Recent studies on pediatric inflammatory bowel disease (IBD) have revealed that early-onset IBD has distinct phenotypic differences compared with adult-onset IBD. In particular, very early-onset IBD (VEO-IBD) differs in many aspects, including the disease type, location of the lesions, disease behavior, and genetically attributable risks. Several genetic defects that disturb intestinal epithelial barrier function or affect immune function have been noted in these patients from the young age groups. In incidence of pediatric IBD in Korea has been increasing since the early 2000s. Neonatal or infantile-onset IBD develops in less than 1% of pediatric patients. Children with “neonatal IBD” or “infantile-onset IBD” have higher rates of affected first-degree relatives, severe disease course, and a high rate of resistance to immunosuppressive treatment. The suspicion of a monogenic cause of VEO-IBD was first confirmed by the discovery of mutations in the genes encoding the interleukin 10 (IL-10) receptors that cause impaired IL-10 signaling. Patients with such mutations typically presented with perianal fistulae, shows a poor response to medical management, and require early surgical interventions in the first year of life. To date, 60 monogenic defects have been identified in children with IBD-like phenotypes. The majority of monogenic defects presents before 6 years of age, and many present before 1 year of age. Next generation sequencing could become an important diagnostic tool in children with suspected genetic defects especially in children with VEO-IBD with severe disease phenotypes. VEO-IBD is a phenotypically and genetically distinct disease entity from adult-onset or older pediatric IBD.

**Key Words:** Very early-onset inflammatory bowel disease, Child, Infant, Mutation

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**INTRODUCTION**

Inflammatory bowel disease (IBD) encompasses a diverse group of complex disorders. There is an increasing amount of evidence that IBD develops in genetically susceptible individuals. Children with IBD not only suffer from the common symptoms of adult-onset IBD, but also exhibit growth failure [1,2]. Studies on pediatric IBD have revealed that early-onset IBD has distinct phenotypic differences...
compared to adult-onset IBD. Particularly very early-onset IBD (VEO-IBD) or infantile-onset IBD differs in many aspects, including the disease subtypes, location of the lesions, disease behavior, and genetically attributable risks. Several genetic defects that disturb intestinal epithelial barrier function or affect immune function have been noted in patients with VEO-IBD [1,3]. This review examines the currently published data on the clinical and genetic characteristics of VEO-IBD, particularly focused on the VEO-IBD in Korea.

**EPIDEMIOLOGY OF PEDIATRIC IBD**

IBD can present at any age, with the most affected patients being in the age range of 15 to 29 years [4]. It develops during childhood or adolescence in approximately 25% of the cases [5]. The incidence of pediatric IBD, particularly Crohn’s disease (CD), has been increasing in both developed and developing nations [6]. The annual incidence of pediatric IBD has been increasing in Western countries, with the annual incidence of 2.2 to 13.3 per 100,000 children [6-8]. In Korea, according to the National Health Insurance Claim Data from 2006 to 2015, the annual incidence of CD is 3.6 per 100,000 at all ages and 5.2 per 100,000 children. The incidence of ulcerative colitis (UC) is 7.7 per 100,000 at all ages and 2.4 per 100,000 children. The incidence of CD in teenagers has been increased, while its incidence in children younger than 6 years has remained stable. Neonatal or infantile-onset IBD develops in less than 1% of pediatric patients [9]. The annual incidence of IBD in children younger than 6 years was reported as 0.4 per 100,000 for CD and 0.9 per 100,000 for UC in 2009 in Canada, which had been increased by 7.4% per year since 1994 [7]. However, this increased rate of diagnosis for pediatric IBD might be partially attributable to improvement in awareness and diagnostic accuracy. In a recent French study, VEO-IBD represented 3% of pediatric IBD cases and its incidence remained stable from 1988 to 2011 [10] as in the Korean nationwide data. The stability of the incidence of VEO-IBD over time implies that this disease might not be strongly influenced by environmental factors.

**AGE OF ONSET**

The pediatric Paris classification uses an age cutoff of < 10 years (A1a) [11] because of the paucity of ileal involvement, serological characteristics in CD, and pancolitis in UC. Children with neonatal-onset IBD or infantile-onset IBD have high rates of affected first-degree relatives, a severe disease course, and a high rate of resistance to immunosuppressive treatment. Recently, subgroups of pediatric-onset IBD (< 17 years), early onset IBD (< 10 years), VEO-IBD (< 6 years), infantile onset IBD (< 2 years), and neonatal onset IBD (< 28 days) have been suggested (Table 1) based on the phenotypic characteristics including disease location and severity, in addition to the presence of monogenic defects [3,12].

