Higher Morbidity of Monogenic Inflammatory Bowel Disease Compared to the Adolescent Onset Inflammatory Bowel Disease

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Purpose: Monogenic inflammatory bowel disease (IBD) patients do not respond to conventional therapy and are associated with a higher morbidity. We summarized the clinical characteristics of monogenic IBD patients and compared their clinical outcomes to that of non-monogenic IBD patients.

Methods: We performed a retrospective cohort study of all children < 18 years old who were diagnosed with IBD between 2005 and 2016. A total of 230 children were enrolled. Monogenic IBD was defined as a presentation age less than 6 years old with confirmation of a genetic disorder. We subdivided the groups into monogenic IBD (n=18), non-monogenic very early-onset IBD (defined as patients with a presentation age < 6 years old without a confirmed genetic disorder, n=12), non-monogenic IBD (defined as all patients under 18 years old excluding monogenic IBD, n=212), and severe IBD (defined as patients treated with an anti-tumor necrosis factor excluding monogenic IBD, n=92). We compared demographic data, initial pediatric Crohn disease activity index/pediatric ulcerative colitis activity index (PCDAI/PUCAI) score, frequency of hospitalizations, surgical experiences, and height and weight under 3rd percentile among the patients enrolled.

Results: The initial PCDAI/PUCAI score (p < 0.05), incidence of surgery per year (p < 0.05), and hospitalization per year (p < 0.05) were higher in the monogenic IBD group than in the other IBD groups. Additionally, the proportion of children whose weight and height were less than the 3rd percentile (p < 0.05 and p < 0.05, respectively) was also higher in the monogenic IBD group.

Conclusion: Monogenic IBD showed more severe clinical manifestations than the other groups.

Key Words: Inflammatory bowel disease, Very early onset, Immunologic deficiency syndromes, Interleukin-10, Crohn disease
INTRODUCTION

Inflammatory bowel diseases (IBDs) are complex, multifactorial disorders characterized by chronic relapsing intestinal inflammation [1]. IBD that develops in a child under 6 years of age is called very early onset-IBD (VEO-IBD) [2,3]. Because VEO-IBD starts earlier in life and has more resistance to immunosuppressive treatment, it is thought to have a strong association with genetic backgrounds. Meta-analyses of association studies have shown the genetic diversity of IBD and found 163 IBD-associated genetic loci [4]. Individually, however, most of them contribute only to a minor portion of the heritability of IBD. With advances in genetic sequencing techniques, approximately 50 genetic disorders have been identified which have been referred to as monogenic IBD [5-8].

Monogenic IBD seems to be different from non-monogenic IBD. Previous studies on monogenic IBD revealed a more severe clinical course and a higher rate of resistance to conventional treatments [4,9]. Even monogenic IBD is known to have different properties from VEO-IBD. However, there is still an insufficient understanding of the clinical features, characteristics, and outcomes of these monogenic IBD cases. In previous studies, we found that there was a significant difference between the two groups by comparing the phenotype of IBD in children who were less than 10 years of age and in children who were 10 years of age or older [10-12]. This was followed by Paris modification of the IBD Montreal classification [13]. Recently, VEO-IBD, which is found in children under the age of 6 years, is thought to have a different phenotype from other IBD types; however, accurate research has not been done [14,15]. Thus, there is no precise understanding of the characteristics of monogenic IBD associated with monogenetic defects in VEO-IBD [16]. As a result, they have not been able to find appropriate treatment options. We therefore wanted to characterize this monogenic IBD by comparing it with other non-monogenic IBDs, severe IBDs, and non-monogenic VEO-IBDs.

The primary goal of this study was to identify a monogenic disease underlying monogenic IBD which would lead to a novel treatment method. We summarized the clinical characteristics of our monogenic IBD group and compared their clinical outcomes to those of the non-monogenic IBD, severe IBD, and non-monogenic VEO-IBD groups.

MATERIALS AND METHODS

We performed a retrospective cohort study of all children < 18 years old who were diagnosed with IBD between 2005 and 2016 at Seoul National University Children’s Hospital. Thus, 230 Korean children diagnosed with IBD below the age of 18 years were enrolled. Diagnoses of Crohn disease (CD), ulcerative colitis (UC), and inflammatory bowel disease unclassified (IBD-U) were confirmed by standard tools including clinical features, laboratory, radiologic, and endoscopic with biopsies at the time of the diagnosis.

