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Novel *FKTN* p. Gly424Asp variant associated with adult-onset dilated cardiomyopathy and seizures in a Chinese patient

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Abstract

Fukuyama congenital muscular dystrophy (FCMD) is a rare autosomal recessive α-dystroglycanopathy typically presenting in infancy with severe hypotonia, intellectual disability, and cortical malformations. Adult-onset phenotypes are uncommon and usually dominated by isolated cardiomyopathy without neurological involvement. We report the first genetically confirmed case of adult-onset *FKTN*-related dilated cardiomyopathy (DCM) in a Chinese patient harboring a novel homozygous *FKTN* missense mutation. We present here a 31-year-old man presented with acute heart failure secondary to dilated cardiomyopathy and subsequently developed a generalized tonic–clonic seizure. Neurological examination revealed mild bilateral gastrocnemius atrophy without weakness, preserved cognition, and normal deep tendon reflexes. Serum creatine kinase was markedly elevated (>7,000 U/L). Echocardiography and cardiac MRI confirmed DCM with non-compaction features. Brain MRI was unremarkable. Genetic testing identified a novel homozygous *FKTN* mutation (c. 1271G>A, p. Gly424Asp). Following treatment with heart failure medication and prophylactic levetiracetam, cardiac function improved, and the patient remained seizure-free during a 12-month follow-up.
Conclusions: This case expands the phenotypic spectrum of *FKTN*-related disorders to include adult-onset DCM accompanied by seizures. While the exact mechanism remains to be fully elucidated, the presence of seizures in the absence of cortical malformations highlights a potential functional neurological involvement. Targeted *FKTN* screening is recommended for adults with unexplained cardiomyopathy and markedly elevated CK.

Keywords: Fukuyama congenital muscular dystrophy; *FKTN* mutation; α-dystroglycanopathy; dilated cardiomyopathy; seizure; muscle biopsy

INTRODUCTION

Fukuyama congenital muscular dystrophy (FCMD) represents the prototypic α-dystroglycanopathy caused by mutations in the *FKTN* gene, which encodes fukutin, a crucial enzyme in α-dystroglycan glycosylation.[1] Classical FCMD is characterized by congenital hypotonia, severe developmental delay, and structural brain abnormalities such as cobblestone lissencephaly and cerebellar cysts, and it is most prevalent in the Japanese population due to a founder retrotransposon insertion in *FKTN*.[2,3] Outside Japan, non-founder *FKTN* variants result in a wider phenotypic spectrum, ranging from lethal Walker–Warburg syndrome to milder limb-girdle muscular dystrophies (LGMD2X).[4]

In contrast to these congenital and early-onset forms, adult-onset presentations are exceedingly rare and typically manifest as isolated dilated cardiomyopathy (DCM), designated as CMD1X, often with minimal or subclinical skeletal muscle involvement.[5] While central nervous system (CNS) involvement is a hallmark of severe congenital *FKTN* mutations, it is generally considered absent in the adult-onset cardiac phenotype.

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Here, we report a Chinese patient harboring a novel homozygous *FKTN* missense mutation (c.1271G>A, p.Gly424Asp). Clinically, the patient presented with adult-onset dilated cardiomyopathy and elevated creatine kinase (CK) levels, consistent with *FKTN*-related cardiomyopathy. Notably, the clinical course was complicated by a generalized tonic–clonic seizure, a feature previously uncharacterized in the adult-onset cardiac spectrum. We discuss the clinical and genetic characteristics of this case in the context of previously reported adult-onset *FKTN*-related cardiomyopathy cases and explore the potential implications for diagnosis and management.

CASE REPORT

A 31-year-old Han Chinese male presented to the Department of Neurology with acute onset dyspnea, orthopnea, and lower limb edema persisting for three months, followed by a generalized tonic–clonic seizure four months later. The seizure episode occurred without obvious triggers and was characterized by loss of consciousness, upward gaze deviation, tonic extension, clonic jerking of all limbs, and tongue biting, without urinary incontinence. He regained full consciousness after several minutes, with postictal confusion lasting 10 minutes.

