



To treat or not to treat: *CUBN*-associated persistent proteinuria

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Background: Persistent proteinuria is an important indicator of kidney damage and requires active evaluation and intervention. However, tubular proteinuria of genetic origin typically does not improve with immunosuppression or antiproteinuric treatment. Recently, defects in *CUBN* were found to cause isolated proteinuria (mainly albuminuria) due to defective tubular albumin reuptake. Unlike most other genetically caused persistent albuminuria, *CUBN* C-terminal variants have a benign course without progression to chronic kidney disease according to the literature. Here, we present Korean cases with persistent proteinuria associated with C-terminal variants of *CUBN*.

Methods: We identified Korean patients with *CUBN* variants among those with an identified genetic cause of proteinuria and evaluated their clinical features and clinical course. We also reviewed the literature on *CUBN*-associated isolated proteinuria published to date and compared it with Korean patients.

Results: All patients presented with incidentally found, asymptomatic isolated proteinuria at a median age of 5 years. The proteinuria was in the subnephrotic range and did not significantly change over time, regardless of renin-angiotensin system inhibition. Initial physical examination, laboratory findings, and kidney biopsy results, when available, were unremarkable other than significant proteinuria. All patients maintained kidney function throughout the follow-up duration. All patients had at least one splicing mutation, and most of the variants were located C-terminal side of the gene.

Conclusion: We report Korean experience of *CUBN*-related benign proteinuria, that aligns with previous reports, indicating that this condition should be considered in cases with incidentally found asymptomatic isolated proteinuria, especially in young children.

Keywords: Chronic proteinuria, Cubilin, *CUBN* variants, Genetic testing

Received: October 6, 2023; **Revised:** March 7, 2024; **Accepted:** March 22, 2024

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Introduction

Persistent proteinuria is an important indicator of kidney damage and a well-known risk factor for progressive kidney impairment [1]. In the pediatric population, however, orthostatic proteinuria needs to be excluded before any further evaluation or management is initiated, because this benign condition is common especially in adolescents. Moreover, tubular proteinuria may also cause proteinuria; representatively, Dent disease, Lowe syndrome, or Donnai-Barrow syndrome is often diagnosed by low-molecular-weight proteinuria due to impaired kidney tubular reabsorption of low-molecular-weight protein from genetic defect of *CLCN5*, *OCRL*, or *LRP2* [2–7]. Unlikely persistent proteinuria of kidney glomerulopathy, tubular proteinuria is not a target of management, thus excluding proteinuria of tubular origin is necessary before ensuing any potentially harmful medication including immunosuppression.

Recently, *CUBN* defect was added to the list of genetic defects inducing tubular proteinuria, but distinctively, mainly albuminuria [8].

CUBN encodes cubilin, an extracellular glycoprotein receptor, composed of a 110 amino acid at N-terminals, followed by eight epidermal growth factor-like domains, and 27 CUB domains at C-terminals (Fig. 1) [9]. Cubilin binds to many ligands and transfers them by endocytosis, partnering with a transmembrane protein amnionless (Fig. 2). Cubilin is expressed in podocyte, proximal tubule, and small intestine, and has a role of albumin reabsorption in the renal proximal tubule and the intrinsic factor-vitamin B12 complex absorption in the small intestine [9–11]. Previously, mutations in *CUBN* have been known to cause Imerslund-Gräsbeck syndrome or megaloblastic anemia 1 which is characterized by selective intestinal vitamin B12 malabsorption and megaloblastic anemia. This condition also has subnephrotic range proteinuria, of which

