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알파 디스트로글리칸 연관 근이영양증에서 임상형과 유전형의 다양성에 대한 연구

Broad spectrum of phenotype and genotype in alpha dystroglycan related muscular dystrophy

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고 영 준

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Abstract

Broad spectrum of phenotype and genotype in alpha dystroglycan related muscular dystrophy

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Background: Alpha dystroglycanopathies are a clinically and genetically heterogeneous group of muscular dystrophies associated with defective glycosylation of alpha dystroglycan (α-DG). Eighteen associated genes have been identified and the relative prevalence of genetic subtypes varies among different populations. We aimed to describe the clinical and genetic characteristics of α-DG-related muscular dystrophy in a tertiary center in Korea.

Materials and Methods: We analyzed the clinical characteristics and mutation profiles of 42 patients with α-DG-related muscular dystrophies. A retrospective medical record review was performed to explore genotype-phenotype correlations.

Results: Among the 42 patients, muscle-eye-brain disease/Fukuyama congenital muscular dystrophy was the most common phenotype (29/42, 69.0%). Homozygous or compound heterozygous mutations were detected in 36 patients from 33 unrelated families (36/42, 85.7%). Mutations were identified in *FKTN* (n = 24), *POMGNT1* (n = 4), *GMPPB* (n = 3), *FKRP* (n = 2), *POMT1* (n = 2), and *ISPD* (n = 1). Compound heterozygous mutations of retrotransposal (RT) insertion and deep-intronic mutations in *FKTN* were the most common genotypes and were associated with severe phenotypes.

Conclusion: This study adds to the clinical and genetic data in alpha dystroglycanopathies in Korean patients. Considering the frequent founder mutations of RT insertion and deep-intronic mutation of *FKTN*, three-primer PCR for RT insertion and Sanger sequencing of deep-intron (c.647+2084G>T) in *FKTN* should be considered in the genetic diagnosis of alpha dystroglycanopathies in Korean patients.

Keywords: Alpha dystroglycanopathy, muscular dystrophy, genotype, phenotype

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List of Abbreviation

α-DG, Alpha dystroglycan

LGMD, Limb-girdle muscular dystrophy

CMD, Congenital muscular dystrophy

MEB, Muscle-eye-brain disease

RT, Retrotransposal

FCMD, Fukuyama CMD

NGS, Next-generation sequencing

IRB, Institutional Review Board

MDDG type A, Muscular dystrophy with dystroglycanopathy type A

MDDG type B, Muscular dystrophy with dystroglycanopathy type B

MDDG type C, Muscular dystrophy with dystroglycanopathy type C

CK, Creatine kinase

WWS, Walker-Warburg syndrome

ID, Intellectual disability

PCR, Polymerase chain reaction

SD, Standard deviation

MRI, Magnetic resonance imaging

Introduction

Alpha dystroglycan (α-DG)-related muscular dystrophies are recognized as a heterogeneous group of autosomal recessive muscular dystrophies characterized by a disrupted *O*-mannosylation pathway resulting in hypoglycosylation of α-DG[1]. Reduced glycosylation of α-DG affects its binding affinity to extracellular matrix ligands, such as laminin, perlecan, and agrin in skeletal muscle and neurexin in the brain[2].

Based on the severity and location of hypoglycosylated α-DG, the clinical manifestation of alpha dystroglycanopathies encompasses a wide spectrum of phenotypic features, ranging from a mild form such as adult-onset limb-girdle muscular dystrophy (LGMD) without brain or eye involvement to a severe form such as congenital muscular dystrophy (CMD) with brain and eye involvement[3].

The differential distribution of causative genes presented according to ethnicity is a special characteristic of alpha dystroglycanopathies. In European and Chinese populations, *FKRP*, *POMGNT1*, *POMT1*, and *POMT2* have been reported as common causative genes[4-6]. In Korean and Japanese patients, *FKTN* is the most common pathogenic gene[7, 8]. In addition, at the initial discovery

of pathogenic genes, genotype and phenotype correlations were represented in distinct ethnic groups with severe phenotypic features[9]. A founder spice-site mutation in *POMGNT1* was associated with muscle-eye-brain disease (MEB) in Finnish populations and a retrotransposal (RT) insertion mutation in *FKTN* was associated with Fukuyama CMD (FCMD) in Japan. With the advent of new genetic technologies such as next-generation sequencing (NGS), at least 18 genes have been shown to cause alpha dystroglycanopathy, namely, *FKTN*, *FKRP*, *POMGNT1*, *POMGNT2*, *POMT1*, *POMT2*, *ISPD*, *GMPPB*, *DAG*, *DPM1*, *DPM2*, *DPM3*, *DOLK*, *POMK*, *TMEM5*, *B3GALNT2*, *B3GNT1*, and *LARGE1*[6]. In addition, the spectrum of phenotypes associated with pathogenic genes has become broaden.

As we presented in 2010, *FKTN* mutations are the most common genetic cause of alpha dystroglycanopathies in Korea. However, since the era of NGS, there have been few further studies of causative genes, except for the *FKTN* mutation and the overall genotype-phenotype spectrum of alpha dystroglycanopathies in Korea[12]. Therefore, our aim was to demonstrate the genotypic and phenotypic features of alpha dystroglycanopathies and their correlation in Korean patients.

Materials and Methods

1. Patients

This study was approved by the Institutional Review Board (IRB) of the Seoul National University Hospital (IRB no. 2007-057-1140). All examinations needed for diagnosis including muscle biopsies or genetic tests were performed with patients' or parents' informed consent. We enrolled a total of 42 patients from 39 unrelated Korean families who were genetically or pathologically diagnosed with α-DG-related muscular dystrophy. All cases were identified from the neuromuscular disorders database in the Seoul National University Children's Hospital from January 2000 to June 2020. The inclusion criteria were the presence of either an α-DG defect on muscle biopsy, biallelic pathogenic variants in α-DG-related genes, or both. For the analysis of the genotype-phenotype spectrum, we recruited 13 Korean patients reported previously[7, 13]. Although one patient (Case 34a) did not meet the inclusion criteria due to unavailability of a biopsy specimen and genetically undiagnosed, he was included in the study because he showed typical clinical findings of FCMD and his older sister with similar symptoms showed a definite decrease of α-DG expression in a muscle specimen. We retrospectively reviewed medical records

including initial symptoms, age of onset, clinical course, development, and seizure history. All examinations were also thoroughly reviewed including laboratory tests for creatine kinase (CK) level, radiographic findings, muscle pathologic findings, ophthalmologic investigations, echocardiography, and pulmonary function tests. Brain imaging data were available in 39 of the 42 patients and were reviewed by focusing on representative findings including cortical malformation (cobblestone lissencephaly, polymicrogyria, and pachygyria), diffuse or patchy white matter changes, posterior fossa defect (cerebellar dysplasia and cyst), and structural defect (ventriculomegaly and cerebellar hypoplasia).

We classified enrolled patients into three categories according to the Online Mendelian Inheritance in Man entries and then subclassified them into seven categories according to the disease course and degree of structural or functional brain involvement[2]. Muscular dystrophy with dystroglycanopathy type A (MDDG type A) is the severe phenotype presented by CMD with brain and eye involvement including Walker-Warburg syndrome (WWS), MEB disease and FCMD. Muscular dystrophy with dystroglycanopathy type B (MDDG type B) is the moderate phenotype presented by CMD with or without intellectual disability (ID). Muscular dystrophy with dystroglycanopathy type C (MDDG type C) is the mild

phenotype presented as LGMD with or without ID[6, 9].