The patient was born to consanguineous parents (first cousins) (Figure 1) and had an unremarkable perinatal history. Early motor and cognitive milestones were reportedly normal. Over the preceding two years, he experienced a progressive decline in fine motor coordination. There was no prior history of neuromuscular disease, cardiomyopathy, seizures, myotoxic drug exposure, or similar symptoms among family members.

On admission, the patient was alert and oriented. Cognitive function was preserved (MoCA 30/30; MMSE 27/30). Cranial nerve, sensory, and cerebellar examinations were unremarkable. Gait was normal. Mild bilateral calf atrophy was noted, but muscle bulk elsewhere was preserved (Figure 2). Muscle strength was full (Medical Research Council grade 5 in all tested muscle groups). Deep tendon reflexes were normal, with no Gower's sign or joint contractures. Cardiac examination revealed a displaced apex beat in the 6th intercostal space at the anterior axillary line and a grade 3/6 pansystolic murmur at the left sternal border. No peripheral cyanosis or hepatomegaly was observed.

Serum CK was persistently elevated (7,041–7,242 U/L; reference <170 U/L). Cardiac biomarkers showed transient elevation (BNP: 806 pg/mL; reference <100 pg/mL; troponin T: 0.068 ng/mL; reference <0.014 ng/mL). Comprehensive metabolic screening, including liver and renal function, electrolytes, lactate, and autoimmune profiles, was unremarkable, ruling out common metabolic causes of seizures.

Electrocardiography revealed sinus rhythm with non - specific ST - T changes. Transthoracic echocardiography demonstrated a dilated left atrium with an internal diameter of 58 mm

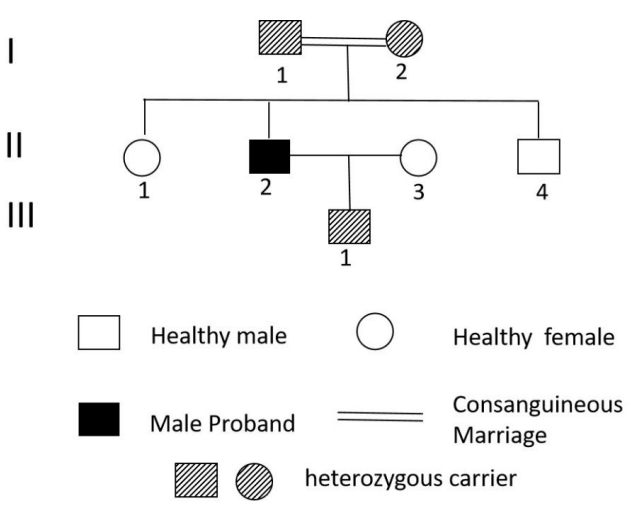

Figure 1. Pedigree of the patient's family.

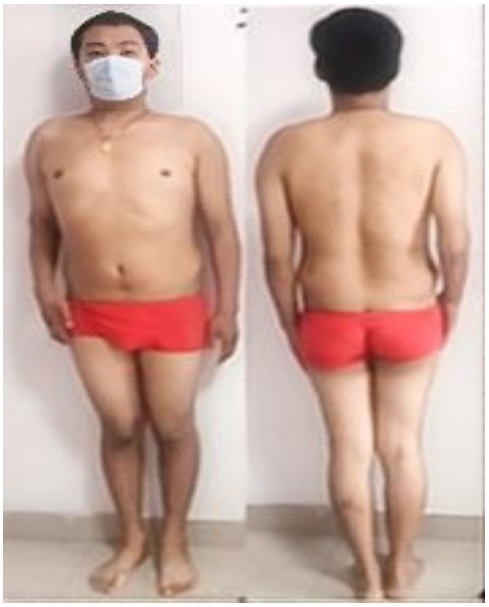

Figure 2. Clinical photograph of the proband's lower legs: Mild bilateral gastrocnemius muscle atrophy is visible; No significant atrophy is observed in other muscle groups.

