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Possible founder variant and spectrum of phenotypic manifestations of Fukuyama congenital muscular dystrophy in five unrelated families in Pakistan: A case series

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Abstract

Fukuyama congenital muscular dystrophy (FCMD) is a rare autosomal recessive dystroglycanopathy caused by pathogenic/likely pathogenic (P/LP) variants also known as mutations in the *FKTN* gene, typically presenting in early childhood with hypotonia, progressive muscle weakness, and variable central nervous system and cardiac involvement. This case series describes five male patients from consanguineous families in different regions of Pakistan, all presenting with features of a progressive muscular dystrophy. Genetic analysis revealed a homozygous pathogenic missense variant, *FKTN*, NM_001079802.1 c.920G>A (p.R307Q), in all five patients, suggesting the presence of a possible founder variant. Despite sharing the same genetic mutation, the patients exhibited significant clinical heterogeneity. This report adds to the limited literature on FCMD in South Asia and emphasizes the phenotypic variability of the disorder, particularly its cardiac manifestations. The development of cardiomyopathy is not uncommon, hence regular cardiac monitoring is crucial. Early genetic diagnosis is vital for appropriate clinical management and genetic counseling in populations with high rates of consanguinity.

Keywords: Muscular dystrophy, fukutin gene, genetic testing, consanguinity, dystroglycan

INTRODUCTION

Congenital Muscular Dystrophies (CMDs) are a group of hereditary disorders primarily affecting the striated muscles, with the pathology being dystrophic in nature. Clinically, they are characterized by hypotonia and muscle weakness that manifests before the development of independent ambulation, resulting in delays or complete arrest in the achievement of motor milestones.[1] The overall prevalence of CMDs is estimated to be 0.6–0.9 per 100.000, with majority of CMDs having an autosomal recessive pattern of inheritance.[2]

Dystroglycan is a component of the dystrophin glycoprotein complex (DGC), which is essential to link the extracellular matrix to the intracellular actin cytoskeleton. Gene abnormalities in alpha-glycosylation pathway of dystroglycan results into a broad category of alpha-dystroglycan related dystrophies, which holds an expanded clinical horizon ranging from syndromic CMDs with severe central nervous system manifestations (including Walker Warberg Syndrome (WWS), Fukutin CMD and Muscle-Eye-Brain disease) to a presentation mimicking limb girdle muscular dystrophy.[3] Phenotypic variability in alpha-dystroglycan related dystrophies is explained by the fact that a single gene may lead to several phenotypes due to the level of glycosylation, leading to prominent proximal muscle weakness, with variable cerebral or ocular involvement.[4]

Fukuyama congenital muscular dystrophy (FCMD), resulting from mutations in *FKTN* causes a deficiency in alpha-dystroglycan which leads to dysfunction in muscle integrity, cortical histogenesis and normal ocular development.[5] *FKTN* encodes the protein- Fukutin, which serves as a ribitol phosphate transferase. The defect in this gene leads to variations in the O-mannose-type sugar chain of dystroglycan.[6]

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This causes impaired binding of laminin and other extracellular matrix components within the basal membrane, leading to disruption in the integrity of myocyte with eventual culmination into muscle fiber degeneration and necrosis.[7]

About half of the cases of FKTN associated muscular dystrophy are reported with severe central nervous system involvement; clinically presenting as intellectual disability and seizure disorders. Consistent with the genotype-phenotype correlation, certain protein-truncating variants result in a more severe phenotype compared to variants caused by a missense variant. Historically, these pathogenic/likely pathogenic (P/LP) variants were first reported in Eastern Asia, particularly in Japan due to the discovery of a founder variant within this population.[8] Currently, it is the second most common form of muscular dystrophy after Duchenne Muscular Dystrophy (DMD) in Japan with an incidence of around 0.7-1.2 cases per 100,000 children.[9]

This case series aims to describe the clinical and genetic features of FCMD in five Pakistani patients. While the core features are consistent with those reported globally, this series is unique in being one of the first genetically confirmed FCMD reports from South Asia and highlights remarkable phenotypic variability, especially in cardiac involvement, underscoring the need for early genetic testing and counseling in highly consanguineous populations.

METHODS

This retrospective case series includes five patients diagnosed with FCMD at Aga Khan University Hospital Karachi, Pakistan. Patient data were collected from medical records, including demographic information, clinical presentation, laboratory investigations, genetic testing, and disease progression. Diagnosis was established by a trained neurologist and genetic specialist and was based on clinical presentation and results from genetic testing. Ethical approval was obtained from the institutional review board, and informed consent was acquired from patients or their guardians where required.