2. Muscle histopathology

Muscle specimens were taken from the quadriceps femoris and processed by appropriate freezing methods with isopentane supercooled by liquid nitrogen. To evaluate the α-DG defect, we used immunohistochemical (IHC) staining or western blot with monoclonal antibodies against α-DG with VIA4-1 (Merck Millipore, Catalogue No. 05-298)[7].

3. Genetic test

Genomic DNA was extracted from peripheral blood leukocytes using a Wizard Genomic DNA Purification Kit, according to the manufacturer's instructions (Promega, Madison, WI, USA). We used a CMD gene panel or LGMD gene panel containing 16 alpha dystroglycanopathy-related genes (*FKTN*, *FKRP*, *POMGNT1*, *POMGNT2*, *POMT1*, *POMT2*, *ISPD*, *GMPPB*, *DPM1*, *DPM2*, *DPM3*, *B3GALNT2*, *LARGE*, *POMK*, *TMEM5*, and *DAG*). All pathogenic variants identified by the gene panel were confirmed by Sanger sequencing and segregation analysis. The clinical significance of each sequence variation was determined according to the Leiden

Muscular Dystrophy Database (http://www.dmd.nl/), genome Aggregation Database (gnomAD: http://gnomad.broadinstitue.org/), the Human Gene Mutation Database Professional, and the American College of Medical Genetics and Genomics recommendations[14].

A three-primer polymerase chain reaction (PCR) using LAT7ura, LAT7-2, and ins385-359 was performed to detect RT insertion mutation in *FKTN*. Direct sequencing of all coding exons and flanking intronic sequences of the *FKTN* gene was performed. PCR was performed in a thermal cycler (Model 9700; Applied Biosystems, Foster City, CA, USA) and cycle sequencing was performed on an ABI Prism 3100xl Genetic Analyzer using the BigDye Terminator Sequencing Ready Reaction Kit (Applied Biosystems). Sequence variations were analyzed via comparison with the wild-type sequence (GenBank Accession No. NM_006731)[7]. Sanger sequencing was also performed to find deep-intronic mutation in *FKTN* (c.647+2084G>T), which is known as founder mutation in Korean patients[7].

Results

1. Clinical results

A summary of clinical problems of the 42 patients is presented in Figure 1 and detailed phenotypic features are shown in Supplementary Table 1. Among the 42 patients, 25 (59.5%) were male and 17 (40.5%) were female. The average age of disease onset was 11.3 months (Standard Deviation [SD] = 38.1, range, 0–20 years old). The mean age at the last visit was 7.6 years old (SD = 5.9, range, 0.1–27.4 years old). Thirty-one patients (73.8%) were classified into MDDG type A, four patients (9.5%) were MDDG type B, and seven patients (16.7%) were MDDG type C. Muscle biopsy data were available in 35 patients (83.3%) and 32 patients (76.2%) were confirmed to have a defect in α-DG on the sarcolemma of the muscle specimen.

Serum CK level was markedly elevated in all patients with the mean level of 6390 IU/L (SD = 4986, range, 689–26099 IU/L). Brain magnetic resonance imaging (MRI) findings were available in 39 patients, and 33 patients (78.6%) had brain structural abnormalities. The abnormal image findings were presented in varying severity of cortical malformation, white matter change, and posterior fossa defect. Cognitive impairment was reported in 36

patients (85.7%) with varying severity. Eye abnormalities were confirmed in 22 patients (52.4%). Myopia (17/42, 40.5%) was the most common ophthalmologic problem and was followed by cataracts (6/42, 14.3%) and retinal detachment (5/42, 11.9%). Among five patients with retinal detachment, three patients received emergency surgery to preserve vision and two patients were not indicated for surgery due to late detection. Nystagmus was rare but shown in two patients (4.8%). Developmental delay was identified in 40 patients (95.2%). Maximal motor performance presented as no head control in 11 patients (26.2%), head control in five patients (11.9%), roll over in one patient (2.4%), sit with support in four patients (9.5%), sit alone in eight patients (19.0%), sit up in two patients (4.8%), stand with assistance in two patients (4.8%), step up in five patients (11.9%), and running in four patients (9.5%). Speech ability was presented as babbling only in 20 patients (47.6%), few words in nine patients (21.4%), sentences in 10 patients (23.8%), and similar as peers in three patients (7.1%). Seizures were reported in 16 patients (38.1%) but were mostly well controlled with antiepileptic drugs. Feeding problems were reported in 12 patients (28.6%) usually as poor sucking or aspiration due to gastroesophageal regurgitation disorder during the neonatal period. Echocardiographic data were available in 33

patients and cardiac involvement presenting with dilated cardiomyopathy was confirmed in only one patient (case 22). The patient showed congenital hypotonia and developmental delay from 4 months and *ISPD* was identified as the causative gene. At the time of the last evaluation, four patients required a home ventilator due to respiratory difficulties. Among them, ventilation was applied to two patients around 2 years of age and another two patients were 12 and 19 years old. Scoliosis was reported in six patients, and two of them (case 13 and case 22) received corrective surgery.

Pathology findings ranged from mild fiber size change to severe dystrophic or degenerating change of myofibers. IHC staining or western blot of α-DG was performed in 32 patients (76.2%) and a definite decrease or absent expression of α-DG was confirmed in all 32 patients. IHC staining and western blot of α-DG are presented in Figure 2.

2. Genotype analysis and correlation of genotype and phenotype

Homozygous or compound heterozygous mutations were detected in a total of 36 patients from 33 unrelated families (36/42,

85.7%). Twenty-four patients had mutations in *FKTN* (55.8%), four in *POMGNT1* (9.3%), three in *GMPPB* (6.9%), two in *POMT1* (4.7%), two in *FKRP* (4.7%), and one in *ISPD* (2.3%). A total of 25 different pathogenic mutations were revealed, 17 of which were novel. Variant subtypes included four nonsense, 11 missense, five frameshift, two insertion/deletion, one splicing-site variant, one synonymous, and one RT insertion variant. Detailed data of pathogenic mutations are shown in Table 1. The genotype distribution of genetically confirmed patients in our study showed significant difference in previous studies in other ethnicities. The comparison of genotype distribution in Korean CMD patients with in other ethnicities is presented in Figure 3.

The frequency of mutations in alpha dystroglycanopathy-related genes according to clinical classification is presented in Figure 4. MDDG type A was the most prevalent in patients with mutations in *FKTN* (22/24, 91.7%). Mutations in *POMGNT1* (3/4, 75%), *FKRP* (1/2, 50%), and *GMPPB* (1/3, 33.3%) were also associated with MDDG type A. Mutations in *POMT1* (n = 2) and *ISPD* (n = 1) were associated with MDDG type B. Mutations in *FKTN* (n = 2), *GMPPB* (n = 2), *POMGNT1* (n = 1), and *FKRP* (n = 1) were identified in a patient with MDDG type C.

3. Six genetically undiagnosed patients

Six patients remained genetically undiagnosed but all except one, who did not have muscle biopsy data available, showed definite α-DG defects on muscle histology. All patients showed mutations of α-DG-related genes in only one allele. The heterozygous variants are presented in Supplementary Table 2. The mutations were identified in two in *FKTN*, two in *POMGNT2*, one in *POMT1*, and one in *POMT2*.