We classified patients with IBD according to the Pediatric Paris modification. We subdivided the groups into monogenic IBD (defined as patients with a presentation age < 6 years old and a confirmed genetic disorder, n=18), non-monogenic VEO-IBD (defined as patients with a presentation age < 6 years old without a confirmed genetic disorder, n=12), non-monogenic IBD (defined as all patients under 18 years old excluding monogenic IBD, n=212), and severe IBD (defined as patients treated with an anti-tumor necrosis factor (TNF) excluding monogenic IBD, n=92) [17].

To analyze the characteristics of monogenic IBD, we compared monogenic IBD with non-monogenic IBD, monogenic IBD with severe IBD, and monogenic IBD with non-monogenic VEO-IBD. We investigated their clinical characteristics including sex, disease type, initial pediatric CD activity index/pediatric ulcerative colitis activity index (PCDAI/PUCAI) score, presence of perianal disease, surgical interventions associated with IBD (such as intestinal resection or perianal abscess removal), frequency of hospitalizations related to IBD, height below 3rd percentile, and weight under 3rd percentile. Disease
type was defined as the original classification of IBD. Disease activity was collected using the initial PCDAI/PUCAI score.

Statistical analysis for the clinical characteristics was performed with chi-square or independent sample t-test using IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA).

This study was approved at Seoul National University Hospital Clinical Research Institute with Institutional Review Board (IRB no. 1712098908).

RESULTS

Classification of monogenic IBD

Of the total eighteen children with monogenic IBD, chronic granulomatous disease (CGD) was identified in three; immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome was identified in two; glycogen storage disease (GSD) was identified in one; congenital neutropenia was identified in two; hyper immunoglobulin (Ig)M syndrome was identified in one; hypogammaglobulinemia was identified in one, and interleukin (IL)-10 signaling defects were identified in eight. All the disease locations of the children were L2 (100%) including one with an oral ulcer according to the Paris classification. The characteristics of the children with monogenic IBD are summarized in Table 1.

Monogenic IBD vs. non-monogenic IBD

Between 2005 and 2016, a total of 230 children diagnosed with IBD were enrolled in the registry, and 60.0% were male, and 40.0% were female. Subtype classification revealed that 78.7% were diagnosed with CD, 17.8% with UC, and 3.5% with IBD-U. The 18 children classified into the monogenic IBD group comprised 7.8% of the entire study population. Among these children, 72.2% had CD and 27.8% IBD-U, and no UC was diagnosis. In the non-monogenic IBD group, 79.2% had CD, 19.3% UC, and 1.4% IBD-U. The UC diagnosis was significantly higher for non-monogenic IBD (0% vs. 19.3%, \( p = 0.04 \)), whereas IBD-U was significantly higher for monogenic IBD (27.8% vs. 1.4%, \( p < 0.005 \)). However, there was

| No. | Group | Syndrome/disorder | CD | UC | IBD-U | Granuloma | Disease location | Perianal fistula/abscess |
|-----|-------|-------------------|----|----|-------|-----------|------------------|------------------------|
| 1   | Phagocyte defects | CGD | +   | +   | L2    |           |                  |                        |
| 2   | CGD   | +     | L2  | +   |       |           |                  |                        |
| 3   | CGD   | +     |     | L2  | +     |           |                  |                        |
| 4   | Glycogen storage disease | + | L2 | + | | | |
| 5   | Congenital neutropenia | + | L2 | | | | |
| 6   | Congenital neutropenia | + | L2 | | | | |
| 7   | T- and B-cell defects | Hyper IgM syndrome | + | L2 | | | |
| 8   | T- and B-cell defects | Hypogammaglobulinemia | + | L2 | | | |
| 9   | Immunoregulation | IPEX | + | L2 | | | |
| 10  | IPEX | + | L2 | | | | |
| 11  | IL-10 | + | L2 | + | | | |
| 12  | IL-10 | + | L2 | + | | | |
| 13  | IL-10 | + | L2 | + | | | |
| 14  | IL-10 | + | L2 | + | | | |
| 15  | IL-10 | + | L2 | + | | | |
| 16  | IL-10 | + | L2 | | | | |
| 17  | IL-10 | + | L2 | | | | |
| 18  | IL-10 | + | L2 | | | | |

CD: Crohn disease, UC: ulcerative colitis, IBD-U: inflammatory bowel disease unclassified, CGD: chronic granulomatous disease, IgM: immunoglobulin M, IPEX: immunodysregulation polyendocrinopathy enteropathy X-linked, IL-10: interleukin, L1: distal 1/3 ileum limited cecal disease, L2: colonic, L3: ileocolonic, L4a: upper disease proximal to the ligament of Treitz, L4b: upper disease distal to the ligament of Treitz and proximal to the distal 1/3 ileum.
no statistical difference among the groups with regards to the percent of patients with a CD diagnosis (72.2% vs. 79.2%, \( p = 0.485 \)).

