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Genomic and Immunologic Drivers of Very Early-Onset Inflammatory Bowel Disease

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Abstract

Purpose of Review: Inflammatory bowel disease (IBD) is a multifactorial disease caused by dysregulated immune responses to commensal or pathogenic intestinal microbes, resulting in chronic intestinal inflammation. However, a subset of patients with IBD diagnosed <6 years of age, known as very early-onset (VEO)-IBD, can be phenotypically and genetically distinct from older onset IBD. We aim to review the clinical presentation of children with VEO-IBD and recent discoveries that point to the underlying genomic and immunologic drivers of disease, and the significant impact on our therapeutic decisions.

Recent Findings: VEO-IBD is increasing in incidence and is associated with more severe disease, aggressive progression, and poor response to most conventional therapies. This article will review some of the genetic findings in this population and the subsequent impact on therapy, with targeted approaches.

Summary: Children with VEO-IBD may present with a different phenotype and more severe disease than older children and adults. An integrated approach combining genetics, immunology, and traditional IBD evaluations can lead to the identification of causal defects that directly impact management. These strategies can also be employed in older onset refractory IBD.

Keywords

very early-onset inflammatory bowel disease; whole-exome sequencing; immunodeficiency

Introduction

The genomic contribution to inflammatory bowel disease (IBD) is complex and polygenic, involving over 200 risk loci identified mainly through genome wide association studies.[1,2] These studies have provided the genetic landscape of IBD and shed light on the delicate interaction between host defense and the gut microbiome in disease development. However,

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genetics can play a more dominant role in the very young children with IBD, diagnosed <6, known as very early-onset IBD (VEO-IBD), particularly in those who present in the first year of life, known as infantile onset IBD. Children with VEO-IBD can have a more severe and refractory disease course than older children and adults with IBD. Over the last decade, using advanced sequencing technology, monogenic defects have been identified in some of these children, often involving primary immunodeficiency genes.[3–5]

Epidemiology

Pediatric IBD has increased in incidence and prevalence, and this phenomenon has included very young children.[6–8] Approximately 6% to 15% of the pediatric IBD population is less than 6-years-old,[7,8] and recent studies have demonstrated a rapid rise in this cohort from 1.3 to 2.1 per 100 000 children from 1994 to 2009, with a mean annual increase of 7.2%.[9] This rise may be, at least in part, secondary to changes in the environment and the gut microbiota, which develops between birth and 3 years of life, coincident with the age of onset of many VEO-IBD cases. Exposures such as route of delivery, gestational age, maternal diet, and infant feeding practices shape the colonization of an infant's microbiota until age 3 and can impact disease risk at all ages.[10] Simultaneously, the immune system develops during the first 3 years of life. The intestine is the largest immune organ, and it is at this interface that the microbiota and immune system shape and regulate one another in function and development. This interaction is well balanced in healthy children; however, disruptions in development may affect the formation of the microbial community structure and function (dysbiosis) and/or immune response, leading to devastating sequelae.[10]

Disease Classification

Because a subset of patients with VEO-IBD present with extensive colonic disease (pancolitis), it can be difficult to differentiate ulcerative colitis (UC) from Crohn's disease (CD).[8,11] In addition, the extent and location of disease can change and progress over time, and patients who present with exclusive colonic disease can later develop perianal and small bowel disease.[12] Therefore, indeterminate colitis is diagnosed more often in patients with VEO-IBD (11%–22%) as compared to older onset IBD (4%–10%).[9,13–15] Because of this colonic involvement, patients with VEO-IBD are also more commonly diagnosed with UC (35%–59%) as compared to older onset IBD (older children > 6 and adults) in which CD is more prevalent (55%–60%). In contrast, only 30% to 35% of VEO-IBD patients are diagnosed with CD.

