



REVIEW ARTICLE

Genetics on early onset inflammatory bowel disease: An update

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Abstract Inflammatory bowel disease (IBD) is more common in adults than in children. Onset of IBD before 17 years of age is referred as pediatric onset IBD and is further categorized as very early onset IBD (VEO-IBD) for children who are diagnosed before 6 years of age, infantile IBD who had the disease before 2 years of age and neonatal onset IBD for children less than 28 days of life. Children presenting with early onset disease may have a monogenic basis. Knowledge and awareness of the clinical manifestations facilitates early evaluation and diagnosis. Next generation sequencing is helpful in making the genetic diagnosis. Treatment of childhood IBD is difficult; targeted therapies and hematopoietic stem cell transplantation form the mainstay. In this review we aim to summarize the genetic defects associated with IBD phenotype. We describe genetic location and functions of various genetic defect associated with VEO-IBD with their key clinical manifestations. We also provide clinical clues to suspect these conditions and approaches to the diagnosis of these disorders and suitable treatment options. Copyright © 2019, Chongqing Medical University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Inflammatory bowel disease (IBD) is a clinical condition which is common among adults. Childhood IBD constitutes about 25% of all patients of IBD.¹ Among these children, there is a subgroup of patients who develop symptoms of

IBD at a very early age and may have an underlying genetic basis.² The affected children have severe manifestations and complicated clinical course of disease. The Montreal classification of IBD defined childhood IBD with disease onset <17 years as pediatric onset IBD.³ This was later modified by Paris classification as A1a group for those with

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onset of IBD <10 years of age and A1b for children with onset of symptoms between 10 and <17 years of age. The A1a group was further subdivided into very early onset IBD (VEO-IBD) for children who are diagnosed before 6 years of age, infantile IBD who developed disease before 2 years of age and neonatal onset IBD for children less than 28 days of life.⁴ Even though VEO-IBD constitutes only a small proportion of the total IBD, it is this subset of children who are most likely to have a genetic basis and early recognition and management is necessary to improve the morbidity and mortality. The current review is thus focused on VEO-IBD which includes the infantile and neonatal disease.

Epidemiology

Childhood IBD constitutes about 20–25% of all IBD patients.⁵ The incidence of childhood IBD is increasing world over.⁶ It may be attributed to increased awareness and better diagnostic tests but may also represent a true increase in the incidence. The annual incidence of childhood IBD is estimated to be 2.2 to 13.3 cases per 100,000 children in Western countries.^{6–8} The VEO-IBD has been reported in about 15% of childhood IBD⁵ with an incidence and prevalence of 4.37 per 100,000 and 14 per 100,000 children respectively.⁶

Clinical presentation

Childhood IBD can have a myriad of clinical manifestations and children usually present with insidious onset, blood and mucus stained small volume diarrhoea. Occasionally, severe large volume diarrhoea can also occur more often seen in children with immunodysregulation polyendocrinopathy enteropathy X linked (IPEX) syndrome.⁹ Intestinal fistula can be seen in children with chronic granulomatous disease (CGD), IL-10 signalling defect and X-linked inhibitor of apoptosis protein (XIAP) due to transmurial inflammation of intestine.¹⁰ In addition to gastrointestinal symptoms, infections at other sites are encountered in children who have IBD associated with significant immune deficiencies.¹¹ There may also be associated somatic defects in skin, hair, teeth and various other ectodermal elements in children with nuclear factor- κ B essential modulator (NEMO) mutation and are helpful clinical clues.¹²

Genetics

Most childhood IBD are polygenic in nature. Approximately 163 genetic loci comprising of 300 candidate genes associated with IBD have been detected by genome-wide association studies. However, it was found that each loci contributed only a small portion to the hereditary nature of IBD.¹³ However, many children with VEO-IBD have an underlying genetic disorder that causes IBD. Till date, approximately, 50 genetic variants have been associated with IBD and these disorders are collectively called as monogenic IBDs.¹⁴

These genetic conditions lead to aberrations in several mechanisms altering the intestinal immune homeostasis. Thus, monogenic IBDs are best studied based on the

following pathophysiological mechanism viz, defective T-cell immune tolerance, epithelial barrier dysfunction, defect in cells regulating inflammation (IL-10 signalling defect), neutrophil dysfunction, combined or isolated defect in T and B-cell, and hyperinflammatory disorders.¹⁵

Defective T-cell immune tolerance

Various mutation can cause defective T-cell tolerance and the prototype example is immune dysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome. Mutations in *FOXP3* gene leads to decrease in regulatory T (Treg) cells and hence defective immune tolerance. This results in T and B-cell immune dysregulation resulting in both antibody and cell-mediated GI injury and inflammation (Fig. 1).¹⁶ The reduced Treg cells leads to autoimmunity which manifests as endocrinopathy, cytopenia, hepatitis and severe eczema.¹⁷ IPEX phenotype can also be caused by various other mutations that decrease Treg cell quantitatively and qualitatively like defect in IL2 signalling due to CD25

