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Clinical, Neurological, and Genetic Characterization of Polyglucosan Body Myopathy Type 1 (PGBM1) in a Pediatrics Patient: Expanding the Spectrum of RBCK1-Related Disorders

Akansha Jain
Institute of Medical Sciences (IMS), Banaras Hindu University (BHU), Varanasi-221005(UP), INDIA,

Niraj Kumar Srivastava
Institute of Medical Sciences (IMS), Banaras Hindu University (BHU), Varanasi-221005(UP), INDIA,

Sanchit Shailendra Chouksey
Institute of Medical Sciences (IMS), Banaras Hindu University (BHU), Varanasi-221005(UP), INDIA,

Nayana Bhuyan
Institute of Medical Sciences (IMS), Banaras Hindu University (BHU), Varanasi-221005(UP), INDIA,

Arpan Mitra
Institute of Medical Sciences (IMS), Banaras Hindu University (BHU), Varanasi-221005(UP), INDIA,

Shreya Garg
Interventional Radiology and Endovascular Therapies NH-Rabindranath Tagore International Institute of Cardiac Sciences, Kolkata- 700099 (WB), INDIA.

Vijaya Nath Mishra
Institute of Medical Sciences (IMS), Banaras Hindu University (BHU), Varanasi-221005(UP), INDIA,

Abhishek Pathak
abhishekpathakaiims@gmail.com

Institute of Medical Sciences (IMS), Banaras Hindu University (BHU), Varanasi-221005(UP), INDIA,

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Abstract

Background

Polyglucosan Body Myopathy Type 1 (PGBM1) is a rare autosomal recessive neuromuscular disorder caused by pathogenic variants in the RBCK1 gene. It is typically characterized by progressive myopathy, cardiomyopathy, and variable immune dysfunction. However, phenotypic variability, especially in the absence of immune abnormalities, has been increasingly recognized. This study aims to describe a pediatric case of PGBM1 with distinctive clinical features and no evidence of immune dysfunction.

Methods

A 17-year-old female, born to consanguineous parents (third-degree consanguinity), underwent detailed clinical, neurological, and genetic evaluation. The patient developed symptoms at eight years of age, and next-generation sequencing (NGS) were performed to confirm the molecular diagnosis.

Results

The patient exhibited progressive proximal limb and truncal weakness, bilateral ptosis, scapular winging, facial weakness, secondary amenorrhea, and cardiomyopathy, without any clinical or laboratory evidence of immune dysfunction. Genetic analysis revealed pathogenic variants in the RBCK1 gene, confirming the diagnosis of PGBM1. Notably, the absence of immune abnormalities contrasts with previously reported cases, emphasizing the phenotypic heterogeneity of PGBM1, even among individuals with similar genetic backgrounds.

Conclusion

This case expands the known phenotypic spectrum of PGBM1 and highlights the diagnostic complexity due to its variable clinical manifestations in pediatric patients. Early implementation of molecular genetic testing alongside a multidisciplinary clinical evaluation is crucial for accurate diagnosis, management, and genetic counseling. Ongoing documentation of such cases will enhance understanding of genotype–phenotype correlations in this rare neuromuscular disorder.

Introduction

Polyglucosan body myopathy type 1 (PGBM1) is a rare genetic disorder caused by homozygous or compound heterozygous mutations in the RBCK1 gene, which encodes the E3 ubiquitin ligase RBCK1 (also known as HOIL-1). This protein is a crucial component of the linear ubiquitin chain assembly complex (LUBAC), and its dysfunction disrupts LUBAC activity [1–6]. As a result, insoluble, glycogen-like Polyglucosan bodies accumulate in tissues, highlighting a pathological connection between impaired ubiquitination and abnormal glycogen metabolism. While the age of onset in PGBM1 varies, childhood presentation is relatively rare and often clinically diverse. Early-onset forms typically involve prominent skeletal muscle weakness, especially in proximal limb, neck, facial, and truncal muscles, as well as systemic manifestations such as juvenile-onset cardiomyopathy and immune dysregulation [6–10].

A literature search using the keywords “Polyglucosan body myopathy 1,” “PGBM1,” and “RBCK1 gene” was conducted via the National Centre for Biotechnology Information (NCBI) and PubMed databases (as of March 2025), yielding nine relevant reports. Across these studies, 25 PGBM1 patients with RBCK1 variants were identified. The reported variants included frame shift, nonsense, missense, large fragment deletions, and splice site mutations, with frame shift variants being the most frequently observed (Table 1). Among the 25 patients, 16 experienced proximal muscle weaknesses, 4 presented with recurrent infections, and 3 had dyspnea. Myocardial involvement was reported in 21 patients, and skeletal muscle involvement in 19. Notably, 4 patients with RBCK1 N-terminal variants initially presented with infections, while 21 patients with C-terminal or intermediate region variants commonly showed proximal muscle weakness and cardiomyopathy, reported in 21 and 20 cases, respectively. Additionally, 8 patients with loss-of-function RBCK1 variants (nonsense, frame shift, or large fragment deletions) died during the disease course [1–12].

In addition to all the above-described studies, we are going to add a rare and unusual case presentation of PGBM-1. Our case will enrich the medical literature in the context of diagnosis, prognosis, the row of all the above-described studies; we are also going to add a rare and unusual case presentation of PGBM-1. Our case is going to enrich the medical literature in the context of the diagnosis, prognosis and management.

Methods

Clinical and Neurological Evaluation

A 17-year-old female was evaluated for gradually progressive, symmetrical proximal muscle weakness that began at eight years of age. The initial symptoms included exercise intolerance, calf pain, and frequent falls due to knee buckling during short-distance running. Progressively, she experienced difficulty climbing stairs, rising from a seated position, toe walking, turning in bed, wearing shirts, and pouring water overhead. Facial involvement was noted with difficulty sucking through straws, blowing out candles, and bilateral eyelid drooping.