(normal value < 35 mm), a dilated right ventricle with an internal diameter of 39 mm (normal value < 25 mm), and a dilated right atrium with a transverse diameter of 66 mm (normal value: 30 - 40 mm), indicating generalized cardiac enlargement. The left ventricular ejection fraction (LVEF) was 44%. There was left ventricular hypertrophy accompanied by impaired systolic and diastolic functions. The pulmonary artery was dilated. Moderate tricuspid regurgitation was present, suggesting moderate pulmonary hypertension. A small amount of pericardial effusion was also noted. Electroencephalography (EEG) performed 48 hours after the seizure was normal, without epileptiform discharges. Nerve conduction studies and electromyography showed no myopathic or neurogenic changes.

Cardiac MRI revealed dilation of the right atrium and right ventricle with an increased number of moderator bands in the right ventricle, along with right atrial fibrosis(Figure 3). There were scattered linear and patchy late gadolinium enhancements in the inferior wall of the left ventricle. The left atrium was slightly enlarged, and the left ventricular myocardium was mildly and homogeneously thickened. Brain MRI was performed to investigate the seizure etiology but revealed no structural abnormalities, specifically no evidence of cortical dysplasia or polymicrogyria typically seen in FCMD (Figure 4).

Open biopsy of the left gastrocnemius showed mild variation in muscle fiber diameter, increased internalized nuclei, and scattered necrotic fibers without regenerative basophilia. No inflammatory infiltrates were identified in hematoxylin–eosin staining (Figure 5A-B). Oil Red O were negative for lipid or glycogen accumulation (Figure 5C). Modified Gomori trichrome (MGT) staining showed no ragged-red fibers or rimmed vacuoles (Figure 5D).

Targeted next-generation sequencing of neuromuscular disease–associated genes identified a novel homozygous missense mutation in *FKTN* (NM_001079802.2: c.1271G>A; p.Gly424Asp) located in exon 12, affecting a conserved glycine residue within the fukutin Golgi-targeting domain (Figure 6). This variant was absent from gnomAD, 1000 Genomes, and ExAC East Asian databases. Multiple in silico prediction tools (SIFT, PolyPhen-2, MutationTaster) suggested pathogenicity, and ACMG/AMP criteria classified it as "Likely Pathogenic" (PM1, PM2, PP1, PP3, PP4).

Sanger sequencing confirmed that both parents (I-1, I-2) and the patient's son (III-1) were heterozygous carriers of the c.1271G>A variant, consistent with autosomal recessive inheritance (Figure 7). No other family members exhibited neuromuscular or cardiac symptoms.

Following the diagnosis, the patient was

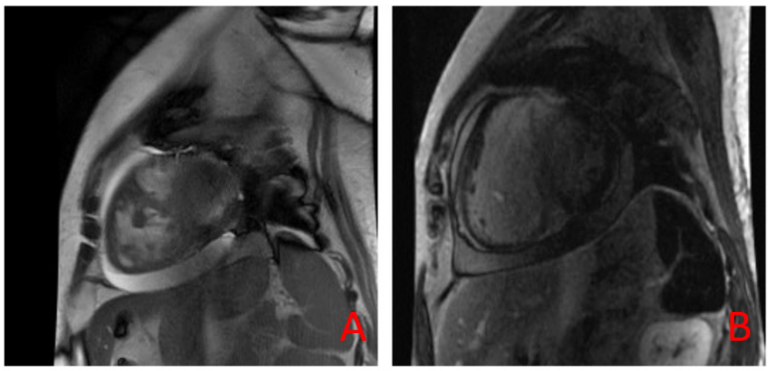

Figure 3. Cardiac MRI findings in the proband: (A) Cardiac cine sequence reveals features consistent with non - compaction cardiomyopathy; (B) Gadolinium - enhanced sequence shows right atrial and right ventricular dilation, an increased number of moderator bands in the right ventricle, and patchy fibrosis in the right atrium.

initiated on standard heart failure therapy, including an ACE inhibitor (enalapril) and a β-blocker (metoprolol), which resulted in significant improvement in cardiac function. Repeat echocardiography after 6 months showed that the left ventricular ejection fraction had increased from 44% to 58%. For seizure prophylaxis, levetiracetam (500 mg twice daily) was administered.

During a 12-month follow-up period, the patient remained seizure-free. Serial neurological examinations showed stable status with no progression of muscle weakness or cognitive decline (Montreal Cognitive Assessment score: 30/30). Repeated video-EEG monitoring at 6 and 12 months revealed no epileptiform discharges.