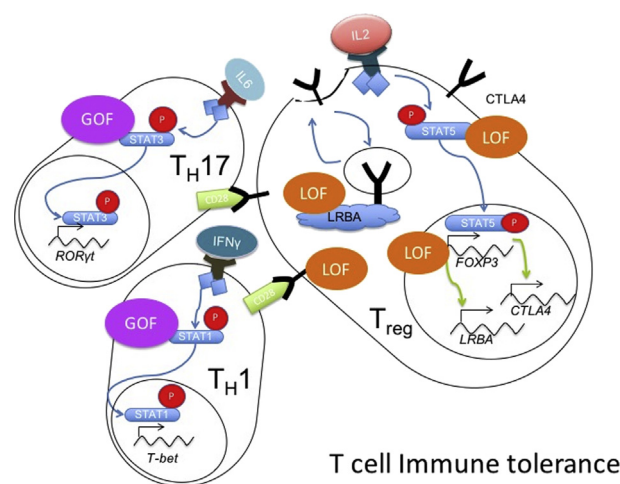


Figure 1 Summarizes the pathways involved in T cell immune tolerance and mutations in various molecules which can cause enteropathy and autoimmunity. Type 1 CD4+ T effector cells (Th1 cells) originate from naive T cells, which differentiate into Th1 cells by engaging Signal Transducer and Activator of Transcription (STAT) STAT1, STAT4, and T-bet transcription factors. STAT1 mediates IFN signalling. Th17 cells originate from naive T cells due to the activation of the transcription factors ROR γ t and STAT3 on receiving IL6 signals. Gain of function mutations in STAT 1 and STAT 3 are associated with inflammatory bowel disease. Naive T cells in presence of IL2, IL10 and T-bet transcription factors get converted to regulatory T cells (Tregs). Within Tregs, STAT5 initiates the transcription of Forkhead box P3 (FOXP3), which in turn regulates transcription of cytotoxic T- lymphocyte-associated protein 4 (CTLA4) and lipopolysaccharide-responsive and beige-like anchor (LRBA). CTLA4 helps in regulating T cell responses. LRBA helps CTLA4 recycling and protectsg CTLA4 from lysosomal degradation. Mutations in STAT5, FOXP3, CTLA4 and LRBA are associated with inflammatory colitis.

mutation,¹⁸ signal transducer and activator of transcription (STAT)-5b,¹⁹ STAT-1 gain-of-function (GOF) mutation,²⁰ STAT-3 GOF mutation,²¹ lipopolysaccharide responsive beige-like anchor protein (LRBA) deficiency,²² and cytotoxic T-lymphocyte-associated protein (CTLA)-4 haploinsufficiency²³ due to Treg dysfunction (Fig. 1).

Epithelial barrier dysfunction

Intestinal immune tolerance is impaired when there is defect in epithelial integrity and function resulting in proinflammatory intestinal milieu and IBD. Tetratricopeptide repeat domain 7A (TTC7A) deficiency leads to inversion of apicobasal polarity and defective epithelial cell differentiation and poor mucosal barrier function causing IBD.²⁴ Apart from TTC7A deficiency, Inhibitor of Kappa Light Polypeptide Gene Enhancer in B cell Kinase Gamma (IKBKG) gene mutation causes IBD like phenotype.²⁵ IKBKG gene encodes for nuclear factor- κ B essential modulator

protein (NEMO) and its deficiency leads to defective NF- κ B signalling and thereby, become sensitive to proinflammatory cytokine-mediated apoptosis of intestinal cells (Fig. 2).²⁶ Moreover, dystrophic epidermolysis bullosa, Kindler syndrome, familial diarrhoea caused by dominant activating mutations in guanylate cyclase C, a disintegrin and metalloproteinase domain 17 (ADAM17) deficiency from biallelic loss of function in ADAM17 gene,²⁷ dyskeratosis congenita (DKC),²⁸ and regulator of telomere elongation helicase 1 (RTEL1) are known to present with varying immune deficiency and enterocolitis as they have defective epithelial barrier²⁹ (Fig. 2).

Defect in cells regulating inflammation (IL10 signalling defect)

IL10 is an immunomodulatory cytokine produced by Treg cells, macrophages and B cells. Loss of function mutation in