Unique Genomics of VEO-IBD

Advances in sequencing technology, such as whole-exome sequencing (WES) and targeted sequencing panels, have radically changed our approach to VEO-IBD and provided an opportunity to investigate its unique genomic etiology.[16–21] Since 2009, single gene defects have been identified in this cohort, and some of the discoveries have led to targeted therapy. Examples include the identification of *IL-10*[22] and *IL-10R*[23,24] gene mutations in infantile IBD, which result in the phenotype of severe perianal disease, colitis, and folliculitis.[5,24] Although refractory to conventional therapies, these patients are successfully treated with

hematopoietic stem cell transplantation (HSCT). Additional underlying immunodeficiencies or genetic disorders have been identified in children with VEO-IBD.[4,11,18,25,26] These include genes integral to intestinal epithelial barrier function, phagocyte bacterial killing, hyper or autoimmune inflammatory pathways, and development and function of the adaptive immune system.[11,18,25,27] These defects can impact the developing gut microbiome and thus progression of intestinal inflammation. As we learn more about this disease we will have the unique opportunity to develop therapeutic strategies that are directed toward the underlying impaired pathway in this cohort.

Genetic Variants in the IL-10-IL-10R Pathway and Related Cytokine Family Members

Homozygous loss-of-function mutations in *IL10* ligand and receptors *IL10RA* and *IL10RB* were the first genes to be identified as causative for VEO-IBD.[23] They are associated with severe intestinal inflammation, particularly in neonatal or infantile IBD, with a phenotype of severe enterocolitis and perianal disease.[22,23] In addition, compound heterozygote loss-of-function mutations of *IL10RA* have been reported with neonatal IBD and enterocolitis.[28] IL-10 is an anti-inflammatory cytokine secreted by a variety of cells, including dendritic cells, natural killer cells, eosinophils, mast cells, macrophages, B cells, and $CD4^+$ T-cell subsets (including Th2 cells, Th1 cells, Th17 cells, and Treg).[29,30] IL-10 maintains homeostasis through suppression of an excessive proinflammatory response and exerts its effect through binding to the IL-10 receptor, IL-10R, which is a tetrameric complex.[31,32] *IL-10* defects are associated with intestinal inflammation, arthritis, folliculitis, and increase risk of lymphoma,[28,33] particularly large B-cell lymphoma. HSCT has proven to be a successful treatment for these patients and potentially life-saving.[34,35]

Genetic Variants Influencing Intestinal Epithelial Barrier Function

It is at the epithelial surface where the interaction between the immune cells and the intestinal environment must be perfectly tuned to prevent inappropriate responses. The intestinal barrier is necessary to maintain a physical separation between commensal bacteria and the host immune system, and any break in this defense can lead to chronic intestinal inflammation.[36,37] Increased translocation of bacteria or translocation of inappropriate bacteria, as in the case in dysbiosis, drives an inflammatory loop.

Defects in the intestinal epithelial barrier function can be involved in VEO-IBD. These processes include loss-of-function mutations in *ADAM17* resulting in ADAM17 deficiency,[38,39] *IKBKG* (encoding NEMO) resulting in X-linked ectodermal dysplasia and immunodeficiency,[40] *COL7A1* resulting in dystrophic epidermolysis bullosa,[41] *FERMT1* resulting in Kindler syndrome,[42–44] and *TTC7A*,[19] or gain-of-function mutations in *GUCY2* resulting in familial diarrhea.[26,45] Many of these results in immune deficiency as well as additional extraintestinal manifestations including changes in skin, hair, and nails.

Homozygous mutations in tetratricopeptide repeat domain 7A (*TTC7A*) gene have been shown to lead to several phenotypes including different forms of severe combined immunodeficiency, multiple intestinal atresia, and infantile onset IBD (Figure 1).[19,46,47] Other phenotypes linked to this gene also include immune deficiency-related enteropathy-lymphocytopenia-alopecia syndrome.[48] There have been cases of severe intestinal disease in

older patients with compound heterozygous mutations in *TTC7A*.[49] Although the mechanism of disease seen in *TTC7A* defects has not been fully elucidated, the protein appears to repress RhoA signaling. Therefore, mutations lead to increased rho kinase activity, disrupting epithelial intestinal cell polarity and growth with subsequent multiple intestinal atresia and impairment of immune cell homeostasis resulting in combined immunodeficiency.[19,46] Future therapeutic developments inhibiting rho kinase may be an effective treatment option for this condition.