4. *FKTN* mutation

Pathogenic mutations in *FKTN*, the most common causative gene, were identified in 24 patients (57.1%, 24/42). Ten patients have been reported previously. Compound heterozygosity of RT insertion mutation and a c.647+2084G>T mutation in the *FKTN* gene were identified in 14 of those patients (14/24, 58.3%) and was the most common genotype. Homozygotes for RT insertion mutation were identified in five patients. Twenty-two patients with homozygotes or compound heterozygotes for RT insertion mutation showed cognitive impairment with a relevant MRI abnormality and had severe phenotypes (20 MEB/FCMD and 2 WWS). Among the 22 patients, 14 patients with compound heterozygosity of RT insertion

mutation and a c.647+2084G>T mutation showed more severe phenotype and radiologic finding including cortical malformation and involvement of cerebellum and brainstem. In addition, half of them (11/22) suffered from seizures. The remaining two patients with compound heterozygotes for point mutations showed the mildest phenotype of LGMD without functional or structural brain involvement. The distribution and correlation of phenotype and genotype in the *FKTN* mutation are presented in Table 2.

5. *POMGNT1* mutation

Four patients had five mutations in the *POMGNT1* gene and two of the five mutations were novel. Homozygous mutations in two patients and compound heterozygous mutations in two patients were identified. All patients showed cognitive impairment and abnormal MRI findings. Three patients showed FCMD/MEB-like phenotype and another patient showed LGMD with cognitive impairment. All patients had ophthalmologic problems and three of four patients (75%) received emergency surgery due to retinal detachment.

6. *GMPPB* mutation

Three patients had mutations in the *GMPPB* gene. Compound

heterozygous mutations in two patients and homozygous mutations in one patient were identified. Two patients showed LGMD without cognitive impairment and normal brain imaging but had cataracts. Another patient showed MEB/FCMD-like phenotype and brain involvement but normal ophthalmologic findings.

7. *FKRP* mutation

Two patients had mutations in the *FKRP* gene. Compound heterozygotes for point mutation and frameshift or small insertion/deletion mutation were identified in two patients. One patient showed MEB/FCMD-like phenotype and the other had LGMD without cognitive impairment.

8. *POMT1* mutation

Two patients had mutations in the *POMT1* gene. Homozygous and compound heterozygous mutations for a small deletion were identified in two patients. Both patients showed CMD with cognitive impairment. They had no parenchymal abnormality on brain imaging but showed severe global developmental delay and feeding problems from birth.

9. *ISPD* mutation (c.894delT/c.964_966del)

This patient showed hypotonia and motor developmental delay since the age of 4 months, but speech and intellectual ability were normal. Brain MRI at 5 years of age revealed no structural abnormality and ophthalmologic examination was also normal. From 10 years of age, a progressive decrease of cardiac function was confirmed by cardiac echocardiography (ejection fraction = 47%). At 12 years old, pulmonary function test showed severely decreased functional vital capacity below 0.45 L and application of noninvasive positive pressure ventilation was planned. He received tracheostomy surgery for invasive ventilation after a respiratory arrest event at 13 years old.

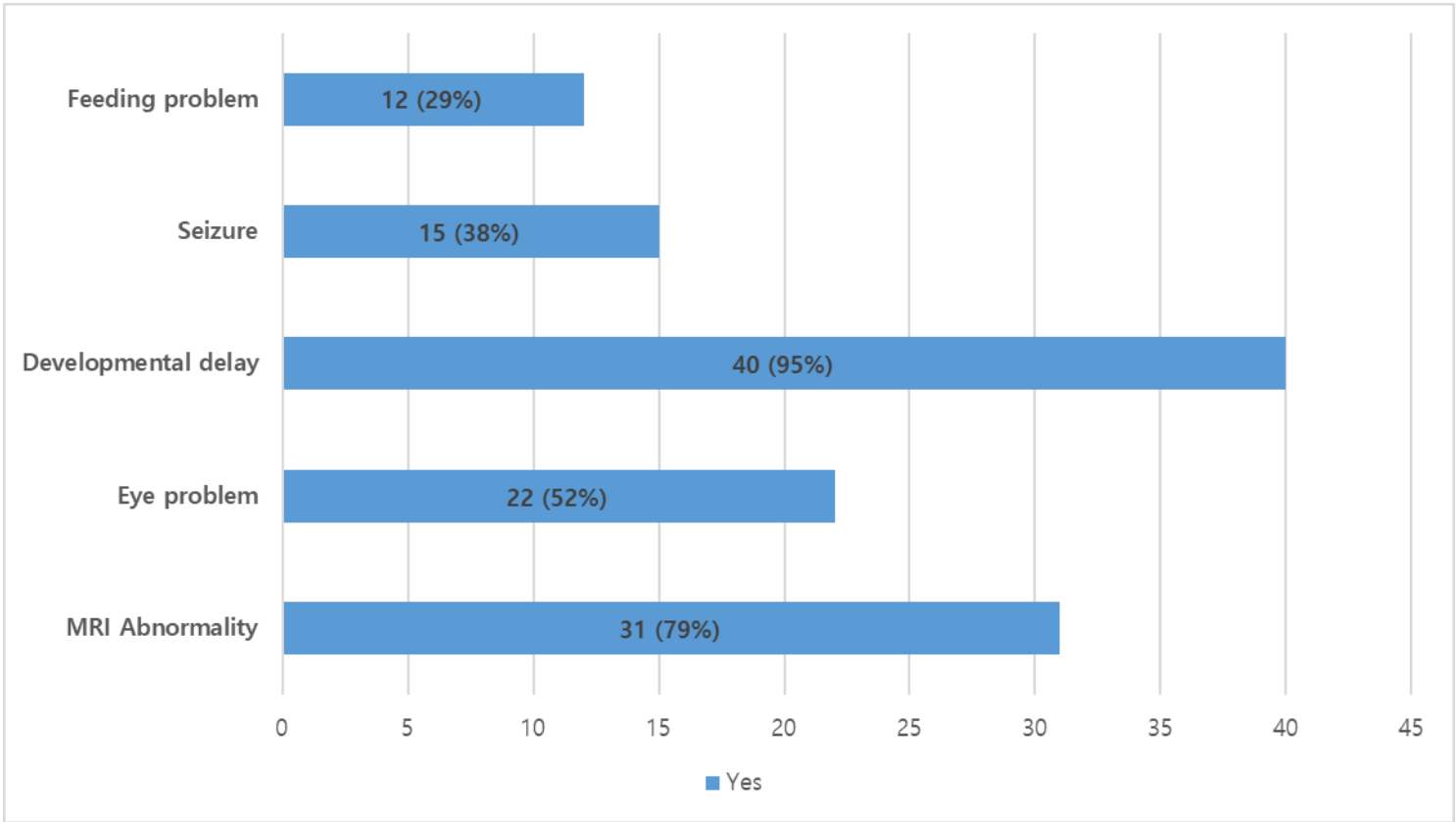

Figure 1. Overall proportions of clinical problems of the 42 patients with alpha dystroglycanopathy (N (%)).