The mean age at diagnosis was 2 years for the monogenic IBD group and 12 years for the non-monogenic IBD group. The median PCDAI level at the initial visit was higher in the monogenic IBD group (median = 70.8) compared with the non-monogenic IBD group (median = 36.4, \( p = 0.04 \)). In the case of UC, the median initial PUCAI score was 33.9 points in the non-monogenic IBD group; however, there was no diagnosis in the monogenic IBD group. Eight (44.4%) and 92 (43.4%) of the children in the monogenic IBD and non-monogenic IBD groups, respectively, had perianal diseases including perianal abscess or perianal fistula. However, there was no statistical difference between the groups with regards to the percent of patients with perianal diseases (\( p = 0.931 \)).

Thirteen (72.2%) and 59 (27.8%) of the children in the monogenic IBD and non-monogenic IBD groups, respectively, underwent surgery because of a poor response to medical management including immunosuppressive therapy. After adjusting for age and the number of incidents per year, there was a statistically significant difference in surgery per year and hospitalization per year. The monogenic IBD group had a higher level compared with the non-monogenic IBD group (\( p < 0.005 \) and \( p < 0.005 \), respectively).

The proportion of children whose weight and height were less than the 3rd percentile (\( p < 0.005 \) and \( p < 0.005 \), respectively) was higher in the monogenic IBD group than in the non-monogenic IBD group. The comparisons of the phenotypes between monogenic IBD and non-monogenic IBD are summarized in Tables 2 and 3.

### Monogenic IBD vs. severe IBD

This investigation also identified the distinct phenotypic characteristics of the monogenic IBD group and compared them with those of the severe IBD group which used anti-TNF.

For the children diagnosed with severe IBD, 89.1% had CD, 9.8% UC, and 1.1% IBD-U. There were no differences in the frequency of CD and UC between the severe IBD group and the monogenic IBD group (90.2% vs. 72.2%, \( p = 0.056 \) and 9.8% vs. 0%, \( p = 0.166 \), respectively). However, more children were diagnosed with IBD-U in the monogenic IBD group (27.8%) compared with 1.1% in the severe IBD group (\( p < 0.005 \)).

The median PCDAI level at the initial visit was higher in the monogenic IBD group (median = 70.8) compared with the severe IBD group (median = 40.8, \( p = 0.047 \)). However, there was no statistical difference between the groups with regards to the percent of patients with perianal diseases (\( p = 0.265 \)).

Fifty-nine (27.8%) of the children in the severe IBD group underwent surgery because of a poor response to medical management. After adjusting for age and number of incidents per year, there was a statistically significant difference in surgery per year

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**Table 2. Demographic Comparison between Monogenic IBD and Non-Monogenic IBD**

| Variable               | Monogenic IBD (n=18) | Non-monogenic IBD (n=212) | All subjects (n=230) |
|------------------------|----------------------|---------------------------|----------------------|
| Male                   | 13 (72.2)            | 125 (59.0)                | 138 (60.0)           |
| Female                 | 5 (27.8)             | 87 (41.0)                 | 92 (40.0)            |
| Male/female (ratio)    | 13/5 (2.6)           | 115/87 (1.32)             | 138/92 (1.5)         |
| Mean age at diagnose (y)| 1.6±2.6              | 11.7±3.3                  | -                    |
| Mean follow-up period (y)| 8.6±4.9              | 4.0±3.4                   | -                    |
| CD                     | 13 (72.2)            | 168 (79.2)                | 181 (78.7)           |
| UC                     | 0 (0)                | 41 (19.3)                 | 41 (17.8)            |
| IBD-U                  | 5 (27.8)             | 3 (1.4)                   | 8 (3.5)              |

Values are presented as number (%), number (ratio), or mean±standard deviation.