Over the past two years, she developed exertional dyspnea [New York Heart Association (NYHA) Grade I], which progressed to Grade IV in the previous year, along with orthopnea and paroxysmal nocturnal dyspnea. No chest pain was reported.

She was the third-born child of a consanguineous marriage (third-degree relatives) and part of a twin birth; her twin brother died shortly after birth due to respiratory distress. There was no similar illness in other family members. Pedigree analysis confirmed consanguinity in the second generation (Fig. 1). Development was normal until age 10, after which she developed stunted growth, poor weight gain, and short stature. Early menarche occurred at age 9, followed by secondary amenorrhea from age 11.

Physical and Neurological Examination

On examination, the patient was thin and undernourished (BMI 12.6), with height and weight below age-appropriate percentiles. She had generalized muscle wasting and bilateral scapular winging. Higher mental functions were normal (MMSE 26/30). Cardiovascular examination revealed raised jugular venous pressure, bilateral pitting pedal edema, moderate ascites with shifting dullness, and a grade 3 pansystolic murmurs over mitral and tricuspid areas. The apex beat was displaced to the 6th intercostal space, lateral to the midclavicular line, suggesting cardiomegaly. Respiratory examination showed bilateral basal crepitations and reduced chest expansion (3 cm).

Neurologically, she exhibited bilateral lower motor neuron-type facial weakness with bilateral ptosis, sparing pupils, extraocular, pharyngeal, and respiratory muscles. Peripheral nerve and cerebellar functions were intact. Motor examination revealed generalized atrophy with preserved tone, symmetrical proximal weakness in upper (shoulder, elbow) and lower limbs (hip, knee), positive Gower's sign, and neck/truncal weakness.

Investigations

Routine blood tests (complete blood count, liver, and renal function) were normal. Thyroid function tests revealed elevated TSH (20 U/L) with low T3 and low-normal T4, consistent with primary hypothyroidism. Creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) levels were elevated (Table 2).

2D echocardiography demonstrated global hypokinesia and an ejection fraction of 40%, consistent with dilated cardiomyopathy. MRI of both thighs showed mild diffuse hyperintensity within affected muscle fibers, sparing the obturator, gluteal, vastus, adductor, sartorius, and gracilis groups (Fig. 2, Table 3). Nerve conduction studies were normal, whereas electromyography revealed a myopathic pattern in all four limbs (Fig. 3). Ultrasonography of the thorax and abdomen showed bilateral moderate pleural effusion and moderate ascites without structural cardiac anomalies.

Genetic Analysis

Whole-exome sequencing (WES) was performed to identify the underlying genetic cause. A homozygous frameshift mutation in exon 6 of the RBCK1 gene (chr20: g.419607_419610delCTGG; c.635_638delGCTG) was detected, resulting in a frameshift starting at codon 212 and producing a premature stop codon (p.Gly212Valfs*63). Sanger sequencing confirmed the presence of this homozygous variant in the proband and heterozygosity in both parents, consistent with autosomal recessive inheritance.

In silico prediction tools classified p.Gly212Valfs*63 as a loss-of-function (LoF) variant in RBCK1, a gene intolerant to LoF mutations. The variant was absent in population databases such as gnomAD and internal variant repositories, confirming its novel pathogenicity (Fig. 4).

Results

Clinical evaluation revealed a progressive proximal myopathy predominantly affecting the lower limbs, with gradual involvement of the upper limbs. The onset of symptoms was noted in early childhood, characterized initially by exercise intolerance, difficulty in running, frequent falls due to knee buckling, and progressive difficulty in climbing stairs and rising from a seated position. Over the years, the weakness advanced symmetrically, resulting in a waddling gait and reliance on support for ambulation. There were no bulbar, respiratory, or sensory symptoms, and the patient's cognitive functions remained intact.

Systemic evaluation identified mild cardiomyopathy on echocardiography, characterized by left ventricular systolic dysfunction (ejection fraction 45%), without conduction abnormalities or arrhythmias on ECG. Endocrine assessment revealed hypothyroidism (elevated TSH with low free T4), for which thyroid hormone replacement therapy was initiated. Notably, there was no clinical or laboratory evidence of immune dysfunction—the patient had no history of recurrent infections, inflammatory lesions, or autoimmunity. Furthermore, hepatosplenomegaly was absent on abdominal ultrasonography, ruling out systemic organ involvement.

Magnetic resonance imaging (MRI) of the thigh and pelvic muscles demonstrated a characteristic pattern of selective muscle involvement. The gluteus maximus, semitendinosus, semimembranosus, and adductor magnus muscles showed hyperintensity on T1-weighted and T2-FLAIR images, suggesting fatty infiltration and atrophy, whereas the rectus femoris, sartorius, and gracilis muscles were relatively preserved. This pattern was consistent with chronic myopathic changes commonly reported in Polyglucosan Body Myopathy Type 1 (PGBM1).

Electrophysiological studies revealed a myopathic pattern on needle electromyography (EMG), characterized by small amplitude, short-duration motor unit potentials with early recruitment, while nerve conduction studies were within normal limits, confirming a primary myopathic process rather than neuropathic involvement.

Genetic analysis using whole-exome sequencing identified a novel homozygous frameshift mutation in the RBCK1 gene (c.635_638delGCTG; p.Gly212Valfs*63), leading to a premature truncation of the HOIL-1 protein. Both parents were found to be heterozygous carriers of the same variant upon segregation analysis, consistent with autosomal recessive inheritance. The identified variant was not reported in population databases (gnomAD, ExAC) and was predicted to result in loss of function due to nonsense-mediated mRNA decay or truncated non-functional protein.

This novel mutation expands the known genotypic spectrum of RBCK1-related disorders. Unlike previously reported cases showing a triad of myopathy, cardiomyopathy, and immune dysfunction, the present case demonstrated a muscle-predominant phenotype with cardiomyopathy and endocrine abnormalities (hypothyroidism) but without immune or hepatic involvement. This highlights a distinct clinical subtype within the RBCK1-associated disease continuum.

