LMNA c.1622G>A mutation and myopathic changes in a family with limb-girdle muscular dystrophy: A case report

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Abstract. The present study reports a case of limb-girdle muscular dystrophy (LGMD) associated with a pathogenic lamin A/C (*LMNA*) mutation (c.1622G>A). Notably, this case expands the phenotypic and genotypic spectrum of LMNA-related LGMD, and provides novel familial clinical and genetic evidence for this rare mutation. Genetic sequencing revealed a heterozygous mutation in both the proband and the mother of the proband, suggesting autosomal dominant inheritance. Electromyography (EMG) revealed reduced nerve conduction velocity and abnormal potentials in the proband and mother, indicating muscle weakness and atrophy. Magnetic resonance imaging (MRI) results showed symmetric muscle atrophy in the proximal muscles of the lower legs, with fatty tissue replacement. Both the proband and mother had elevated creatine kinase levels, whereas the father had normal levels. Transthoracic echocardiography ruled out severe heart disorders in the proband and mother. In conclusion, EMG and MRI findings indicated myopathic changes in the proband and the mother of the proband, confirming the significance of this mutation in LGMD. This familial case adds novel clinical, electrophysiological and imaging data to the existing literature on LMNA-associated LGMD. Further genetic and clinical evaluations are required to understand the long-term prognosis and potential treatment strategies for LMNA-related LGMD.

Introduction

Limb-girdle muscular dystrophy (LGMD) is a group of hereditary muscle disorders characterized by progressive muscle weakness and atrophy that severely impair the daily activities and overall quality of life of patients. LGMD represents a genetically heterogeneous group of conditions, with >30 identified subtypes (1), each associated with distinct genetic causes and clinical presentations, posing notable challenges for early diagnosis and management. Lamin A/C (*LMNA*) gene mutations are among the numerous known genetic factors that cause LGMD (2). *LMNA* is also involved in a wide variety of cellular processes, including the regulation of cell stability, cell motility, mechanosensing, gene regulation, chromosome organization, DNA damage repair, telomere protection and cell differentiation, including myogenesis (3-8). *LMNA* genes encode lamin A and C proteins, which are critical for maintaining muscle cell stability and normal function (9). Notably, *LMNA* mutations have been linked to a spectrum of tissue-specific disorders collectively referred to as laminopathies, which include cardiac, skeletal and metabolic manifestations beyond isolated muscle disease (10). A previous study has shown that lamins A and C are important for regulating nuclear maturation, functional responses and the gene expression patterns of neutrophils in murine models (11).

The present study reports the case of a patient with congenital LGMD accompanied by an *LMNA* gene c.1622G>A mutation. The pathogenicity of this mutation was confirmed using genetic sequencing and clinical assessment. The results showed that this mutation was present in the proband and the mother of the proband, but not the father, confirming the importance of *LMNA* mutations in LGMD.

Case report

A 43-year-old female patient (mother of the proband) was admitted to the Department of Respiratory Medicine, Affiliated Banan Hospital of Chongqing Medical University (Chongqing, China) in May 2024, due to a pulmonary infection. When the patient was 30 years old, they developed problems in the left leg. The core focus of this case report is the proband, who was hospitalized in May 2024 at the age of 16 years for clinical manifestation evaluation for LGMD; the mother's hospitalization is presented as secondary familial background information. The proband's father was in good health and the proband belonged to a Chinese family with a history of LGMD. The 16-year-old daughter of the patient was the proband, who was 10 years and 11 months old at the time of her initial diagnosis of LGMD via genetic testing in August 2018. This date marked the proband's first hospital visit for the disease,

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with the mother and father first accompanying the proband for diagnosis and treatment on the same date. The proband was a girl with no abnormalities during the neonatal period; at 10 years old, the proband began to exhibit clinical features, including a slender body type, reduced subcutaneous fat, aortic valve abnormalities, aortic dilation, ventricular premature beats, second-degree atrioventricular block, elevated serum creatine kinase (CK: 388 U/l; reference range: 40-200 U/l) and myodystrophy. The present study was approved by the Ethics Committee of Banan Hospital, Chongqing Medical University (approval no. BNLL-KY-2025-074). Written informed consent was obtained from the proband and the parents of the proband.

Test results during the hospitalization in May 2024 indicated higher levels of CK in the proband and increased CK and CK-MB levels in the mother, while the father's CK and CK-MB levels were normal (Table I). The mother presented with clinical symptoms of lower limb pain and diminished physical activity at this time, which suggested an underlying muscle disease. Further diagnostic investigations were then conducted to determine the nature of the muscle damage.

Both the proband and parents underwent electromyography (EMG) examination. A myoelectric evoked potentiometer (Dantec Keypoint) was used to detect sensory nerve conduction velocity in the tibial, ulnar and peroneal nerves. Motor nerve conduction velocity and amplitude were measured and the detected muscles included bilateral biceps obolus, deltoid, supraspinous, subscapularis, quadriceps, biceps femoris, anterior tibialis and fat bowel muscles. In the proband, mild myogenic damage in specific muscles such as the right iliopsoas was suspected, as evidenced by abnormal potentials on the EMG and a slight decrease in nerve conduction velocity. However, most of the nerve conduction tests were normal, indicating no extensive nerve damage (Fig. 1A-C). The EMG for the proband's mother showed myogenic damage, characterized by fibrillation and short spiky polyphasic waves, indicating muscle disease or injury. Despite this, the nerve conduction velocity test results were normal, suggesting that peripheral nerve function remained intact (Fig. 1D-F). These findings indicated a myopathic rather than neurogenic process, necessitating further diagnostic evaluations to clarify the underlying muscle pathology. The father did not show any signs of myopathic or peripheral neuropathic electrophysiological changes (Fig. 1G-I).