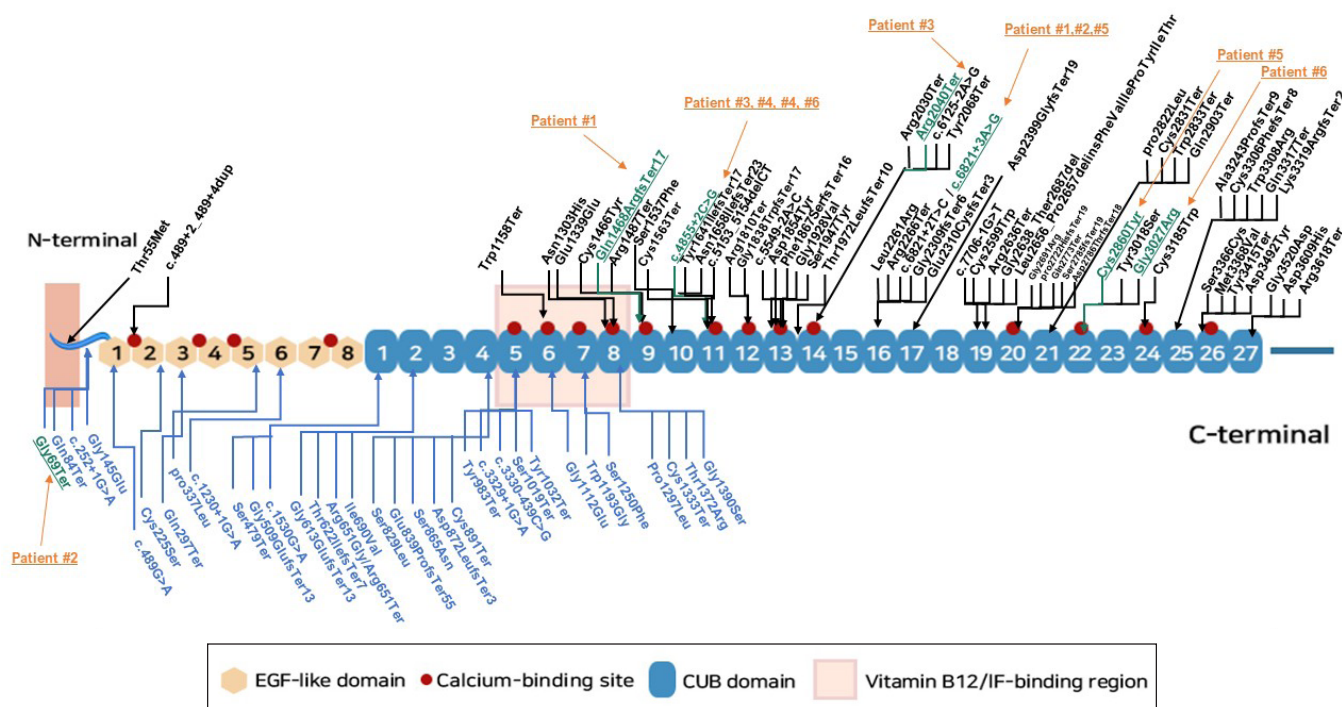


Figure 1. Position of *CUBN* variants along the cubilin protein. The cubilin protein structure consists of eight epidermal growth factor (EGF)-like (yellow) and 27 CUB domains (blue), consisting of complement C1r/C1s, EGF-related sea urchin protein and bone morphogenic protein 1. The red dots represent the theoretical Ca²⁺-binding sites. This figure includes previously reported data until 2022 [8,13,15,18–19]. Variants written in blue are associated with Imerslund-Gräsbeck syndrome in the Human Mutation Database, while variants written in black are previously identified variants causative of isolated proteinuria. Variants identified in this study are written in green and annotated with orange color. IF, intrinsic factor.

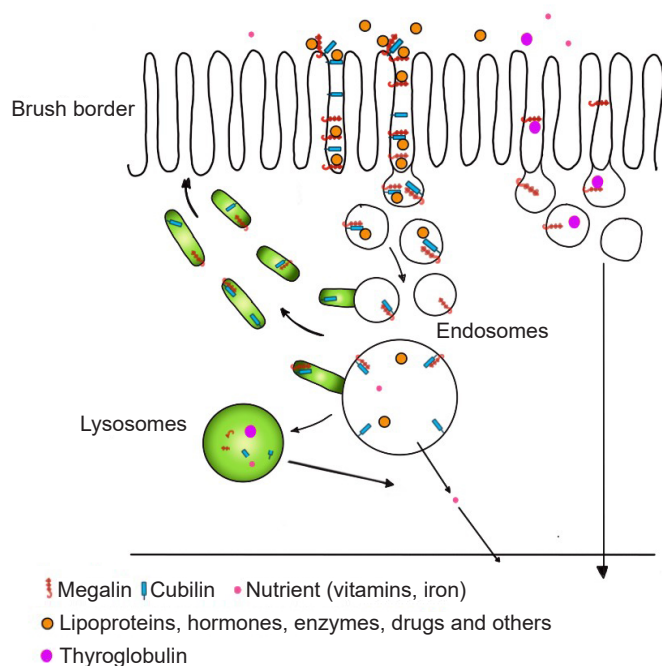


Figure 2. Endocytic megalin and cubilin-amnionless complex in the apical membrane of the renal proximal tubule.