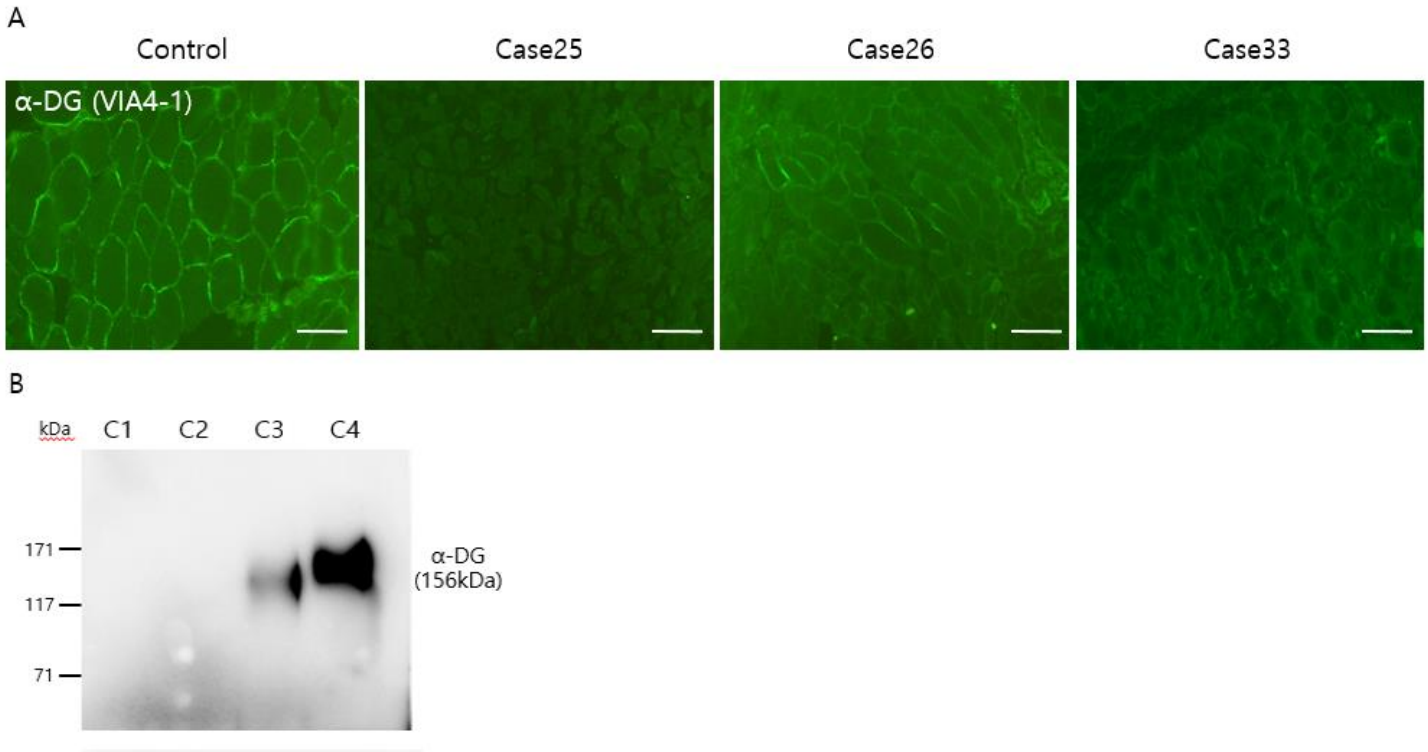

Figure 2. Immunohistochemistry staining and western blot of alpha DG. A. Immunofluorescence images from the muscle biopsies reveal decrease or absence of staining for α-dystroglycan with glycoepitope-dependent antibody (VIA4-1). Case25 muscle shows complete loss of functional glycosylated α-dystroglycan. Scale bar, 100 μm. **B.** Protein blot analysis of muscle biopsy with the glycoepitope-dependent α-dystroglycan antibody (VIA4-1). C1 is case29, C2 is case17a, C3 is case26, C4 is normal control. C1 and C2 shows complete loss and C3 shows decrease of functional glycosylated α-dystroglycan as compared with control.

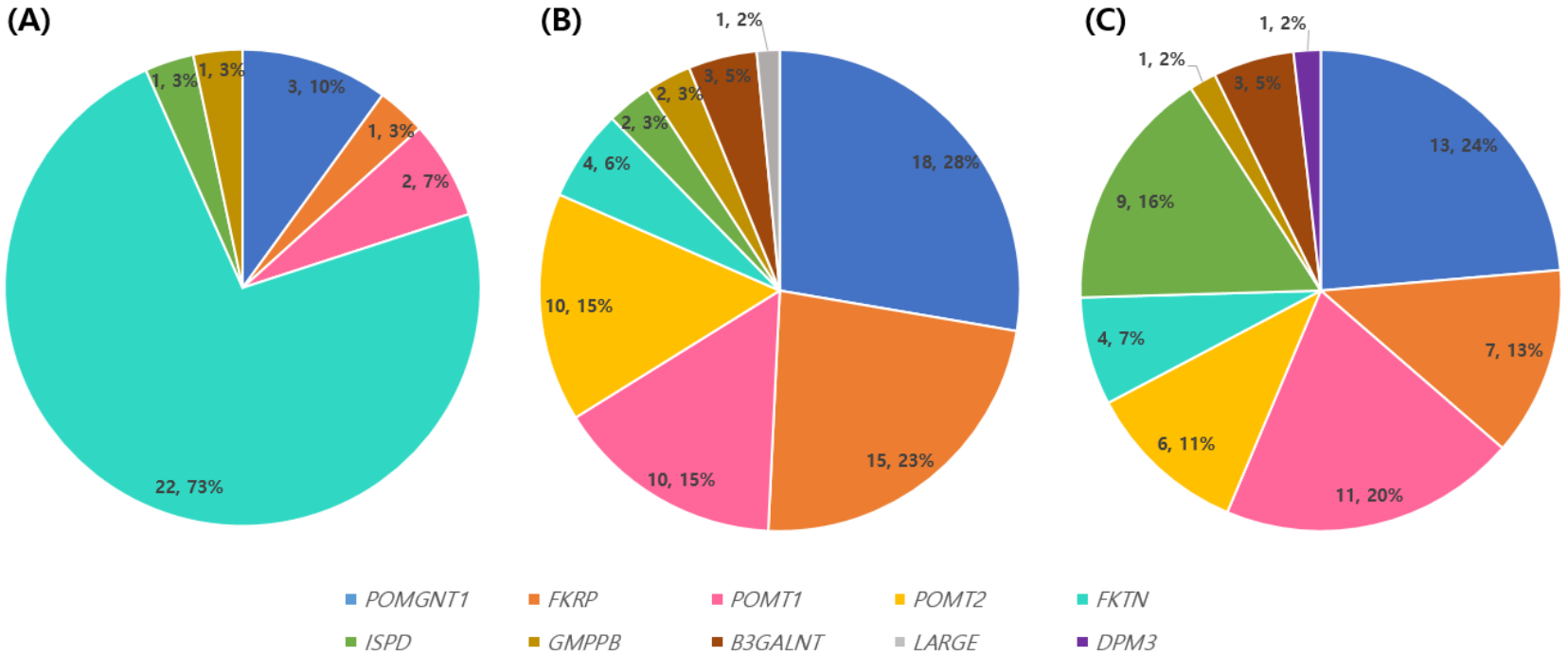

Figure 3. Genotype distribution of alpha DG patients with CMD according to ethnicity. A, Genotype distribution in genetically confirmed 30 Korean patients with CMD (N, %). B, Genotype distribution of alpha DG in 66 UK patients with CMD (N, %)[4]. C, Genotype distribution of alpha DG in 55 Chinese patients with CMD (N, %)[6].

