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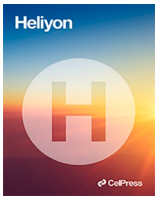

Case report

Duchenne muscular dystrophy caused by a deletion (c.5021del) in exon 35 of the DMD gene: A case report and review of the literature

Yue Liu [a,c,d], Yanhui Tang [b], Hui Zhang [a,c,d], Hongying Chen [b], Qing Luo [a,c,d], Jinbo Liu [a,c,d,*]

[a] Department of Laboratory Medicine, The Affiliated Hospital of Southwest Medical University, Luzhou, China
[b] Department of Pediatric, The Affiliated Hospital of Southwest Medical University, Luzhou, China
[c] Sichuan Province Engineering Technology Research Center of Molecular Diagnosis of Clinical Diseases, Luzhou, China
[d] Molecular Diagnosis of Clinical Diseases Key Laboratory of Luzhou, Luzhou, China

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ABSTRACT

Duchenne muscular dystrophy (DMD MIM#310200) is a degenerative muscle disease caused by mutations in the dystrophin gene located on Xp21.2. The clinical features encompass muscle weakness and markedly elevated serum creatine kinase levels. An 8-year-old Chinese boy was diagnosed with Duchenne muscular dystrophy (DMD). Whole exome gene sequencing was conducted and the Sanger method was used to validate sequencing. A deletion (c.5021del) in exon 35 of the dystrophin gene was identified, which was predicted to generate a frameshift mutation and create an early termination codon (p.Leu1674CysfsTer47). It has a pathogenic effect against dystrophin in the muscle cell membrane of the patient. As such, prednisone treatment at a dose of 0.75 mg/kg.d was administered. After one month, a notable reduction in fall frequency was observed. Our new finding will expand the pathogenic mutation spectrum causing DMD.

1. Introduction

Duchenne muscular dystrophy (DMD) is a common, progressive and fatal X-linked recessive neuromuscular disorder, predominantly affecting males with an incidence of approximately 1 in 5000 live male births globally [1,2]. The underlying cause of the disease lies in mutations within the Dystrophin gene, located at locus Xp21.2, leading to subsequent Dystrophin deficiency [3]. Dystrophin, a cytoplasmic protein situated at the sarcolemma (muscle fiber membrane), plays a crucial role as a link between the cytoplasmic compartment of muscle fibers and the extracellular matrix. This contribution is essential for the stabilization of muscle cell membranes during contraction sessions [4]. Clinical symptoms in individuals with DMD may manifest at any point from birth to the age of 8, including motor delays, abnormal gait, frequent falls, and an inability to climb stairs [5]. Rapid progression often leads to the loss of independent ambulation by age 13, necessitating wheelchair use. Mortality typically occurs around age 20, usually due to respiratory or cardiac complications, imposing immense suffering on affected individuals and their families [6].

Although DMD is still not completely curable, early diagnosis and timely intervention play crucial roles in mitigating disease progression and enhancing long-term outcomes. The therapeutic approach to managing DMD encompasses a range of strategies,

* Corresponding author. Department of Laboratory Medicine, The Affiliated Hospital of Southwest Medical University, Luzhou, China.
E-mail address: liujb7203@swmu.edu.cn (J. Liu).

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including the use of glucocorticoids, gene addition, exon skipping, stop codon read-through, genome editing, and a variety of other types of therapy. Corticosteroids remain among the most effective methods for managing complications, significantly increasing the longevity of these patients [7,8].

Here, we present a case of DMD in China and unveil an exon mutation within the dystrophin gene. To the best of our knowledge, the occurrence of DMD associated with a deletion (c.5021del) in the dystrophin gene has not been previously reported in the gnomAD database. This case study can contribute to delineating the DMD phenotype, raising awareness among clinicians about the link between this condition and the dystrophin gene, enhancing clinical suspicion, and optimizing early therapeutic interventions.