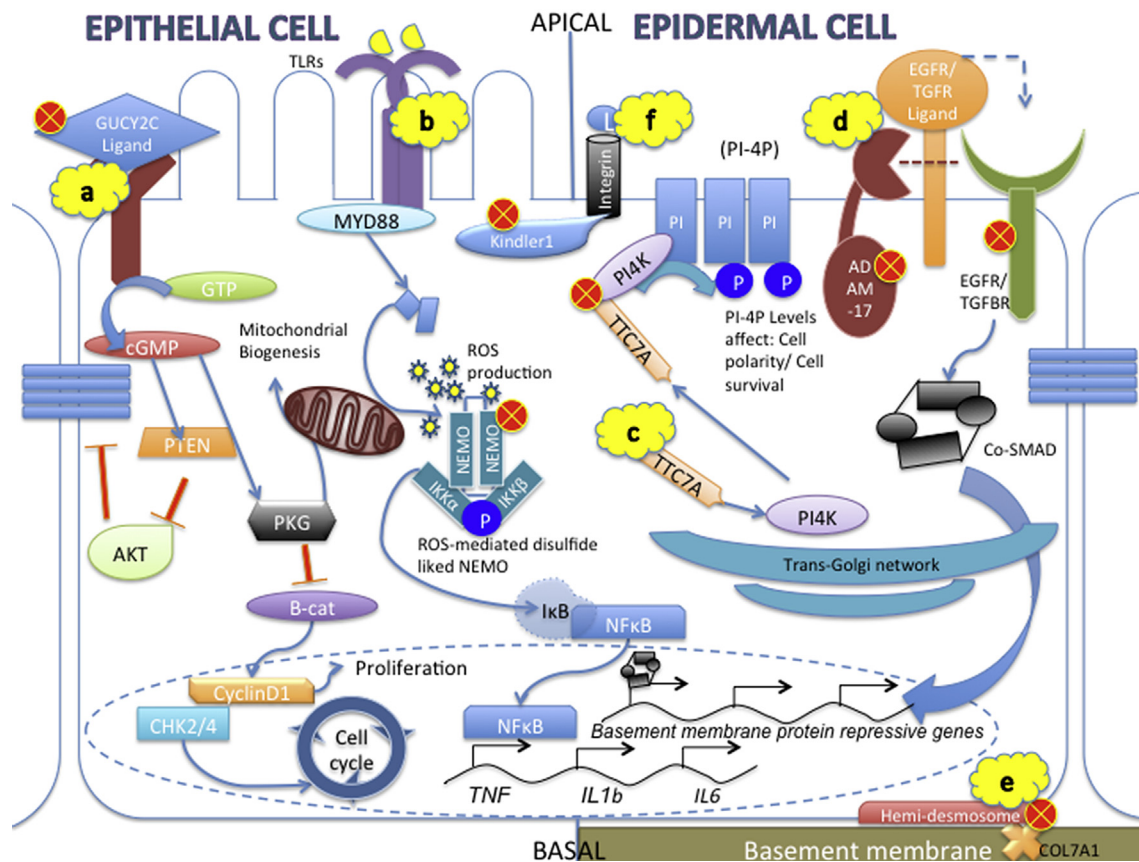


Figure 2 Epithelial and Epidermal barrier dysfunction: Various molecules involved in the signaling pathways shown in figure are maintaining the epithelial and epidermal barrier. Defects in the molecules indicated through red circles has a potential to disrupt these pathways and cause dysfunction. a. Signaling through GUCY2C activates PTEN which inhibits AKT and thereby, inhibits tight Junction expression. It also promotes proliferation, mitochondrial biogenesis, and helps in continuation of cell cycle. b. Toll-Like Receptors, on receiving signals, activate NEMO through Reactive Oxygen Species (ROS). NEMO along with IKK- α and IKK- β activates Inhibitory kappa B (I κ B) and initiates its ubiquitination to release NF κ B. c. TTC7A helps in protein trafficking. Here, it takes PI4K from trans-golgi network near cell membrane so that PI4K can activate PI and helps in accumulation of PI-4P, which is further involved in maintaining cell polarity and cell survival. d. ADAM-17 cleaves the membrane bound EGFR/TGFR ligands. This helps in receptor-ligand binding and initiation of signaling of EGFR/TGFR mediated pathway. e. COL7A1 helps hemi-desmosomes to keep the cell bound to the basement membrane. f. Kindler 1 protein increases the integrin and integrin-ligand binding.

IL10 and its receptor (IL10RA and IL10RB) results in breakdown of immune tolerance and defective IL10 signalling. It leads to differentiation of macrophage into inflammatory phenotype with excess IL-1 β production and inflammation of intestine.³⁰ Defective IL10 signalling also leads to extraintestinal manifestations like folliculitis, arthritis, recurrent infections and predispose to B-cell lymphoma.^{31–33}

Neutrophil dysfunction

Chronic granulomatous disease (CGD) is characterised by phagocytic dysfunction due to genetic defect in components of NADPH oxidase complex viz, gp91-phox (CYBB), p22-phox (CYBA), p47-phox (NCF1), p67-phox (NCF2), and p40-phox (NCF4). CGD is known to cause intestinal inflammation and IBD like phenotype. The defect in NADPH oxidase leads to defect in NF- κ B signalling, activation of inflammasome and neutrophil apoptosis, ultimately, leading to hyperinflammation.³⁴ Recently, missense variant of NCF2 affecting RAC2 binding sites are also noted to manifest as VEO-IBD.³⁵ Moreover, several heterozygous hypomorphic variants in components of NOX2 NADPH oxidase complex were detected in patients with VEO-IBD.³⁶ In addition to CGD, a number of other neutrophil defects are associated with intestinal

inflammation. Defects in glucose-6-phosphate-translocase (SLC37A4) and glucose-6-phosphatase-catalytic subunit 3 (G6PC3) predispose individuals to IBD along with neutropenia. Defect in any of these two genes create hypoglycolytic monocytes and neutrophils lending them with defective microbial killing capacity.^{37,38} Some patients with leukocyte adhesion deficiency type 1 (mutation in ITGB2 encoding CD18) are also reported to have IBD like manifestations as they have persistent inflammation due to defective neutrophil migration to the site of inflammation.³⁹ Lastly, glycogen storage disease type Ib, characterized by neutropenia and neutrophil granulocyte dysfunction also has IBD like manifestations⁴⁰ (Fig. 3).