Patient 1

An 11-month-old boy was referred to our clinic due to delay in motor milestones. Prior to the diagnosis, the patient was able to hold his neck up and sit without support but struggled to rise independently from a sitting position. Patient's anthropometric measurements indicated a healthy weight and height above the 50th percentile. Birth history revealed an uneventful full-term delivery via elective cesarean section due to a breech presentation, with no reported complications. The patient, who had a birthweight of 2.5kg, is the younger of two siblings from a consanguineous union, with no reported family history of congenital conditions (Figure 1). Clinical examination revealed visible calf hypertrophy without fasciculations, accompanied by intact deep tendon reflexes. Laboratory investigations showed elevated serum creatine kinase (CK) levels at 3300 IU/L (normal < 200 IU/L). MLPA testing for DMD revealed no deletions or duplications. Subsequent electromyography (EMG) and nerve conduction studies revealed no abnormal findings. Echocardiography was normal. Patient was advised to have neurorehabilitation and follow-up.

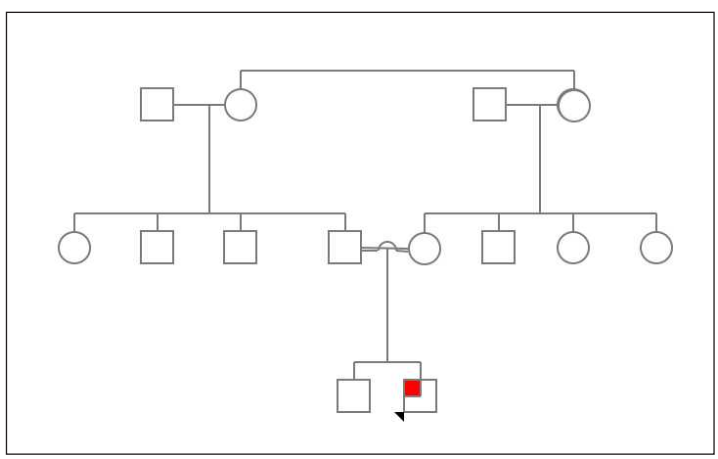

Figure 1. Pedigree of Patient 1.

Patient 2

This patient presented at the age of 6 years with symptoms of proximal weakness in all four limbs and a non-progressive gait abnormality. He also had bilateral inversion contractures of the feet, necessitating the use of ankle-foot-orthoses for mobility assistance. Motor milestones were notably delayed. Anthropometric assessment revealed the patient to be below the 3rd percentile for weight-for-age and slightly above the 3rd percentile for height-for-age. Born into a consanguineous union, he was the only affected individual amongst the siblings (Figure 2). Despite initiating walking at the age of 2 years, symptoms of frequent tripping and difficulty climbing stairs were reported. Clinical examination revealed thin limbs in proportion to height in addition to weakness. Additionally, the patient exhibited a high-arched palate, bilateral facial weakness, mild scapular winging and exaggerated lumbar lordosis. There was no history of abnormal movements, seizures, or cognitive impairments. Laboratory investigations revealed elevated serum CK levels at 4409 IU/L (normal < 200 IU/L). While an echocardiogram was recommended for monitoring cardiac function, results were not available at the time of this report.

Patient 3

The third patient was an 18-year-old male, who presented with progressive weakness in his limbs, making walking and standing from a seated position difficult. These symptoms began around the age of 10 years. He also experienced mild dyspnea and chest heaviness during exertion, along with generalized body aches. He was at the 20th percentile for his height but well below the 3rd percentile for weight. He had an unremarkable antenatal and birth history. This patient was the youngest of three siblings born to a consanguineous couple with both older siblings exhibiting similar clinical manifestations and age of symptoms onset (Figure 3). Clinical examination revealed significant lower limb atrophy, rendering the patient unable to walk without external support. Echocardiography was indicative of dilated cardiomyopathy, with an ejection fraction of 30%. However, serum CK levels were within normal limits at 110 IU/L. Patient was advised supportive care and follow-up with a cardiac specialist.

Patient 4

Another male, 22 years old, was referred to the genetics clinic from the cardiology department due to dilated cardiomyopathy with ejection fraction of 20%. He had complaints of dyspnea and orthopnea starting at the age of 20 years. He also reported difficulty in walking, characterized by tip-toeing due to distal limb weakness that started manifesting around the age of 16, resulting in severe limitation in walking. Patient 4 was the third of the four siblings born to a consanguineous union and the first to exhibit symptoms, followed shortly by his younger sister, who presented with similar features (Figure 4). Serum CK levels were elevated at 1227 IU/L (normal < 200 IU/L) upon investigation. He was advised to do rehabilitation and follow-up.