Magnetic resonance imaging (MRI) was performed using a Siemens Verio 3.0T superconducting MR scanner, including orthogonal body coils, bilateral axial, coronal and sagittal scans of the thigh. The scanning sequence was turbo spin echo (TSE) T1Wl, repetition time (TR) 600 msec; TSE T2Wl, TR 4,140 msec and echo time (TE) 109 msec; short tau inversion recovery sequence of short inversion, TR 3,670 msec, TE 95 msec and Tl 130 msec; and layer thickness 5 mm, layer spacing 5 mm and field of view 360 mm. MRI results obtained at the initial diagnosis of the proband's mother indicated symmetrical muscle atrophy in the medial posterior muscle groups of the middle upper segments of both lower legs, with muscle replacement with fatty tissue, which may be associated with hereditary muscle diseases. In addition, the mother had a small amount of fluid in the knee and ankle joints, which might indicate mild joint inflammation or injury (Fig. 2A-E). The lower limb MRI scans of the proband and father showed no abnormalities (Fig. 2F-I).

Concomitant with the initial diagnosis in September 2018, Sanger sequencing (12) was performed to confirm the LMNA variants identified by next-generation sequencing. For next generation sequencing, peripheral blood samples were collected from the proband and parents via sterile venipuncture. The samples were transferred to ethylenediaminetetraacetic acid-coated (EDTA) tubes to prevent coagulation and preserve DNA integrity. Genomic DNA was extracted from peripheral blood samples using the QIAamp DNA Blood Mini Kit (cat. no. 51104; Qiagen GmbH). DNA concentration and purity were assessed using a NanoDrop One spectrophotometer (Thermo Fisher Scientific, Inc.), with acceptable A260/A280 ratios between 1.8 and 2.0 and A260/A230 ratios >1.8. DNA integrity was then verified by 1% agarose gel electrophoresis. Library concentration was quantified using the KAPA Library Quantification Kit (Roche Diagnostics) on a QuantStudio 5 Real Time PCR System (Thermo Fisher Scientific, Inc.), and the final library was loaded at 1.8 nM. Subsequently, targeted next generation sequencing was carried out on an Illumina platform as paired end 150 bp bidirectional sequencing with the NovaSeq 6000 SBS Reagent Kit (cat. no. 20028312; Illumina, Inc.). Sequencing data were processed using RTA v3.4.4 (Illumina, Inc.) for base calling, BWA MEM v0.7.17 (http://bio-bwa.sourceforge.net/; https://github.com/lh3/bwa) for read alignment, GATK4 v4.2.6.1 (https://gatk.broadinstitute.org/) for variant calling, and ANNOVAR v2021 05 01 (http://annovar.openbioinformatics.org/) for variant annotation.

For Sanger sequencing, the EDTA-coated blood collection tubes containing peripheral blood samples from the proband and parents were immediately stored at 4˚C until further processing. DNA amplification was performed via polymerase chain reaction (PCR) using DreamTaq DNA Polymerase (Thermo Fisher Scientific, Inc.) and the thermocycling conditions were 95˚C for 5 min, followed by 35 cycles at 95˚C for 30 sec, 58˚C for 30 sec and 72˚C for 45 sec, and a final extension at 72˚C for 7 min. PCR amplification of selected candidate variants (*LMNA*, c.1622G>A) from the exome sequence analysis was conducted using gene-specific PCR primers targeting the *LMNA* gene (5'-3' forward: CCATGTCCCCACCAGGAA; 5'-3' reverse: TGGTTGAGGACGACGAGGA) (13). Purification was performed using a BigDye XTerminator purification kit (Thermo Fisher Scientific, Inc.), electrophoretic analysis was performed using the Applied Biosystems 3500 Genetic Analyzer (Thermo Fisher Scientific, Inc.) and chromatograms were analyzed using FinchTV software version 1.4.0 (Geospiza Inc.).

The sequences of the proband and parents were compared using the *LMNA* gene reference sequence (NCBI: NM_170707.4). The proband and mother were both heterozygous (G/A) at the variant locus, whereas the father carried the homozygous wild-type (G/G) allele, consistent with autosomal dominant inheritance and confirming the variant's co-segregation with the disease phenotype in this family. Using Sanger sequencing, a specific point mutation in the *LMNA* gene was confirmed: *LMNA* (NM_170707.4) c.1622G>A p.Arg541His (Fig. 3). According to the 2015 guidelines of the American College of Medical Genetics and Genomics (ACMG), this variant is classified as

Table I. Results of the CK and CK-MB analysis.