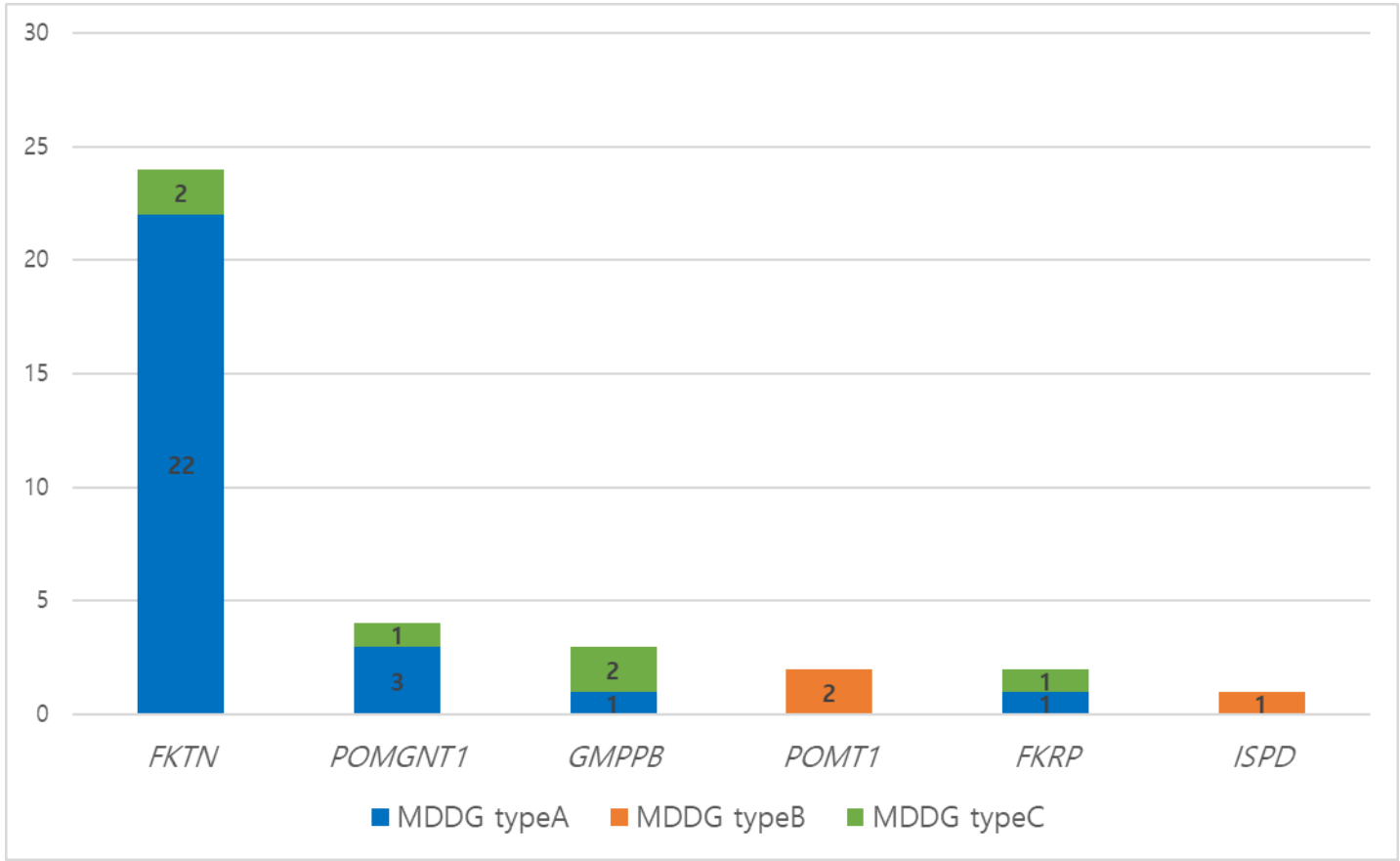

Fig 4. Frequency of mutations in alpha dystroglycanopathy related genes according to clinical classification.

Table 1. Summary of pathogenic mutations of genetically confirmed 36 patients with alpha dystroglycanopathy

Case	Gene	Location	Nucleotide change	Amino acid change	Mutation type	ACMG classification	ACMG category
1	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		Intron6	c.647+2084G>T	p.Arg216Serfs*10	frameshift	Pathogenic	PVS1 PS3
2	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		Intron6	c.647+2084G>T	p.Arg216Serfs*10	frameshift	Pathogenic	PVS1 PS3
3a	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		Intron5	c.647+2084G>T	p.Arg216Serfs*10	frameshift	Pathogenic	PVS1 PS3
3b	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		Intron5	c.647+2084G>T	p.Arg216Serfs*10	frameshift	Pathogenic	PVS1 PS3
4	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		Intron5	c.647+2084G>T	p.Arg216Serfs*10	frameshift	Pathogenic	PVS1 PS3
5	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		Intron5	c.647+2084G>T	p.Arg216Serfs*10	frameshift	Pathogenic	PVS1 PS3
6	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		Intron5	c.647+2084G>T	p.Arg216Serfs*10	frameshift	Pathogenic	PVS1 PS3
7	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		Intron5	c.647+2084G>T	p.Arg216Serfs*10	frameshift	Pathogenic	PVS1 PS3
8	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		Intron5	c.647+2084G>T	p.Arg216Serfs*10	frameshift	Pathogenic	PVS1 PS3
9	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		Intron5	c.647+2084G>T	p.Arg216Serfs*10	frameshift	Pathogenic	PVS1 PS3
10	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		Intron5	c.647+2084G>T	p.Arg216Serfs*10	frameshift	Pathogenic	PVS1 PS3
11	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		Intron5	c.647+2084G>T	p.Arg216Serfs*10	frameshift	Pathogenic	PVS1 PS3
12	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		Intron5	c.647+2084G>T	p.Arg216Serfs*10	frameshift	Pathogenic	PVS1 PS3
13	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		Intron5	c.647+2084G>T	p.Arg216Serfs*10	frameshift	Pathogenic	PVS1 PS3