Genetic Variants Influencing Bacterial Recognition and Clearance

Chronic granulomatous disease (CGD) is a result of defective phagocytes, specifically the granulocytes responsible for bacterial killing and clearance.[50] The NADPH oxidase complex within neutrophils is responsible for killing of ingested microbes through its production of the respiratory burst. Mutations in any part of the complex molecules, including X-linked and autosomal recessive inheritance (*CYBB, CYBA, NCF1, NCF2, NCF4*) can result in intestinal inflammation, autoimmune disease, and immunodeficiency.[51,52] In addition to susceptibility to systemic bacterial and fungal infections, intestinal inflammation can be observed in as high as 40% of patients with CGD.[53–56] Several variants have been associated with VEO-IBD, in particular defective NCF2 results in altered binding to RAC2.[57] These patients can present in the neonatal or first year of life. With colitis, severe fistulizing perianal disease, and stricturing.[57] Histology frequently demonstrates multiple granulomas that may not have associated inflammatory change.[16,58] Other neutrophil defects that are associated with VEO-IBD include leukocyte adhesion defect, due to mutation in *ITGB2*.[59,60] These patients can present with an IBD phenotype, history of bacterial infection, and increased peripheral blood granulocytes.[61] Glycogen storage disease Type 1b, with the unique combination of neutropenia and neutrophil granulocyte dysfunction, can also present with intestinal inflammation.[62]

Therapies used to treat patients with these defects need to be carefully considered. For example, anti-TNFα therapy, an effective therapy for IBD, is contraindicated in CGD. These agents can increase the risk of severe infections in patients with CGD and can be fatal.[63] Other therapies include sargramostim, antibiotics, and allogenic HSCT, which have demonstrated some success.[64] IL-1R antagonists have been used in these patients with some positive results, by restoring autophagy and directly limiting inflammation.[65]

Genetic Variants Impairing Development of the Adaptive Immune System

Several genetic variants can alter the development or function of adaptive immune cells in a cell-intrinsic or -extrinsic manner. Multiple gene defects that impact the development or function of the adaptive immune system have been associated with severe combined immune deficiency (SCID).[27,66,67] Defects that affect development or function of B cells and T cells by blocking either early lymphocyte survival or recombination of the B-cell receptor or T-cell receptor[68–70] can occur with loss-of-function mutations in recombination activating genes (*RAG1* or *RAG2*) or the IL-7 receptor (*IL7R*) causing Omenn syndrome and the *PTEN* gene causing PTEN syndrome.[71] Omenn syndrome, a recessive form of SCID, can also be associated with intestinal disease as well as severe eczematous rash.[67,72] Laboratory studies can show increased oligoclonal T cells and reduced B cells, and histology can show

an intestinal graft versus host appearance, including epithelial cell apoptosis, eosinophilic and neutrophilic infiltrates, and villous atrophy in the small bowel.[73,74] Defects in B-cell development lead to an absence of circulating mature B cells and antibody production, which have been linked to an IBD phenotype.[66] This includes agammaglobulinemia, including X-linked agammaglobulinemia,[75] common variable immune deficiency and IgA deficiency. These are complex and heterogeneous diseases, with the responsible mutations known for only a minority of cases.[76] Even a mild immune deficiency such as IgA deficiency has a significantly higher rate of IBD than the general population.[77] This may reflect changes to the microbiome due to the lack of selective pressure,[78] increased microbial translocation, compromised signaling within the gastrointestinal tract, or stimulation of an aberrant response due to active infection.

Loss-of-function mutation in LRBA, resulting in multiple defects in immune cell populations, can result in a VEO-IBD phenotype with enteropathy in addition to autoimmune cytopenia, lymphoproliferation, immune deficiency, as well as endocrine manifestations.[79] LRBA is responsible for regulating CTLA4, which is recycled by immune cells in order to control immune responses. Abatacept, a CTLA4 immunoglobulin fusion drug, has been effective in treating LRBA deficiency, but HSCT can be an option for severe cases.

In addition to hypogammaglobulinemia, defects leading to overproduction of immunoglobulins including hyper-IgM, hyper-IgD, and hyper-IgE syndromes have been associated increased infections, intestinal inflammation, dermatologic manifestations, and perianal disease.[80]

Wiskott-Aldrich syndrome (WAS) results from a loss-of-function mutation in Wiskott-Aldrich syndrome protein (*WASP*), affecting actin filament formation. These patients can exhibit thrombocytopenia, eczema, eosinophilia, and immune deficiencies along with intestinal inflammation.[81] The clinical manifestation of patients with VEO-IBD with this genetic defect can be pancolitis in addition to other autoimmune processes. Genetic defects in *ARPC1B* can also result in a similar phenotype to WAS with intestinal inflammation.