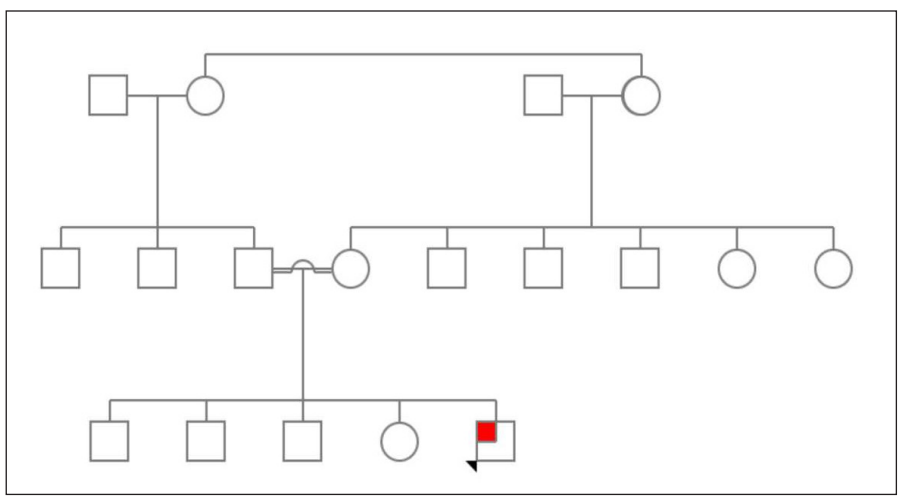

Figure 2. Pedigree of Patient 2.

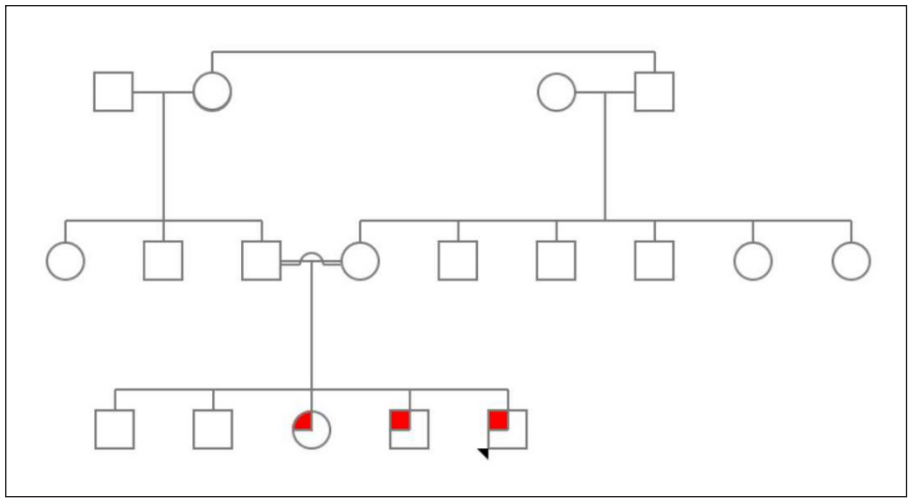

Figure 3. Pedigree of Patient 3.

Case 5

This patient was a 17-year-old male presented with generalized muscle weakness that began progressively at the age of 3. He reported profound weakness, particularly in the proximal upper limbs. Later, he also developed difficulty in climbing stairs and rising from seated position. He was diagnosed initially as having DMD, based on clinical grounds. The severity of his symptoms increased until the age of 12. Additionally, he experienced shortness of breath, prompting consideration for echocardiography. Anthropometric evaluation revealed the patient's stature and weight to be approximately in the 15th and 10th percentiles, respectively. He was the youngest of four siblings born to a non-consanguineous couple in two of his first paternal cousins having similar symptoms (Figure 5). Serum CK levels were elevated at 753 IU/L (normal < 200 IU/L), and echocardiography revealed findings consistent with dilated cardiomyopathy, characterized by a reduced ejection fraction of 15%. The patient's condition eventually progressed to acute decompensated heart failure.