Combined or isolated T and B cell defect

IBD phenotype is one of the common manifestations of T cell or B cell defect. Hypomorphic mutation of genes such as DCLRE1C, ZAP70, RAG2, IL2RG, LIG4, ADA, and CD3G can lead to leaky SCID with some residual dysregulated, autoreactive and oligoclonal T cells. These variant of SCID is known to present with VEO-IBD.^{41,42} Another primary immunodeficiency disease that is associated with VEO-IBD is Wiskott-Aldrich syndrome (WAS). It is an X-linked, recessive disease caused by subnormal expression of WASP due to

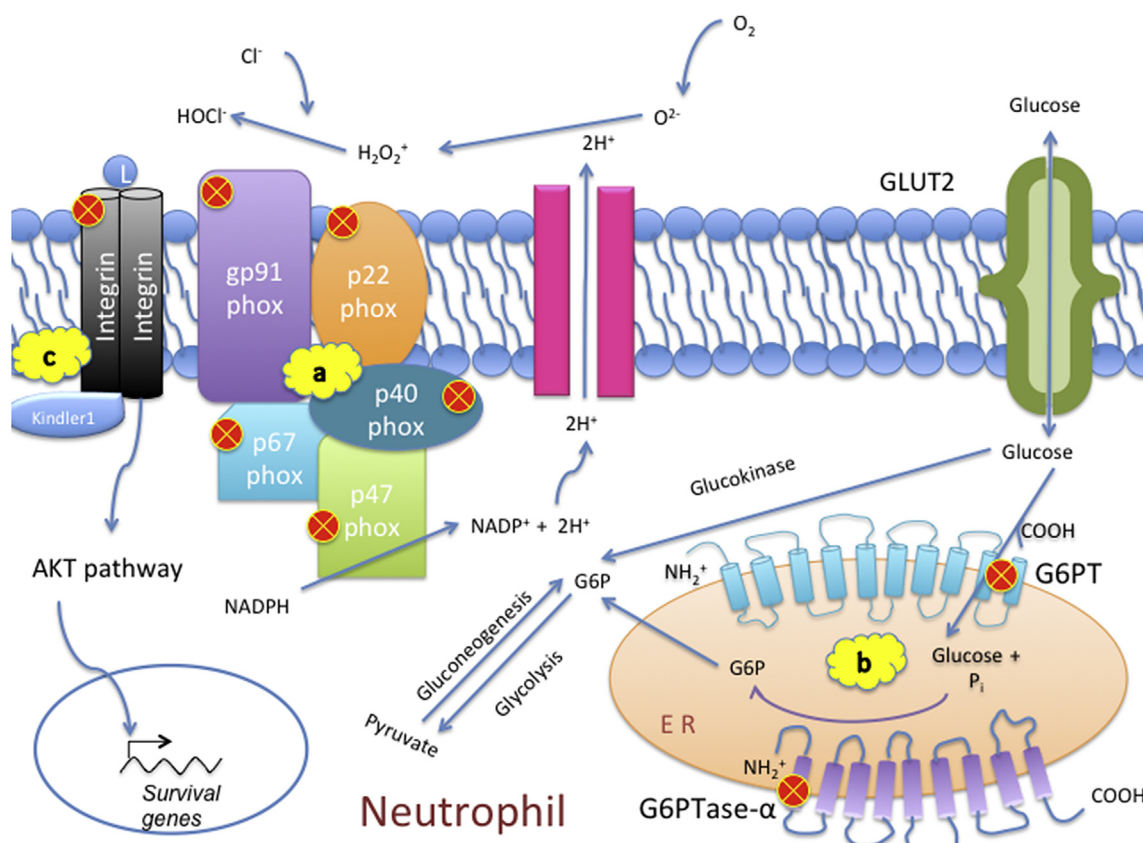


Figure 3 Neutrophil dysfunction: involvement of molecules, indicated through red circles which can cause inflammatory bowel disease. a. Subunits of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase are involved in secreting reactive oxygen species (ROS). b. Glucose-6-phosphate dehydrogenase (G6PT) transports glucose from cytoplasm to endoplasmic reticulum. G6PTase- α phosphorylates glucose to continue glycolysis. c. Integrin on binding to its substrate, initiates AKT pathway and helps in cell survival.

Table 1 Different monogenic defects identified with their inheritance pattern and location with common extraintestinal manifestations.