2. Case presentation

An 8-year-old Chinese boy was admitted to the Affiliated Hospital of Southwest Medical University with a complaint of "tiptoe walking, a distinctive duck-like gait and frequent falls". The child is currently in elementary school and is struggling with poor grades. While language development followed a normal trajectory, with the child gradually becoming able to speak from the age of 1, there were noticeable delays in motor skills. The child achieved independent walking at 12 months, but by 15 months, gait wasn't as steady as that of peers of the same age. During this period, the child experienced frequent falls, adopted an abnormal posture, walked on tiptoe, and reported pain in the feet after prolonged walking. Additionally, the child encountered difficulty rising independently from a supine position, requiring assistance. Upon closer observation, family members noted the presence of hardened muscles in both calves. This is his first visit to the hospital for medical treatment. Physical examination revealed bilateral gastrocnemius pseudohypertrophy, diminished tendon reflexes, and weakened knee reflexes (Fig. 1). Laboratory examination was conducted on blood samples, and the results are presented (Table 1). Among them, extremely high blood creatine kinase (CK) levels were noted at 31,406 U/L (reference range: 50–310 U/L). Using the MRC (Medical Research Council) scale for strength assessment, the findings indicated the following muscle strength levels: bilateral upper limbs exhibit grade IV + strength in the distal region and grade IV strength in the proximal region, while bilateral lower limbs demonstrate grade IV + strength in the distal region and grade III + strength in the proximal region. Pathological findings were inconclusive, while electromyography profiles mirrored myogenic damage. Sinus tachycardia was evident on electrocardiogram. Collectively, these findings substantiated the diagnosis of DMD. Echocardiography showed no abnormalities in the intracardiac structures (supplementary file). Clinical Practice Guidelines for Duchenne progressive muscular dystrophy [9] necessitate a diagnosis based on clinical presentation, physical findings, serum CK levels, and gene sequencing Thus, gene sequencing was pursued.

In contrast, considering the genotypic and phenotypic extreme heterogeneity of muscular dystrophies, whole exome sequencing proves to be a more feasible approach for identifying candidate genes. This is because whole exome sequencing enables the comprehensive screening of all genes associated with muscular dystrophies [7]. It exposed a hemizygous nucleotide deletion c.5021del within dystrophin gene exon 35. This alteration led to the replacement of leucine at codon 1674 with cysteine, prematurely terminating dystrophin gene translation due to a termination codon at position 47 post-mutation (Table 2). Notably, this variant had not previously been documented in the gnomAD database. Accordingly, we incorporated this new mutation into the ClinVar database (SUB12878480). Subsequent bioinformatics algorithms were engaged to predict pathogenicity (Table 3). According to the "Standards and Guidelines for interpretation of genetic variants" outlined by the American Society of Medical Genetics and Genomics (ACMG), the variant was initially classified as pathogenic [10]. To guarantee the reliability of WES results, DNA was extracted from the peripheral

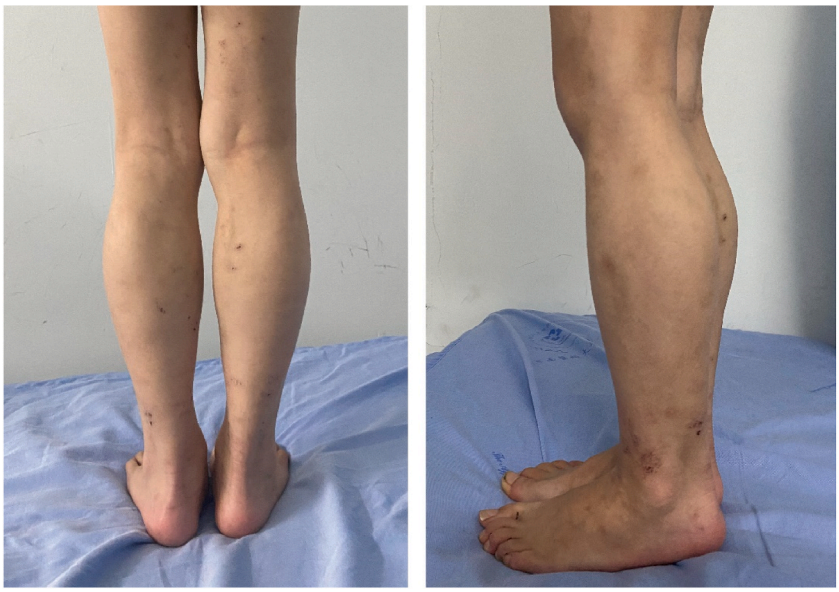

Fig. 1. Lower limb illustration depicting bilateral gastrocnemius muscle pseudohypertrophy.

