



The role of monogenic disease in children with very early onset inflammatory bowel disease

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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

immunodeficiency, very early onset inflammatory bowel disease, whole exome sequencing

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 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 (VEO)-IBD.

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 heterogeneous [6] 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 2.1/100 000 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

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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 provides 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.

with the age of onset of many VEO-IBD cases. This population, which has until now been understudied, 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 from Crohn disease [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 with older onset IBD (4–10%) [6,13–15]. Because of this colonic involvement, patients with VEO-IBD are also more commonly diagnosed with ulcerative colitis (35–59%) as compared with older onset IBD (older children >6 and adults) in which Crohn disease is more prevalent (55–60%). In contrast, approximately, 30–35% of VEO-IBD patients are diagnosed with Crohn disease.

UNIQUE GENOMICS OF VERY EARLY ONSET INFLAMMATORY BOWEL DISEASE

Advances in sequencing technology, such as whole exome sequencing have radically changed our approach to VEO-IBD and provided an opportunity to investigate its unique genomic cause [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 interleukin 10 (*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]. Although refractory to conventional therapies, these patients are successfully treated with bone marrow transplantation. 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 [7,18,25,27]. 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 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], inhibitor of nuclear factor kappa-B kinase subunit gamma (encoding NEMO) resulting in X-linked ectodermal dysplasia and immunodeficiency [32], *COL7A1* resulting in dystrophic epidermolysis bullosa [33], *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 clearance [38]. 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 [41–44]. Several variants have been associated with VEO-IBD, in particular defective NCF2 results in altered binding to RAC2 [45]. These patients can present in the neonatal or first year of life with colitis, severe fistulizing perianal disease and structuring [45]. 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, because of mutation in ITGB2 [47,48]. These patients can present with an IBD phenotype, history of bacterial infection and laboratory studies remarkable for increased peripheral granulocytes [49]. Glycogen storage disease Type 1b, with the unique combination of neutropenia and neutrophil granulocyte dysfunction, can also present with intestinal inflammation [50].

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 fatal [51]. Other therapies include leukine, antibiotics, and allogeneic hematopoietic stem cell transplantation, which have demonstrated some success [52]. IL-1R antagonists have been used in these patients with some positive results, by restoring autophagy and directly limiting inflammation [53].

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 or T-cell receptor [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 phenotype [54]. This includes agammaglobulinemia, which can also occur in X-linked agammaglobulinemia [63], common variable immune deficiency and IgA deficiency, a complex and heterogeneous disease, with the responsible mutations known for only a minority of cases [64]. 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 because of 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 because of 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 phenotype [66].

Wiskott–Aldrich syndrome results from a loss-of-function mutation in Wiskott–Aldrich syndrome protein (*WASP*), and patients can exhibit thrombocytopenia, eczema, immune deficiencies and intestinal inflammation [67]. 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 (Tregs) 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 [60,68–70]. There are over 20 mutations in *FOXP3* that have been identified in patients with IPEX [69], and patients frequently present with neonatal severe secretory diarrhea, failure to thrive, infection (because of defects in immunoregulation), skin rash, insulin-dependent diabetes, thyroiditis, cytopenias, and other autoimmune disorders [60]. 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 Tregs [60]. Further, Zeissig *et al.* identified a novel loss-of-function mutation in *CTLA4*, a surface molecule of Tregs that directly suppresses effector T-cell populations, in VEO-IBD [72].

Genetic variants in the IL-10–IL-10R pathway and related cytokine family members

Homozygous loss of function in *IL-10* or *IL-10* receptors, IL-10Ra and IL-10b were the first genes to be identified as causative for VEO-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 enterocolitis [73]. IL-10 is an antiinflammatory 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) [74,75]. 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 [76]. It is composed of two distinct chains, two molecules of IL-10R1 (α chain) and two molecules of IL-10R2 (β chain) [77]. IL-10 binding to IL-10R activates the JAK1/STAT3 cascade, which subsequently limits proinflammatory gene expression [77]. In addition to intestinal inflammation, IL-10 defects are associated with arthritis, folliculitis, and predispose 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 lifesaving [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 deficiency [81], mutations in *NLRC4* [82^{***}], familial Mediterranean fever [83,84], Hermansky–Pudlak syndrome, [85] and X-linked lymphoproliferative syndrome (type 1 and 2) [18,86–88]. Although there are many additional clinical manifestations in these patients, 20% 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-IBD [89]. *XIAP* is involved in NOD2-mediated NF κ 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 [90,91]. Therefore, in *XIAP* deficiency, because of 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 lymphohistiocytosis [92].

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

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, HSCT, or leukemia 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 such as whole exome sequencing 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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Conflicts of interest

There are no conflicts of interest.

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- of outstanding interest

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