more than 50% being albuminuria. While most cases of Imerslund-Gräsbeck syndrome have mutations located at the N-terminal of *CUBN* affecting the interaction with amnionless or the intrinsic factor-vitamin B12, recently found *CUBN* variants of isolated proteinuria are located at C-terminal of *CUBN* [8].

CUBN-associated isolated proteinuria was first reported in a case study in 2011 [12] and confirmed by large-scale European cohort studies for genetic diagnosis of patients with proteinuria [8,13]. In addition, a meta-analysis through a genome-wide association study in general and diabetic populations also highlighted the relationship between *CUBN* and proteinuria [14]. Detailed phenotypes of this condition were revealed by following studies [15–21], demonstrating that most *CUBN* variants in the C-terminal had a benign course without progression to chronic kidney disease up to the age of 66 years despite the significant amount of proteinuria (urine protein-to-creatinine ratio [uPCR], 0.5 to >2.0 mg/mg; 24 hours urine protein, 0.4–0.8 g/day).

In this study, we present Korean patients with persistent proteinuria associated with C-terminal variants of *CUBN* along with detailed genotype and phenotype description.

In addition, we reviewed published literature on *CUBN*-associated isolated proteinuria to assess the necessity of treatment of this condition.

Methods

This study was approved by the Institutional Review Board of the Seoul National University Hospital (No. H-2011-048-1171). Informed consent was obtained from all individual participants and/or their parents. As previously published [22,23], pediatric patients with suspected genetic renal disease were recruited from major pediatric nephrology centers in Korea and performed genetic testing by targeted exome sequencing or whole exome sequencing (WES). The details of DNA extraction and analysis of targeted exome sequencing and WES data have also been previously described [22,23].

Among the Korean patients who were confirmed to have genetic cause of proteinuria under the care of the authors, those who have *CUBN* variants were identified and evaluated. In these cases, genetic testing has been performed in cases with proteinuria not explained clinically or pathologically; for example, asymptomatic proteinuria of significant amount with normal serum albumin and/or normal kidney pathology. To confirm the segregation of the *CUBN* variants, available parents and/or other family members were tested by Sanger sequencing. Those with additional pathogenic or likely-pathogenic variants in other related genes were excluded.

A total of six cases were identified and their laboratory results and medical records were retrospectively reviewed. When available, kidney biopsy findings were acquired. The pathogenicity of the mutations was reviewed based on the American College of Medical Genetics and Genomics criteria and the Genome Aggregation Database (gnomAD) using VarSome (<https://varsome.com/>).

Results

Demographic characteristics (Table 1)

Proteinuria was incidentally discovered through school health screening in three cases and through routine examination during hospital visits in the rest. The median age at the initial diagnosis of proteinuria was 5 years (range, 18

Table 1. Demographic and clinical characteristics of patients with *CUBN* variants

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	Male	Male	Male	Female	Female	Female
Age at the initial proteinuria detection	8 yr	8 yr	3 yr	18 mo	7 yr	20 mo
Age at the <i>CUBN</i> variants diagnosis	18 yr	13 yr	5 yr	24 mo	7 yr	26 mo
Follow-up duration	11 yr	8 yr	5 yr	3 yr	2 yr	6 mo
Age at last follow-up period	19 yr	16 yr	8 yr	4 yr	9 yr	2 yr
Initial proteinuria detection	School health screening	School health screening	Incidentally detected during evaluation for the cause of fever	Incidentally detected during preoperative evaluation	School health screening	Incidentally detected during evaluation for the cause of fever

