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The Role of Monogenic Disease In Children With 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. Patients diagnosed with IBD occurring before the age of 5 are a unique population, known as Very Early Onset (VEO)-IBD and 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 genomic drivers of disease that may impact 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 the advances in sequencing technology that have led to identification of novel gene variants associated with disease and potentially new targeted therapeutic options.

Summary—Children with VEO-IBD may present with a different phenotype and more severe disease than older children and adults. Identification of the causal gene or pathways these children may allow for true precision medicine with targeted therapy and improved disease course.

Keywords

very early-onset IBD (VEO-IBD); 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 (GWAS).^{1,2} These studies have provided the genetic landscape of IBD and demonstrate the interaction between host defense and the gut microbiome in disease development. The effect size of each variant in these studies is rather small, however, and it has been difficult to define the precise pathophysiologic contribution related to each independent variant. On the other side of the spectrum, monogenic disorders occur in which the penetrance of IBD is high, such as in the very young children, known as very early-onset IBD (VEO-IBD).

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Pediatric IBD has increased in incidence and prevalence and this phenomenon has included very young children^{3–5}. Approximately 6–15% of the pediatric IBD population is less than 6 years old and disease in the first year of life is rare^{4,5}. The phenotype of VEO-IBD is heterogeneous⁶ and while some children have mild disease, others can present with extensive colonic involvement and greater disease severity than older onset IBD.^{7,8} It is because of the aggressive phenotype, early age of onset, and strong family history, that a subset of VEO-IBD is thought to be a monogenic disease, often involving genes associated with primary immunodeficiencies.^{9–11} At the same time, presence of environmental risk factors is supported by the increase in incidence of pediatric IBD overall and VEO-IBD in particular, which has gone from 1.3 to 2.1 per 100,000 children from 1994 to 2009, with a mean annual increase of 7.4%.⁶ In particular, a role for the gut microbiota is suggested by its development between birth and 3 years of life, coincident with the age of onset of many VEO-IBD cases. This population, which has until now been under-studied, may potentially have the most to benefit from the results of high-throughput genomic analyses that can lead to a precision medicine approach to their care.

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 disease (CD)^{5,7}. Additionally, 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%)^{6,13–15}. 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, approximately 30–35% of VEO-IBD patients are diagnosed with CD.

Unique genomics of VEO-IBD

Advances in sequencing technology, such as whole exome sequencing (WES), 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 these children and some of the discoveries have led to targeted therapy. Examples include the identification of *IL-10*²² and *IL-10* receptor^{23,24} gene mutations in infantile VEO-IBD, which result in the phenotype of severe perianal disease and colitis.^{11,24} While refractory to conventional therapies, these patients are successfully treated with bone marrow transplantation (BMT). Additional underlying immunodeficiencies or genetic disorders have been identified in VEO-IBD patients.^{7,10,18,25,26} These include intestinal epithelial barrier function, phagocyte bacterial killing, hyper or autoimmune inflammatory pathways and development and function of the adaptive immune system.^{27,25,18} 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 influencing intestinal epithelial barrier function—It is at the epithelial surface where immune responses 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^{28,29}. Increased translocation of bacteria or translocation of inappropriate bacteria, as is 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^{30,31}, *IKBKG* (encoding NEMO) resulting in X linked ectodermal dysplasia and immunodeficiency³², *COL7A1* resulting in dystrophic epidermolysis bullosa³³, *FERMT1* resulting in Kindler syndrome^{34–36}, and *TTC7A*¹⁹, or gain-of-function mutations in *GUCY2* resulting in familial diarrhea^{26,37}.

Genetic variants influencing bacterial recognition and clearance—Chronic granulomatous disease (CGD) is a result of defective intestinal phagocytes, specifically the granulocytes responsible for bacterial killing and clearance³⁸. The NADPH oxidase complex is responsible for killing of ingested microbes through its production of the respiratory burst. Mutations in any part of the complex molecules (CYBB, CYBA, NCF1, NCF2, NCF4) can result in intestinal inflammation as well as autoimmune disease.^{39,40} Intestinal inflammation can be observed in as high as 40% of patients with CGD^{41,42,43,44}. Several variants have been associated with VEO-IBD, in particular defective NCF2 results in altered binding to RAC2⁴⁵. These patients can present in the neonatal or first year of life with colitis, severe fistulizing perianal disease and stricturing⁴⁵. Histology frequently demonstrates multiple granulomas that may not have associated inflammatory change.^{16,46} Other neutrophil defects that are associated with VEO-IBD include leukocyte adhesion defect, due to mutation in ITGB2.^{47,48} These patients can present with an IBD phenotype, history of bacterial infection and laboratory studies remarkable for increased peripheral granulocytes⁴⁹. Glycogen storage disease Type 1b, with the unique combination of neutropenia and neutrophil granulocyte dysfunction, can also present with intestinal inflammation⁵⁰.

