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.

Introduction

Inflammatory bowel disease (IBD) is a clinical condition which is common among adults. Childhood IBD constitutes about 25% of all patients of IBD. 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. 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. This was later modified by Paris classification as A1a group for those with...
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. 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. The incidence of childhood IBD is increasing world over. 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. The VEO-IBD has been reported in about 15% of childhood IBD with an incidence and prevalence of 4.37 per 100,000 and 14 per 100,000 children respectively.

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 immunedysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome. 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 transmural inflammation of intestine. In addition to gastrointestinal symptoms, infections at other sites are encountered in children who have IBD associated with significant immune deficiencies. There may also be associated somatic defects in skin, hair, teeth and various other ectodermal elements in children with nuclear factor-kB essential modulator (NEMO) mutation and are helpful clinical clues.

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. 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.

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.

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). The reduced Treg cells leads to autoimmunity which manifests as endocrinopathy, cytopenia, hepatitis and severe eczema. 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

![T cell Immune tolerance](image-url)
Mutation,\textsuperscript{18} signal transducer and activator of transcription (STAT)-5\textsuperscript{b},\textsuperscript{19} STAT-1 gain-of-function (GOF) mutation,\textsuperscript{20} STAT-3 GOF mutation,\textsuperscript{21} lipopolysaccharide responsive beige-like anchor protein (LRBA) deficiency,\textsuperscript{22} and cytotoxic T-lymphocyte-associated protein (CTLA)-4 haploinsufficiency\textsuperscript{23} 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 (TTCA7A) deficiency leads to inversion of apicobasal polarity and defective epithelial cell differentiation and poor mucosal barrier function causing IBD.\textsuperscript{24} Apart from TTCA7A deficiency, Inhibitor of Kappa Light Polypeptide Gene Enhancer in B cell Kinase Gamma (IKBKG) gene mutation causes IBD like phenotype.\textsuperscript{25} IKBKG gene encodes for nuclear factor-κB essential modulator protein (NEMO) and its deficiency leads to defective NF-κB signalling and thereby, become sensitive to proinflammatory cytokine-mediated apoptosis of intestinal cells (Fig. 2).\textsuperscript{26} Moreover, dystrophic epidermolysis bullosa, Kindler syndrome, familial diarrhea 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,\textsuperscript{27} dyskeratosis congenita (DKC),\textsuperscript{28} and regulator of telomere elongation helicase 1 (RTEL1) are known to present with varying immune deficiency and enterocolitis as they have defective epithelial barrier\textsuperscript{29} (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

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**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-alpha and IKK-beta activates Inhibitory kappa B (IκB) and initiates its ubiquitination to release NFκB. 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/TGFβ ligands. This helps in receptor-ligand binding and initiation of signaling of EGFR/TGFβ 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 break-down of immune tolerance and defective IL10 signalling. It leads to differentiation of macrophage into inflammatory phenotype with excess IL-1b production and inflammation of intestine. Defective IL10 signalling also leads to extraintestinal manifestations like folliculitis, arthritis, recurrent infections and predispose to B-cell lymphoma.

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-κB signalling, activation of inflammasome and neutrophil apoptosis, ultimately, leading to hyper-inflammation. Recently, missense variant of NCF2 affecting RAC2 binding sites are also noted to manifest as VEO-IBD. Moreover, several heterozygous hypomorphic variants in components of NOX2 NADPH oxidase complex were detected in patients with VEO-IBD. 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 leading them with defective microbial killing capacity. Some patients with leukocyte adhesion deficiency 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.

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. 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

![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.](image-url)
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                                                      |
|-------|------------------------------------------------------------------------|-------------|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| 1.    | Defects in IL10 and IL-10R                                             | AR          | **IL10/IL10**           | Secreted; involved in anti-inflammatory responses                                                                arto-                                                                                                                                                                      | Enterocolitis, perianal fistula, furuncles, arthritis, lymphoma                               |
|       |                                                                         | AR          | **IL10RA/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          | **IL10RB/IL10R2**       | Cell Surface; essential for the active interleukin 10 receptor complex                                                                                         |                                                                                              |
| 2.    | TTC7A deficiency                                                        | AR          | **TTC7A/TTC7A**         | 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    | **IKBKG/NEMO**          | Cytoplasm; regulatory subunit of the inhibitor of IκB kinase (IKK) complex, which activates NF-κB                                                                   | Ectodermal dysplasia, conical teeth, space, brittle hair, recurrent bacterial, viral and mycobacterial infections |
| 4.    | ADAM17 deficiency                                                       | AR          | **ADAM17/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          | **COL7A1/COL7A1**       | Cell surface; anchoring fibril between the external epithelia and the underlying stroma                                                                               | Blister formations                                                                         |
| 6.    | Kindler syndrome                                                       | AR          | **FERMT1/Kindlin-1**    | Cell surface; interactions between actin and extra-cellular matrix                                                                                               | Congenital acral skin blisters, photosensitivity, poikiloderma, skin atrophy                |
| 7.    | Familial diarrhea                                                      | AD          | **GUCY2C/GUCY2C**       | Cell surface; key receptor for heat-stable enterotoxins                                                                                                             | Secretory diarrhoea without congenital malformations                                         |
| 8.    | Neonatal inflammatory skin and bowel disease 2                        | AR          | **EGFR/EGFR**           | Cell Surface; binds to epidermal growth factor                                                                                                                     |                                                                                              |
| 9.    | Loeys-Dietz syndrome                                                   | AD          | **TGFBR1/TGFBR1**       | 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                                                   |