Written informed consent was obtained from the patient for publication of this report, including all clinical details, genetic findings, medical images, and pedigree data. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University. All personally identifiable information has been anonymized.

DISCUSSION

This report describes the first genetically confirmed case of adult-onset *FKTN*-related disorder in a Chinese patient carrying a novel homozygous *FKTN* mutation (c. 1271G>A, p. Gly424Asp). The clinical phenotype is characterized by predominant DCM and markedly elevated serum CK, consistent with the diagnosis of *FKTN*-related cardiomyopathy. However, the co-occurrence of a late-onset

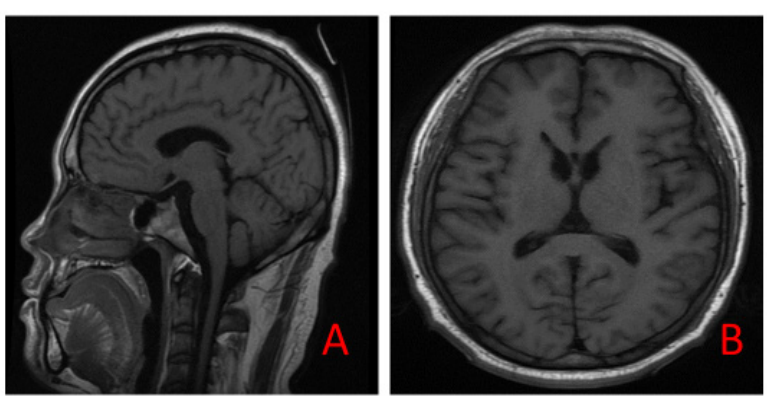

Figure 4. Brain MRI of the proband demonstrating normal structural appearance: (A) Axial T2-FLAIR images; (B) Sagittal T1-weighted images. No evidence of cobblestone lissencephaly, cerebellar cysts, or white matter abnormalities is detected.

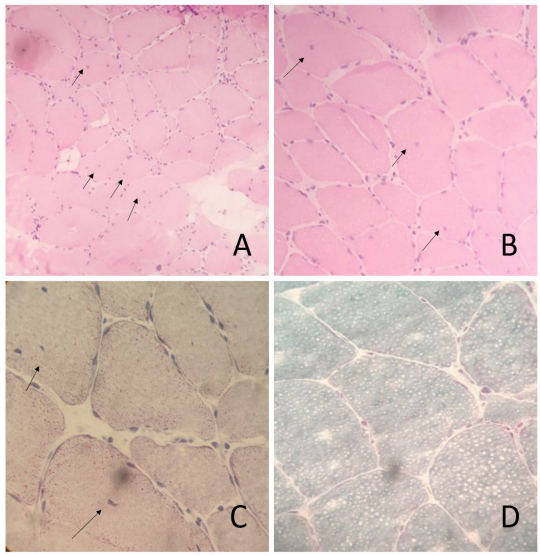

Figure 5. Histopathological findings from left gastrocnemius muscle biopsy: (A) Hematoxylin–eosin (HE) staining, ×100: Mild variation in myofiber diameter with scattered small, round fibers; increased internalized nuclei; (B) HE, ×400: Internalized nuclei and scattered necrotic fibers; (C) Oil Red O (ORO) staining, ×400: No abnormal lipid droplet accumulation; (D) Modified Gomori trichrome (MGT) staining, ×400: No ragged-red fibers or rimmed vacuoles observed.

generalized seizures, in the absence of structural brain abnormalities, distinguishes this case from the classical cardiac-only presentation of adult-onset *FKTN* variants.