Table 2. Summarized clinical and laboratory characteristics

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
At diagnosis						
Urine stick albumin	+	1+	1+	2+	3+	1+
uPCR (mg/mg)	0.94	1.13	1.50	1.37	0.63	1.17
uACR (mg/mg)	0.70	Not done	Not done	0.75	0.34	0.70
uB2MG (ng/mL) ^a	0.28	<0.10	0.20	0.20	0.01	Not done
Serum albumin (mg/dL)	4.8	4.7	4.7	3.9	4.8	4.5
eGFR (mL/min/1.73 m ²)	136.0	84.9	117.0	89.0	102.8	165
Treatment	ENL 2.5–5 mg/day (during 5.5 mo) → stop due to PC	ENL 2.5 mg/day	Losartan 12.5 mg/day	Losartan 12.5 mg/day + steroid (during 1 mo)	ENL 2.5–5 mg/day	None
Kidney biopsy	15 yr, nonspecific change	9 yr, nonspecific change	Not done	Not done	Not done	Not done
Last visit						
Urine stick albumin	3+	3+	+/-	1+	2+	1+
uPCR (mg/mg)	0.75	0.75	1.25	1.04	0.83	1.175
Serum albumin (mg/dL)	4.7	4.7	4.5	4.3	4.4	4.5
eGFR (mL/min/1.73 m ²)	124.0	87.0	97.3	80.0	98.3	147.5
Vitamin B12 (pg/mL)	Not done	434 (wnl)	1,051 (wnl)	835.1 (wnl)	Not done	Not done
Hemoglobin (g/dL)	13.6	12.6	12.7	12.9	13	12.6

eGFR, estimated glomerular filtration rate; ENL, enalapril; PC, poor compliance; uACR, urine albumin-to-creatinine ratio; uB2MG, urine β 2-microglobulin; uPCR, urine protein-to-creatinine ratio; wnl, within normal limits.

Subnephrotic range proteinuria is defined as a uPCR of 0.2–2.0 mg/mg, while nephrotic range proteinuria is defined as a uPCR of greater than 2.0 mg/mg.

^aNormal level, <0.3 ng/mL.

months to 8 years), and the median age at the detection of *CUBN* variants was 6 years (range, 2–18 years). After the median follow-up duration of 4 years (range, 6 months to 11 years), the median age at the last follow-up was 8.5 years (range, 2–19 years). All six patients are of Korean ethnicity but come from different families. Two patients had a family history of renal disease: Patient 1's great aunt had end-

stage kidney disease and Patient 3's sister has proteinuria, diagnosed with the same variants as Patient 3.

Clinical characteristics (Table 2)

The amount of proteinuria in the first-morning urine ranged from uPCR 0.63 to 1.5 mg/mg and urine albu-

min-to-creatinine ratio 0.34 to 0.75 mg/mg. The proportions of albumin in the proteinuria of patients, when measured, were 53% to 73%. Serum albumin levels (4.3–4.7 g/dL), estimated glomerular filtration rate (eGFR; 84.9–165 mL/min/1.73 m²), and blood pressure were all within the normal range during the follow-up period. None of the patients showed anemia with hemoglobin levels ranging from 12.6 to 13.6 g/dL. Their serum vitamin B12 levels were not lower than the normal range. In addition, they all did not show any signs of tubular dysfunction such as electrolyte abnormality or metabolic acidosis. Two patients underwent kidney biopsies to investigate the cause of proteinuria, and the biopsy results were unremarkable for both.

Upon recognition of persistent proteinuria, five patients started angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). However, ACEIs or ARBs did not lower the amount of proteinuria. Patient 4, who was suspected to have idiopathic nephrotic syndrome, was prescribed steroid therapy for one month but showed no response, and the steroid was stopped immediately after confirmation of the *CUBN* mutations. As shown in Fig. 3, uPCRs remained in the subnephrotic range throughout the follow-up period regardless of medication.

Variants of *CUBN*

The loci and the pathogenicity of *CUBN* variants are sum-

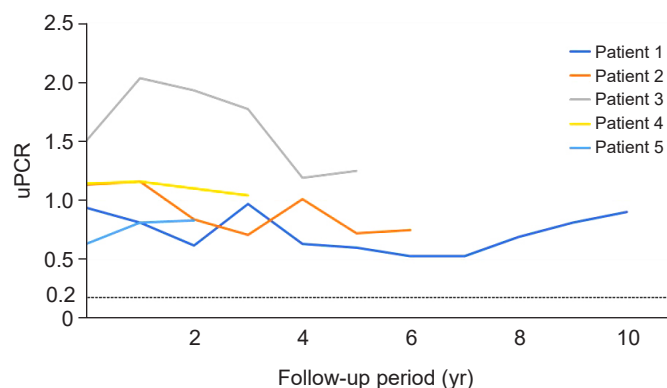


Figure 3. Changes in proteinuria over the patient's follow-up period. Six patients were followed up for a period of 2 to 10 years. Among all patients, proteinuria remained similar during the follow-up period. However, Patient 6 had a follow-up duration of less than 1 year, and thus the patient's data are excluded from this chart.