	Proband		Mother		Father	
Variable	Result	Reference range	Result	Reference range	Result	Reference range
CK, U/l	295	40-200	851	40-200	96	50-310
CK-MB, U/l	20	0-24	47	0-24	14	0-24

CK, creatine kinase.

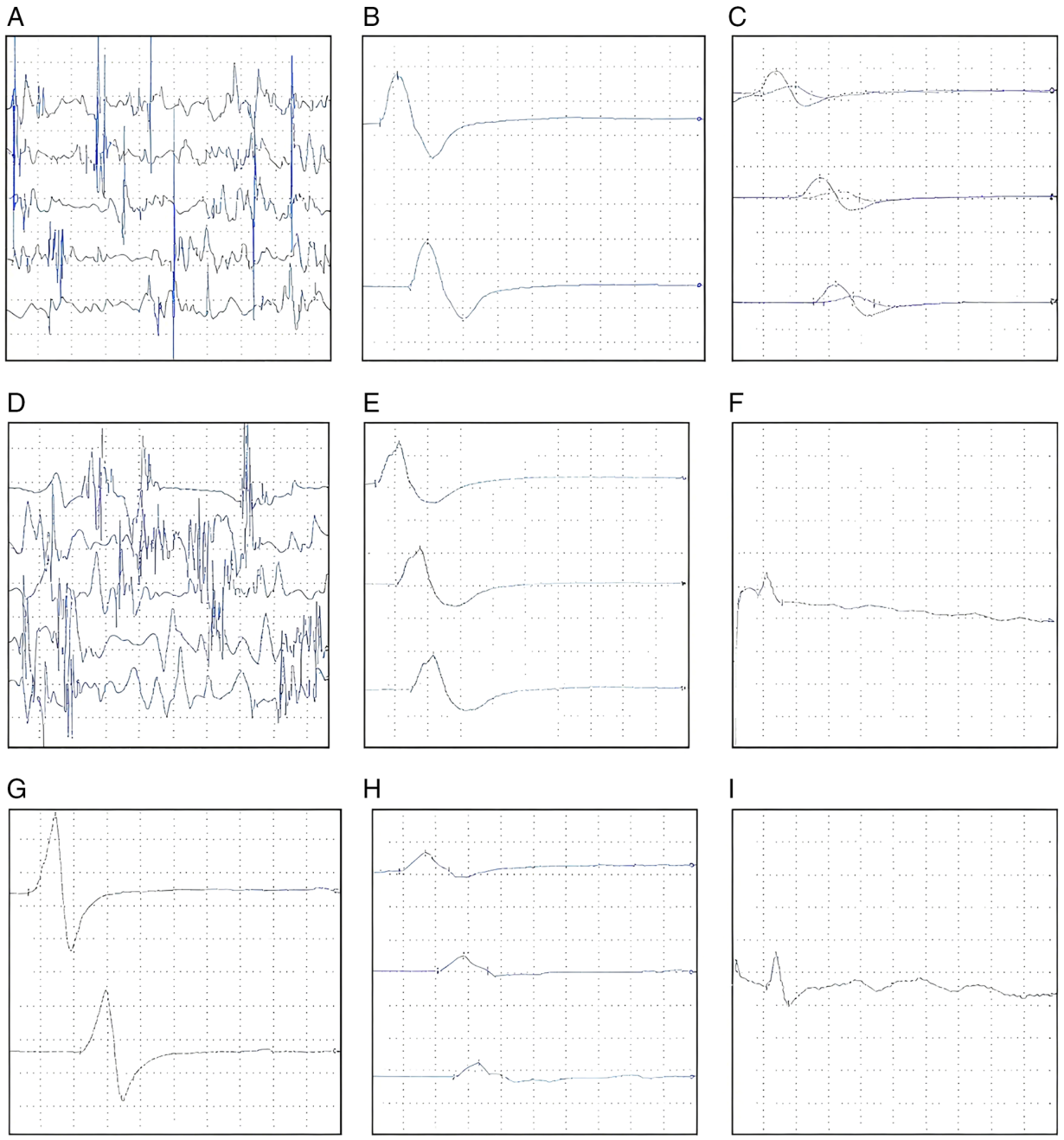

Figure 1. EMG and NCV data. (A) Proband EMG recording: EMG of iliopsoas muscle shows multi-phase potentials, irregular waveforms and reduced amplitude. (B) Proband NCV recording: NCV of the common peroneal nerve shows reduced amplitude and conduction velocity. (C) Proband F-wave response: F-wave shows normal or slightly delayed latency. (D) Mother EMG recording: EMG shows multi-phase potentials and irregular waveforms with amplitude changes. (E) Mother NCV recording: NCV of the tibial nerve shows normal amplitude and conduction velocity. (F) Mother F-wave response: F-wave shows normal latency. (G) Father EMG recording: Needle EMG of the tested muscles shows no abnormal spontaneous activity or myopathic/neurogenic changes. (H) Father NCV recording: Tibial nerve NCV shows normal parameters. (I) Father F-wave response: F-wave shows normal latency. EMG, electromyogram; NCV, nerve conduction velocity;