Therapies used to treat patients with these defects need to be carefully considered. For example, anti-TNF α therapy is contraindicated in CGD. Though effective for intestinal disease, these agents can increase the risk of severe infections in these patients, and can be fatal⁵¹. Other therapies include leukine, antibiotics, and allogeneic hematopoietic stem cell transplantation, which have demonstrated some success⁵². IL-1R antagonists have been used in these patients with some positive results, by restoring autophagy and directly limiting inflammation⁵³.

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 SCID.^{27,54,55} 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 (BCR) or T cell receptor (TCR)^{56–58} can occur with loss-of-function mutations in recombination activating genes (*RAG1* or *RAG2*)

or the *IL-7R* (*IL7R*) causing Omenn syndrome and the *PTEN* gene causing PTEN syndrome.⁵⁹ Omenn syndrome, a recessive form of SCID, can also be associated with intestinal disease as well as severe eczematous rash^{55,60}. Laboratory studies can show increased oligoclonal T cells and reduced B cells, and histology can show an intestinal graft vs host appearance^{61,62}. Defects in B cell development lead to an absence of circulating mature B cells and antibody production, which have been linked to an IBD phenotype⁵⁴. This includes agammaglobulinemia, which can also occur in X-linked agammaglobulinemia (XLA),⁶³ common variable immune deficiency (CVID) and IgA deficiency, a complex and heterogeneous disease, with the responsible mutations known for only a minority of cases⁶⁴. Even a mild immune deficiency such as IgA deficiency has a significantly higher rate of IBD than the general population (Ludvigsson 2014 Journal of Clinical immunology 34:444). This may reflect changes to the microbiome due to the lack of selective pressure (Palm 2014, Cell 158:1000) 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.⁶⁵ Aberrant function of immunoglobulins, such as in hyper IgM and Hyper IgE syndromes can also result in intestinal inflammation and an IBD phenotype⁶⁶.

Wiskott-Aldrich syndrome (WAS) results from a loss of function mutation in Wiskott-Aldrich syndrome protein (*WASP*), and patients can exhibit thrombocytopenia, eczema, immune deficiencies and intestinal inflammation⁶⁷. The clinical manifestation of patients with VEO-IBD with this genetic defect can be pancolitis in addition to other autoimmune processes.

Genetic variants impairing regulatory T cells—Defects in regulatory T cells can clinically present as colonic disease 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^{60,68,69,70}. There are over 20 mutations in *FOXP3* that have been identified in patients with IPEX⁶⁹, 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 disorders⁶⁰. 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.⁷¹ 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 Tregs⁶⁰. Further, Blumberg and colleagues 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-IBD⁷².

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 VE-IBD (NEJM 2009). They are associated with severe intestinal inflammation, particularly in neonatal or infantile VEO-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 Crohn's disease and enterocolitis⁷³. IL-10 is an anti-inflammatory cytokine secreted by a variety of cells, including dendritic cells, natural killer (NK) cells, eosinophils, mast cells, macrophages, B cells and CD4⁺ T cell subsets (including Th2 cells, Th1 cells, Th17 cells and Treg)^{74,75}. IL-10 maintains homeostasis through suppression of an excessive pro-inflammatory response and exerts its effect through binding to the IL-10 receptor, IL-10R, which is a tetrameric complex⁷⁶. It is composed of 2 distinct chains, 2 molecules of IL-10R1 (α chain) and 2 molecules of IL-10R2 (β chain)⁷⁷. IL-10 binding to IL-10R activates the JAK1/STAT3 cascade, which subsequently limits pro-inflammatory gene expression⁷⁷. In addition to intestinal inflammation, IL-10 defects are associated with arthritis, folliculitis and pre-dispose to lymphoma^{73,78}, particularly Large B cell lymphoma. Hematopoietic stem cell transplantation has proven to be a successful treatment for this patients and potentially life-saving^{79,80}.

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 deficiency⁸¹, mutations in *NLRC4*⁸², familial Mediterranean fever (FMF)^{83,84}, Hermansky-Pudlak syndrome⁸⁵ and X-linked lymphoproliferative syndrome (type 1 and 2)^{18,86–88}. While there are many additional clinical manifestations in these patients, twenty percent of patients with X-linked lymphoproliferative syndrome that have a loss of function defect in the gene X-linked inhibitor of apoptosis protein (*XIAP*), present with VEO-IBD⁸⁹. *XIAP* is involved in NOD2 mediated NFκB 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^{90,91}. 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^{89,91}. Children with these mutations can present with severe colonic and perianal fistulizing disease^{18,92}, and of great concern, EBV infection can result in fatal hemophagocytic lymphohistiocytosis⁹².

TRIM22 has recently been identified as a causal single gene defect in patients with a phenotype of severe perianal disease and granulomatous colitis.⁹³ 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.

Conclusion

While 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 towards the specific defect, such as IL-1 antagonists, colchicine, HSCT, or leukine can be used if the defect is determined. Additionally, monitoring for potential complications associated with a genetic defect is essential, such as in XIAP, 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 (NGS) 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