S.No.	Defects	Inheritance	Genes/encoding proteins	Location of protein and function	Common extraintestinal manifestations
Defects in IL-10 signaling					
1.	Defects in IL10 and IL-10R	AR	<i>IL10</i> /IL10	Secreted; involved in anti-inflammatory responses	Enterocolitis, perianal fistula, furuncles, arthritis, lymphoma
		AR	<i>IL10RA</i> /IL10R1	Cell Surface; mediate the immunosuppressive signal of interleukin 10, promote survival of progenitor myeloid cells through the insulin receptor substrate-2/PI 3-kinase/AKT pathway	
		AR	<i>IL10RB</i> /IL10R2	Cell Surface; essential for the active interleukin 10 receptor complex	
Epithelial-barrier dysfunction					
2.	TTC7A deficiency	AR	<i>TTC7A</i> /TTCA	Cytoplasm; protein transport, phosphate turnover, and protein trafficking or secretion, and they can act as chaperones	Intestinal atresia, recurrent infections
3.	X-linked ectodermal immunodeficiency (NEMO deficiency)	X-linked	<i>IKBKG</i> /NEMO	Cytoplasm; regulatory subunit of the inhibitor of IκB kinase (IKK) complex, which activates NF-κB	Ectodermal dysplasia, conical teeth, sparse, brittle hair, recurrent bacterial, viral and mycobacterial infections
4.	ADAM17 deficiency	AR	<i>ADAM17</i> /ADAM17	Cytoplasm; trims TNFα from the cell surface, and from within the intracellular membranes of trans-Golgi network	Generalized pustular rash
5.	Dystrophic epidermolysis bullosa	AR	<i>COL7A1</i> /COL7A1	Cell surface; anchoring fibril between the external epithelia and the underlying stroma	Blister formations
6.	Kindler syndrome	AR	<i>FERMT1</i> /Kindlin-1	Cell surface; interactions between actin and extra-cellular matrix	Congenital acral skin blisters, photosensitivity, poikiloderma, skin atrophy
7.	Familial diarrhea	AD	<i>GUCY2C</i> /GUCY2C	Cell surface; key receptor for heat-stable enterotoxins	Secretory diarrhoea without congenital malformations
8.	Neonatal inflammatory skin and bowel disease 2	AR	<i>EGFR</i> /EFGR	Cell Surface; binds to epidermal growth factor	
9.	Loeys-Dietz syndrome	AD	<i>TGFBR1</i> /TGFB R1	Cell surface; binds TGF-beta & regulate the transcription of genes related to cell proliferation, cell cycle arrest, wound healing, immunosuppression, and tumorigenesis	Vascular aneurysm, Marfan-like syndrome
		AD	<i>TGFBR2</i> /TGFB R2		

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Table 1 (continued)

S.No.	Defects	Inheritance	Genes/encoding proteins	Location of protein and function	Common extraintestinal manifestations
Defective T cell immune tolerance					
10.	Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX)	X-linked	<i>FOXP3/FOXP3</i>	Nucleus; Transcription regulator	Autoimmune endocrinopathy, nail dystrophy, eczema, alopecia, bullous pemphigoid, cytopenia, hepatitis
11.	CD25 deficiency	AR	<i>CD25/CD25</i>	Cell membrane; play an important role in cell survival and maintaining homeostasis	Autoimmune endocrinopathy, cytopenia, eczema, viral infections
12.	STAT5b deficiency	AR	<i>STAT5B/STAT5B</i>	Cytoplasm and Nucleus; Transcription regulator	Autoimmune endocrinopathy, eczema, short stature, chronic pulmonary disease (lung fibrosis, lymphoid interstitial pneumonia), alopecia, varicella and herpes zoster infections
13.	STAT1 GOF mutation	AD	<i>STAT1/STAT1</i>	Cytoplasm and Nucleus; Transcription regulator	Mucocutaneous candidiasis, eczema, autoimmune endocrinopathy, sinopulmonary infection, cancers
14.	STAT3 GOF mutation	AD	<i>STAT3/STAT3</i>	Cytoplasm and Nucleus; Transcription regulator	Autoimmunity, short stature, lymphoproliferation, infection, cytopenia
15.	LRBA deficiency	AR	<i>LRBA/LRBA</i>	Cytoplasm; helps in recycling surface proteins (e.g. CTLA4) from vacuole to surface	Autoimmunity, cytopenia, recurrent sinopulmonary infection, organomegaly, hypogammaglobulinemia
16.	CTLA4 haploinsufficiency	AD	<i>CTLA4/CTLA4</i>	Cell Surface; helps in immune-regulation after the inflammatory responses	Autoimmunity, lymphoproliferation, hypogammaglobulinemia, lymphocytic interstitial pneumonia, recurrent infection
Neutrophil dysfunction					
17.	Chronic Granulomatous Disease (CGD)	AR	<i>CYBA/p22phox</i> <i>CYBB/gp91phox</i>	Mitochondrial and Cell membrane; primary component of the microbicidal oxidase system of phagocytes to generate superoxide	Recurrent abscess from catalase positive organisms, lymphadenitis, pneumonia, liver abscess, osteomyelitis
		X-linked			
		AR			
		AR			
18.	Glycogen storage disease 1b	AR	<i>NCF1/p47phox</i> <i>NCF2/p67phox</i> <i>NCF4/p67phox</i>	Cytoplasm of Neutrophils; produces a burst of superoxide which is delivered to the lumen of the neutrophil phagosome	Recurrent bacterial infections, hypoglycemic seizures, hepatomegaly
		AR			
			<i>SLC37A4/G6PT1</i>	Endoplasmic Reticulum membrane; maintain glucose homeostasis, ATP-mediated calcium sequestration in the lumen of ER	