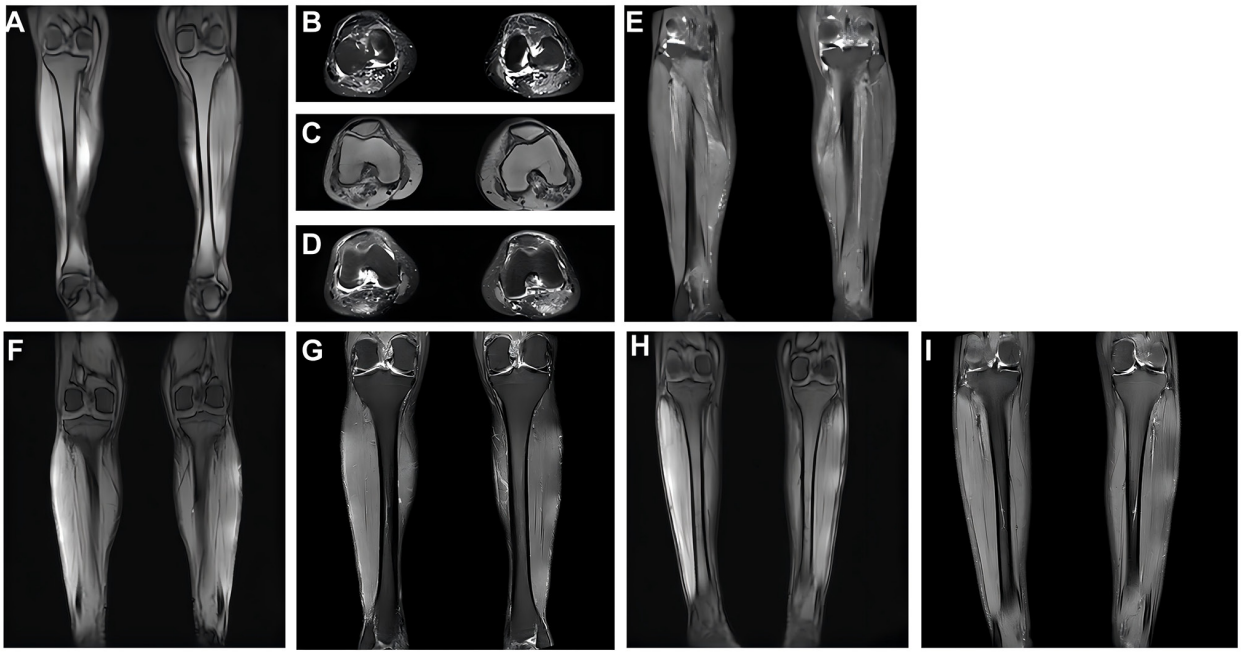

Figure 2. Magnetic resonance imaging of calf muscles. Proband's mother: (A) The quick scan shows the inside structure of the lower legs; (B) Short tau inversion recovery images show bright areas in the back muscles of the lower legs; (C) T1WI images show fat replacing tissue in the back muscles of the lower legs; (D) T2WI images show changes in muscle structure after fat has replaced it; (E) T2 FSE coronal images show changes in the water content of the back muscles in the lower legs. Proband's father: (F) The fast gradient recalled echo sequence shows the inside structure of the lower leg; (G) T2 FSE Dixon coronal images of the lower limbs reveal normal anatomical structures. Proband: (H) The quick scan clearly shows the inside structure of the lower leg; (I) T2 FSE Dixon coronal images of both legs. FSE, fast spin echo.