Table 1
Biochemical analyses for the patient show muscle-specific changes.

Lab finding	Values	Normal ranges
CK (U/L)	31406	50–310
ALT (U/L)	401.6	7–30
AST (U/L)	645.2	14–44
LDH (U/L)	2180.6	120–250

CK: creatine kinase; ALT: alanine transaminase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase.

Table 2
Mutation site details.

Gene name	Location	Genomic variation	Transcripts; Exon	Protein defect	Amino acid change/ Variation type	American college of medical genetics classification
DMD	chrX:3238 3141–32383141	c.5021del	NM_004006.3; exon 35	p. Leu1674CysfsTer47	frame shift mutation	Pathogenic PVS1+PM2_Supporting + PP4

PVS1: the variant is a zero-effect variant (frame shift mutation) that may cause loss of gene function; PM2_Supporting: frequency in the normal population database; PP4: the patient's phenotype or family history is highly specific to a single genetic basis for the disease.

Table 3
Bioinformatics prediction results.

Variation	Bioinformatic Prediction			
c.5021del	Polyphen2 _HDIV	Mutation Taster	Mutation Assessor	SIFT
	1	Prediction disease causing	–	0.01

blood of the child. Primers for PCR were designed, and Sanger sequencing was conducted (Fig. 2a). The above results confirmed our conjecture that the child was diagnosed with DMD.

To assess the sequence conservation of Leu1674, a range of species available in the UCSC database were selected. The strict conservation of this mutation site was evident (Fig. 2b), underscoring the significance of Leu1674 for dystrophin protein integrity. Furthermore, SWISS-MODEL software was harnessed to construct pre- and post-frameshift mutation models, subsequently visualized through PyMol software (Fig. 2c–d). The resultant hemizygous mutation precipitated the formation of a truncated dystrophin protein, thereby meriting classification as "pathogenic".

Regrettably, the mother succumbed to uremia during pregnancy, while the father declined examination. Consequently, the origins and inheritance pattern of the mutation could not be validated. Given that DMD is an X-linked muscular dystrophy impacting up to 3,500 male births, it can be inferred that the mother bears the causative gene. Randomized controlled trials [11] have demonstrated the efficacy of glucocorticoids in enhancing muscle strength and respiratory function, significantly prolonging independent ambulation time [12]. Two corticosteroids, prednisone and felazort, are the most commonly used in the treatment of DMD [13]. Therefore, a dose of 0.75 mg/kg/day of prednisone was given. One month later, we followed him up. A significant decrease in the frequency of falls was observed, with no immediate side effects. The entire family expressed satisfaction with the outcome.

3. Discussion

Dependence on abnormal clinical presentations as triggers for the diagnostic workup of DMD has resulted in a delayed diagnosis of this genetic disorder [14]. Often, parents mistakenly perceive the child as delicate and may not initially take the symptoms seriously. This delay has contributed to a mean age of diagnosis of 4.9 years in typical cases, but in this particular instance, the child was not diagnosed until the age of 8 years.

The DMD gene boasts one of the most extensive known human genomes, encompassing approximately 2.4 Mb, 79 exons, 78 introns, and 8 promoters. It is because this gene is so huge that it has a high mutation rate, $>8 \times 10-5$ (OMIM: 300376) [15]. The ClinVar database houses records of over 8,000 genetic mutations, reflecting a diversity of mutation types: deletions (16.9%), duplications (8.2%), indels (0.4%), insertions (7.7%), and single nucleotide variations (66.8%). Within the context of our study, we have unveiled a c.5021del mutation within the dystrophin gene in a Chinese individual with muscular dystrophy, inducing a frameshift mutation. Among the 589 cases of frameshift mutations documented in the ClinVar database, this variant comprises roughly 13%.