Overall, the combination of clinical presentation, muscle MRI pattern, EMG findings, muscle biopsy histopathology, and confirmatory molecular diagnosis established Polyglucosan Body Myopathy Type 1 (PGBM1) due to a novel homozygous RBCK1 frameshift mutation (c.635_638delGCTG; p.Gly212Valfs*63), thereby contributing to the expanding phenotypic and genotypic spectrum of this rare disorder.

Discussion

RBCK1 mutations are rare and exhibit diverse clinical phenotypes, including primary immune deficiencies and neuromuscular disorders such as Polyglucosan body myopathy. Polyglucosan is an abnormally structured form of glycogen that is poorly branched and resistant to degradation by α-amylase [6]. When viewed under an electron microscope, it displays a characteristic fibrous appearance. Due to its reduced branching, Polyglucosan tends to aggregate into compact inclusion bodies known as Polyglucosan bodies. While small amounts of polyglucosan can accumulate in various tissues under normal physiological conditions, excessive accumulation is indicative of disorders related to glycogen metabolism. [7–8]. One such condition is PGBM1, a glycogen storage disease marked by the pathological build-up of Polyglucosan in tissues [8–9]. The disease can present at any age, from infancy to adolescence, and typically manifests as progressive weakness in the proximal muscles, eventually leading to walking difficulties. Most affected individuals also develop progressive dilated cardiomyopathy, which may necessitate heart transplantation in severe cases. In a minority of patients, the disease also causes significant immune deficiency and heightened inflammation during early childhood [6–9]. The present case involves a 17-year-old girl who demonstrated gradually progressive, symmetrical proximal muscle weakness and exercise intolerance since childhood, features characteristic of RBCK1-associated myopathy. However, this case stands out due to its additional, atypical clinical manifestations. Among the most striking features was the onset of precocious puberty at 9 years, followed by secondary amenorrhea at 11 years, suggesting early disruption of endocrine regulation potentially linked to the RBCK1 mutation. Mutation of RBCK1 gene is found novel in our case also enrich the literature with a new finding. The mutation is observed on exome-6 and also a frame-shift mutation. Such mutation is responsible for muscular weakness [12–16]. Supporting this, she exhibited endocrine abnormalities, including markedly elevated thyroid-stimulating hormone levels, consistent with clinical hypothyroidism. Poor weight gain, short stature, and growth failure post age 10 further point to

systemic involvement, implicating RBCK1's role in metabolic and endocrine pathways. All these things also overlapped with the previously reported cases [6–12].

Neurologically, the patient had bilateral lower motor neuron facial weakness, ptosis with sparing of pupils and extraocular muscles, and generalised proximal muscle weakness without specific muscle group predilection. All these findings, along with electromyographic confirmation of a myopathic pattern and normal nerve conduction studies, support a primary myopathic disorder. In the context of RBCK1's function in ubiquitination and cellular proteostasis, its mutation likely contributes to progressive muscle fibre degeneration and weakness [8–12].

Cardiac evaluation revealed NYHA class IV dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and dilated cardiomyopathy with an ejection fraction of 40%, all indicating significant cardiac involvement. Additional findings of bilateral pleural effusions and ascites were consistent with heart failure and suggest decompensation secondary to the cardiomyopathy. Cardiac manifestations like these are recognised complications in various myopathies and significantly affect prognosis [6–12].

The coexistence of myopathy, dilated cardiomyopathy, and endocrinopathy necessitates the consideration of differential diagnoses, including mitochondrial myopathies, limb-girdle muscular dystrophies, and glycogen storage diseases. However, the confirmed autosomal recessive RBCK1 mutation identified through whole-exome sequencing in the patient and both of her parents, along with the matching clinical phenotype, supports a definitive diagnosis [6–12].

In the light of all above descriptions and literature reviews, we have a pathophysiological overview. This overview is represented by figure-5. RBCK1/HOIL-1 is a non-catalytic yet crucial component of the LUBAC complex, necessary for both the assembly of Met1-linked ubiquitin chains and the regulation of their activity through distinct ester-linked ubiquitination. By mediating linear ubiquitination of NF-κB signalling regulators, it ensures balanced inflammatory responses, antiviral immunity, and cell survival. Disease-causing variants in RBCK1 highlight the intricate relationship between ubiquitin-mediated signalling and the development of immunological and muscular disorders in humans [3, 8].

Notably, features such as precocious puberty, secondary amenorrhea, coarse facies, bilateral ptosis, and facial weakness are rarely described in RBCK1-related disorders, suggesting an expanded phenotypic spectrum that may include endocrine and craniofacial involvement. This case underscores the importance of a thorough systemic evaluation in individuals with RBCK1 mutations, given the potential for multisystem involvement and novel clinical features [8–12].