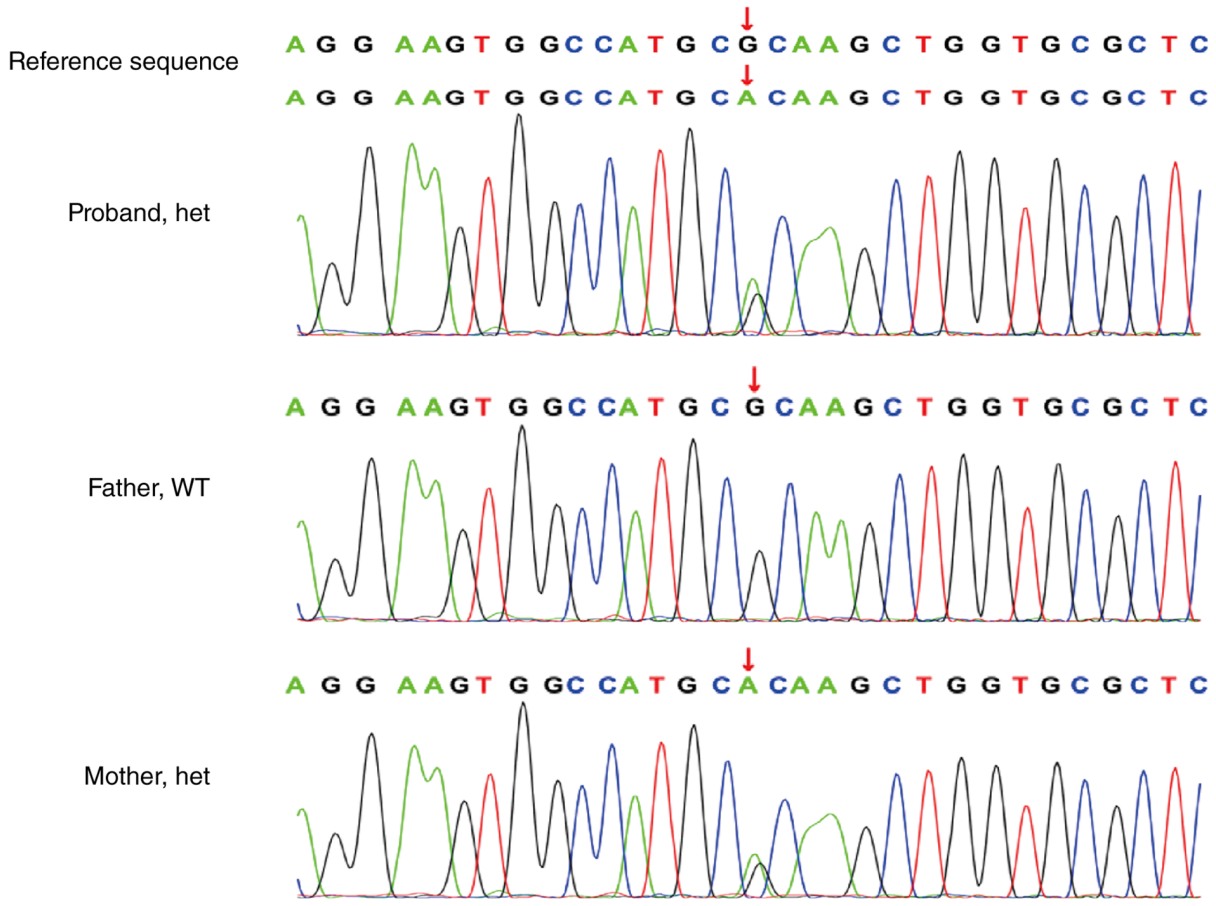

Figure 3. Sanger sequencing verification conducted on the proband and family members. The reference sequence (top) shows the WT G and mutant A bases at the variant position (red arrow). The proband and mother were het for the G>A substitution and displayed overlapping G and A peaks at the variant site. The father was homozygous for the WT G base, confirming a *de novo* or maternally inherited origin of the variant in the proband. WT, wild-type; het, heterozygous.