In this study, our focus centered on "Duchenne muscular dystrophy [Title] and mutation [topic]" by Web of Science and PubMed. Subsequently, we refined the search to specifically include "deletion". Through this process, we identified a total of 45 research papers (Table 4). He X et al. [16] conducted comprehensive whole-exome sequencing, uncovering a hemizygous mutation in the DMD gene (c.5571del, p. Lys1857AsnfsTer8). Takizawa H et al. [17] presented a case study involving a 14-year-old DMD patient with a nonsense mutation in exon 70. Despite still being ambulant, the patient initiated ataluren treatment at 12 years of age and maintained stability for the subsequent two years. Wang Y et al. [18] reported the identification of a proband carrying a c.6794delG mutation in exon 47 of

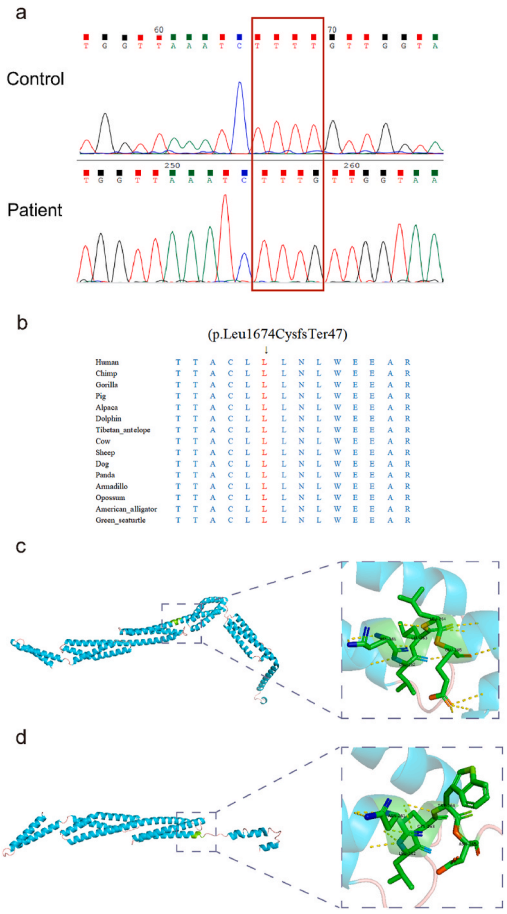

Fig. 2. Sanger sequencing, conservation analysis, and three-dimensional (3D) modeling of the DMD protein structure. *a* Sanger sequencing of partial DNA sequence of DMD gene. Boxes indicate missing loci. *b* Leu1674 is highly conserved among Human, Chimp, gorilla, pig, Alpaca, Dolphin, Tibetan antelope, Cow, Sheep, Dog, Panda, Armadillo, Opossum, American alligator and Green seaturtle. *c* DMD wild-type exon 31 to exon 40 protein sequence. Amino acid and hydrogen bond at position 352 of wild-type protein. *d* Truncated protein due to the mutation site. Amino acid and hydrogen bond alteration at position 1674 due to the variation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

the Dystrophin gene, resulting in a frameshift and a premature stop codon (p.G2265EfsTer6). Gibbs EM et al. [19] documented two individuals with significant in-frame 5' deletions (exon 3–23 and exon 3–28), encompassing a substantial portion of the N-terminal region, including segments of the actin-binding and central rod domains. Dinh LT et al. [20], employing sequencing of 79 exons through MLPA against the dystrophin gene, revealed a 2-nucleotide deletion of c.2032_2033delCA, leading to p. Q678DfsTer41. Loss of function variants in the DMD gene have been previously linked to pathogenicity. However, all the mentioned instances differ from the findings reported in this article. Here, a hemizygous nucleotide deletion c.5021del within exon 35 of the DMD gene was observed, leading to premature stop codons and precluding protein translation, deviating from the wild-type length of 3,685 amino acid residue.

In addition, we encountered challenges in verifying the origin and mode of inheritance of this mutation. Unfortunately, the mother's death during pregnancy from uremia and the father's refusal to undergo testing have impeded our ability to gather conclusive information in this regard.

4. Conclusions

In summary, we present a pathogenic DMD gene mutation, providing useful insights to the DMD gene mutation database. In this way, we want to raise awareness among parents and provide comprehensive assistance to each patient to the best of our abilities.