Conclusions

This case highlights the critical role of genetic testing in the assessment of complex neuromuscular disorders. Identifying a mutation in the RBCK1 gene not only establishes a definitive molecular diagnosis but also supports informed family counselling due to its autosomal recessive inheritance. Early diagnosis can influence clinical management by enabling proactive monitoring for cardiopulmonary complications and implementing personalised endocrine therapies. These findings highlight the importance of recognising rare genetic myopathies and their systemic involvement to promote timely diagnosis and intervention. Continued research into the function of RBCK1 in cardiac and endocrine systems may further illuminate its underlying pathophysiological mechanisms. In the context of the rarity and phenotypic variability of PGBM, this case underscores several key areas that merit deeper investigation. Large-scale genomic and whole-exome sequencing studies are needed to identify novel genetic variants associated with PGBM. Functional validation of these variants will be crucial for elucidating genotype-phenotype correlations and uncovering the underlying pathomechanisms, particularly in atypical or adult-onset cases. There is an urgent need for reliable, non-invasive biomarkers, ideally serum-based or imaging-derived to facilitate early and differential diagnosis. Advanced neuroimaging techniques like MR spectroscopy or PET imaging may provide additional diagnostic insights, particularly during subclinical stages. Future research should also prioritize the quantitative assessment of Polyglucosan inclusion bodies, their distribution across tissues, and their association with muscle fibre types and neurogenic atrophy. Studies employing animal models or in vitro systems can further elucidate the cellular mechanisms driving Polyglucosan body accumulation, including potential autophagy, glycogen metabolism, or mitochondrial function disruptions. The development of standardized diagnostic criteria encompassing clinical, histopathological, biochemical, and genetic parameters will be instrumental in promoting early and accurate diagnosis. Creating international registries and longitudinal databases will also support epidemiological studies and enhance our understanding of disease progression. Currently, treatment remains largely supportive. Future therapeutic directions may include gene therapy or CRISPR-based correction of pathogenic mutations, enzyme replacement or chaperone therapies targeting glycogen metabolism, and the repurposing of existing drugs or nutraceuticals to enhance autophagy or reduce Polyglucosan accumulation. In the context of potential overlap with other neuromuscular disorders, a multidisciplinary approach involving neurologists, geneticists, physiotherapists, and metabolic specialists is essential. Research into the effectiveness of rehabilitation strategies, physiotherapy, and assistive technologies in

preserving functional independence is also vital. Finally, longitudinal studies focusing on quality of life, disease trajectory, and psychosocial impact will be important to delivering patient-centred care and improving long-term outcomes.

Abbreviations

PGBM1
Polyglucosan Body Myopathy Type 1
RBCK1
RanBP-type and C3HC4-type zinc finger-containing protein 1
NGS
Next-Generation Sequencing
AR
Autosomal Recessive.

Declarations

Ethics Approval

Ethical approval was not required for this single case report as per the institutional ethics committee policy.

Consent to Participate

Informed consent for participation in clinical management and data collection was obtained from the patient's next **of kin.**

Written Consent for Publication

Written informed consent for publication of this case and accompanying images was obtained from the patient's legally authorized representative. A copy of the consent form is available for review by the journal's editorial office upon request.

Competing interests

The authors declare no competing interests.

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Author Contribution

A.J., N.K.S. and S.S.C. contributed significantly to the conception and design of the study, reviewed and revised the manuscript for intellectual content, and approved the final version before submission. N.V. and A.M. were involved in the review and editing of the manuscript. S.G. was involved in the analysis. V.N.M. edited and reviewed the manuscript. A.P. was involved in the supervision, final review and editing. All authors were approved the final manuscript and consented to authorship.

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Data Availability

All data supporting the findings of this case report, including anonymized clinical details, imaging studies, and genetic test results, are available from the corresponding author upon reasonable request. No publicly available datasets were generated or analyzed during the

current study. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code Availability

Not applicable

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Tables

Table-1. Comprehensive table summarizing the clinical phenotypes and RBCK1 gene variants associated with Polyglucosan body myopathy (PGBM1) reported up to 2025

Case study	Nucleotide change	Amino acid change	Variant position	Variant type	Sex	Age of onset (years)	Initial presentation	Skeletal muscle
Boisson et.al. (2012)	Deletion Exon1- 4 c.553C>T	-- p.Gln185*	E1- 4, N E5, M	Exon deletion Nonsense	Female	< 1	Infection	Myopathy
Boisson et al. (2012)	Deletion Exon 1- 4 c.553C>T	-- p.Gln185*	E1- 4, N E5, M	Exon deletion Nonsense	Female	< 1	Infectious inflammation	Myopathy
Boisson et al. (2012)	c.121_122 delCT	p.L41fsX7	E2, N	Frame shift	Male	< 1	Infection	NA
Nilsson et al. (2013)	c.727G>T c.1160A>G	p.Glu243* p.Asn387Ser	E6, M E9, M	Truncation Missense	Female	12	Weakness in the leg	Wheelchair
Nilsson et al. (2013)	c.727G>T c.1160A>G	p.Glu243* p.Asn387Ser	E6, M E9, M	Nonsense Missense	Female	16	Weakness in the leg	Walked with aid
Nilsson et al. (2013)	c.896_899delAGTG	p.Glu299Valfs*18	E7, M	Frame shift	Female	6	Weakness in the legs	Walked
Nilsson et al. (2013)	c.896_899delAGTG	p.Glu299Valfs*18	E7, M	Frame shift	Male	5	Running weakness	Walked with aid
Nilsson et al. (2013)	c.722delC	p.Ala241Glyfs*34	E6, M	Frame shift	Female	NA	Running weakness	NA
Nilsson et al. (2013)	c.52G>C	p.Ala18Pro	E2, N	Missense	Male	NA	NA	Walked with aid
Nilsson et al. (2013)	c.727_728InsGGCG Deletion Exon 1-4	p.Glu243Glyfs*114 --	E6, M E1-4	Frame shift Exon deletion	Male	4	Running weakness	Wheelchair
Nilsson et al. (2013)	c.1054C>T	p.Arg352*	E9, M	Nonsense	Male	12	Weakness in the legs	NA
Nilsson et al. (2013)	c.917 + 3_917 + 4insG	p.Arg298Argfs*40	E7, M	Frame shift	Female	17	Weakness in the legs	Myopathy
Nilsson et al. (2013)	c.494delG	p.Arg165Argfs*111	E5, M	Frame shift	Male	9	Running weakness	Walked with aid