IBD: inflammatory bowel disease, CD: Crohn disease, UC: ulcerative colitis, IBD-U: IBD unclassified.
Table 3. Comparison of Clinical Manifestation of Monogenic IBD and Non-Monogenic IBD (n=230)

| Variable                        | Monogenic IBD (n=18) | Non-monogenic IBD (n=212) | p-value |
|---------------------------------|----------------------|---------------------------|---------|
| Male female ratio               | 13/5 (2.6)           | 115/87 (1.32)             | 0.270   |
| CD                              | 13 (72.2)            | 168 (79.2)                | 0.485   |
| UC                              | 0 (0)                | 41 (19.3)                 | 0.04    |
| IBD-U                           | 5 (27.8)             | 3 (1.4)                   | <0.005  |
| Initial PCDAI (median)          | 70.8                 | 36.4                      | 0.04    |
| Initial PUCAI (median)          | -                    | 33.9                      | -       |
| Perianal lesion (abscess/fistula)| 8 (44.4)             | 92 (43.4)                 | 0.931   |
| Surgery                         | 13 (72.2)            | 59 (27.8)                 | -       |
| Surgery (y)                     | 0.21                 | 0.03                      | <0.005  |
| Hospitalization (y)             | 2.30                 | 0.41                      | <0.005  |
| Height (<3rd percentile)        | 12 (66.7)            | 17 (8.0)                  | <0.005  |
| Weight (<3rd percentile)        | 14 (77.8)            | 48 (22.6)                 | <0.005  |

Values are presented as number (%) or number only.
IBD: inflammatory bowel disease, CD: Crohn disease, UC: ulcerative colitis, IBD-U: IBD unclassified, PCDAI: pediatric Crohn disease activity index, PUCAI: pediatric ulcerative colitis activity index.

Table 4. Demographic Comparison between Monogenic IBD and Severe IBD

| Variable                        | Monogenic IBD (n=18) | Severe IBD (n=92) | All subjects (n=110) |
|---------------------------------|----------------------|-------------------|---------------------|
| Male                            | 13 (72.2)            | 56 (60.9)         | 69 (62.7)           |
| Female                          | 5 (27.8)             | 36 (39.1)         | 41 (37.3)           |
| Male female ratio               | 13/5 (2.6)           | 56/36 (1.6)       | 69/41 (1.7)         |
| Mean age at diagnose (y)        | 1.6±2.6              | 13.0±2.5          | 69±1.7             |
| Mean follow-up period (y)       | 8.6±4.9              | 5.0±4.2           | -                  |
| CD                              | 13 (72.2)            | 82 (89.1)         | 95 (86.4)           |
| UC                              | 0 (0)                | 9 (9.8)           | 9 (8.2)            |
| IBD-U                           | 5 (27.8)             | 1 (1.1)           | 6 (5.5)            |

Values are presented as number (%) or mean±standard deviation.
IBD: inflammatory bowel disease, CD: Crohn disease, UC: ulcerative colitis, IBD-U: IBD unclassified.

and hospitalization per year. The monogenic IBD group had a higher level compared with the severe IBD group (p<0.005 and p<0.005, respectively). Moreover, the proportion of children whose weight and height were less than the 3rd percentile (p<0.005 and p<0.005, respectively) was still higher in the monogenic IBD group than in the severe IBD group. The comparisons of the phenotypes between monogenic IBD and severe IBD are summarized in Tables 4 and 5.

Monogenic-IBD vs. non-monogenic VEO-IBD
This study also identified the distinct phenotypic characteristics of the monogenic IBD group and compared them with those of the non-monogenic VEO-IBD group.

For the children diagnosed with non-monogenic VEO-IBD, 58.3% had CD and 41.7% UC, and none had IBD-U. There was no statistical difference for the diagnosis of CD between the non-monogenic VEO-IBD group (58.3%) and the monogenic IBD group (72.2%, p=0.429). However, more children in the non-monogenic VEO-IBD group (41.7%, p<0.005) were diagnosed with UC, whereas more children in the monogenic group were diagnosed with IBD-U (27.8%, p=0.046).