Genetic Variants Impairing Regulatory T Cells

Defects in regulatory T cells (Tregs) can clinically present with colonic inflammation and well as an enteropathy. The prominence of villous atrophy is a clue to these disorders. Immunodysregulation, polyendocrinopathy, enteropathy X-linked syndrome (IPEX) is most often secondary to mutations of Forkhead box protein 3 (*FOXP3*) gene, a transcription factor that is essential for the development and immunosuppressive activity of CD4 Foxp3$^+$ Tregs.[72,82–84] There are over 20 mutations in *FOXP3* that have been identified in patients with IPEX,[83] and patients frequently present with neonatal severe secretory diarrhea, failure to thrive, infection (due to defects in immunoregulation), skin rash, insulin dependent diabetes, thyroiditis, cytopenias, and other autoimmune disorders.[72] Tregs are absent or dysfunctional in these patients, and in the intestine, histologic analyses may reveal infiltration of inflammatory cells in the lamina propria and submucosa of the small bowel and colon as well as changes in the mucosa of the small bowel (ie, villous blunting).[85] Other genetic defects have been found to cause IPEX-like disease, including loss-of-function mutations

impacting IL-2-IL-2R interactions, *STAT5b*, and ITCH, or gain-of-function mutations in *STAT1*, all of which critically influence the development and function of Tregs.[72] Furthermore, Zeissig et al. identified a novel loss-of-function mutation in *CTLA4*, a surface molecule of regulatory T cells that directly suppresses effector T-cell populations, in VEO-IBD.[86]

Autoimmune and Autoinflammatory Disorders

Immunologic considerations.—Autoimmune disease in general is strongly associated with variants related to immune deficiency, and VEO-IBD is similarly enriched with gene defects related to primary immune deficiencies. The study of primary immune deficiencies and their association with VEO-IBD has illuminated the critical and delicate interaction of the immune system with the luminal contents of the gastrointestinal tract.

Several autoimmune/autoinflammatory diseases have been linked with intestinal inflammation in children with VEO-IBD. These include mevalonate-kinase deficiency,[87] mutations in *NLRC4*,[88] familial Mediterranean fever,[89,90] Hermansky-Pudlak syndrome,[91] and X-linked lymphoproliferative syndrome (type 1 and type 2).[18,92–94] Although there are many additional clinical manifestations in these patients, 20% of patients with X-linked lymphoproliferative syndrome who have a loss-of-function defect in the gene X-linked inhibitor of apoptosis protein (*XIAP*) present with VEO-IBD.[95] *XIAP* is involved in NOD2-mediated NF-?B signaling, and therefore these children may have an impaired ability to sense bacteria. In addition, as an inhibitor of apoptosis, it prevents apoptosis of activated T cells, thus allowing for expansion and survival of T cells in response to pathogens.[96,97] Therefore, in XIAP deficiency, due to the inability to clear pathogens, there is a hyperinflammatory state, with increased production of cytokines resulting in an IBD phenotype.[95,97] Children with these mutations can present with severe colonic and perianal fistualizing disease[18,98] (Figure 2(A) to (C)), and of great concern, EBV infection can result in fatal hemophagocytic lymphohistiocytosis (HLH).[98] HSCT is curative for the immune deficiency, prevents the risk of development of HLH, and in most cases, appears to be curative for the intestinal disease.

TRIM22 has recently been identified as a causal single gene defect in patients with a phenotype of severe perianal disease and granulomatous colitis.[99] Tripartite motif (TRIM) proteins are important components of both the innate and adaptive immune system, including cell proliferation, apoptosis, and autoimmunity. Defects in these proteins are involved in malignancies, autoimmune disease, and familial Mediterranean fever and Opitz syndrome type 1. TRIM22 mutations result in impaired NOD2 binding and signaling. Monogenic defects can result in VEO-IBD and can play a role on older onset disease as well.