19.	Leucocyte adhesion defect (LAD)	AR	<i>ITGB2</i> / <i>ITGB2</i>	Cell surface; cell adhesion as well as cell-surface mediated signaling	Neutrophilia, oral ulcer, recurrent bacterial infections with no pus formation, delayed separation of umbilical cord
20.	Congenital neutropenia	AR	<i>G6PC3</i> / <i>G6PC3</i>	Endoplasmic Reticulum; Catalyzes the hydrolysis of proteins in the last step of the gluconeogenic and glycogenolytic pathways	Cutaneous vascular malformation and cardiac defect, infection
Hyperinflammatory disorder					
21.	X-linked inhibitor of apoptosis (XIAP) deficiency	X-linked	<i>BIRC4</i> / <i>XIAP</i>	Cell Membrane, Cytoplasm, Nucleus; anti-apoptotic function	Perianal fistula, recurrent HLH, EBV, CMV infections, hypogammaglobinemia
22.	NLRC4 GOF mutation	AD	<i>NLRC4</i> / <i>NLRC4</i>	Cytoplasm; assemble the inflammasome complex that promotes production of inflammatory cytokines	Rash and enterocolitis
23.	Familial cold autoinflammatory syndrome 2	AD	<i>NLRP12</i> / <i>NAL12</i>	Nucleus; attenuating factor of inflammation in activated monocytes	Abdominal pain
24.	Phospholipase C- γ 2 defects	AD	<i>PLCG2</i> / <i>PLCG2</i>	Cell membrane; Catalyzes the conversion of 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate to 1D-myo-inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG)	Cold-induced urticaria, susceptibility to infection and autoimmunity
25.	Familial hemophagocytic lymphohistiocytosis type 5	AR	<i>STXBP2</i> / <i>Syntaxin</i>	Cytoplasm; control intracellular protein trafficking, and the release of cytotoxic granules	HLH, sensorineural hearing loss
26.	Mevalonate kinase deficiency	AR	<i>MVK</i> / <i>KIME</i>	Cytoplasm; Catalyzes the phosphorylation of mevalonate to mevalonate 5-phosphate, a key step in isoprenoid and cholesterol biosynthesis	Recurrent fever, rash, abdominal pain
27.	Familial Mediterranean	AR	<i>MEFV</i> / <i>Pyrin</i>	Cytoplasm; regulation of innate immunity and the inflammatory response in response to IFNG/IFN-gamma, initiation of autophagy	Recurrent fever, abdominal pain, arthralgia, peritonitis
28.	Hermansky-Pudlak syndrome	AR AR	<i>HPS1</i> / <i>HPS1</i> <i>HPS4</i> / <i>HPS4</i>	Cytoplasm; Component of the BLOC-3 complex, a complex that acts as a guanine exchange factor (GEF) for RAB32 and RAB38; channelize the lysosome-like compartment's trafficking to pathogen containing vacuole.	Partial albinism, bleeding tendency, granulomatous colitis, recurrent infection, and immunodeficiency

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Table 1 (continued)

S.No.	Defects	Inheritance	Genes/encoding proteins	Location of protein and function	Common extraintestinal manifestations
		AR	<i>HPS6/HPS6</i>	Cytoplasm; involved in organelle biogenesis associated with melanosomes, platelet dense granules, and lysosomes.	
T and/or B cell defect					
29.	X-linked agammaglobulinemia	X-linked	<i>BTK/BTK</i>	In Vesicles; crucial role in B lymphocyte development, differentiation and signaling	Recurrent sinopulmonary infection
30.	Agammaglobulinemia	AR	<i>PIK3R1/P85A</i>	Cytoplasm; important role in the metabolic actions of insulin	Recurrent sinopulmonary infection
31.	CVID	AR	<i>ICOS/ICOS</i>	Cell surface; Enhances all basic T-cell responses to a foreign antigen	Heterogeneous group of defects with sinopulmonary infections, autoimmunity, lymphoproliferation, and variable T cell immune defect
32.	IL-21 deficiency (CVID-like)	AR	<i>IL21/IL21</i>	Secreted; differentiation, proliferation and activity of multiple target cells including macrophages, natural killer cells, B cells and cytotoxic T cells	Diarrhea, oral ulcers recurrent and severe upper and lower respiratory tract infections
33.	X-linked hyper IgM	X-linked	<i>CD40L/CD40L</i>	Cell surface; binds to CD40 on the B cell surface and regulates B cell function. Co-stimulates T-cell proliferation and cytokine production	Recurrent infection, lymphoproliferation
34.	Autoimmune Polyendocrinopathy Candidiasis	AR/AD	<i>AIRE/AIRE</i>	Cytoplasm; regulate the expression of autoantigens and negative selection of autoreactive T-cells in the thymus	Malabsorption, diarrhea, chronic atrophic gastritis
35.	Hyper IgM syndrome	AR	<i>AICDA/AICDA</i>	Nucleus; somatic hypermutation, gene conversion, and class-switch recombination of immunoglobulin genes	Sinopulmonary infections, Otitis media, lymphoproliferation
36.	Wiskott-aldrich syndrome	X-linked	<i>WAS/WASP</i>	Cytoplasm; Downstream protein for Rho-type GTPases and further interacts with Actin related Proteins (ARP1/2), which recruits actin filaments actin polymerization	Eczema, recurrent infection, autoimmunity, microplatelets, thrombocytopenia
37.	Omenn syndrome	AR	<i>DCLRE1C/Artemis</i>	Nucleus; V(D)J recombination, regulation of cell cycle in response to DNA damage & also has single-strand-specific 5'-3' exonuclease activity	Generalized erythroderma, hepatosplenomegaly, lymphadenopathy, infections

