulomatous disease. Nat Commun. 2018;9:4447.

233. Trefzer R, Elpeleg O, Gabrusskaya T, Stepensky P, Mor-Shaked H, Grosse R, et al. Characterization of a L136P mutation in Formin-like 2 (FMNL2) from a patient with chronic inflammatory bowel disease. PLoS One. 2021;16:e0252428.

234. Zeissig Y, Petersen BS, Milutinovic S, Bosse E, Mayr G, Peuker K, et al. XIAP variants in male Crohn's disease. Gut. 2015;64:66-76.

235. Rigaud S, Fondanèche MC, Lambert N, Pasquier B, Mateo V, Soulas P, et al. XIAP deficiency in humans causes an X-linked lymphoproliferative syndrome . Nature. 2006;444:110-4.

236. Yang X, Kanegane H, Nishida N, Imamura T, Hamamoto K, Miyashita R, et al. Clinical and genetic characteristics of XIAP deficiency in Japan. J Clin Immunol. 2012;32:411-20.

237. Aguilar C, Lenoir C, Lambert N, Bègue B, Brousse N, Canioni D, et al. Characterization of Crohn disease in X-linked inhibitor of apoptosis-deficient male patients and female symptomatic carriers. J Allergy Clin Immunol. 2014;134:1131-41.e9.

238. Tang J, Zhou X, Wang L, Hu G, Zheng B, Wang C, et al. Eosinophilic colitis in a boy with a novel XIAP mutation: a case report. BMC Pediatrics. 2020;20:171.

239. Erzin Y, Cosgun S, Dobrucali A, Tasyurekli M, Erdamar S, Tuncer M. Complicated granulomatous colitis in a patient with Hermansky-Pudlak syndrome, successfully treated with infliximab. Acta Gastroenterol Belg. 2006;69:213-6.

240. Carmona-Rivera C, Golas G, Hess RA, Cardillo ND, Martin EH, O'Brien K, Tsilou E, et al. Clinical, molecular, and cellular features of non-Puerto Rican Hermansky-Pudlak syndrome patients of Hispanic descent. J Invest Dermatol. 2011;131:2394-400.

241. Mahadeo R, Markowitz J, Fisher S, Daum F. Hermansky-Pudlak syndrome with granulomatous colitis in children. J Pediatr. 1991;118:904-6.

242. Hussain N, Quezado M, Huizing M, Geho D, White JG, Gahl W, et al. Intestinal disease in Hermansky-Pudlak syndrome: occurrence of colitis and relation to genotype. Clin Gastroenterol Hepatol. 2006;4:73-80.

243. Omoyinmi E, Rowczenio D, Sebire N, Brogan PA, Eleftheriou D. Vasculitis in a patient with mevalonate kinase deficiency (MKD): a case report. Pediatr Rheumatol Online J. 2021;19:161.

244 Bader-Meunier B, Martins AL, Charbit-Henrion F, Meinzer U, Belot A, Cuisset L, et al. Mevalonate kinase deficiency: A

cause of severe very-early-onset inflammatory Bowel Disease. Inflamm Bowel Dis. 2021;27:1853-7.

245. Zhou Q, Lee GS, Brady J, Datta S, Katan M, Sheikh A, et al. A hypermorphic missense mutation in PLCG2, encoding phospholipase Cγ2, causes a dominantly inherited autoinflammatory disease with immunodeficiency. Am J Hum Genet. 2012;91:713-20.

246. Li Q, Lee CH, Peters LA, Mastropaolo LA, Thoeni C, Elkadri A, et al. Variants in TRIM22 that affect NOD2 signaling are associated with very-early-onset inflammatory bowel disease. Gastroenterology. 2016;150:1196-207.

247. Uchida K, Nakajima A, Ushijima K, Ida S, Seki Y, Kakuta F, et al. Pediatric-onset chronic nonspecific multiple ulcers of small intestine: A nationwide survey and genetic study in Japan. J Pediatr Gastroenterol Nutr. 2017;64:565-8.

248. Ito N, Kudo T, Eguchi H, Jimbo K, Furuhata A, Okuno T, et al. Attenuated expression of SLCO2A1 caused by DNA methylation in pediatric inflammatory bowel disease. Inflamm Bowel Dis. 2023;29:1920-8.

249. Lam MT, Coppola S, Krumbach OHF, Prencipe G, Insalaco A, Cifaldi C, et al. A novel disorder involving dyshematopoiesis, inflammation, and HLH due to aberrant CDC42 function. J Exp Med. 2019;216:2778-99.

250. Vardi I, Barel O, Sperber M, Schvimer M, Nunberg M, Field M, et al. Genetic and structural analysis of a SKIV2L mutation causing Tricho-hepato-enteric syndrome. Dig Dis Sci. 2018;63:1192-9.

251. Fabre A, Charroux B, Martinez-Vinson C, Roquelaure B, Odul E, Sayar E, et al. SKIV2L mutations cause syndromic diarrhea, or trichohepatoenteric syndrome. Am J Hum Genet. 2012;90:689-92.

252. Kammermeier J, Drury S, James CT, Dziubak R, Ocaka L, Elawad M, et al. Targeted gene panel sequencing in children with very early onset inflammatory bowel disease--evaluation and prospective analysis. J Med Genet. 2014;51:748-55.

253. Kahr WH, Pluthero FG, Elkadri A, Warner N, Drobac M, Chen CH, et al. Loss of the Arp2/3 complex component ARPC1B causes platelet abnormalities and predisposes to inflammatory disease. Nat Commun. 2017;8:14816.

254. Ziegler A, Duclaux-Loras R, Revenu C, Charbit-Henrion F, Begue B, Duroure K, et al. Bi-allelic variants in IPO8 cause a connective tissue disorder associated with cardiovascular defects, skeletal abnormalities, and immune dysregulation. Am J Hum Genet. 2021;108:1126-37.

255. Cananzi M, Wohler E, Marzollo A, Colavito D, You J, Jing H, et al. IFIH1 loss-of-function variants contribute to very early-onset inflammatory bowel disease. Hum Genet. 2021;140:1299-312.

256. Ouahed J, Spencer E, Kotlarz D, Shouval DS, Kowalik M, Peng K, et al. Very early onset inflammatory bowel disease: A clinical approach with a focus on the role of genetics and underlying immune deficiencies. Inflamm Bowel Dis. 2020;26:820-42.