Histopathological findings associated with VEO-IBD and immunodeficiencies.—The diagnostic histopathology of children with VEO-IBD may provide some further understanding of the underlying etiology of the disease and may help guide the subsequent evaluation. In a recent clinical and histological review of subjects with VEO-IBD and older onset pediatric IBD, we identified findings characteristic of primary immunodeficiency in

the VEO-IBD cohort on diagnostic endoscopic biopsies. Some of these features include increased frequency of apoptosis, moderate to severe chronic architectural changes, small intestinal villous blunting often in the absence of inflammation, and eosinophils in the crypts, lamina propria, and surface epithelium on the biopsies.[100] These findings have been previously associated with immunodeficiencies and disorders of immune regulation, such as severe combined immunodeficiency or common variable immunodeficiency. Therefore, their presence in the histology of VEO-IBD patients may be indicators of different disease drivers than older onset IBD and should signal further investigation in these patients.[16]

A larger cohort study characterized the phenotypic and genotypic features of patients with infantile onset IBD (IO-IBD) diagnosed before 2 years of age. Of these subjects, 77% exhibited extensive disease with significant inflammation of both the upper and lower gastrointestinal tract. Similar to the aforementioned study, the epithelial abnormalities observed in these patients included abundant epithelial cell apoptosis as well as epithelial shedding and tufting. Furthermore, villous blunting was identified in at least 40% of the unclassifiable IO-IBD cases, similar to what we detected in our review.[101]

Conclusion

Although this is not an exhaustive description of the rare genomic drivers of VEO-IBD, this review highlights the different components of the immune system, including innate and adaptive response, involved in VEO-IBD. Treatments guided toward the specific defect, such as IL-1 antagonists, colchicine, sargramostim, or HSCT may lead to remission or even cure in some cases. In addition, identifying a defect will allow for essential monitoring for the associated potential complications, such as risk of HLH in XIAP, risk of lymphoma in IL-10 gene variants, and CGD. In addition to these monogenic diseases, VEO-IBD has been shown to have a high degree of genetic heterogeneity. It is therefore likely that there are more pathways involved in VEO-IBD, and the outcome of therapeutic intervention can be improved through further study and identification of the associated variants. Utilizing next-generation sequencing such as WES can improve detection of variants and diagnosis of disease. The combination of these genomic findings with translational studies looking at the functions of these genes will allow for better mechanistic insight into the role of immune dysregulation in intestinal inflammation and provide an opportunity to deliver true precision medicine to children with VEO-IBD.

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Key Points

- Children with VEO-IBD can present with a different phenotype and more severe disease than older children and adults, in some cases secondary to a monogenic defect.
- Advances in sequencing technology have allowed for identification of causal gene defects in a subset of patients with VEO-IBD.
- Identification of these causal variants has radically changed the approach in these children and provide an opportunity for true precision medicine by targeting the pathway responsible for disease.
- It is critical to understand the underlying defect in children with VEO-IBD. Conventional therapy may not only be unsuccessful, but, as in cases of immunodeficiency, can be inappropriate as well.