38.	Sever Combined Immunodeficiency (SCID)	AR	<i>RAG1/RAG1</i>	Nucleus; activation of immunoglobulin V-D-J recombination, also involved in recognition of the DNA substrate	
		AR	<i>RAG2/RAG2</i>	Nucleus; initiation of V(D)J recombination during B and T cell development, can form double-strand breaks by cleaving DNA at conserved recombination signal sequences	
		X-linked	<i>IL-2RG/IL-2RG</i>	In vesicles; important signaling component of many interleukin receptors, including those of interleukin -2, -4, -7 and -21	
		AR	<i>ZAP70/ZAP70</i>	Cytoplasm; Regulates motility, adhesion and cytokine expression of mature T-cells & thymocytes, & development and activation of primary B-lymphocytes.	
		AR	<i>LIG4/Ligase IV</i>	Nucleus; essential for V(D)J recombination and DNA double-strand break (DSB) repair through nonhomologous end joining (NHEJ)	
		AR	<i>ADA/ADA</i>	Cytoplasm; Catalyzes the hydrolytic deamination of adenosine and 2-deoxyadenosine, purine metabolism and in adenosine homeostasis	
		AR	<i>CD3γ/CD3G</i>	Cell surface; forms the T-cell receptor-CD3 complex, Coupling antigen recognition to several intracellular signal-transduction pathways.	
39.	Hyper IgE syndrome	AR	<i>IL-7Ra/IL7RA</i>	Cell surface; receptors of various cytokines, including interleukins 2, 4, 7, 9, and 15 & also involved in V(D)J recombination during lymphocyte development	
		AR	<i>DOCK8/DOCK8</i>	Centrosome and Cytoplasm; activates small GTPase CDC42 by exchanging bound GDP for free GTP, involved in cell migration in response to chemokine stimulation	Eczema, pneumonia, cold abscess

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Table 1 (*continued*)

S.No.	Defects	Inheritance	Genes/encoding proteins	Location of protein and function	Common extraintestinal manifestations
40.	TACI deficiency	AR/AD	<i>TNFRSF13B/TACI</i>	Cell membrane and Cytoplasm; activation of the transcription factors NFAT, AP1, and NF-kappa-B and plays a crucial role in humoral immunity by interacting with a TNF ligand	Recurrent infection, hypogammaglobulinemia,
41.	Congenital disorder of glycosylation, type 3	AR	<i>COG6/COG6</i>	Nucleus Golgi complex; maintain structure and function of the Golgi complex	Anal anteposition, recurrent diarrhea, IBD
42.	Hoyeraal-Hreidarsson S.	X-linked	<i>DKC1/Dyskerin</i>	Nucleus; telomerase stabilization and maintenance, as well as recognition of snoRNAs containing H/ACA sequences, nucleo-cytoplasmic shuttling, DNA damage response, and cell adhesion	Cerebellar hypoplasia, growth retardation, pancytopenia
		AR	<i>RTEL1/RTEL1</i>	Nucleus; stability, protection and elongation of telomeres and interacts with proteins in the shelterin complex known to protect telomeres during DNA replication	
Others					
43.	MASP2 deficiency	AR	<i>MASP2/MASP2</i>	Golgi Apparatus; cleaves complement components C2 and C4 in order to generate C3 convertase in the lectin pathway of the complement system, role in the coagulation cascade through cleavage of prothrombin to form thrombin	Autoimmunity, infection, skin lesions, arthritis
44.	Caspase 8 deficiency	AR	<i>CASP8/CASP8</i>	Cytoplasm & Nucleoplasm; execution of cell apoptosis.	Splenomegaly, lymphadenopathy, recurrent sinopulmonary infections, viral infection, hypogammaglobulinemia
45.	Autoimmune disease, multisystem with facial dysmorphism	AR	<i>ITCH/ITCH</i>	Nucleus; Acts as an E3 ubiquitin-protein ligase then directly transfers the ubiquitin to targeted proteins, erythroid and lymphoid cell differentiation and the regulation of immune responses	Enteropathy, chronic diarrhea, malabsorption, gastrostomy tube feeding

46.	Trichohepatoenteric syndrome	AR	SKIIV2L/SKIV2	Nucleus; Helicase having ATPase activity. Component of the SKI complex which is thought to be involved in exosome-mediated RNA decay and associates with transcriptionally active genes in a manner dependent on PAF1 complex (PAF1C).	Wooly hair, hepatitis, coarse facies
		AR	TTC37/TTC37	Nucleus; Component of the SKI complex which is thought to be involved in exosome-mediated RNA decay and associates with transcriptionally active genes in a manner dependent on PAF1 complex (PAF1C).	

mutation in the WAS gene. Children with this disorder can have ulcerative colitis like manifestation during infancy along with eczema, recurrent infections and thrombocytopenia. Defective actin remodeling in WAS mutants affects the T and B cell signaling thereby, having delayed response to gut infection and have persistent inflammation.^{43,44} Moreover, B-cell defects like X-linked agammaglobulinemia (Bruton tyrosine kinase mutation), common variable immunodeficiency (CVID) and Hyper IgM syndrome can also present with IBD. These defects has abnormal B cells function and thus defective immunoglobulin production resulting in prolonged inflammation.^{45,46}