**GENETICS OF VEO-IBD**

Genetic predisposition might play an important role in development of IBD particularly in young children. Twin and family studies suggested that the risk of developing CD in another sibling is 26-fold higher than in an unrelated person, compared with a 9-fold increase for UC development [13]. Large-scaled genome-wide association studies (GWAS) have detected 250 single-nucleotide polymorphisms associated with IBD, and a recent trans-ancestry association study identified 38 additional new loci influencing the risk of developing IBD [14,15]. Ethnic differences have also been reported, since NOD2/...

| Subgroup            | Previous classification                  | Age of onset |
|---------------------|-----------------------------------------|--------------|
| Pediatric-onset IBD | Montreal classification A1               | < 17 y       |
|                     | Paris classification A1b                |              |
| Early-onset IBD     | Paris classification A1a                | < 10 y       |
| Very early-onset IBD| Paris classification A1a                | < 6 y        |
| Infantile-onset IBD | Paris classification A1a                | < 2 y        |
| Neonatal IBD        | Paris classification A1a                | < 28 day of age |
CARD15 was reported as a susceptible gene locus in Caucasians, but not in Asians, while ATG16L2 and IL17REI were reported as susceptible loci in Korean [16]. A GWAS in children showed similar results as in adults [17]. Older children and adults shares similar polygenic forms of IBD. The main limitation of GWAS is that the evidence of causality is largely absent and it tend to find common variants, so it may overlook functionally detrimental variations imposed by rare mutations. VEO-IBD patients may carry a wide spectrum of low frequency gene variants.

Glocker et al. [18] were the first to identify mendelian mutations of IL10RA IL10RB in children with infantile-onset IBD, which provided a new insight into the pathogenesis of IBD. Interleukin 10 (IL-10) is critical in maintaining the balance of the immune system, where it restricts and terminates immune responses by limiting the secretion of pro-inflammatory cytokines such as tumor necrosis factor-α, IL-1, IL-6, IL-12, and controls both the differentiation and proliferation of macrophages, T cells and B cells. Due to its unique role in balancing the immune system, IL-10 has a long history as the focal point in IBD research. Shim et al. [19,20] reported 7 cases of Korean children with IL10RA mutations among 14 children with infantile-onset IBD. Children with IL10RA mutations showed Crohn’s phenotypes, had anal fistulae, and required early surgical interventions since they exhibited a poor response to medical therapy. They also had recurrent infections, and folliculitis.

Whole exome sequencing (WES) has greatly expanded the list of genes associated with IBD risk beyond those identified during the GWAS era. Sequential candidate gene sequencing according to the disease phenotype could not identify new causative variants. WES allows the identification of causative mutations in rare diseases, although extensive filtering and bioinformatics are required to exclude the large numbers of benign variants and variants of unknown significance that tend to be identified by this approach [1].

Studies using WES have identified mutations in the gene encoding X-linked inhibitor of apoptosis (XIAP) in infants with aggressive colitis, perianal fistulae, and refractory IBD [21,22]. Such symptoms often present between 2 and 6 years of age. XIAP regulates apoptosis and nuclear factor-κB activation, and it is expressed in all hematopoietic cells; therefore, mutations in this protein may also cause the development of an X-linked lymphopoietic syndrome and hemophagocytic lymphohistiocytosis.

To date, approximately 60 monogenic mutations associated with IBD and IBD-like colitis have been identified (Table 2) [1,3,23-73]. Mutations related in genes associated with epithelial barrier function, such as TTC7A have been identified [33]. Monogenic mutations have also been observed in diseases with phagocyte defects, such as chronic granulomatous disease (CYBB, CYBA, NCF1, NCF2, and NCF4) [34-36] and congenital neutropenia (G6PC3) [38]. About 40% of chronic granulomatous disease cases develop CD-like inflammation [3]. Other IBD-associated mutations have been implicated in hyper- or auto-inflammatory disorders, including XIAP deficiency. Genetic disorders involving defects in T and B cell function, such as Wiskott-Aldrich syndrome (WAS) [74] and severe combined immunodeficiency disorder [59] can present with IBD-like phenotypes. Furthermore, mutations associated with X-linked immune dysregulation, polyendocrinopathy, and enteropathy (IPEX) have been found such as those in FOXP3 [75].