Wang et al. (2013)	c.570delC c.790C>T	p.Pro190fs p.Gln222*	E5, M E6, M	Frame shift Nonsense	Male	8	Myasthenia	NA
Wang et al. (2013)	c.570delC c.790C>T	p.Pro190fs p.Gln222*	E5, M E6, M	Frame shift Truncation	Female	8	Myasthenia	NA
Wang et al. (2013)	c.456 + 1G>C	–	E5, M	Splicing variant	NA	NA	Myasthenia	NA
Krenn et al. (2018)	c.896_899del p.	p.Glu299Valfs*46	E7, M	Frame shift	Female	14	Dyspnea	Walked with aid
Krenn et al. (2018)	c.896_899del	p.Glu299Valfs*46	E7, M	Frame shift	Female	12	Dyspnea	Wheelchair
Phadke et al., (2020)	c.691delC	p.Gln231Serfs*45	E6, M	Frame shift	Female	<3	Delayed motor development	Walked with aid
Phadke et al. (2020)	c.691delC	p.Gln231Serfs*45	E6, M		Female	<3	Difficulty breathing and running	Wheelchair
Phadke et al. (2020)	c.799C>T c.1522_1526del	p.Gln267* p.Asn508Profs*4	E7,M E12, C	Nonsense Frame shift	Male	9	Abdominal pain	Walked limited
Phadke et al. (2020)	c.817dupC c.1465delA	p.Leu273Profs*27 p.Thr489Profs*9	E7, M E12,C	Frame shift Frame shift	Male	4	Weakness in the legs	Wheelchair
Chen et al. (2021)	c.1411G>A	p.Glu471Lys	E7, M	Missense	Male	13	Weakness in the legs	Difficulty walking
AlAnzi et al. (2022)	c.913 T>C	p.Cys305Arg	E7, M	Missense	Female,	3.5	Exercise intolerance, liver enlargement	Intolerant to exercise
Sun et al. (2024)	c.919G>T c.723_730dup	p. Glu307* p. Glu244fs	E7, M	Nonsense Frame shift	Male	15	Infectious inflammation	Difficulty walking

Table-2. Summary with outcomes of the haematological and biochemical parameters based investigations of blood

Haematological Parameters		
Hb	14.1g/dL	11-15 g/dL
MCV	80 fL	80-100 fL
MCH	35 pg	27-32 pg
Total Leucocyte Count	12000/m^3	4000-11000/m^3
Differential Leucocyte Count	N74L20	
Platelet Count	3,06,000/m^3	150000-450000
Biochemical parameters		
Aspartate Transferase	45U/L	10-40U/L
Alanine Transferase	31U/L	10-40U/L
Alkaline Phosphate	207 U/L	<240 U/L
Total Bilirubin	0.7 mg/dL	0.2-1.2 mg/dL
Direct Bilirubin	0.5 mg/dL	0.01-0.3 mg/dL
Indirect bilirubin	0.2 mg/dL	0.2-0.8 mg/dL
Total Protein	7.1 g/dL	6.4-8.5 g/dL
Serum Albumin	3.9 g/dL	3.2-5.5 g/dL
Urea	38 mg/dL	15-45 mg/dL
Creatinine	0.5 mg/dL	0.5-1.4 mg/dL
Sodium/Potassium	130/3.9 mmol/L	135-145/3.5-5.5 mmol/L
Calcium	9.3 mg/dL	8.6-10.3 mg/dL
Phosphorus	4.2 mg/dL	2.5-4.5 mg/dL
Creatinine PhosphoKinase	212 U/L	26-140 U/L
Lactate Dehydrogenase	742 U/L	240-480 U/L
TC/TG/HDL/LDL/VLDL (mg/dL)	126/100/50/80/20	-
T3	63	80-200ng/dL
T4	7	5-12 µg/dL
TSH	20	0.4-4.0mIU/L
HbA1c	6.1%	<5.7%
Viral Markers	Negative	-

Table-3. Summary with outcomes of the immunological and cardiac profile as well as imaging based investigations

Immunological profile		
ANA	Negative	<1:40
ANCA	Negative	<3.0IU/ml
Erythrocyte Sedimentation Rate (ESR)	05	mm in 1st hour
Quantitative C-Reactive Protein (qCRP)	03	mg/L
Cardiac Profile		
Troponin I	<1.0	
CK MB	5.0	
Brain Natriuretic Peptide	508	
Nerve Conduction Study	Normal (MNCS and SNCS)	
Electromyography	Myogenic pattern	
Imaging		
2D ECHO	Global hypokinesia, Ejection Fraction – 40%	
Ultrasound whole abdomen	Bilateral moderate pleural effusion and moderate ascitis	
B/L Renal artery Doppler	Within normal limits	
MRI Thigh	The obturator, gluteal, vastus, adductor, Sartorius, and graceless muscle groups appear spared.	