14	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
15	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
16	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
17a	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
17b	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
18	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		Exon3	c.49A>C	p.Ser17Arg	Missense	Likely pathogenic	PM1 PM2 PP3 PP4
19	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		Exon3	c.49A>C	p.Ser17Arg	Missense	Likely pathogenic	PM1 PM2 PP3 PP4
20	*FKTN*	3′ UTR	RT	–	RT	Pathogenic	PVS1 PS3
		Exon5	c.346C>T	p.Gln116*	Nonsense	Pathogenic	PVS1 PM2 PP3 PP4
21	*FKTN*	Exon3	c.49A>C	p.Ser17Arg	Missense	Likely pathogenic	PM1 PM2 PP3 PP4
		Intron4	c.165+6T>C	–	Spicing	Likely pathogenic	PM2 PM3 PP3 PP4
22	*FKTN*	Exon9	c.1044G>A	p.Lys348=	Synonymous	Likely pathogenic	PM1 PM2 PP3 PP4
		Exon10	c.1112A>G	p.Tyr371Cys	Missense	Likely pathogenic	PM1 PM2 PP3 PP4
23a	*POMGNT1*	Exon15	c.1274G>C	p.Trp425Ser	Missense	Likely pathogenic	PM1 PM2 PP3 PP4
		Exon15	c.1274G>C	p.Trp425Ser	Missense	Likely pathogenic	PM1 PM2 PP3 PP4
23b	*POMGNT1*	Exon15	c.1274G>C	p.Trp425Ser	Missense	Likely pathogenic	PM1 PM2 PP3 PP4
		Exon15	c.1274G>C	p.Trp425Ser	Missense	Likely pathogenic	PM1 PM2 PP3 PP4
24	*POMGNT1*	Exon11	c.1011dupT	p.Asp338*	Nonsense	Pathogenic	PVS1 PM1 PP3 PP4
		Exon16	c.1385T>A	p.Leu462His	Missense	Likely pathogenic	PM1 PM2 PP3 PP4
25	*POMGNT1*	Exon11	c.1011dupT	p.Asp338*	Nonsense	Pathogenic	PVS1 PM1 PP3 PP4
		Exon20	c.1768T>C	p.Trp590Arg	Missense	Likely pathogenic	PM1 PM2 PP3 PP4
26	*GMPPB*	Exon4	c.391G>T	p.Gly131Cys	Missense	Likely pathogenic	PM1 PM2 PP3 PP4
		Exon4	c.391G>T	p.Gly131Cys	Missense	Likely pathogenic	PM1 PM2 PP3 PP4
27	*GMPPB*	Exon4	c.391G>T	p.Gly131Cys	Missense	Likely pathogenic	PM1 PM2 PP3 PP4
		Exon8	c.787G>A	p.Gly263Ser	Missense	Likely pathogenic	PM1 PM2 PP3 PP4

28	*GMPPB*	Exon4	c.343T>C	p.Phe115Leu	Missense	Likely pathogenic	PM1 PM2 PM3
		Exon8	c.787G>A	p.Gly263Ser	Missense	Likely pathogenic	PM1 PM2 PP3 PP4
29	*POMT1*	Exon5	c.357delC	p.Tyr120Thrfs*3	Frameshift	Pathogenic	PVS1 PM2 PP4
		Exon20	c.2208delG	p.Trp736*	Nonsense	Pathogenic	PVS1 PM2 PP4
30	*POMT1*	Exon20	c.2167delG	p.Asp723Thrfs*21	Frameshift	Pathogenic	PVS1 PM2 PP4
		Exon20	c.2167delG	p.Asp723Thrfs*21	Frameshift	Pathogenic	PVS1 PM2 PP4
31	*FKRP*	Exon4	c.1170_1171delCG	p.Gly391Leufs*72	Frameshift	Pathogenic	PVS1 PM2 PP4
		Exon4	c.1136G>C	p.Arg379Pro	Missense	Likely pathogenic	PM1 PM2 PP3 PP4
32	*FKRP*	Exon4	c.501_502delinsCC	p.Arg167_Cys168delinsSerArg	Indel	Likely pathogenic	PM1 PM2 PP3 PP4
		Exon4	c.1176C>G	p.Phe392Leu	Missense	Likely pathogenic	PM1 PM2 PM3
33	*ISPD*	Exon6	c.894delA	p.298fs*8	Frameshift	Pathogenic	PVS1 PM2 PP4
		Exon7	c.964_966del	p.His322del	Deletion	Pathogenic	PM1 PM2 PM3

FKTN, fukutin; gnomAD, genome aggregation database, RT, retrotransposal insertion mutation; UTR; untranslated region,

Table 2. The distribution and correlation of phenotype and genotype in *FKTN* mutation

Genotype	N	Phenotype	Maximal motor performance					Epilepsy	Eye problem	
			None	Head	Sit	Stand	Walk		Myopia	Retina
Homo RT	5	MEB/FCMD			4	1		2		
RT/c.647+2084G>T	14	MEB/FCMD	5	3	5	1		7	9	2
RT/c.49A>C	2	MEB/FCMD			2			1		
RT/c.346C>T	1	MEB/FCMD		1				1	1	
c.49A>C/c.165+6T>C	1	LGMD no CI					1	0		
c.1044G>A /c.1112A>G	1	LGMD no CI	5	4	11	2	1	0		

FCMD, Fukuyama congenital muscular dystrophy; LGMD no CI, limb-girdle muscular dystrophy without cognitive impairment; MEB, muscle-eye-brain disease; RT, retrotransposal insertion mutation

Supplementary Table 1. Clinical features of the 42 patients with alpha dystroglycanopathy

Case	Sex	Age at onset (mon)	Age at last visit (year)	Clinical Phenotype	CK (IU/L)	a-DG	Brain MRI	Eye problem	Best motor ability	Speech	Seizure	Feeding problem
1	M	0.0	4.7	MEB/FCMD	3798	Decrease	Cortmalf Diffuse WMC Cbllcyst and WMC	Cataract	No HC	Babble	+	+
2	F	2.7	8.2	MEB/FCMD	8556	Decrease	Cortmalf Diffuse WMC Cbll hypoplasia	NA	No HC	Babble	-	+
3a	M	0.0	1.6	WWS	4900	Decrease	Cortmalf Diffuse WMC Cbllcyst	Myopia	No HC	Babble	-	-
3b	M	1.9	7.3	MEB/FCMD	6117	NA	Cortmalf Diffuse WMC Cbllcyst and WMC	High myopia/ RD	HC	Babble	-	-
4	F	4.0	1.4	MEB/FCMD	15468	Decrease	Cortmalf Diffuse WMC Cbllcyst and WMC Pons hypoplasia	NA	No HC	Babble	-	-
5	M	2.9	12.2	MEB/FCMD	9208	Decrease	Cortmalf Diffuse WMC Cbllcyst and WMC Pons hypoplasia	Myopia/ RD	Sit alone	Words	+	+
6	F	0.0	0.1	WWS	6999	NA	Cortmalf Diffuse WMC Cbllcyst and WMC	NA	No HC	Babble	-	-

7	M	3.5	9.2	MEB/FCMD	3507	Decrease	Cortmalf Diffuse WMC Cbllcyst Pons hypoplasia	Myopia	Sit alone	Babble	+	−
8	F	3.9	7.9	MEB/FCMD	4727	Decrease	Cortmalf Diffuse WM Cbllcyst and WM	High myopia	Sit alone	Sentence	+	−
9	M	4.1	7.1	MEB/FCMD	8640	Decrease	Cortmalf Diffuse WM Cbllcyst and WM Pons hypoplasia	Myopia	Sit alone	Babble	+	−
10	M	4.1	7.1	MEB/FCMD	3611	Decrease	Cortmalf Diffuse WMC Cbllcyst and WMC	Myopia	HC	Babble	+	−
11	F	3.8	6.2	MEB/FCMD	4857	Decrease	Cortmalf Diffuse WMC Cbllcyst and WMC Pons hypoplasia	Myopia	Sit alone	Words	+	+
12	M	4.2	4.1	MEB/FCMD	7261	NA	Cortmalf Diffuse WMC Cbllcyst and WMC	Normal	HC	Babble	−	−
13	M	4.7	3.2	MEB/FCMD	14580	NA	Cortmalf Diffuse WMC Cbllcyst and WMC	Myopia	Sit alone	Words	−	−
14	F	4.3	17.9	MEB/FCMD	4712	Decrease	Cortmalf WM patchy	Normal	Stand with assist	Sentence	−	−
15	M	6	10	MEB/FCMD	3824	NA	Cortmalf WM patchy	NA	Stand with assist	Sentence	+	−