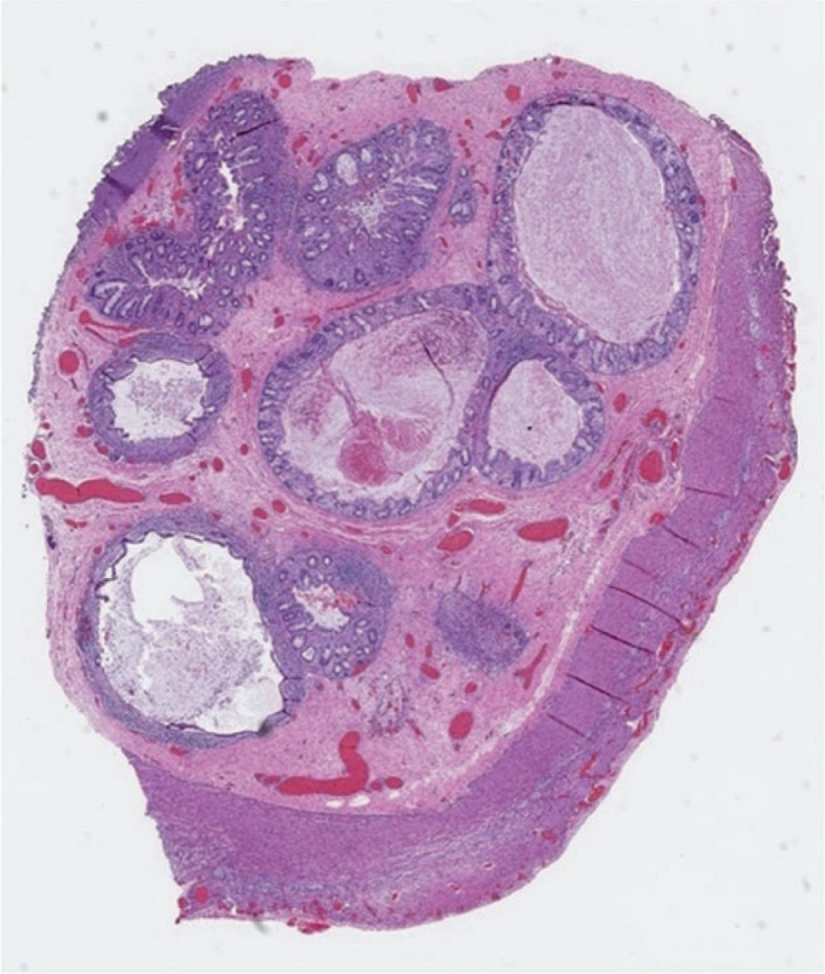

Figure 1.

Ascending colon resected from a male infant with biallelic mutation in TTC7A, multiple intestinal atresias, and severe combined immunodeficiency. Luminal obstruction was attributable to multiple minute lumina lined by mucosa and muscularis mucosae with expanded submucosa.