Figures

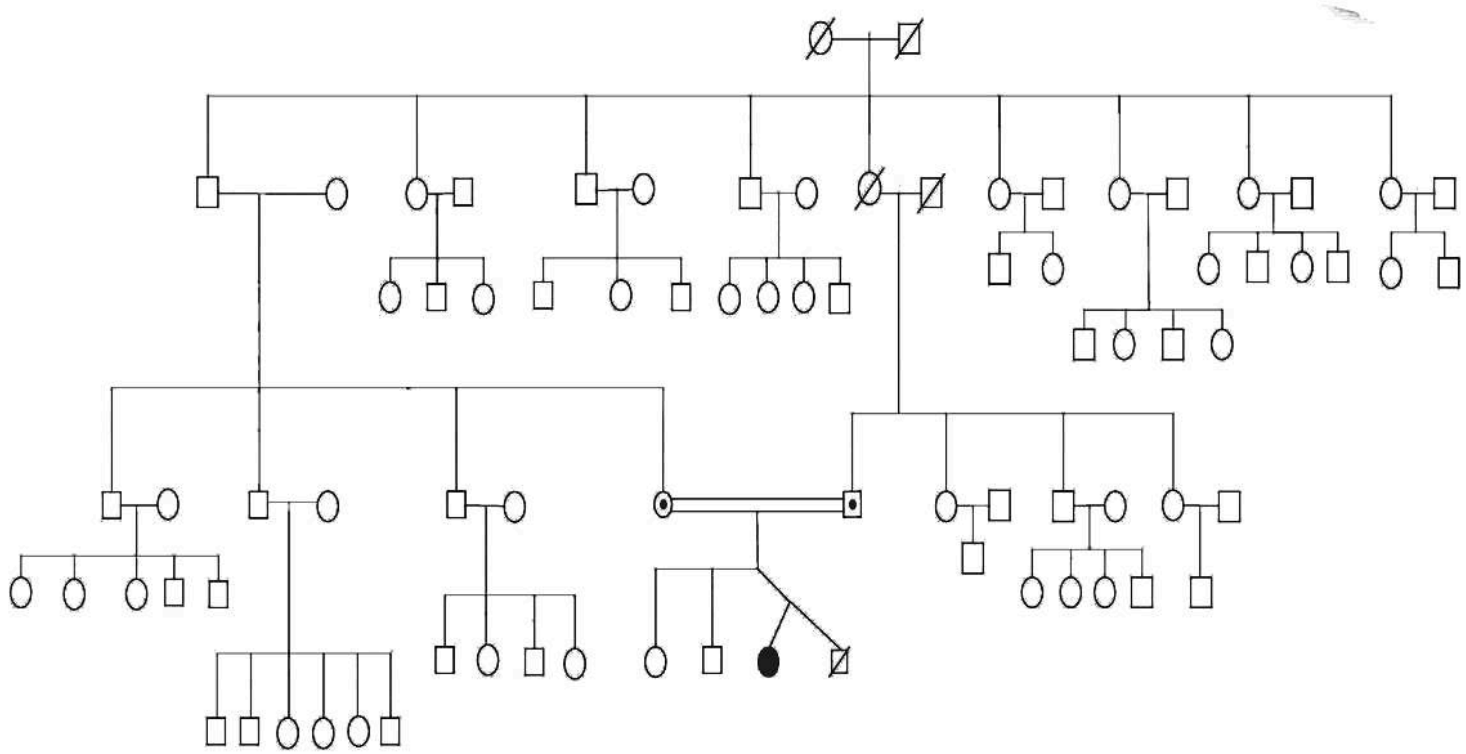


Figure 1

The pedigree chart indicates consanguinity marriage, with both parents originating from the same familial ancestry. They have three surviving children. Among them are two older non-twin siblings, a boy and a girl, and a set of opposite-sex fraternal twins. The male twin passed away in infancy, while his twin sister, who survived, has been diagnosed with Polyglucosan Body Myopathy-1 (PGBM-1) due to a homozygous pathogenic mutation in the RBCK1 gene.

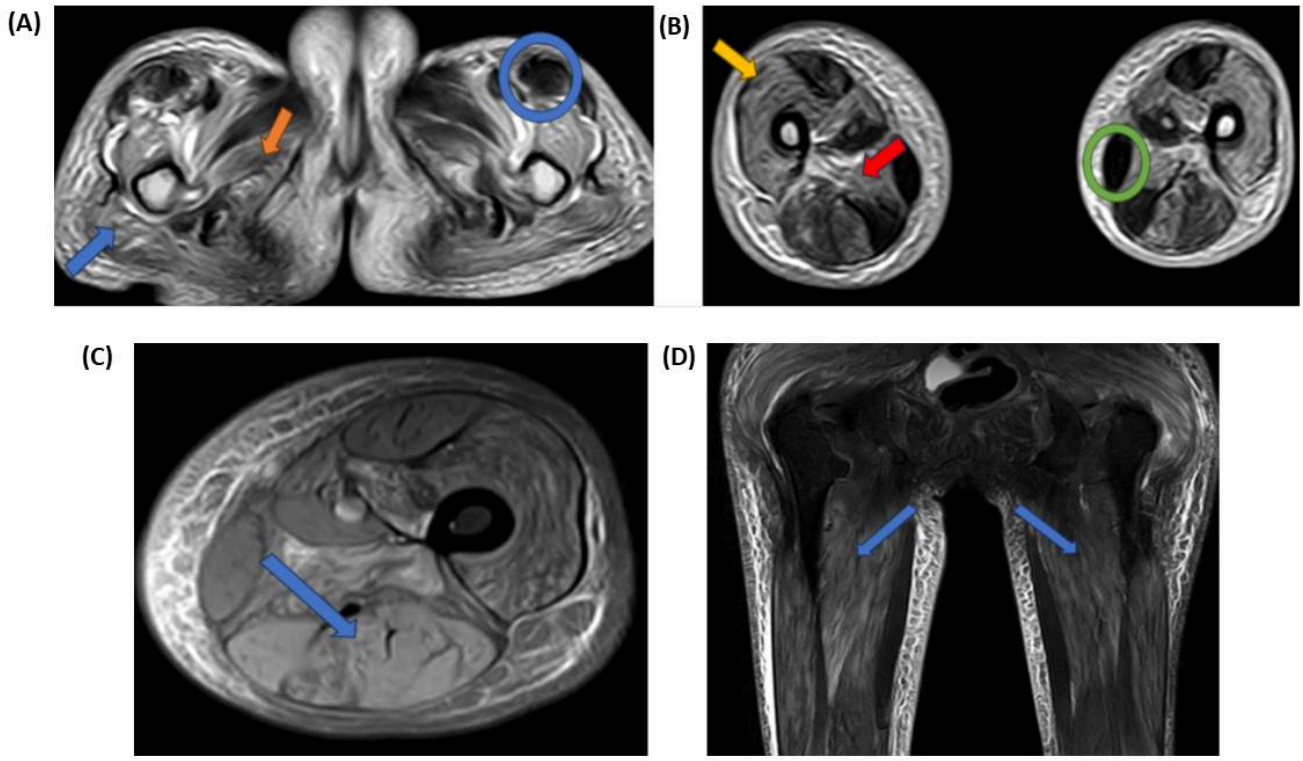


Figure 2

A. Axial PD Fat-Saturated image of the left thigh and **B.** Coronal T2 STIR image of the bilateral thighs demonstrate mild, diffuse hyperintensity within the affected muscle fibers. The involved muscle groups are indicated by colored arrows: Orange arrow – Obturator muscles; Blue arrow – Gluteal muscles; Yellow arrow – Vastus muscles; Red arrow – Adductor muscles. Muscles spared include the Sartorius (blue circle) and Gracilis (green circle). **C.** Axial PD Fat-Saturated image of the left thigh and **D.** Coronal T2 STIR image of the bilateral thighs again show mild, diffuse hyperintensity within the affected muscle fibers (arrows).