To contextualize our findings, we systematically compared our patient's phenotype with previously reported adult-onset *FKTN*-related cardiomyopathy cases (Supplementary Table 1). Notably, all documented cases—including those with founder (e.g., 3-kb insertion) and non-founder mutations (e.g., p.Arg179Thr, p.Gln358Pro)—presented with isolated DCM and elevated CK levels (range: 343–3,000 U/L), but none exhibited seizures

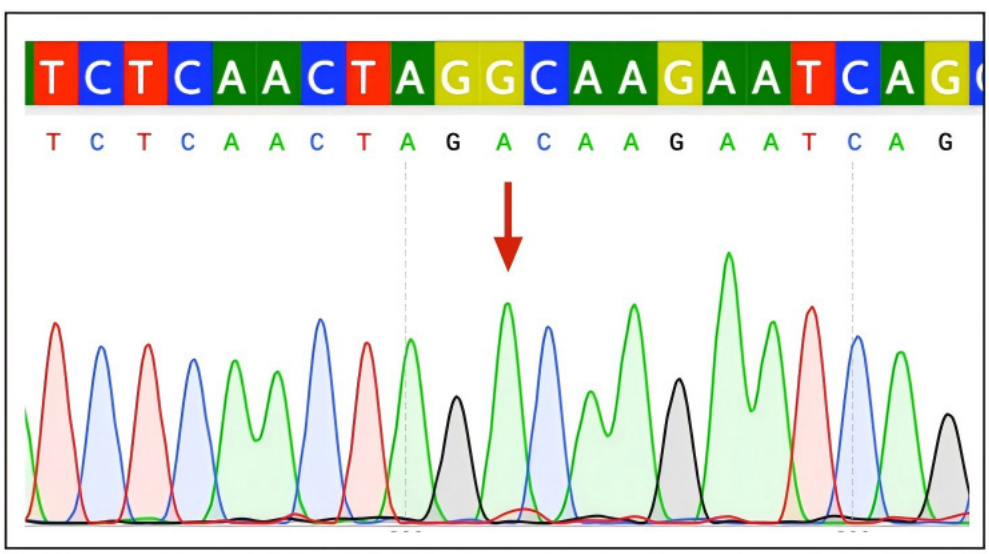

Figure 6. Genetic analysis of the proband by Ampliseq multiplex PCR and next-generation sequencing. The proband (II-2) harbored a homozygous FKTN c.1271G>A (p.Gly424Asp) variant.

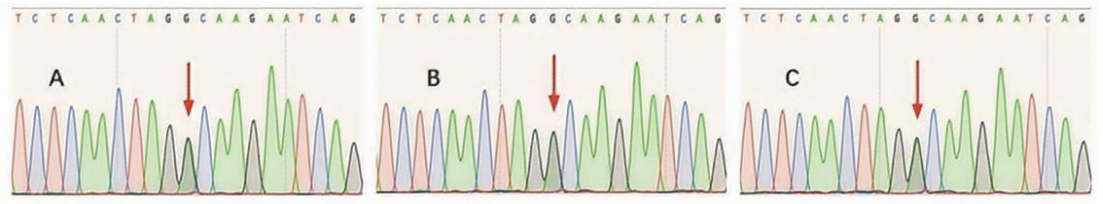

Figure 7. Sanger sequencing for family segregation analysis of the FKTN c.1271G>A variant: (A) Father (I-1): heterozygous variant; (B) Mother (I-2): heterozygous variant; (C) Son (III-1): heterozygous variant. All chromatograms are shown in the forward direction.

or other CNS manifestations. In contrast, our patient's markedly elevated CK (>7,000 U/L) and DCM phenotype align with this cohort, yet the occurrence of a generalized tonic-clonic seizure—absent in all prior cases—represents a novel clinical observation.

The relationship between the *FKTN* variant and the observed seizure warrants cautious interpretation. Classically, seizures in FCMD are attributed to cortical migration defects such as polymicrogyria.[6] However, the absence of structural abnormalities in our patient's brain MRI implies that if the seizure is indeed pathogenetically linked to the *FKTN* variant, it would likely involve non-structural mechanisms rather than cortical malformations. While the seizure could represent an incidental event (lifetime risk: 8–10% in the general population)[7] or transient cerebral hypoperfusion secondary to earlier cardiac decompensation, its timing four months after stable cardiac status makes these explanations less likely. Alternatively, emerging evidence suggests that α-dystroglycanopathy may contribute to functional neuronal dysfunction independent of gross malformations. Hypothetical mechanisms include α-dystroglycan-mediated synaptic instability causing cortical hyperexcitability, or tau hyperphosphorylation disrupting microtubule dynamics, as observed in mild dystroglycanopathy models.[8] This observation is supported by Smogavec *et al*., who documented subclinical EEG abnormalities in an *FKTN* carrier with normal neuroimaging, suggesting that neuronal hyperexcitability can occur without overt anatomical defects.[9]