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Table 4
Summary of genetic variations and corresponding amino acid changes as reported by various authors.

Reference	Year	Region	Variation site	Amino acid changes
He X et al. [16]	2022	China	c.5571del	p. Lys1857AsnfsTer8
Aiello GM et al. [21]	2022	U.S.	exon 45-50	
Pasca L et al. [22]	2021	Italy	exon 70	
Takizawa H et al. [17]	2021	Japan	exon 45-54	
Wang L et al. [23]	2021	China	exon 49-52	
Xia Y et al. [24]	2021	China	exon 50	
Wang Y et al. [18]	2020	China	c.6796del	p.Ile2266PhefsTer5
Guan J et al. [25]	2019	China	exons 49-50	
Gibbs EM et al. [19]	2019	U.S.	exon 3–23 and exon 3-28	
Tsurumi F et al. [26]	2018	Japan	exon 44	
Dinh LT et al. [27]	2018	Vietnam	c.2032_2033del	p.Gln678AspfsTer41
Mukherjee S et al. [28]	2018	Italy	exon 43-52	
Finsterer J et al. [29]	2018	Australia	exon 12-29	
Bianco B et al. [30]	2017	Brazil	exon 2-47	
Takeshita E et al. [31]	2017	Japan	exon 48–50 and exon 51-53	
Kaczorowska E et al. [32]	2015	Poland	c.9055del	
Strmecki L et al. [33]	2013	U.S.	exon 45-52	
Donkervoort S et al. [34]	2013	U.S.	exon 48-50	
Balci-Hayta B et al. [35]	2012	Turkey	exon 43-50	
Schänzer A et al. [36]	2012	Germany	exon 49-52	
López-Hernández LB et al. [37]	2011	Mexico	exon 24-41	
Yoon J et al. [38]	2011	Korea	exon 44	
Ou Z et al. [39]	2010	China	exon 46-47	
Rajakulendran S et al. [40]	2010	U.K.	exon 3-13	
Jiang YH et al. [41]	2009	U.S.	exon 30-43	
Nakamura A et al. [42]	2008	Japan	exon 45-55	
Korngut L et al. [43]	2008	Canada	exon 6	
Purushottam M et al. [44]	2008	India	exon 45	
Vondracek P et al. [45]	2007	Chech	c.3609-3612del	p.K1204LfsTer11
Katayama Y et al. [46]	2006	Japan	exon 12-19	
Takeshima Y et al. [47]	2005	Japan	exon 20	
Todorova A et al. [48]	2003	Bulgaria	exon 44	
Becker K et al. [49]	2003	U.K.	c.10099_10101del	p.E3367del
Gussoni E et al. [50]	2002	U.S.	exon 44-45	
Patria SY et al. [51]	1999	Japan	exon 46-54	
Quan F et al. [52]	1996	U.S.	exon 50	
Takenaka T et al. [53]	1995	Japan	exon 46-50	
Uchino M et al. [54]	1994	Japan	exon 45	
Mostacciuolo ML et al. [55]	1994	Italy	exons 10-44	
Mostacciuolo ML et al. [55]	1994	Italy	exon 45	
Wallgren-Pettersson C et al. [56]	1993	U.K.	exon 35-43	
Clemens PR et al. [57]	1992	U.S.	exon 48	
Matsuo M et al. [58]	1991	Japan	exon 19	

Consent for publication

Written informed consents were obtained from the parents of the patient for the publication of this case report and any accompanying images.

Data availability statement

Data associated with this study has been deposited into the ClinVar database (SUB12878480). The data are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Yue Liu: Writing – original draft, Software, Methodology. **Yanhui Tang:** Investigation, Methodology, Validation. **Hui Zhang:** Data curation, Software. **Hongying Chen:** Resources, Investigation. **Qing Luo:** Data curation, Formal analysis. **Jinbo Liu:** Writing – review & editing, Conceptualization, Methodology, Project administration, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

DMD	Duchenne muscular dystrophy
CK	blood creatine kinase
MRC	Medical Research Council
ACMG	American Society of Medical Genetics and Genomics
3D	three-dimensional

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28677.

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