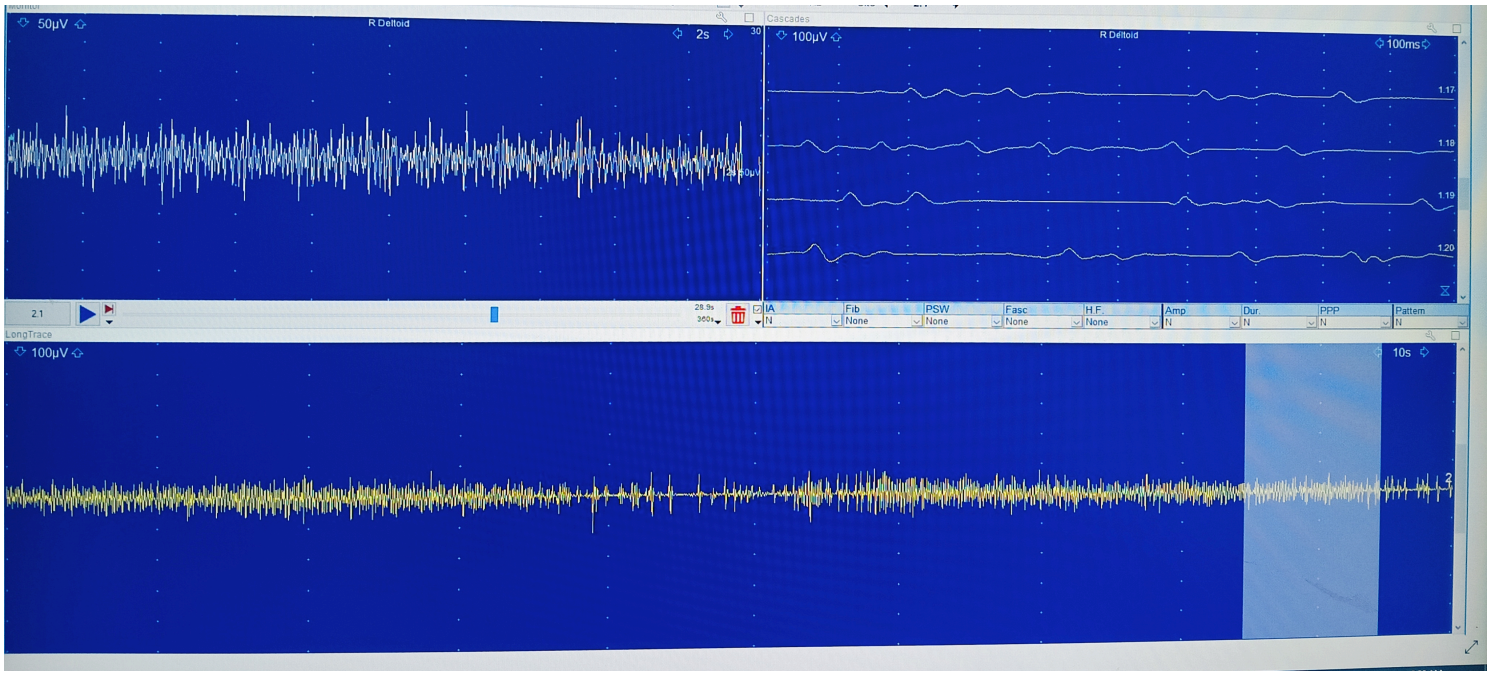
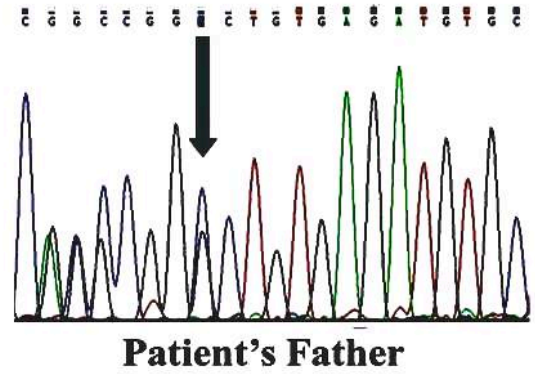


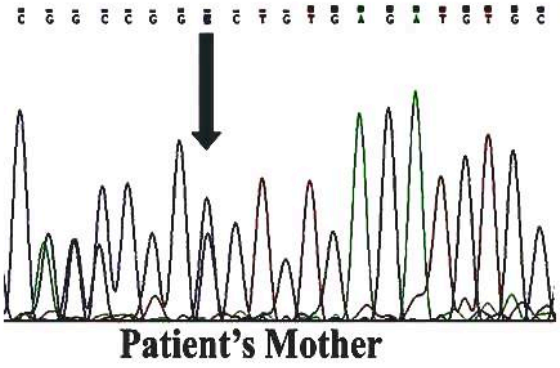
Figure 3

The EMG pattern showed predominantly small-amplitude motor unit potentials (approximately 50 µV per division) with short durations (10 ms/cm), along with an increased proportion of polyphasic MUPs. All patients demonstrated early recruitment and a mixed interference pattern.