Regarding treatment, our patient responded favorably to conventional heart failure management with ACE inhibitors and β-blockers, consistent with prior reports in adolescent FCMD cohorts.[10] Seizure control was achieved with levetiracetam, with no recurrence within 12 months. Future therapeutic avenues may include ribitol supplementation, shown to restore α-dystroglycan glycosylation in murine models of *FKRP* deficiency, and adeno-associated virus (AAV)-mediated *FKTN* gene delivery, which improved cardiac function in dystrophic mice.[11,12] Given the likely residual enzymatic activity in adult-onset variants, such interventions could have enhanced efficacy.[13]

Our study has several limitations. First, the absence of functional assays precludes definitive confirmation of the p.Gly424Asp variant's pathogenic impact on fukutin function. Second, while the muscle biopsy revealed non-specific histopathological changes, immunohistochemical analysis of α-dystroglycan glycosylation could not be performed due to specimen exhaustion after routine diagnostic staining; the patient declined a repeat biopsy, precluding further mechanistic studies of dystroglycanopathy. Third, the 12-month follow-up period may be insufficient to assess long-term cardiac and neurological outcomes, particularly the potential recurrence of seizures or progression of cardiomyopathy. Larger cohort studies with extended follow-up are needed to validate the association between this variant and seizure susceptibility.

In summary, we report a novel *FKTN* variant associated with adult-onset dilated cardiomyopathy and a seizure event in a Chinese patient. This case highlights the importance of including *FKTN* in the genetic panel for adults with unexplained cardiomyopathy and elevated CK. While the association with seizures requires further validation in larger cohorts, clinicians should be aware of potential neurological involvement even in the absence of structural brain defects.

REFERENCES

1. Lee SJ, Joo HJ, Jo DH, *et al.* Ophthalmologic manifestations associated with Fukutin (FKTN) variant subtypes in Korean patients with Fukuyama congenital muscular dystrophy: a single-center

retrospective case series. *BMC Ophthalmol* 2025. 25(1): 616. DOI: 10.1186/s12886-025-04432-x.
2. Kobayashi K, Kato R, Kondo-Iida E, *et al.* Deep-intronic variant of fukutin is the most prevalent point mutation of Fukuyama congenital muscular dystrophy in Japan. *J Hum Genet* 2017. 62(11): 945-8. DOI:10.1038/jhg.2017.71.
3. Abhishek P, Reddy KS, Khaleel MA. Diagnosing a cobblestone lissencephalic malformation with other associated disorders in a tier II tertiary referral center. *Int J Curr Pharmaceutic Rev Res* 2025; 17(6): 56-9. DOI: 10.1038/jhg.2017.71.
4. Safwat S, Flannery KP, El Beheiry AA, Mokhtar MM, Abdalla E, Manzini MC. Genetic blueprint of congenital muscular dystrophies with brain malformations in Egypt: A report of 11 families. *Neurogenetics* 2024. 25(2): 93-102. DOI: 10.1007/s10048-024-00745-z.
5. Sugiyama R, Takeshita E, Shimizu-Motohashi Y, Komaki H. Holter electrocardiography findings in Fukuyama congenital muscular dystrophy. *Neuromuscul Disord* 2025; 46:105273. DOI: 10.1016/j.nmd.2024.105273.
6. Bouzková K, Kubánek M, Krebsová A, *et al.* Fukutinopathy as a rare cause of dilated cardiomyopathy and subclinical skeletal myopathy – a case report and review of cardiac involvement in skeletal muscle disease. *Cor et Vasa* 2022; 64:468-73. DOI: 10.33678/cor.2021.119.
7. Pohlmann-Eden B, Beghi E, Camfield C, Camfield P. The first seizure and its management in adults and children. BMJ 2006; 332(7537): 339-42. DOI: 10.1136/bmj.332.7537.339.
8. Jahncke JN, Miller DS, Krush M, Schnell E, Wright KM. Inhibitory CCK+ basket synapse defects in mouse models of dystroglycanopathy. *bioRxiv* 2023: 2022.01.26.477791. DOI: 10.1101/2022.01.26.477791.
9. Smogavec M, Zschüntzsch J, Kress W, *et al*. Novel fukutin mutations in limb-girdle muscular dystrophy type 2M with childhood onset. *Neurol Genet* 2017; 3(4): e167. DOI: 10.1212/NXG.0000000000000167.
10. Nakanishi T, Sakauchi M, Kaneda Y, *et al*. Cardiac involvement in Fukuyama-type congenital muscular dystrophy. *Pediatrics* 2006; 117(6): e1187-e1192. DOI: 10.1542/peds.2005-2469.
11. Gicquel E, Maizonnier N, Foltz SJ, *et al.* AAV-mediated transfer of FKRP shows therapeutic efficacy in a murine model but requires control of gene expression. *Hum Mol Genet* 2017; 26(10): 1952-65. DOI: 10.1093/hmg/ddx066.
12. Wu B, Lu PJ, Drains M, *et al*. Ribitol treatment rescues dystroglycanopathy mice with common L276I mutation. *PLoS One* 2025; 20(8): e0325239. DOI: 10.1371/journal.pone.0325239.
13. Cataldi MP, Vannoy CH, Blaeser A, *et al*. Improved efficacy of FKRP AAV gene therapy by combination with ribitol treatment for LGMD2I. *Mol Ther* 2023; 31(12): 3478-89. DOI: 10.1016/j.ymthe.2023.10.022.