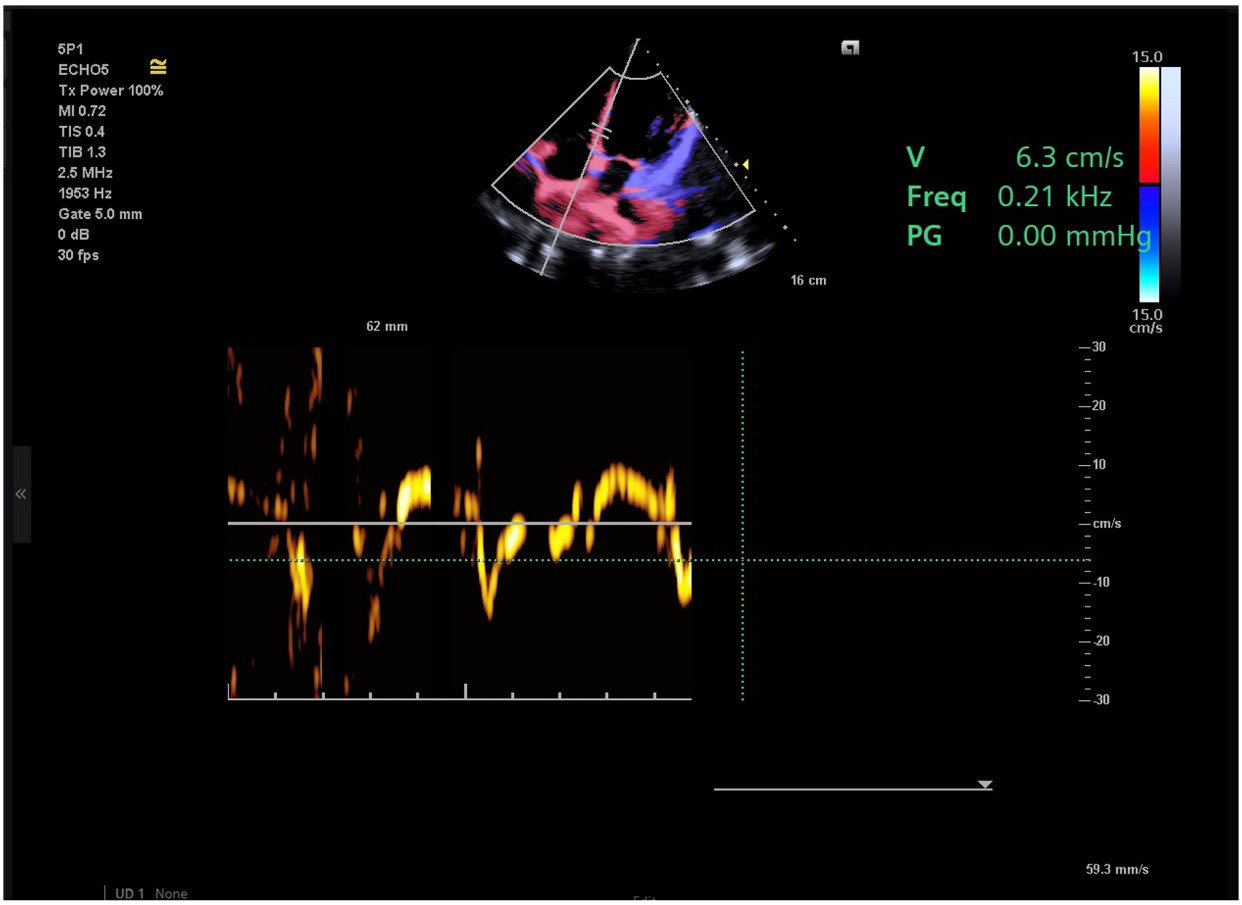

Figure 4. Transthoracic echocardiogram of the proband. Upper panel: Color Doppler imaging (apical four-chamber view) demonstrating normal cardiac chamber dimensions and intracardiac flow with mild aortic sinus widening and no pericardial effusion. Lower panel: Pulsed-wave Doppler tracing confirms preserved left ventricular diastolic function.

pathogenic (14). The variant c.1622G>A (p.Arg541His) was categorized based on the ACMG guidelines as follows: i) The same amino acid change as identified in pathogenic variants in previous studies (15,16) and databases (ClinVar, https://www.ncbi.nlm.nih.gov/clinvar/; Human Gene Mutation Database, https://www.hgmd.cf.ac.uk/) for strong evidence of disease (PS1: Same amino acid change as a known pathogenic variant). ii) The missense variant was located in a well-studied functional domain without any benign variations, as assessed using the gnomAD v3.1 (https://gnomad.broadinstitute.org/), providing moderate evidence of the disease (PM1: Variant resides in a critical functional domain or mutational hotspot lacking benign variants). iii) The minor allele frequency was <0.005, classifying it as a low-frequency variant for moderate evidence of disease (PM2: Variant shows extremely low allele frequency in general population databases). According to public population databases, including gnomAD v3.1, the c.1622G>A (p.Arg541His) variant of *LMNA* has not yet been identified in the East Asian subgroup. Consistent with this, no instances of the c.1622G>A variant have been detected in large-scale Chinese population databases (including ChinaMAP) (17,18), indicating that the minor allele frequency in the Chinese population is extremely low (estimated to be $<1x10^{-5}$). iv) Co-segregation among family members supported the pathogenicity and possible evidence of disease (PP1: Variant co-segregates with disease phenotype within affected family members) of this variant, and v) two computational prediction methods, performed in the present study, indicated that the variant affects gene and protein structure. PolyPhen-2 (version 2.2.3r408; https://genetics.bwh.harvard.edu/pph2/) classified the *LMNA* p.Arg541His variant as 'Probably Damaging' with a HumDiv score of 1.000, indicating a high probability of disrupting protein function. Furthermore, analysis using the 100 Vertebrates Conservation track in the UCSC Genome Browser (GRCh38/hg38; https://genome.ucsc.edu/) revealed that the variant is located at a highly evolutionarily conserved site with a phyloP score close to 4.0, supporting functional importance of this residue (PP3: Multiple computational algorithms predict a damaging impact on protein function). This mutation was the sole finding in the *LMNA* gene, providing a key clue for understanding the genetic background of LGMD in this family.

The proband underwent a follow-up visit in March 2023, with transthoracic echocardiography and CK testing conducted at this visit; the echocardiography test showed that the cardiac chambers of the proband were of normal size, with intact left ventricular systolic and diastolic functions. There was only mild dilation of the aortic sinus and no pericardial effusion (Fig. 4), with a detected CK level of 266 U/l and Holter result indicating non-sustained ventricular tachycardia. For the