Monogenic mutations have been found mostly in children with an age of onset under 6 years, whereas conventional polygenic IBD more commonly has an age of onset older than 7 years.

**CLINICAL ASPECTS OF VEO-IBD AND MONOGENIC IBD**

In many cases of VEO-IBD, we should consider the potential differential diagnoses of cow milk protein allergy, eosinophilic gastroenteritis, infectious causes, and primary immune deficiency with intestinal inflammation. High levels of immunoglobulin E or eosinophilia can also be found in patients with monogenic IBD and IBD-like phenotype (defects in
| Disorder | Gene | Study (year) |
|----------|------|-------------|
| Immune dysregulation | **IPEX** | **FOXP3** | Barzaghi et al. (2012) [23] |
| IPEX-like | **IL2RA** | Caudy et al. (2007) [24] |
| IL-10 signaling defects | **STAT1** | Uzel et al. (2013) [25] |
| IL-10 signaling defects | **IL10RA** | Glocke et al. (2009) [18] |
| IL-10 signaling defects | **IL10** | Kotlarz et al. (2012) [26] |
| NOD2 signaling defects | **TRIM22** | Li et al. (2016) [27] |
| Epithelial barrier function defects | **ADAM17** deficiency | **ADAM17** | Blaydon et al. (2011) [28] |
| Dystrophic epidermolysis bullosa | **COL7A1** | Freeman et al. (2008) [29] |
| Epithelial NADPH oxidases defect | **NOX1, DUOX2** | Hayes et al. (2015) [30] |
| Familial diarrhea | **GUCY2C** | Fiskerstrand et al. (2012) [31] |
| Kindler syndrome | **FERMT1** | Freeman et al. (2008) [29] |
| X-linked ectodermal immunodeficiency (NEMO) | **IKBK** | Cheng et al. (2009) [32] |
| TTC7A deficiency | **TTC7A** | Avizur et al. (2014) [33] |
| Phagocyte defects | **CYBB, CYBA** | Schäppi et al. (2001) [34] |
| Chronic granulomatous disease | **NCF1, NCF2, NCF4** | Matute et al. (2009) [35] |
| Congenital neutropenia | **LACCI** | Al-Bousaif et al. (2006) [36] |
| Glycogen storage disease 1b | **G6PC3** | Huang et al. (2016) [37] |
| Leukocyte adhesion deficiency 1 | **ITGB2** | Visser et al. (2000) [39] |
| Hyperinflammatory and autoimmune disorders | **CTLA4** | Kuehn et al. (2014) [41] |
| Autoimmune lymphoproliferative syndrome type 5 | **STXBP2** | Meeths et al. (2010) [42] |
| Familial hemophagocytic lymphohistiocytosis type 5 | **XIAP** | Zeissig et al. (2015) [43] |
| XLP2 | **SH2DIA** | Booth et al. (2011) [44] |
| Familial Mediterranean fever | **MEFV** | Sari et al. (2008) [45] |
| Hermansky-Pudlak 1,4,6 | **HPS1** | Villani et al. (2009) [46] |
| Multisystem autoimmune disease | **HPS4** | Hazzan et al. (2006) [47] |
| Mevalonate kinase deficiency | **HPS6** | Anderson et al. (2003) [48] |
| Phospholipase C-2 defects | **HPS6** | Mora and Wolfsch (2011) [49] |
| T-cell, B-cell, and complex function defect | **PLCG2** | Flanagan et al. (2014) [50] |
| Agammaglobulinemia | **BTK, PIK3R1** | Bader-Meunier et al. (2011) [51] |
| CVID 1 | **ICOS** | Conley et al. (2012) [54] |
| CVID 8 | **LRBA** | Takahashi et al. (2009) [55] |
| IL-21 deficiency (CVID-like) | **IL21** | Burns et al. (2012) [56] |
| Hoyeraal-Hreidarsson syndrome | **DKC1** | Salzer et al. (2014) [57] |
| Hyper immunoglobulin E syndrome | **DOCK8** | Knight et al. (1999) [58] |
| Hyper immunoglobulin M syndrome | **CD40LG** | Ballew et al. (2013) [59] |
| Immunodeficiency 17 | **AICDA** | Sanal et al. (2012) [60] |