Supplementary Table 1. Summary of Adult-Onset Cardiac-Predominant or Cardiomyopathy-Associated *FKTN*-Related Cases

Author (Year)	Patient / Cohort	Age at Onset (Years)	FKTN Genotype (Founder vs. Non-founder)	Seizures/ Epilepsy (Yes/No)	Serum CK Level (U/L)	Brain MRI Findings
Present Case (2024)	Chinese male	31 (Acute heart failure)	**Homozygous**: c.1271G>A (p.Gly424Asp) **missense mutation (Non-founder)**	**Yes** (Generalized tonic-clonic seizures)	**>7,000** (Markedly elevated)	**No structural abnormalities**
Murakami et al. (2006) Patient 1 [1]	Japanese male	17 (DCM onset)	**Compound heterozygous**: **3-kb insertion (Founder)** + c.1073A>C (p.Gln358Pro) **missense (Non-founder)**	Not reported	400–3,000 (Range)	Not reported
Murakami et al. (2006) Patient 2 [1]	Japanese female	20 (DCM onset)	**Compound heterozygous**: **3-kb insertion (Founder)** + c.1073A>C (p.Gln358Pro) **missense (Non-founder)**	Not reported	1,500–1,800 (Range)	Not reported
Murakami et al. (2006) Patient 3 [1]	Japanese female	46 (DCM onset)	**Compound heterozygous**: **3-kb insertion (Founder)** + c.536G>C (p.Arg179Thr) **missense (Non-founder)**	Not reported	1,200–2,000 (Range)	Not reported
Murakami et al. (2006) Patient 4 [1]	Japanese female	30 (DCM onset)	**Compound heterozygous**: **3-kb insertion (Founder)** + c.536G>C (p.Arg179Thr) **missense (Non-founder)**	Not reported	1,139	Not reported
Matsui et al. (2015) [2]	Japanese male	23 (DCM onset)	**Compound heterozygous**: **3-kb insertion (Founder)** + c.536G>C (p.Arg179Thr) **missense (Non-founder)**	**No** (Not reported)	343	Not reported

Note: Adult-onset was defined as symptom appearance at ≥16 years of age.

References

[1] Murakami T, Hayashi YK, Noguchi S, et al. Fukutin gene mutations cause dilated cardiomyopathy with minimal muscle weakness. ANNALS OF NEUROLOGY. 2006. 60(5): 597-602.

[2] Matsui M, Endo T, Matsumura T, Saito T, Fujimura H. [A case of limb-girdle muscular dystrophy 2M diagnosed by the occurence of dilated cardiomyopathy]. Rinsho shinkeigaku = Clinical neurology. 2015. 55(8): 585-8.