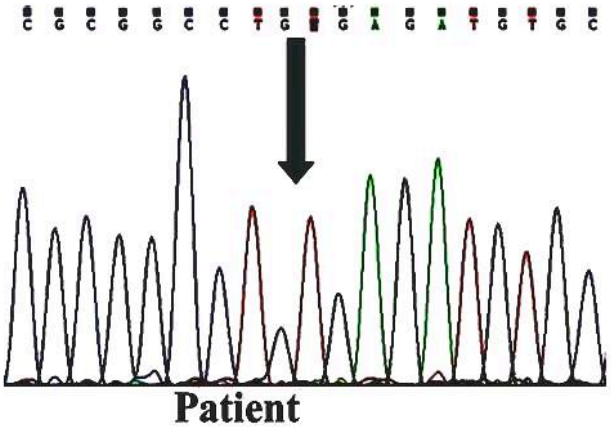
Patient's Father

Gene	Location	Variant	Inheritance	Remark
RBCK1 (NM_031229.4)	Exon 6	c.635_638delGCTG; p.Gly212Valfs*63	Autosomal Recessive	Present (Heterozygous)



Patient's Mother

Gene	Location	Variant	Inheritance	Remark
RBCK1 (NM_031229.4)	Exon 6	c.635_638delGCTG; p.Gly212Valfs*63	Autosomal Recessive	Present (Heterozygous)



Patient

Gene	Location	Variant	Inheritance	Remark
RBCK1 (NM_031229.4)	Exon 6	c.635_638delGCTG; p.Gly212Valfs*63 (chr20: g.419607_419610delCTGG)	Autosomal Recessive	Present (Homozygous)

Figure 4

RBCK1 variants were identified in both the patient and her parents. The patient was found to carry heterozygous variants in the RBCK1 gene, inherited from each parent. Specifically, a deletion of the nucleotide sequence **CCTG** at position **c.635_638**was detected in the RBCK1 gene.

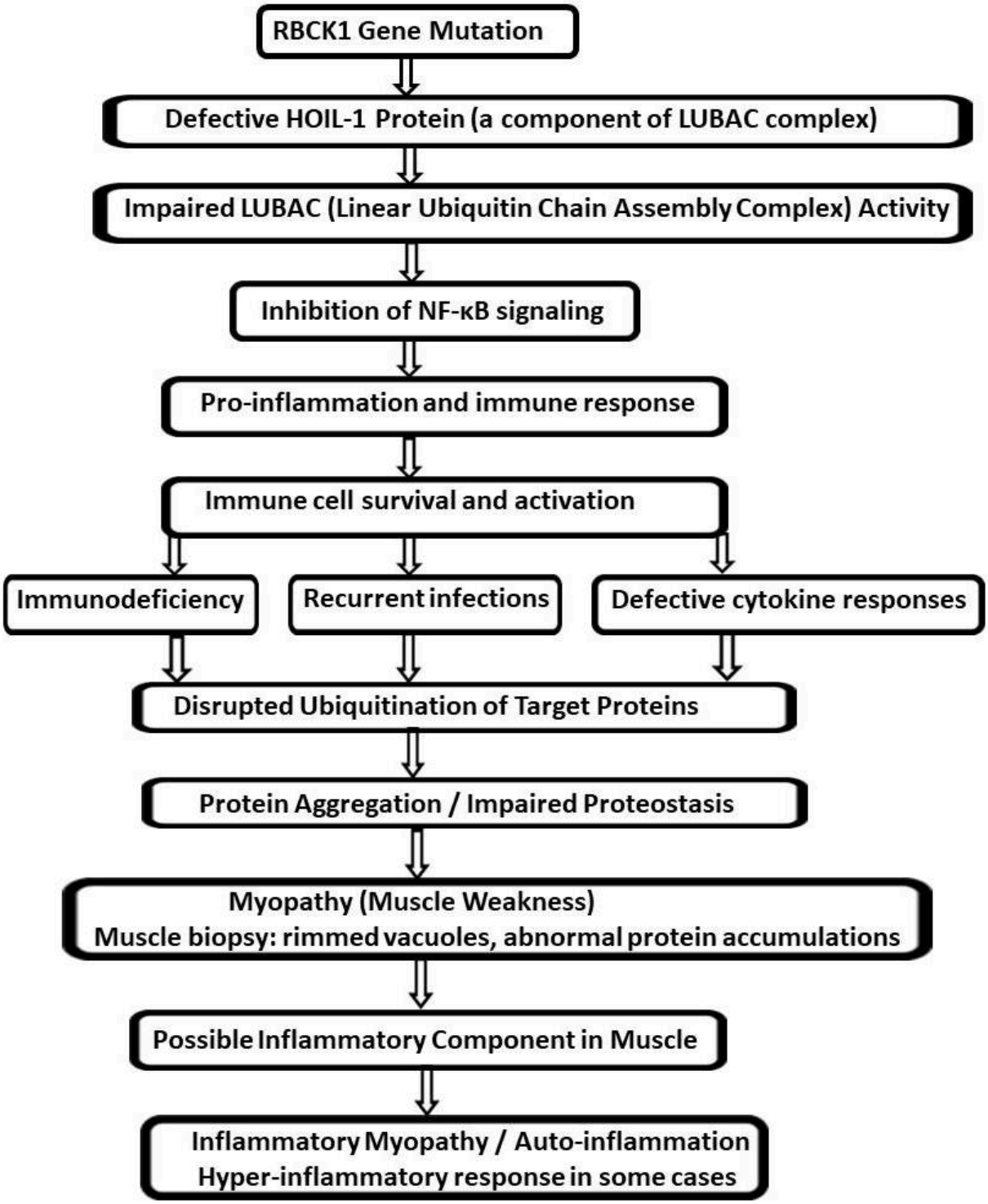


Figure 5

Pathophysiology based mechanistic route of mutation due to RBCK1 gene is presented. Mutations in RBCK1 cause a breakdown in linear ubiquitination, impairing NF-κB–mediated immune signaling. This causes a spectrum of clinical phenotypes ranging from immunodeficiency and auto-inflammation **to** progressive muscular and cardiac pathology**,**depending on the mutation type and residual LUBAC activity.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- NCVINVESTIGATION.jpg