Molecular Genetics and Metabolism Reports 43 (2025) 101203

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

A novel pathogenic variant c.44A > G (p. Asp15Gly) in *TPM3* causing the phenotype of CMYP4A: A case report

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ARTICLE INFO

Keywords:
Tropomyosin 3
TPM3
Congenital myopathy
CMYP4A
Congenital fiber-type disproportion

ABSTRACT

Tropomyosin 3 (*TPM3*) encodes the slow α-tropomyosin isoform (Tpm3.12), an actin-binding protein that plays a critical role in the regulation of muscle contraction. Mutations in *TPM3* are associated with the characteristic features of congenital myopathy (CM).

A 15-year-old boy had a history of developmental delay, he had long narrow face with a myopathic facial appearance, mild scoliosis of the spine, grade IV muscle strength in the extremities, low muscle tone, absent bilateral knee tendon reflexes, and negative pathological findings. MRI revealed fat infiltration in the leg muscles and the surrounding muscle spaces. Muscle biopsy indicated muscle fiber type disproportion. A novel heterozygous mutation of unknown significance, c.44A > G(p.Asp15Gly), in *TPM3* gene was identified. This mutation was confirmed to be de novo and was not present in the proband's parents or sister. According to the guidelines of the American College of Medical Genetics and Genomics (ACMG), this variant was classified as pathogenic. PyMOL software analysis indicated that the variant affects the intermolecular interactions within the Tpm3.12. Interestingly, we also found that the patient has been mouth-breathing since infancy, along with a skeletal open bite. This phenotype that has not been previously described.

Our study expands the mutation spectrum of *TPM3* and offers valuable insights for the clinical diagnosis and genetic counseling of children with CMYP4A.

1. Introduction

Mutations in genes encoding sarcomeric proteins are frequently the underlying cause of CM, a group of neuromuscular disorders characterized by variable clinical, histological, and genetic features [1]. Common features include early symptom onset, slow disease progression, musculoskeletal abnormalities, low or normal plasma creatine kinase (CK) levels, and distinct morphological features observed in muscle biopsies, which aid in disease classification [2]. Despite these similarities, molecular subtyping remains challenging due to the involvement of numerous genes in CM and the phenotypic heterogeneity [3,4]. However, advancements in gene sequencing technology have illuminated how mutations in the same gene can result in different phenotypes and how mutations in different genes can lead to similar phenotypes [4].

Tropomyosin (Tpm) constitutes a class of proteins that play a vital role in muscle contraction and the stability of the cytoskeleton. In recent years, various myopathies have been linked to mutations in the tropomyosin genes *TPM1*, *TPM2*, and *TPM3*, which encode the skeletal muscle isoforms α-tropomyosin (Tpm1.1), β-tropomyosin (Tpm2.2), and slow α-tropomyosin (Tpm3.12), respectively [5]. *TPM1* is predominantly expressed in Type II fibers (fast-twitch muscle fibers), exhibiting lower expression levels in skeletal muscle compared to cardiac muscle.

Abbreviations: TPM3, Tropomyosin 3; ACMG, American College of Medical Genetics and Genomics; CMYP4A, Congenital myopathy 4A; CMYP4B, Congenital myopathy 4B; CM, Congenital myopathies; CK, Creatine kinase; Tpm1.1, α-tropomyosin; Tpm2.2, β-tropomyosin; Tpm3.12, slow α-tropomyosin; Trio-WES, Trio-based whole exome sequencing; PASP, Pulmonary artery systolic pressure; MRC, Medical Research Council; NM, Nemaline myopathy; CFTD, Congenital fiber-type disproportion; CD, Cap myopathy; H&E, Hematoxylin and Eosin; NADH, Nicotinamide Adenine Dinucleotide Hydride; NSE, Neuron-Specific Enolase; ORO, Oil Red O; MHC-f, Fast myosin heavy chains; MHC-s, Slow myosin heavy chains.

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https://doi.org/10.1016/j.ymgmr.2025.101203
Received 1 December 2024; Received in revised form 23 January 2025; Accepted 24 February 2025

TPM2 is primarily found in Type I fibers (slow-twitch muscle fibers), with limited expression also detected in Type II fibers. *TPM3* encodes the Tpm3.12 isoform, which is chiefly expressed in Type I fibers [5,6]. These isoforms collaborate to ensure the normal contraction and metabolic functions of skeletal muscle. *TPMs* mutations may lead to different types of muscular fiber disorders, resulting in CM.