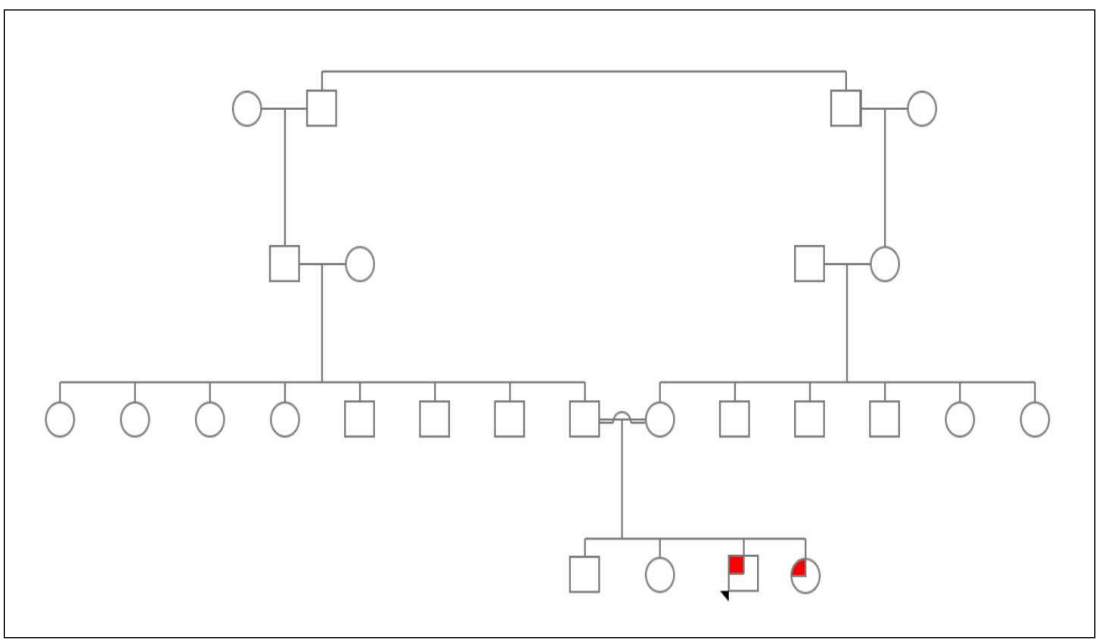

Figure 4. Pedigree of Patient 4.

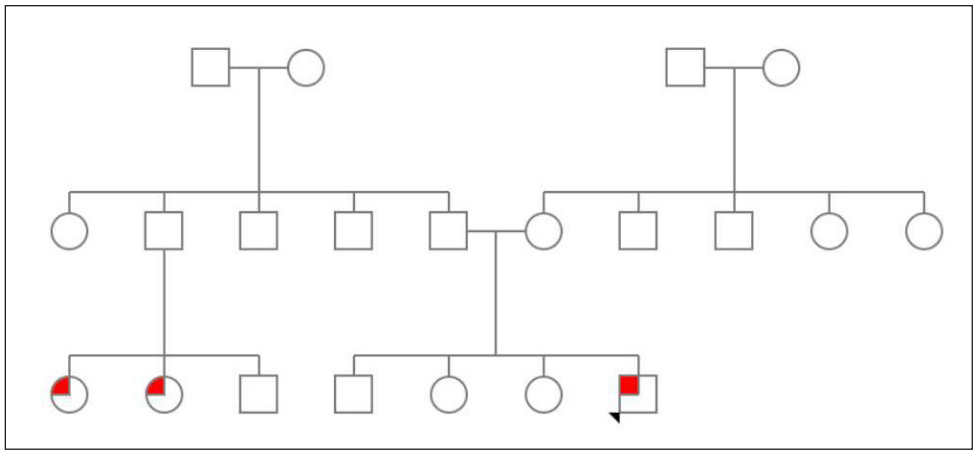

Figure 5. Pedigree of Patient 5.

All five patients harbored homozygous, well-established pathogenic missense variant, *FKTN*, NM_001079802.1 c.920G>A (p.R307Q), (gnomAD MAF 0.001204%, rs119463992), leading to a diagnosis of FCMD. Table 1 shows a summary of cases of FCMD with their demographics and clinical presentation.

DISCUSSION

FCMD is a rare and well-recognized autosomal recessive dystroglycanopathy, traditionally linked to specific founder mutations, especially in Japanese populations. A so-called founder variant in *FKTN*, a 3-kb homozygous insertion mutation in the 3′ untranslated region, is present in 87% of individuals with FCMD. Heterozygous P/LP variants, which combine a founder variant with a point mutation, are seen in the remaining cases.[10] Patients who are compound heterozygous for the ancestral variant and a more severe loss-of-function variant on the other allele have a more severe disease severity, whereas patients homozygous for the ancestral Japanese variant (insertion of a retrotransposon) in *FKTN* have a relatively milder phenotype (FCMD).