Other disorders

IBD and IBD like phenotype have been reported in various others disorders. Loss of function mutations in Transforming Growth Factor B 1 (TGFβ1) have been identified to cause infantile IBD.⁴⁷ TGF β regulate various cellular functions like inflammatory responses, cell proliferation, apoptosis and extracellular matrix remodelling.⁴⁸ VEO-IBD has also been reported with loss of function mutation of intestinal alkaline phosphatase.⁴⁹ It maintain gut homeostasis by increasing tolerance towards commensal bacteria by dephosphorylating lipopolysaccharide (LPS), outer membrane component of gram negative bacteria. LPS, thereby, unable to bind to toll like receptor 4 (TLR4), which prevents the downstream proinflammatory signalling.^{50,51} Another entity called Receptor Interacting Serine/Threonine Kinase1 (RIPK1) also has a role in VEO-IBD. RIPK1 is a cytosolic protein kinase that mediates signal transduction for apoptosis, necroptosis and inflammation which gets activated through TLRs pathway. RIPK1 either gets ubiquitylated and activates NF-κB and proinflammatory signalling or phosphorylated and activates necroptosis of the cell.⁵² RIPK1 deficiency due to homozygous mutations in RIPK1 is characterised by recurrent infections, lymphopenia, early onset IBD and polyarthritis.⁵³ VEO-IBD is also described in several other immunodeficiency and autoinflammatory disorder like defects in the Itchy E3 Ubiquitin Protein Ligase activity encoded by ITCH gene and defects in E3 ubiquitin ligase HOIL-1 encoded by HOIL1.^{54,55} The genetic basis of monogenic IBD are summarised with gene location and function in Table 1.

Clinical clues to very early onset/monogenic IBD

The onset of colitis presenting at very early age, particularly below 2 years should raise a suspicion of VEO-IBD. The history of consanguinity or family history of VEO-IBD gives an additional clue to the underlying genetic etiology. The presence of other associated symptoms of ectodermal changes like trichorrhexis nodosa, superficial skin abscesses, bullous epidermolysis and eczematous skin lesions point towards monogenic IBD. Children may have recurrent or atypical infections with severe and early onset perianal fistulas due to underlying immune deficiencies and may occasionally be the presenting manifestation. There may be associated autoimmune haemolytic anemia, thyroiditis, arthritis, sclerosing cholangitis, serosal inflammation,

arthritis, diabetes. Lastly, hamartomas, non-Hodgkin lymphoma, skin and thyroid cancers can develop at an early age in children with monogenic IBD.²

Molecular diagnosis in VEO-IBD

Different sequencing techniques can be employed to make a genetic diagnosis of VEO-IBD.

- a. **Targeted panel:** Gold standard and has high diagnostic accuracy with maximum coverage. However, this technique is restricted to a few numbers of genes at a time.
- b. **Whole Exome sequencing:** This has high coverage with most of the clinically significant genes. However, there is issue with the genes having pseudo-gene copies like NCF1 and also restricted to exonic parts of genome.
- c. **Whole Genome sequencing:** This technique has even coverage and ability to pick up copy number variations. However, it has comparatively higher cost.
- d. **RNA-seq:** Pseudo-gene coverage, rare variants, splice site variants, and cell-specific gene expression analysis are the advantages of this technique over other techniques. However, cost increases if multiple cell types are analysed.

Management protocols for putative immunodeficiency in VEO-IBD

Children with VEO-IBD usually respond poorly to conventional immunosuppressive therapy of IBD. Many therapeutic options including biologics have given promising results in this disorder. The understanding of underlying pathogenic mechanisms and genetic defects help to employ a targeted therapy. Colitis in CGD has been found to be responsive to anakinra, an IL-1b antagonist.⁵⁶ Anakinra inhibits inflammasome and thereby, augments autophagy. Still, treatment response may not sustain for long and satisfactory response is obtained in only a subgroup of CGD associated colitis.⁵⁷ Abatacept shows good results in children with colitis in LRBA deficiency and CTLA4 haploinsufficiency as it blocks T-cell costimulatory pathway.⁵⁸ Similarly, colitis associated with STAT3 GOF mutation is responsive to tocilizumab, an IL-6 receptor blocking antibody.⁵⁹ Sirolimus improves Treg cell function and has been used in IPEX and its phenocopies.⁶⁰ Children who respond poorly to medical therapy may benefit from colectomy and hematopoietic stem cell transplantation (HSCT). In IPEX and IL-10 signalling defects, HSCT has been shown to improve colitis and gastrointestinal fistulas.^{61,62} However, IBD associated with primary ectodermal defects (NEMO, TTC7a deficiency) fails to improve and may even worsen following HSCT.^{24,63} Lastly, gene therapy is a future prospect in the management of monogenic IBD.^{64,65}

Current challenges in VEO-IBD

Even though these disorders are rare, they are increasingly being recognised due to better awareness among physicians. Yet, they remain a diagnostic challenge. Identifying the underlying genetic disorder is imperative for

introducing optimal therapeutic options. Biologic therapy is effective but, not a curative modality of treatment for VEO-IBD. Long term data of children on biologic therapy is scarce in literature. Experience of curative HSCT in certain conditions is promising however, it should always be individualised.

To conclude, monogenic IBD has high morbidity and mortality. Among children presenting with colitis at very early age, a high index of suspicion for monogenic IBD must be entertained. Early institution of genetic diagnosis should be made to assess prognosis and plan for appropriate therapeutic modalities.

Conflict of interest

The authors declare no conflict of interest.

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