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| S.No. | Defects                                                                 | Inheritance | Genes/encoding proteins | Location of protein and function | Common extraintestinal manifestations                                                                 |
|-------|-------------------------------------------------------------------------|-------------|-------------------------|-----------------------------------|--------------------------------------------------------------------------------------------------------|
| 10.   | Defective T cell immune tolerance                                       | X-linked    | FOXP3/FOXP3             | Nucleus; Transcription regulator  | Autoimmune endocrinopathy, nail dystrophy, eczema, alopecia, bullous pemphigoid, cytopenia, hepatitis    |
| 11.   | CD25 deficiency                                                         | AR          | CD25/CD25               | Cell membrane; play an important role in cell survival and maintaining homeostasis                  | Autoimmune endocrinopathy, cytopenia, eczema, viral infections                                       |
| 12.   | STAT5b deficiency                                                       | AR          | STAT5B/STAT5B           | 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          | STAT1/STAT1             | Cytoplasm and Nucleus; Transcription regulator                                                   | Mucocutaneous candidiasis, eczema, autoimmune endocrinopathy, sinopulmonary infection, cancers         |
| 14.   | STAT3 GOF mutation                                                      | AD          | STAT3/STAT3             | Cytoplasm and Nucleus; Transcription regulator                                                   | Autoimmunity, short stature, lymphoproliferation, infection, cytopenia                                |
| 15.   | LRBA deficiency                                                         | AR          | LRBA/LRBA               | Cytoplasm; helps in recycling surface proteins (e.g. CTLA4) from vacuole to surface               | Autoimmunity, cytopenia, recurrent sinopulmonary infection, organomegaly, hypogammaglobulinemia        |
| 16.   | CTLA4 haploinsufficiency                                                | AD          | CTLA4/CTLA4             | Cell Surface; helps in immune-regulation after the inflammatory responses                          | Autoimmunity, lymphoproliferation, hypogammaglobulinemia, lymphocytic interstitial pneumonia, recurrent infection |
| 17.   | Neutrophil dysfunction                                                  | AR          | CYBA/p22phox            | Mitochondrial and Cell membrane; primary component of the microbial oxidase system of phagocytes to generate superoxide | Recurrent abscess from catalase positive organisms, lymphadenitis, pneumonia, liver abscess, osteomyelitis |
|       | Chronic Granulomatous Disease (CGD)                                    | X-linked    | CYBB/p91phox            |                                                                                                 |                                                                                                       |
|       |                                                                         | AR          | NCF1/p47phox            |                                                                                                 |                                                                                                       |
|       |                                                                         | AR          | NCF2/p67phox            |                                                                                                 |                                                                                                       |
|       |                                                                         | AR          | NCF4/p67phox            |                                                                                                 |                                                                                                       |
| 18.   | Glycogen storage disease 1b                                             | AR          | SLC37A4/G6PT1           | Endoplasmic Reticulum membrane; maintain glucose homeostasis, ATP-mediated calcium sequestration in the lumen of ER | Recurrent bacterial infections, hypoglycemic seizures, hepatomegaly                                  |
| No. | Condition                                                                 | Mode of Inheritance | Gene(s) | Function/Pathway                                                                 | Clinical Features                                                                 |
|-----|---------------------------------------------------------------------------|---------------------|---------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| 19  | Leucocyte adhesion defect (LAD)                                           | AR                  | ITGB2/ITGB2 | 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                  | G6PC3/G6PC3 | Endoplasmic Reticulum; Catalyzes the hydrolysis of proteins in the last step of the gluconeogenic and glycolgenolytic pathways | Cutaneous vascular malformation and cardiac defect, infection                      |
|     | **Hyperinflammatory disorder**                                            |                     |          |                                                                                 |                                                                                   |
| 21  | X-linked inhibitor of apoptosis (XIAP) deficiency                         | X-linked            | BIRC4/XIAP | Cell Membrane, Cytoplasm, Nucleus; anti-apoptotic function                       | Perianal fistula, recurrent HLH, EBV, CMV infections, hypogammaglobulinemia        |
| 22  | NLRC4 GOF mutation                                                        | AD                  | NLRC4/NLRC4 | Cytoplasm; assemble the inflammasome complex that promotes production of inflammatory cytokines | Rash and enterocolitis                                                            |
| 23  | Familial cold autoinflammatory syndrome 2                                 | AD                  | NLRP12/NAL12 | Nucleus; attenuating factor of inflammation in activated monocytes              | Abdominal pain                                                                    |
| 24  | Phospholipase C-γ2 defects                                                | AD                  | PLCG2/PLCG2 | Cell membrane; Catalyzes the conversion of 1-phosphatidylinositol 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                  | STXBP2/Syntaxin | Cytoplasm; control intracellular protein trafficking, and the release of cytotoxic granules | HLH, sensorineural hearing loss                                                   |
| 26  | Mevalonate kinase deficiency                                              | AR                  | MVK/KIME | 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                  | MEFV/Pyrin | 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                  | HPS1/HPS1 | 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, granulomatus colitis, recurrent infection, and immunodeficiency |