uPCR, urine protein-to-creatinine ratio.

marized in Table 3. All patients had at least one splicing mutation, and most of the variants were located C-terminal side of the gene (Fig. 1).

Discussion

In this first Korean report of *CUBN*-related proteinuria, we found that phenotypes of these cases of *CUBN* variants mostly located in the C-terminal regions are similar to previous reports, with subnephrotic range proteinuria, normal serum albumin level, and normal kidney function (Table 4). Since patients with *CUBN* C-terminal variants have benign phenotypes, unlike other genetic kidney diseases mostly progressing to chronic kidney disease, we expect these cases would not experience worsening kidney function despite significant proteinuria. Still, there may be other causes of proteinuria in these cases; thus, we are going to monitor any signs of deterioration of kidney function or worsening of proteinuria in these cases.

It is indeed controversial whether the *CUBN* mutation is truly benign or not. Some researchers have reported abnormal renal pathologic findings among *CUBN*-mutated patients [8,13,15–21]. According to the literature summarized in Table 4, 35 of 74 cases underwent a kidney biopsy, and nine patients had abnormal pathologic findings; one minimal change disease (MCD), six focal segmental glomerulosclerosis (FSGS), and two Alport syndrome features which shows podocyte changes and glomerular basement membrane alteration. All patients except one FSGS patient had normal kidney function at the last follow-up (up to the age of 66 years) and all patients except the MCD patient showed proteinuria of the subnephrotic range. The case of FSGS with decreased kidney function had an eGFR of 70 mL/min/1.73 m² at age 51 years along with comorbidities of type 2 diabetes and obesity [8]. The patient with MCD pathology had a huge amount of proteinuria (uPCR, 22 mg/mg), which was reduced to the subnephrotic range (uPCR, 0.9 mg/mg) after treatment with corticosteroid, cyclophosphamide, and cyclosporine [8]. The clinical courses of these two cases were thought to be coincidental findings rather than the clinical course of *CUBN* mutation [8]. Similarly, kidney biopsy findings of two cases of our study with pathology data were not diagnostic, and clinical courses of all the cases were compatible with the previous studies with no deterioration of kidney function through

Table 3. Pathogenicity of *CUBN* variants

Patient No.	cDNA	Protein	ACMG	Father	Mother
1	c.4402del	p.Q1468Rfs*17	LP	c.4402del	c.6821+3A>G
	c.6821+3A>G	-	LP		
2	c.205G>T	p.G69*	P	NA	NA
	c.6821+3A>G	-	LP		
3	c.6118C>T	p.R2040*	LP	c.6118C>T	c.4855+2C>G
	c.4855+2C>G	-	LP		
4	c.4855+2C>G	-	LP	NA	NA
	c.4855+2C>G	-	LP		
5	c.8579G>A	p.C2860Y	LP	NA	c.6821+3A>G (also sister)
	c.6821+3A>G	-	LP		
6	c.4855+2C>G	-	LP	c.9079G>A	c.4855+2C>G
	c.9079G>A	p.G3027R	LP		

ACMG, American College of Medical Genetics and Genomics; cDNA, complementary DNA; NA, not available; P, pathogenic; LP, likely pathogenic. Novel mutations are written in bold.