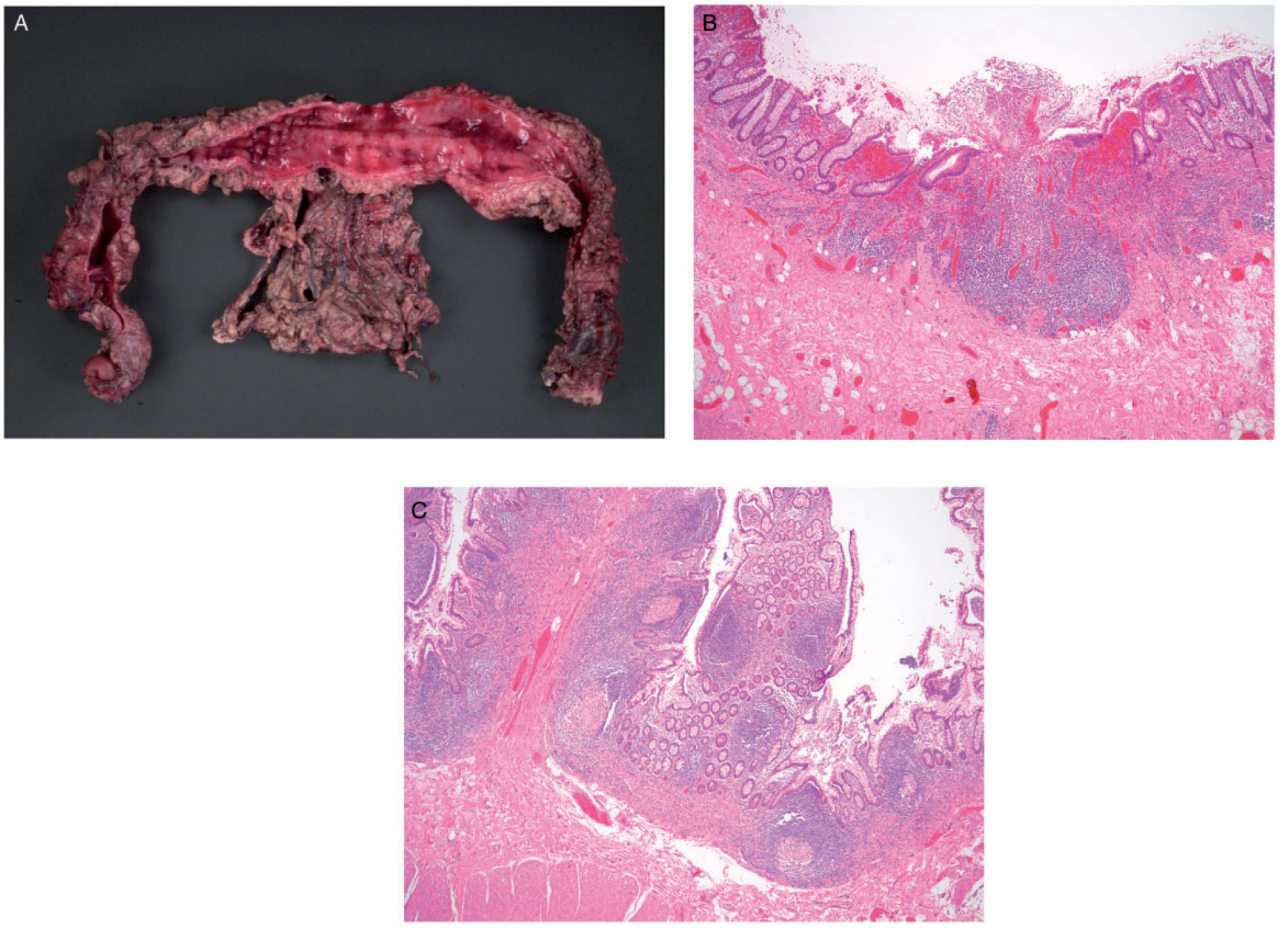

Figure 2.

Terminal ileum and colon from a male patient with infantile onset IBD, identified as XIAP deficiency at age 16 years. A, Colon resection from the patient at age 10 years: Extensive mucosal hemorrhage with nodule formation and structuring. B, Sections from the colon reveal a diffuse active chronic colitis with ulcerations. C, Sections from separately submitted segment of terminal ileum reveals multiple well-formed granulomas in the mucosa.

Table 1.

Genetic Findings Associated With Very Early-Onset Inflammatory Bowel Disease.

Gene	Disease	Pathogenic Inheritance	Phenotypic Features
Defect in epithelial barrier function			
ADAM17		Autosomal recessive	Psoriasiform erythroderma, pustules, broken hair, abnormal nails, small bowel, and colonic involvement
IKBKG	NEMO	X-linked	Hypodontia, thin hair, frontal bossing, recurrent infections, and enteropathy
COL7A1	Epidermolysis bullosa	Autosomal recessive	Recurrent blistering or erosions, esophageal stricture, anal fissures and stenosis, enteropathy, and hair and nail abnormalities
FERMT1	Klinder syndrome	Autosomal recessive	Recurrent skin blisters, esophageal strictures, and colonic involvement
TTC7A	Hereditary multiple intestinal atresia	Autosomal recessive	Intestinal atresia, dermatitis, alopecia, and immunodeficiency
GUCY2		Autosomal dominant Gain of function	Diarrhea, esophagitis, electrolyte abnormalities, ileal obstruction, dilated small bowel, and secretory diarrhea
Defect in NADPH oxidase complex			
CYBA	Chronic granulomatous disease	Autosomal recessive	Life threatening bacterial and fungal infections, excessive inflammation characterized by granulomas in any organ including small and large intestine, gastric outlet obstruction, and perianal disease
CYBB		X-linked	
NCF1		Autosomal recessive	
NCF2		Autosomal recessive	
NCF4		Autosomal recessive	
NOX1		Autosomal recessive Loss of function	Bacterial infections and colonic involvement
Defect in adaptive immunity			
IL-10	IL-10 deficiency	Autosomal recessive	Neonatal onset, folliculitis, panenteric, perianal disease, and lymphoma
IL-10RA			
IL-10RB			
RAG1	Severe combined immunodeficiency (typically T-B-)	Autosomal recessive	Recurrent severe infections, chronic diarrhea, failure to thrive, and variable intestinal involvement
RAG2		Autosomal recessive	
ZAP70	Omenn syndrome	Autosomal recessive	Skin inflammation and variable intestinal involvement
IL7R		Autosomal recessive	
PTEN	PTEN hamartoma tumor syndrome	Autosomal dominant	Thyroiditis, autoimmune hemolytic anemia, hamartomas, adenopathy, adenoid lymphoid hyperplasia, thymic hyperplasia, developmental delay, and enteropathy
LRBA	LRBA deficiency	Autosomal recessive	Enteropathy, lymphoproliferation, and immune deficiency
WASP	Wiskott Aldrich syndrome	X-linked, autosomal recessive	Thrombocytopenia, eczema, eosinophilia, immune deficiency, and colonic involvement
ARPC1B		Loss of function	