*Note: HPS4 (Hermansky-Pudlak syndrome 4) is the gene associated with Hermansky-Pudlak syndrome.*
| S.No. | Defects                                | Inheritance | Genes/encoding proteins | Location of protein and function                                                                                                                                                                                                 | Common extraintestinal manifestations                                                                 |
|-------|----------------------------------------|-------------|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
|       |                                        | AR          | HPS6/HPS6               | 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    | BTK/BTK                | In Vesicles; crucial role in B lymphocyte development, differentiation and signaling                                                                                                                                               | Recurrent sinopulmonary infection                                                                                                                                   |
| 30.   | Agammaglobulinemia                     | AR          | PIK3R1/P85A             | Cytoplasm; important role in the metabolic actions of insulin                                                                                                                                                                      | Recurrent sinopulmonary infection                                                                                                                                   |
| 31.   | CVID                                   | AR          | ICOS/ICOS              | 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          | IL21/IL21              | 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    | CD40L/CD40L            | 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     | AIRE/AIRE              | 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          | AICDA/AICDA            | Nucleus; somatic hypermutation, gene conversion, and class-switch recombination of immunoglobulin genes                                                                                                                        | Sinopulmonary infections, Otitis media, lymphoproliferation                                                                                                |
| 36.   | Wiskott-aldrich syndrome               | X-linked    | WAS/WASP               | 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          | DCLRE1C/Artemis        | 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                                                                                         |
| Genotype                        | Allele (AR) | Gene                        | Function                                                                 |
|--------------------------------|-------------|-----------------------------|--------------------------------------------------------------------------|
| **38. Sever Combined Immunodeficiency (SCID)** | AR          | RAG1/RAG1                   | Nucleus; activation of immunoglobulin V-D-J recombination, also involved in recognition of the DNA substrate |
|                                | AR          | RAG2/RAG2                   | 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    | IL-2RG/IL-2RG               | In vesicles; important signaling component of many interleukin receptors, including those of interleukin –2, –4, –7 and –21 |
|                                | AR          | ZAP70/ZAP70                 | Cytoplasm; Regulates motility, adhesion and cytokine expression of mature T-cells & thymocytes, & development and activation of primary B-lymphocytes. |
|                                | AR          | LIG4/Ligase IV              | Nucleus; essential for V(D)J recombination and DNA double-strand break (DSB) repair through nonhomologous end joining (NHEJ) |
|                                | AR          | ADA/ADA                     | Cytoplasm; Catalyzes the hydrolytic deamination of adenosine and 2-deoxyadenosine, purine metabolism and in adenosine homeostasis |
|                                | AR          | CD3γ/CD3G                   | Cell surface; forms the T-cell receptor-CD3 complex, Coupling antigen recognition to several intracellular signal—transduction pathways. |
|                                | AR          | IL-7Ra/IL7RA                | Cell surface; receptors of various cytokines, including interleukins 2, 4, 7, 9, and 15 & also involved in V(D)J recombination during lymphocyte development |
| **39. Hyper IgE syndrome**     | AR          | DOCK8/DOCK8                 | 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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| S.No. | Defects                           | Inheritance | Genes/encoding proteins | Location of protein and function                                                                 | Common extraintestinal manifestations                      |
|-------|-----------------------------------|-------------|--------------------------|---------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| 40.   | TACI deficiency                   | AR/AD       | TNFRSF13B/TACI           | 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          | COG6/COG6                | Nucleus Golgi complex; maintain structure and function of the Golgi complex                         | Anal anteposition, recurrent diarrhea, IBD                 |
| 42.   | Hoyeraal-Hreidarsson S.           | X-linked    | DKC1/Dyskerin            | 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          | RTEL1/RTEL1              | 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          | MASP2/MASP2              | 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          | CASP8/CASP8              | Cytoplasm & Nucleoplasm; execution of cell apoptosis.                                              | Splenomegaly, lymphadenopathy, recurrent sinopulmonary infections, viral infection, hypogammaglobulinemia |
| 45.   | Autoimmune disease, multisystem with facial dysmorphism | AR          | ITCH/ITCH                | 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 |
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. 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.

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. TGFβ regulate various cellular functions like inflammatory responses, cell proliferation, apoptosis and extracellular matrix remodelling. VEO-IBD has also been reported with loss of function mutation of intestinal alkaline phosphatase. 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. 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. RIPK1 deficiency due to homozygous mutations in RIPK1 is characterised by recurrent infections, lymphopenia, early onset IBD and polyarthritis. 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. 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,
arthritides, 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-1β antagonist.⁶⁶ 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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