Our study reports a pathogenic missense variant, *FKTN*, NM_001079802.1 c.920G>A (p.R307Q) (gnomAD MAF 0.001204%, rs119463992), identified in all five patients diagnosed with FCMD from different regions in Pakistan. This finding also provides novel insights into the genetic landscape of FCMD in this population and reinforces the pathogenicity of this specific variant in disease manifestation. The c.920G>A (p.R307Q) variant alters a conserved arginine residue within the protein, which is likely to disrupt its enzymatic function, consistent with prior reports of missense variants in FCMD-associated phenotypes.[11] The discovery of the p.R307Q variation in Pakistani population raises the possibility of ethnic and geographical diversity in the genetic spectrum of FCMD, even though the condition is traditionally linked to founder variants that are common in Japan. This finding is consistent with previous research indicating that, despite their rarity, *FKTN* P/LP variants may be identified outside of Japan, indicating the need for more studies into their distribution and potential phenotypic effects.[12]

The presence of identical variation in all five cases also raises the possibility of a founder effect or shared ancestry among the afflicted people. Our findings suggest the pathogenic function of rs119463992 in FCMD, especially in the South Asian population, given its exceptionally low minor allele frequency (MAF) South Asian = 0.007776%, total across populations= 0.001010%, zero homozygotes) in gnomAD, version 4.1.[13] To clarify its origin and inheritance pattern in this cohort, more research would be helpful, including haplotype analysis and segregation studies.

Interestingly, despite the similar genotype, patients exhibit significant phenotypic variability in the clinical presentation. Clinically, the five patients exhibited a spectrum of symptoms ranging from early-onset motor delays to progressive muscular weakness. The severity of the disease appeared to correlate with age, with the older patients exhibiting more pronounced symptoms, including cardiomyopathy. The presence of dilated cardiomyopathy (CMP) in three of the five cases suggests a possible late-onset cardiac involvement in FCMD. This aligns with prior studies that highlight the progressive nature of

Table 1: Summary of cases of Fukuyama CMD

	Age at presentation / Sex	Clinical features	Geographical location	Family history	Creatine kinase IU/l	Presence of cardiomyopathy	Functional status at last follow-up
Patient 1	11m / M	Delay in motor milestones	Sindh	Consanguineous parents. No known affected relatives.	3300	Record not available	Lost to follow-up
Patient 2	10 yrs / M	Delay in motor milestones, Gait difficulty with contractures	Sindh	Consanguineous parents. No known affected relatives.	4409	Record not available	Walking with aid
Patient 3	13 yrs / M	Progressive gait difficulty, Exertional dyspnea	Gilgit / Baltistan	Consanguineous parents. Two elder siblings of the patient had similar presentation.	110	Dilated CMP (EF: 30%)	Expired at age of 16 years
Patient 4	22 yrs / M	Exertional dyspnea & orthopnea, Progressive gait difficulty	Gilgit / Baltistan	Consanguineous parents. One younger sibling of the patient had a similar presentation.	1227	Dilated CMP (EF: 20%)	Lost to follow-up
Patient 5	17 yrs / M	Progressive proximal weakness in upper & lower limbs, Exertional dyspnea	Sindh	Non-consanguineous parents (Hindu). Two paternal cousins of the patient had a similar presentation.	753	Dilated CMP (EF: 15%)	Able to walk few steps only (indoor)

dystroglycanopathies and their impact on cardiac function, necessitating the need for cardiac surveillance.[14,15] Interestingly, the creatine kinase (CK) levels varied widely among the patients, with higher levels observed in younger cases (3300 IU/L in Patient 1 and 4409 IU/L in Patient 2) and relatively lower levels in the older patients (110–1227 IU/L). This pattern is consistent with prior observations in muscular dystrophies, where CK levels are typically elevated in the early stages due to ongoing muscle degeneration but may decline as muscle mass is progressively lost.[16]

In conclusion, this case series underscores the importance of expanding genetic screening beyond traditionally affected populations and integrating molecular diagnostics into neuromuscular disease evaluation in regions with limited prior genetic characterization. Identification of pathogenic *FKTN* variants in South Asian patients emphasizes the need for population-specific databases to improve diagnostic accuracy and genetic counseling for affected families.

DISCLOSURE

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Conflict of interest: None

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