The median PCDAI level at the initial visit was higher in the monogenic IBD group (median=70.8) compared with the non-monogenic VEO-IBD group (median=33.12, p<0.005). However, in the mono-
Table 5. Comparison of Clinical Manifestation of Monogenic IBD and Severe IBD

| Variable                        | Monogenic IBD (n=18) | Severe IBD (n=92) | p-value |
|---------------------------------|----------------------|-------------------|---------|
| Male/female ratio               | 13/5 (2.6)           | 56/36 (1.56)      | 0.362   |
| CD                              | 13 (72.2)            | 83 (90.2)         | 0.056   |
| UC                              | 0 (0)                | 9 (9.8)           | 0.166   |
| IBD-U                           | 5 (27.8)             | 1 (1.1)           | <0.005  |
| Initial PCDAI (median)          | 70.8                 | 40.8              | 0.047   |
| Initial PUCAI (median)          | -                    | 42.8              | -       |
| Perianal lesion (abscess/fistula)| 8 (44.4)             | 54 (58.7)         | 0.265   |
| Surgery                         | 13 (72.2)            | 31 (33.7)         | -       |
| Surgery (/y)                    | 0.21                 | 0.04              | <0.005  |
| Hospitalization (/y)            | 2.30                 | 0.64              | <0.005  |
| Height (<3rd percentile)        | 12 (66.7)            | 11 (12.0)         | <0.005  |
| Weight (<3rd percentile)        | 14 (77.8)            | 19 (20.7)         | <0.005  |

Values are presented as number (%) or number only.
IBD: inflammatory bowel disease, CD: Crohn disease, UC: ulcerative colitis, IBD-U: IBD unclassified, PCDAI: pediatric Crohn disease activity index, PUCAI: pediatric ulcerative colitis activity index.

Table 6. Demographic Comparison between Monogenic IBD and Non-Monogenic VEO-IBD

| Variable                        | Monogenic IBD (n=18) | Non-monogenic VEO-IBD (n=12) | All subjects (n=30) |
|---------------------------------|----------------------|-------------------------------|---------------------|
| Male                            | 13 (72.2)            | 6 (50.0)                      | 19 (63.3)           |
| Female                          | 5 (27.8)             | 6 (50.0)                      | 11 (36.7)           |
| Male/female (ratio)             | 13/5 (2.6)           | 6/6 (1.0)                     | 19/11 (1.72)        |
| Mean age at diagnose (y)        | 1.6±2.6              | 3.5±1.8                       | 7.5±3.7             |
| Mean follow-up period (y)       | 8.6±4.9              | 7.5±3.7                       | -                   |
| CD                              | 13 (72.2)            | 7 (58.3)                      | 20 (66.6)           |
| UC                              | 0 (0)                | 5 (41.7)                      | 5 (16.7)            |
| IBD-U                           | 5 (27.8)             | 0 (0)                         | 5 (16.7)            |

Values are presented as number (%), number (ratio), or mean±standard deviation.
IBD: inflammatory bowel disease, VEO-IBD: very early onset-IBD, CD: Crohn disease, UC: ulcerative colitis, IBD-U: IBD unclassified.

In the monogenic IBD group, there were no UC children, and the initial PUCAI score could not be compared with the non-monogenic VEO-IBD group (median=23.75).

There was no statistical difference between the groups with regards to the percent of patients with perianal diseases (p=0.114).

Three (25.0%) of the children in the non-mono-
genic IBD group underwent surgery because of a poor response to medical management. After adjusting for age and the number of incidents per year, there was a statistically significant difference in surgery per year and hospitalization per year between the two groups. As in the case of the previous comparison, the monogenic IBD group had a higher level compared with the non-monogenic VEO-IBD group (p=0.012, p=0.015, respectively). Moreover, the proportion of children whose weight and height were less than the 3rd percentile (p<0.005 and p<0.005, respectively) was still higher in the monogenic IBD group than in the non-monogenic VEO-IBD group (Tables 6 and 7).

**DISCUSSION**

Monogenic IBD represents a distinctive phenotype within pediatric IBD. The occurrence of a monogenic IBD phenotype has been reported in CGD, hyper IgM syndrome, hypogammaglobulinemia, IPEX syndrome, GSD, congenital neutropenia and in particular IL-10 signaling defect; thus, monogenic IBD
Table 7. Comparison of Clinical Manifestation of Monogenic IBD and Non-Monogenic VEO-IBD