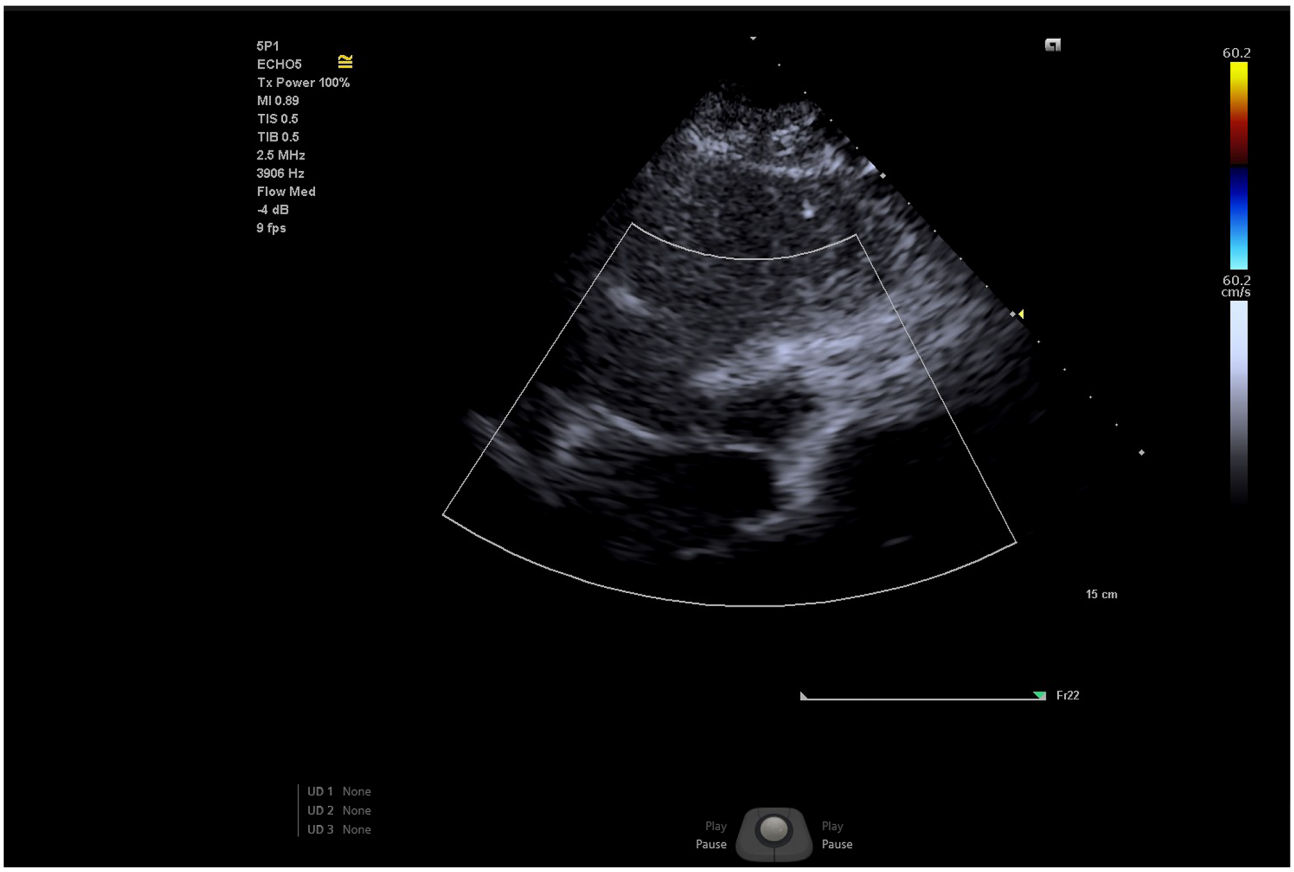

Figure 5. Transthoracic echocardiogram of the proband's mother. This grayscale two-dimensional echocardiogram (parasternal long-axis view) demonstrates normal cardiac chamber dimensions with reduced early diastolic relaxation function of both the left and right ventricles, consistent with subclinical myocardial dysfunction. No pericardial effusions or significant valvular abnormalities were observed.

mother, transthoracic echocardiography confirmed a normal cardiac chamber size but identified reduced early diastolic relaxation function of both the left and right ventricles (Fig. 5), suggestive of subclinical myocardial dysfunction, with no sustained arrhythmias or conduction disturbances documented during clinical follow-up. The proband's brother was found to have notably elevated CK levels of 1,145 U/l (reference range: 50-310 U/l) and died at the age of 14 years; further investigation of this case was not possible.

The last follow-up was conducted on August 30, 2024. At that time, the proband and mother had been receiving long-term continuous treatment with coenzyme Q10 [10 mg three times a day (tid)], metoprolol tartrate (40 mg tid) and fructose diphosphate sodium oral liquid (1 g tid) since the initial diagnosis in 2018. The overall clinical status of both individuals remained stable during follow-up, with no deterioration in muscular symptoms or adverse cardiac events. As no specific curative treatment is currently available for LGMD caused by *LMNA* heterozygous mutation, the long-term prognosis remains challenging. Regular cardiology follow-up is essential to monitor for arrhythmias and progressive myocardial dysfunction. Physical therapy and limb function training are recommended to slow the progression of motor dysfunction and strenuous exercise should be avoided to prevent muscle damage and cardiac events. Genetic counselling is advised for the family to reduce the risk of hereditary transmission in future pregnancies.

Discussion

The long-term prognosis of *LMNA*-related muscular dystrophy is poor, with high disability and mortality rates owing to progressive dyskinesia, contractures, spinal deformity, respiratory insufficiency, cardiomyopathy and various cardiac arrhythmias (19-21). Defects in lamin A/C protein assembly in *LMNA*-related congenital muscular dystrophy are responsible for increased disease severity (22,23). The present study provides a comprehensive analysis of a family affected by LGMD. A heterozygous pathogenic mutation (c.1622G>A) in the *LMNA* gene was identified in the genomes of both the proband and the mother of the proband. The *LMNA* mutations identified in the present study were consistent with the ACMG pathogenicity criteria (14). The mother and proband had the mutation, but the father did not, indicating that *LMNA*-related muscular dystrophy was inherited in an autosomal dominant manner (19).

At present, possible therapeutic approaches under study for LGMD caused by genetic defects include molecular and genetic methods. Autologous stem cell transplantation or allogeneic stem cell transplantation involves injecting healthy stem cells into the patient's body to restore deficient proteins (24-26). Exon skipping using antisense oligonucleotides may bypass the exon regions in genes that cause LGMD, thereby enabling effective treatment (27). LGMD may also be treated by directly transmitting healthy genes (28,29). Finally, the use of

nucleases to eliminate disease-causing genes and gene editing could potentially become effective methods for treating LGMD (30-32). Unfortunately, owing to the relatively small number of cases, there are currently no effective molecular or genetic treatment methods for LGMD caused by *LMNA*. The primary treatment approach involves symptomatic care of the heart and lungs.