16	F	3.6	12.3	MEB/FCMD	5002	Decrease	Cortmalf Diffuse WMC Cbllcyst	NA	Sit alone	Sentence	+	−
17a	F	4.9	6.8	MEB/FCMD	5852	Decrease	Cortmalf WM patchy Cbllcyst	NA	Sit alone	Sentence	−	−
17b	M	3.8	5.0	MEB/FCMD	26099	NA	Cortmalf WM patchy Cbllcyst	NA	Sit alone	Words	−	−
18	F	3.9	4.7	MEB/FCMD	6275	Decrease	Cortmalf WM patchy Cbllcyst and WMC Pons hypoplasia	NA	Sit alone	Babble	+	−
19	F	0.7	1.3	MEB/FCMD	9895	Decrease	Cortmalf Diffuse WMC Cbllcyst and WMC Pons hypoplasia	Normal	Sit	Babble	−	+
20	M	0.0	13.6	MEB/FCMD	3710	Decrease	Cortmalf WM patchy Cbllcyst and WMC Pons hypoplasia	Myopia	Roll over	Babble	+	+
21	M	12	3.1	LGMD no CI	5315	Decrease	Normal	NA	Run	Sentence	−	−
22	M	243.4	27.4	LGMD no CI	689	NA	NA	NA	Run	Normal	−	−
23a	F	3.5	14.8	MEB/FCMD	948	NA	Cortmalf Diffuse WMC Cbllcyst and WMC Pons hypoplasia	Cataract/ Myopia/ RD	Step up	Sentence	−	−

23b	F	NA	NA	MEB/FCMD	NA	NA	NA	Myopia/ RD	Step up	Words	NA	NA
24	M	13.5	17.7	LGMD+CI	4905	Decrease	Cortmalf WM patchy Cbllcyst and WMC Pons hypoplasia	Myopia/ RD	Step up	Sentence	+	−
25	M	3.1	4.6	MEB/FCMD	2743	Decrease	Cortmalf Diffuse WMC Cbllcyst and WMC Pons hypoplasia	Cataract/ High myopia	Sit	Words	−	−
26	M	35.4	7.0	LGMD no CI	2253	Decrease	Normal	Cataract	Run	Normal	−	−
27	M	13.2	14.4	LGMD no CI	4764	Decrease	Normal	Cataract	Step up	Sentence	+	−
28	M	0.0	1.4	MEB/FCMD	1366	Decrease	Cortmalf WM patchy	Normal	No HC	Babble	+	+
29	F	0.0	4.9	CMD+CI	6316	Decrease	Normal	Myopia	No HC	Babble	−	+
30	F	0.0	3.8	CMD+CI	4821	Decrease	Diffuse VM	NA	No HC	Babble	−	+
31	M	0.0	1.1	MEB/FCMD	7529	Decrease	Cortmalf WM patchy Cbllcyst and WMC	Normal	HC	Babble	−	+

32	F	15.2	2.3	LGMD no CI	19160	Decrease	Normal	NA	Step up	Words	−	−
33	M	4.1	15.1	CMD no CI	7411	Decrease	Normal	Normal	Stand with assist	Sentence	−	−
34a	M	0.0	5.8	MEB/FCMD	11388	NA	Cortmalf Diffuse WMC Cbllcyst and WMC Pons hypoplasia	Nystagmus	No HC	Babble	+	−
34b	F	0.0	7.3	MEB/FCMD	2864	Decrease	Cortmalf Diffuse WMC Cbllcyst and WMC Pons hypoplasia	Nystagmus	No HC	Words	+	−
35	M	3.1	1.8	CMD+CI	2174	Decrease	Mild atrophy	Myopia	No HC	Babble	−	+
36	M	15.3	16.3	LGMD no CI	2941	Decrease	NA	NA	Run	Normal	−	−
37	F	0.0	1.6	MEB/FCMD	3473	Decrease	Diffuse WMC	NA	HC	Babble	−	+
38	M	0.0	9.8	MEB/FCMD	3334	Decrease	Thin corpus callosum	Cataract/ Myopia	Sit alone	Words	−	−

a−DG, alpha−dystroglycan; Cbllcyst, cerebellar cysts; CI, cognitive impairment; CK, creatine kinase; Cortmalf, cortical malformation; CMD, congenital muscular dystrophy; FCMD, Fukuyama congenital muscular dystrophy; HC, head control; LGMD, limb−girdle muscular dystrophy; MEB, muscle−eye−brain disease; MRI, magnetic resonance image; NA, not available; RD, retinal detachment; VM, ventriculomegaly; WMC, white matter change; WM patchy, focal white matter change; WWS, Walker−Warburg syndrome.

Supplementary Table 2. Only one heterozygous variant list in 6 patients

Case	Gene	Exon	Nucleotide change	Amino acid change	Mutation type	ACMG classification	ACMG category
34a	*FKTN*	3′ UTR	RT, heterozygote	-	RT	Pathogenic	PS1 PS3
34b	*FKTN*	3′ UTR	RT, heterozygote	-	RT	Pathogenic	PS1 PS3
35	*POMT2*	Exon19	c.1997A>G, heterozygote	p.Tyr666Cys	Missense	Pathogenic	PS1 PS3
36	*POMT1*	Exon12	c.1192G>A, heterozygote	p.Gly398Arg	Missense	VUS	PM1 PP3 PP4
37	*POMGNT2*	Exon2	c.466G>A, heterozygote	p.Ala156Thr	Missense	VUS	PM1 PM2 PP4
38	*POMGNT2*	Exon2	c.295T>g, heterozygote	p.Asn99His	Missense	Likely pathogenic	PM1 PM2 PP3 PP4

Discussion

Alpha dystroglycanopathies are the second most common muscular dystrophy subtype with a broad spectrum of clinical phenotypes[4]. As genetic diagnostic techniques have developed and as new causative genes have been discovered, so the clinical heterogeneity related to specific genotypes has broadened[6].

In this study, we demonstrated the overall phenotypic and genotypic spectrum of 42 patients with alpha dystroglycanopathies in a Korean population. There was a broad range of clinical and genetic heterogeneity of α-DG-related muscular dystrophies. Compared with data in the literature, there were no significant differences in clinical manifestation including cognitive impairment, brain MRI, motor and language ability, ophthalmologic findings, and epilepsy[4-6]. Laboratory measurements of circulating CK were not correlated with clinical severity. Decreases in pulmonary and cardiac function were relatively infrequent in line with previous studies and no association with phenotypic classification was found in our cohort[16].