| Variable                          | Monogenic IBD (n=18) | Non-monogenic VEO-IBD (n=12) | p-value |
|-----------------------------------|----------------------|-----------------------------|---------|
| Male/female ratio                 | 13/5 (2.6)           | 6/6 (1)                     | 0.216   |
| CD                                | 13 (72.2)            | 7 (58.3)                    | 0.429   |
| UC                                | 0 (0)                | 5 (41.7)                    | <0.005  |
| IBD-U                             | 5 (27.8)             | 0 (0)                       | 0.046   |
| Initial PCDAI (median)            | 70.8                 | 33.12                       | <0.005  |
| Initial PUCAI (median)            | -                    | 23.75                       | -       |
| Perianal lesion (abscess/fistula) | 8 (44.4)             | 2 (16.7)                    | 0.114   |
| Surgery                           | 13 (72.2)            | 3 (25.0)                    |         |
| Surgery (±)                       | 0.21                 | 0.05                        | 0.012   |
| Hospitalization (±)               | 2.30                 | 0.48                        | 0.015   |
| Height (<3rd percentile)          | 12 (66.7)            | 0 (0)                       | <0.005  |
| Weight (<3rd percentile)          | 14 (77.8)            | 1 (8.3)                     | <0.005  |

Values are presented as number (%) or number only.

IBD: inflammatory bowel disease, VEO-IBD: very early onset-IBD, CD: Crohn disease, UC: ulcerative colitis, IBD-U: IBD unclassified, PCDAI: pediatric Crohn disease activity index, PUCAI: pediatric ulcerative colitis activity index.

may be a complex immunodeficiency disorder [18]. It has been suggested that monogenic IBD may not only have a different phenotype but also a different genetic structure [4].

In this study, we identified monogenic IBD in Korean children with IBD. The monogenic IBD group had a higher incidence of surgery and hospitalization than that of the non-monogenic IBD and severe IBD groups and showed a higher trend for the initial PCDAI/PUCAI score. Additionally, the proportion of children whose weight and height were less than the 3rd percentile was still higher in the monogenic IBD group. These findings suggest that monogenic IBD has different clinical characteristics than that of the other IBDs. Even when monogenic IBD and non-monogenic VEO-IBD were compared, monogenic IBD showed more severe clinical symptoms suggesting that genetics has a greater impact than that of age. A poor response to immunosuppressive therapy in 13 (72.7%) of the monogenic IBD patients resulted in surgical treatment early in life. In addition, VEO-IBD is generally known to be caused more often by genetic mutations in the pathogenesis of IBD [13]. However, children who did not have an underlying genetic disorder required less surgical management and hospitalization. Therefore, in the case of the monogenic IBD group, the resistance to conventional therapy seems to be due to a genetic effect which is why the morbidity is increased.

Treatment of monogenic IBD should be different from that of existing treatments. Particularly, 44.4% of our children with monogenic IBD had IL-10 mutations. Monogenic IBD due to an IL-10 mutation is known to be more resistant to conventional therapy. These patients showed greater resistance to steroids, immunomodulatory therapy, anti-TNF and surgical treatment. In this case, treatment with hematopoietic stem cell transplantation has been successfully used to induce remission [5,8,19]. One of the classifications of hyperinflammatory monogenic disorders, especially mevalonate kinase deficiency, was found to produce an excess amount of IL-1β, and IL-1β antagonists were used as a remedy [20-22]. Therefore, to properly treat monogenic IBD, it is necessary to understand the clinical features and genetic defects of monogenic IBD patients.

As in the previous studies, pure colonic location [L2] was the most prevalent in our monogenic IBD patients according to the Paris classification [13]. However, unlike previous papers, the ratio of CD to monogenic IBD was higher than that of UC [11,12,23,24]. For this reason, in our study, the presence of perianal disease was more likely to be diagnosed as CD, and...
the proportion of UC was reduced. However, in our study, the presence of perianal disease and the disease severity did not differ with respect to the age of onset [25,26].

Our study has some strengths and limitations. To date, the present investigation is the first report of a monogenic IBD phenotype analysis in Korea. Our study identified distinct phenotypic characteristics in monogenic IBD patients compared with non-monogenic IBD, severe IBD, and even with non-monogenic VEO-IBD patients. Because monogenic IBD represents a small part of the pediatric population, there is not much difference in demographic data and clinical features from non-monogenic IBD due to lack of clinical data [12]. However, it is clear that monogenic IBD does not respond well to conventional therapy. Careful consideration should be taken when interpreting our results because this study was a single center study and had a very low prevalence of monogenic IBD.

In conclusion, monogenic IBD is genetically and phenotypically different from other pediatric IBDs. It has a stronger association with genetic defects. Therefore, physicians should consider genotyping the genes in patients with early-onset IBD. Additionally, this might lead to the development of novel therapies.

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