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Gene	Disease	Pathogenic Inheritance	Phenotypic Features
BTK	X-linked agammaglobulinemia	X-linked	Recurrent infections after first few months of life and variable intestinal involvement
DKC1	Dyskeratosis congenita	X-linked	Microcephaly, IUGR, nail dystrophy, abnormal skin pigmentation, leukoplakia of oral mucosa, enteropathy, and stricture formation
ITGB2	Leukocyte adhesion deficiency-1	Autosomal recessive	Delayed separation of umbilical cord, recurrent bacterial infections, leukocytosis, lack of pus and impaired wound healing, and enteropathy
ICOS	ICOS deficiency	Autosomal recessive	Common variable immunodeficiency, splenomegaly, autoimmune disease, recurrent bacterial infections, and enteropathy
DOCK8	Hyper-IgE syndrome	Autosomal recessive	Skin abscesses, eczema, allergic diseases, sinopulmonary infections, broad nasal base and bridge, frontal bossing, deep set eyes, retained primary teeth, fractures, scoliosis, and enteropathy
PIK3CD	Activated PI3K-delta syndrome	Autosomal recessive	Simopulmonary infections, chronic active viral infections, lymphadenopathy and nodular lymphoid hyperplasia, risk of B-cell lymphoma, and enteropathy
Impaired regulatory T cells			
FOXP3	IPEX	X-linked	Neonatal-onset secretory diarrhea, failure, infection, skin rash, diabetes, thyroiditis, cytopenia, other autoimmune conditions, and enteropathy
IL-2RA	IPEX-like	X-linked	Enteropathy, eczema, and autoinflammatory disease
STAT1	IPEX-like	Autosomal dominant gain of function	Enteropathy and arthritis
STAT3	STAT3 GOF IPEX-like	Autosomal recessive Gain of function	Lymphadenopathy, autoimmune cytopenia, multiorgan autoimmunity, infection, eczema, short stature, and enteropathy
STAT5b	STAT5b deficiency	Autosomal recessive	Growth failure, IGF-I deficiency, chronic pulmonary disease, and enteropathy
ITCH	ITCH deficiency	Autosomal recessive	Autoimmune inflammatory cell infiltration of lungs, liver, gut, growth failure, diarrhea, hepatosplenomegaly, and enteropathy
IL-21		Autosomal recessive	
IL-21R			
CTLA4	Complex immune dysregulation syndrome	Autosomal dominant	Enteropathy and autoimmune disease
Autoinflammatory and hyperinflammatory defects			
MVK	Hyperimmunoglobulin D syndrome	Autosomal recessive	Episodic nausea, fever, abdominal pain, oral ulcers, arthritis, splenomegaly, and enteropathy
NLRC4		Autosomal dominant GOF	Inflammasome activation hemophagocytic lymphohistiocytosis, episodic inflammation, and panenteric disease
MEFV	Familial Mediterranean fever	Autsomal dominant or Autosomal recessive	Serositis, periodic fevers, rash, arthritis, and enteropathy
HPS1	Hermansky Pudlak syndrome	Autosomal recessive	Oculocutaneous albinism, pulmonary fibrosis, bleeding disorder, and colitis
HPS4			
XIAP	X-linked lymphoproliferative syndrome	X-linked	Infectious mononucleosis or hemophagocytic lymphohistiocytosis secondary to EBV, splenomegaly, abnormal immunoglobulins, lymphoma, and enteropathy
TRIM22		Autosomal recessive	Granulomatous colitis and severe perianal disease

Gene	Disease	Pathogenic Inheritance	Phenotypic Features
SKIV2L		Autosomal recessive	IUGR, failure to thrive, trichorrhexis nodosa, frontal bossing, and villous atrophy
STXBP2		Autosomal recessive	Hemophagocytic lymphohistiocytosis and enteropathy
CASP8	Caspase-8 deficiency	Autosomal recessive	Lymphadenopathy, splenomegaly, recurrent bacterial and viral infections, especially sinopulmonary infections, hypogam-maglobuilnemia, and enteropathy

Abbreviations: EBV, Epstein-Barr virus; GOF, gain-of-function; IPEX, immunodysregulation, polyendocrinopathy, and enteropathy X-linked syndrome; IUGR, intrauterine growth restriction; NAPDH, nicotinamide adenine dinucleotide phosphate.