Table 4. Literature review of patients with *CUBN* mutations

Study (year)	Year	No. of patients	Onset age (yr)	uPCR (mg/mg)	Biopsy	Patients with RASi (%), response to RASi	Age at last FU (yr)	Impaired kidney function at last FU
Bedin et al. [13] (3 cohorts)	2020	14	10.87 ± 11.99	0.69 ± 0.45	18 normal	38%, no response	19.87 ± 15.94 (0–54.06)	No
		13	6.37 ± 5.12	0.76 ± 0.68	1 FSGS		10.48 ± 6.47 (0–24.45)	
		12	7.85 ± 3.11	1.00 ± 0.61			26.00 ± 20.27 (0–71.17)	
Domingo-Gallego et al. [8]	2022	15	4 (1–44)	0.8 (0.5 to >2.0)	4 normal	80%, no response	2.7–53	1 FSGS (GFR 70.2 mL/min/1.73 m ²)
				MCD 22	1 MCD			
				FSGS 1.91	1 FSGS			
Cicek et al. [15]	2023	6	6 (5–12)	0.9 (0.6–1.3)	3 normal	83%, no response	5.1–20.4	No
					1 FSGS			
Jayasinghe et al. [18]	2019	2	4, 8	92, 89.4 (mg/mmol)	1 Nonspecific	100%, uPCR 74.6, 73.8 (mg/mmol)	8, 12	No
Yang et al. [16]	2022	3	6, 8, 11	0.354, 0.536, 0.462	3 FSGS	uPCR (mg/mg) 0.187, 0.338, 0.197 after tacrolimus over 3 mo	ND	No
Gan et al. [17]	2023	2 families	8/ND	0.414, 0.485 (g/24 hr)	ND	ND	ND	ND
Shi et al. [19]	2023	2	8, 7	0.72, 0.61	No	100%, no response	15, 14	No
Ran et al. [20]	2023	2	4, 12	0.62, 0.65 (g/24 hr)	No	100%, no response	14, 22	No
Madureira Gomes et al. [21]	2023	2	7, 3	2.7, 1.2	2 r/o AS	100%, no response	10, 10	No
Current study	2024	6	5 (2–9)	1.1 (0.6–1.5)	2 normal	100%, no response	8.5 (2–19)	No

Continuous data are expressed as mean ± standard deviation or median (range).

AS, Alport syndrome; FSGS, focal segmental glomerulosclerosis; FU, follow-up; GFR, glomerular filtration rate; MCD, minimal change disease; ND, no data; RASi, renin-angiotensin system inhibitor; r/o, rule out; uPCR, urine protein-to-creatinine ratio.

follow-ups up to 8 years. Until now, reported outcomes of *CUBN*-associated proteinuria are excellent regardless of the pathology findings; Therefore, if there is no other indication of biopsy such as decreased kidney function or edema, we reckon that kidney biopsy might not be indicated.

Since there is no evidence that an immunosuppressive agent would ameliorate proteinuria, we definitely would not manage these cases with immunosuppression. The efficacy of conservative management with renin-angiotensin system inhibitor (RASi) has not been proven yet, either; none of the cases that were managed with RASi showed a reduction of proteinuria according to our experience and the literature alike [8,13,15–21]. Considering that the main mechanism of antiproteinuric, renoprotective action of RASi is by reducing intraglomerular pressure and hyperfiltration, it seems natural that proteinuria of *CUBN* defect with impaired tubular reabsorption of protein would not be affected by RASi. On the other hand, proteinuria and albuminuria itself may have detrimental effects on the tubules by inducing reactive oxygen species and inflammation that might be mitigated with RASi [24]. Therefore, the prescription of RASi in these cases might still be justified. To answer the question of how to manage *CUBN*-associated proteinuria, more data and experience are required, to where this Korean report would contribute.

The shortcoming of this work is that the number of cases or follow-up duration is not beyond that of previous studies. However, the discovery of *CUBN*-associated persistent proteinuria and confirming this condition in the Korean population would be helpful for expanding the knowledge of the field.

In conclusion, we confirmed in this study that the Korean population does have *CUBN*-associated persistent proteinuria, which is considered as a benign condition so far, not requiring treatment. We suggest that *CUBN* defect needs to be considered in case of otherwise unexplained persistent proteinuria, especially in young, healthy cases.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

This study was supported and funded by a grant from the

Korean Nephrology Research Foundation 2021 and SNUH Lee Kun-hee Child Cancer & Rare Disease Project, Republic of Korea (grant number: 22C-010-0100).

Data sharing statement

The data presented in this study are available from the corresponding author upon reasonable request.

Authors' contributions

Conceptualization: HGK, HKL

Data curation, Formal analysis: YYC, YHA, EP, JHK

Funding acquisition: HGK

Writing—original draft: All authors

Writing—review & editing: All authors

All authors read and approved the final manuscript.

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