Of note, there was a significant difference in the distribution of causative genes compared with previous studies in European and Chinese populations[4-6]. Founder mutations in the *FKRP* gene are

the most common genetic cause of alpha dystroglycanopathies in the UK and Chinese populations where more than half of patients show a mild phenotype of CMD or LGMD. Furthermore, almost all patients have a founder mutation in the *FKRP* gene in the American and Brazilian population[17, 18]. In our cohort, *FKRP* mutations were rare while *FKTN* was the most common pathogenic gene. As noted in our previous study, this difference might result from founder mutations in the *FKTN* gene in Korea[7, 8]. More than half of the patients (52.4%, 22/42) carried heterozygous founder mutations in *FKTN* and showed a more severe phenotype with brain and eye involvement and seizures. These findings are in line with previous studies of founder mutations in *FKTN* that are associated with FCMD or a more severe phenotype[7, 11, 19]. As shown in the results, in the *FKTN* gene, compound heterozygotes for RT insertion and deep-intronic mutations were the absolute majority in our cohort. This finding can be compared with that in Japanese patients where there is a close ethnic relationship with Koreans. Although a deep-intronic point mutation in *FKTN* was recently reported as a second common variant for FCMD in the Japanese population, homozygotes for RT insertion mutation in *FKTN* are known to account for a large majority of this genotype in Japanese patients[8, 20]. These differences in genotype prevalence in *FKTN* may explain the more

severe phenotype in our Korean patients compared with Japanese patients[7, 20]. *FKTN* founder mutations, such as RT insertions or deep-intronic mutations are not covered by the NGS panel or WES. Rather, they should be identified by three-primer PCR for RT insertion and Sanger sequencing for deep-intron (c.647+2084G>T) in *FKTN*. In this study, the prevalence of founder mutations in *FKTN* was present in up to 52.4% (22/42) of cases. Considering the high prevalence of founder mutations of *FKTN*, three-primer PCR for RT insertion and Sanger sequencing of deep-intron (c.647+2084G>T) in *FKTN* should be considered as a first-line screening test for the genetic diagnosis of alpha dystroglycanopathies with a severe phenotype, especially in Korean and Japanese populations.

In 24 patients with an *FKTN* mutation, genotype and phenotype correlation was unequivocal. However, except for the *FKTN* mutation, there was only a small number of cases for each gene mutation. As a result, there was a limitation in the analysis of the association between genotype and phenotype for the other genes. Nonetheless, we found specific clinical manifestations associated with *POMGNT1*. All four patients with a *POMGNT1* mutation showed brain and eye involvement regardless of clinical severity. All four patients had myopia and three of four patients (75%) had a

retinal detachment. Compared with patients with other mutations, prevalent retinal detachment in patients with *POMGNT1* mutation suggests specific retinal expression of *POMGNT1*. In a previous study, retinal degeneration was confirmed in patients with *POMGNT1* mutation and *POMGNT1* was reported as essential for retinal cell survival and stability[21]. Furthermore, nonsyndromic retinitis pigmentosa was also reported in cases of residual POMGNT1 enzyme activity[22]. While this finding is yet to be confirmed in a large cohort study, it may be prudent in real practice to consider regular ophthalmologic examinations and close monitoring of the retinal state in patients with *POMGNT1* mutations. Furthermore, considering half of patients with alpha DG related dystrophy showed ophthalmologic problems, ophthalmologic evaluation should be considered in diagnostic evaluation and management of patients with alpha dystroglycanopathies.

Compared with previous studies where the rate of genetic diagnosis was 50% to 60%, our diagnostic rate of 85.7% is considerably higher. Although there were differences in study design, our improved diagnostic rate may be the result of the availability of advanced genetic technologies combined with founder mutations in Korean patients. However, although our study found that 85.7% of the genetic cause is known in alpha

dystroglycanopathies, we could not account for the genetic etiology of the remaining 14.3% of patients with a clear α-DG defect and clinical findings. This means there are still unknown genes related to alpha dystroglycanopathies or that we have reached a technical limitation. Interestingly, we found heterozygous mutations in α-DG-related genes in all six genetically undiagnosed patients. This suggests the possibility of mutations in another allele, and we are processing RNA sequencing for some of them to identify mutations in another allele. By application of further genetic analysis such as RNA sequencing or whole-genome sequencing, we may detect missed variants or structural abnormalities in the NGS panel or WES[23, 24].

Even in the genomic era, muscle pathology is important not only as a complementary diagnostic resource of genetic tests but for future analysis. Stored frozen muscle may be useful for RNA sequencing or complementary DNA analysis. Furthermore, fibroblast or myoblast culture, derived from muscle specimens, may be required for confirmation of pathogenicity of novel variants or functional study[23, 25].

To our knowledge, this is the largest cohort study describing the spectrum of genotype and phenotype of Korean patients with α-DG-related muscular dystrophy. Furthermore, because of the

child-oriented nature of our cohort, the mild phenotype associated with adult-onset alpha dystroglycanopathies might be underappreciated. Further study on an expanded cohort, including adult patients, will be needed.

Like most muscular disorders, there is no evident treatment or cure for alpha dystroglycanopathies. Even so, an early genetic diagnosis might help patients and their families by providing informed genetic counseling and future family planning through prenatal diagnosis and preventive pregnancy[26].

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국문초록

알파 디스트로글리칸 연관 근이영양증에서 임상형과 유전형의 다양성에 대한 연구

알파 티스트로글리칸병증은 알파 디스트로글리칸의 당화 결손으로 인해 발생하는 근이영양증의 한 형태로 다양한 임상 및 유전 양상을 보이는 것으로 알려져 있다. 알파 디스트로글리칸병증과 관련된 18개의 유전자가 최근까지 밝혀졌고 원인유전자의 구성 분포 및 비율이 민족간에 다양하게 나타나는 것이 특징이다. 본 연구에서는 국내 알파 디스트로글리칸 연관 근이영양증으로 진단받은 환자들의 임상적, 유전적 특징을 분석하고자 한다. 서울대학교 어린이병원에서 알파 디스트로글리칸 연관 근이영양증으로 진단받은 환자 42명의 임상적 특징과 유전변이에 대한 분석을 통해 연구를 진행하였다. 유전형과 임상형의 연관성을 찾기위해 환자들의 근육생검, 혈액 및 영상검사를 포함하여 후향적 의무기록 분석을 시행하였다. 42명의 연구대상 환자에서 근육-눈-뇌병/후쿠야마형 선천성 근이영양증 (29/42, 69.0%)이 가장 흔한 임상형이었다. 동형접합 또는 복합 이형접합 변이가 총 36명 (33가족, 85.7%)에서 확인되었다. 발견된 원인 유전자는 *FKTN* (24명), *POMGNT1* (4명), *GMPPB* (3명), *FKRP* (2명), *POMT1* (2명), *ISPD* (1명)이었다. *FKTN*의 복합 이형접합 변이

(레트로트렌스포존 삽입과 심부 인트론 변이)가 가장 흔한 유전형으로 중증의 임상형과 연관이 있었다. 본 연구를 통해 국내 알파 디스트로글리칸병증 환자들의 임상적, 유전적 다양성을 제시하였다. 특히, 국내 환자에서 확인된 *FKTN*에서 높은 빈도의 창시자 돌연변이를 고려할 때, 국내 알파 디스트로글리칸 환자의 유전적 진단에 있어 *FKTN*의 레트로트렌스포존 삽입에 대한 삼-프라이머 중합효소연쇄반응 검사 및 심부 인트론 변이에 대한 생어 염기서열 분석법을 우선적으로 고려해야 한다.

주요어: 알파 디스트로글칸, 근이영양증, 임상형, 유전형