*Note: This table lists select gene mutations associated with monogenic very early-onset inflammatory bowel disease (IBD) and IBD-like colitis. Additional mutations are not included for the sake of brevity.*
Table 2. Continued

| Disorder | Gene | Study (year) |
|----------|------|--------------|
| SCID | ZAP70, IL2RG, LIG4, ADA, CD3g, CD3D, CD3E | Chan et al. (2016) [64] de Saint-Basile et al. (1992) [65] Felgentreff et al. (2011) [66] Olgur et al. (2008) [67] de Saint Basile et al. (2004) [68] |
| SCID/hyper immunoglobulin M syndrome | RAG2, DCLREIX, DCLRE1C | Felgentreff et al. (2011) [66] Rohr et al. (2010) [69] Moshous et al. (2001) [70] |
| Omenn syndrome | WAS | Catucci et al. (2012) [71] |
| Wiscott-Aldrich syndrome | MASP2, SKIV2L, TTC37 | Stengaard-Pedersen et al. (2003) [72] Fabre et al. (2012) [73] |
| Others | | |

IPEX: X-linked immune dysregulation, polyendocrinopathy, and enteropathy, IL: interleukin, XLP: X-linked lymphoproliferative syndrome, CVID: common variable immunodeficiency, SCID: severe combined immunodeficiency.
The diagnostic approach to monogenic very early onset IBD. Some data were adapted from Uhlig et al. [3] and others were updated.

The frequency of IBD-unclassified was reported as 7% in VEO-IBD, compared to 2% in early onset (EO)-IBD [10]. Furthermore, in 25% of the children with VEO-IBD originally diagnosed as UC or IBD-unclassified, the diagnosis was reclassified to CD over time [76]. Children with VEO-IBD more commonly showed rectal bleeding and mucous stools, whereas weight loss and abdominal pain were more frequent in those with EO-IBD. Isolated colonic disease was more common among the patients with VEO-CD [10].

The next concern is why monogenic IBD is important. Monogenic IBD usually presents with refractory IBD or fistulous CD, so early treatment with biologics, or an unconventional approach such as hematopoietic stem cell transplantation (SCT) might be needed. Patients that do not respond to conventional treatment, those with high mortality, and those that have an increased susceptibility to hematopoietic cancers such as patients with IL-10 signaling defects, IPEX, WAS, and XIAP deficiency can be candidates for SCT [3]. However, in a child with TTC7A deficiency, multiple intestinal atresia recurred after SCT, and he died [77]. Therefore, it is important to determine the genetic basis of the disease for each patient before selecting SCT.

When we suspect monogenic IBD, the most important clinical sign is a young age of onset. In addition, lack of a response to conventional medication, a family history of IBD, autoimmunity, recurrent infections, perianal disease, hemophagocytic lymphohistiocytosis, intestinal obstruction, skin lesions, and tumors can be signs of monogenic IBD.

To diagnose monogenic IBD, sequential candidate gene sequencing can be costly and time-consuming. WES can be used for the analysis of patients with suspected monogenic IBD despite some limitations. The targeted next-generation sequencing of multiple candidate genes can also be an alternative option.

**MONOGENIC IBD VERSUS VEO-IBD**

In a Canadian nationwide epidemiology study, there was no difference in the rate of surgery over time between children aged less than 6 years and children aged between 6 and 9 years [78]. Meanwhile, in the aforementioned study by Shim and Seo [19], the clinical courses of children with VEO-IBD involving IL10RA mutations were refractory, whereas those of children with VEO-IBD without such mutations were not different from those of children with EO-IBD. Kim et al. [79] reported that patients with monogenic VEO-IBD showed a higher morbid-
ity than those with non-monogenic VEO-IBD or non-monogenic pediatric IBD. Whether VEO-IBD patients have low response rates to conventional therapy, or a more aggressive phenotype is controversial. It seems that the age of onset itself does not sufficiently predict the severity of the disease or the response to therapy. Crucially, the main determinant of an individual prognosis is the specific causative gene mutation.

CONCLUSION

Monogenic IBD in patients with VEO-IBD is a different disease entity from EO-IBD, pediatric IBD, and adult-onset IBD. Monogenic VEO-IBD has high rates of morbidity and mortality, and it might require different treatment strategies. Moreover, monogenic VEO-IBD might be a fundamentally different disease entity from non-monogenic forms of VEO-IBD. Well-designed global studies are needed to investigate this hypothesis.

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