In addition to LGMD, the dominant mutation in *LMNA* may also cause diseases such as Emery-Dreifuss muscular dystrophy (EDMD) and myofibrillar myopathy (MFM) (33,34). EDMD is a hereditary muscular dystrophy syndrome caused by the deletion of nuclear membrane protein-coding genes. The patient presents with a triad of muscle atrophy, joint contracture and heart disease, of which heart disease is the most serious and mainly manifests as conduction defects, atrial fibrillation or flutter and atrial stasis. Heart failure due to left ventricular dysfunction is a notable cause of death, particularly in patients with *LMNA* mutations (35). MFM is a group of inherited muscle disorders characterized by abnormal accumulation of myofibrillar dissolution and degradation products, ectopic protein aggregation and a unique pattern of myofibrillar disorganization (34). Patients typically present with progressive muscle weakness that begins in the distal muscle and spreads to the proximal muscle. Since *LMNA* plays a role in DNA replication and affects various cellular mechanisms that maintain genome integrity and innate immune responses, mutations in *LMNA* may lead to muscle diseases such as MFM (36).

The c.1622G>A mutation identified in the present study has also been shown to play a role in two other phenotypes of laminopathy, EDMD and AD-dilated cardiomyopathy with conduction defect type 1A (DCM1A) (37-39), with these phenotypes uniformly characterized by prominent and often severe cardiac involvement, including high-grade atrioventricular block, life-threatening arrhythmias, severe left ventricular dilation and systolic dysfunction and high rates of cardiac intervention or transplantation (33,35,38-40). Vytopil *et al* (37) identified the p.Arg541His variant as a highly penetrant cardiac pathogenic mutation in patients with cardiomuscular phenotypes. By contrast, no notable structural or severe functional cardiac defects were found in the LGMD proband and mother carrying this heterozygous mutation in the present study. Long-term follow-up from 2018 to 2024 only detected mild aortic sinus widening in the adolescent proband and subclinical ventricular diastolic relaxation dysfunction in the 43-year-old mother, with no sustained arrhythmias, conduction disturbances or structural cardiac dilation observed in either individual. This phenotypic divergence expands the clinical spectrum of the *LMNA* c.1622G>A mutation and challenges the established genotype-phenotype correspondence for this variant, providing a new perspective for exploring the heterogeneity of *LMNA*-related laminopathies. This discrepancy may be attributable to the distinct mutation site of p.Arg541His. Unlike DCM1A-associated p.N195K and p.R225X mutations that disrupt the nuclear membrane anchoring domain, the p.Arg541His variant is located in the C-terminal globular domain, potentially exerting tissue-specific functional impacts that predominantly affect skeletal muscle rather than cardiac muscle (41-43). Additional potential explanations include population-specific genetic modifiers, as this variant is absent in East Asian and large-scale Chinese population databases (17,18), and the early disease stage of the proband with possible delayed cardiac penetrance of the mutation (20). This finding underscores that the same *LMNA* mutation can drive divergent pathological processes in skeletal and cardiac muscle and highlights the need for further research into population-specific modifier genes and long-term prospective follow-up to clarify the late cardiac prognosis of East Asian carriers of this variant. Therefore, these genetic mutations are potential therapeutic targets. Future studies should focus on determining how changes in the *LMNA* gene affect the immune system and whether certain treatments can help with LGMD. The present study focused on a single Chinese family and future studies with larger sample sizes are required to confirm the conclusions. Further research is needed to track how the immune systems of patients with LGMD function over time and understand how treatment affects their health.

In conclusion, the results of the present study showed a heterozygous mutation, c.1622G> A, in the *LMNA* gene of the proband and mother. These genetic changes may be related to LGMD. This discovery will help us to gain a deeper understanding of the genes involved in LGMD disorders and develop potential targeted treatments.

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Availability of data and materials

The next-generation sequencing data generated in the present study may be found in the Genomic Sequence Archive under accession number HRA011651 or at the following URL: https://ngdc.cncb.ac.cn/gsa-human/browse/HRA011651. This accession number contains a total of nine datasets, among which HRS1919542, HRS1919543, HRS1919544 and HRS1919545 belong to the mother, HRS1919546, HRS1919547 and HRS1924549 belong to the father, and HRS1919548 and HRS1919549 correspond to the proband enrolled in this case report. All other relevant data generated in the present study may be requested from the corresponding author.

Authors' contributions

QW collected the patient data. YZ analyzed and interpreted the patient data, and drafted the manuscript. TZ supervised the study design, performed data analysis and interpreted of the results. YZ and QW confirm the authenticity of all the raw data. All the authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study adhered to the Declaration of Helsinki and was approved by the Ethics Committee of Banan Hospital, Chongqing Medical University, allowing the publication of case details (approval no. BNLL-KY-2025-074). Written

informed consent was obtained from all participants involved in the present study, including the parents of the minor participant.

Patient consent for publication

The proband and parents provided written informed consent for the publication of this case report and the related images.

Competing interests

The authors declare that they have no competing interests.

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