Tpms in skeletal muscle not only participates in the calcium-dependent regulation of actin-myosin interactions but also regulates thin filament length through interactions with tropomyosin regulatory proteins [7]. The N-terminal segment of tropomyosin aligns with the tips of the thin filaments, pointing towards the center of the sarcomere, and mutations in this region may affect the regulation of thin filament length [8,9]. Mutations in the *TPMs* can result in nemaline myopathy [10,11], congenital fiber-type disproportion (CFTD) [12–14], cap myopathy (CD) [15–17] and cap myopathy coexisting with nemaline myopathy (NM) [18]. These CMS were defined by the observation of significant structural abnormalities in muscle biopsies. *TPM3* located at 1q21.3, spans 42 kb and consists of 13 exons. Currently, there are 42 variants documented in the HGMD database, with the majority being missense variants. Tpm3.12 is an indispensable regulatory factor for muscle contraction in Type I fibers. *TPM3* mutations responsible for causing autosomal dominant CMYP4A (OMIM 255310) and autosomal recessive congenital myopathy 4B (CMYP4B, OMIM 609284).

In this study, we identified a novel heterozygous mutation c.44A > G (p.Asp15Gly) in *TPM3* (NM_152263.4). This mutation was found in a Chinese teenager who presented with CMYP4A, and it was the subject of a comprehensive analysis of both the clinical features and genetic etiology.

2. Case presentation

2.1. Clinical presentation and examination

The patient was admitted to the pediatric intensive care unit of Zhanjiang Central People's Hospital's Pediatrics department due to fatigue and dyspnea. He presented with symptoms of limb weakness, fatigue, and nocturnal dyspnea. He had a history of developmental delay, initiating walking and speaking around the age of 2 years, with the need for rest after short periods of walking. He frequently experienced shortness of breath, dyspnea, and cyanosis at night, and had open-mouthed breathing and elongated molars since childhood, preventing him from fully closing his mouth. Family history was negative. Upon admission, the patient height, body weight, head circumference, and chest circumference were 160 cm (10th percentile), 30 kg (<3rd percentile), 90 %, 55.2 cm (normal), and 64 cm (<3rd percentile), respectively. His saturation of peripheral oxygen was 90 %, and exhibited clear consciousness but a poor mental state. B-type natriuretic peptide (28.04 pmol/L), blood routine (white blood cell count 4.9*10^9/L, red blood cell count 5.18*10^12/L, platelet count 175*10^9/L), liver function tests (alanine aminotransferase 9.4 U/L and aspartate aminotransferase 15.5 U/L), lactic acid (2.1 mmol/L), and CK (40.7 U/L) levels were within normal ranges. Blood gas analysis indicated that partial pressure of carbon dioxide was 107.00 mmHg, partial pressure of oxygen was 161.00 mmHg, and pH was 7.24. The initial treatment with piperacillin sodium and tazobactam sodium for anti-infection led to significant carbon dioxide retention. Subsequent high-flow nasal cannula oxygen therapy gradually improved of the patient's condition.

The patient presented a long narrow face, myopathic face, micrognathia with retrusion of the jaw, a mild flat thoracic cage (Fig. 1A, B), open mouth breathing (Fig. 1B), mild scoliosis and scapula alata (Fig. 1C). X-ray images revealed that the patient has dental skeletal open bite, with tooth 15 missing, teeth 25, 18, and 28 being highly impacted, tooth 46 having a residual crown, and teeth 38 and 48 being low horizontal completely impacted and causing bone obstruction. The teeth are numbered using the FDI International Tooth Numbering System (Fig. 1D, E). Cranial MRI was negative. Chest CT demonstrated scattered inflammation in both lungs. Echocardiography indicated a slight enlargement of the right heart, a widened pulmonary artery, mild tricuspid valve regurgitation, and normal left ventricular systolic and diastolic function. Pulmonary artery systolic pressure (PASP) was 27 mmHg, which was higher than the normal value. He reported fatigue and weakness in all four limbs. Muscle strength was assessed using the

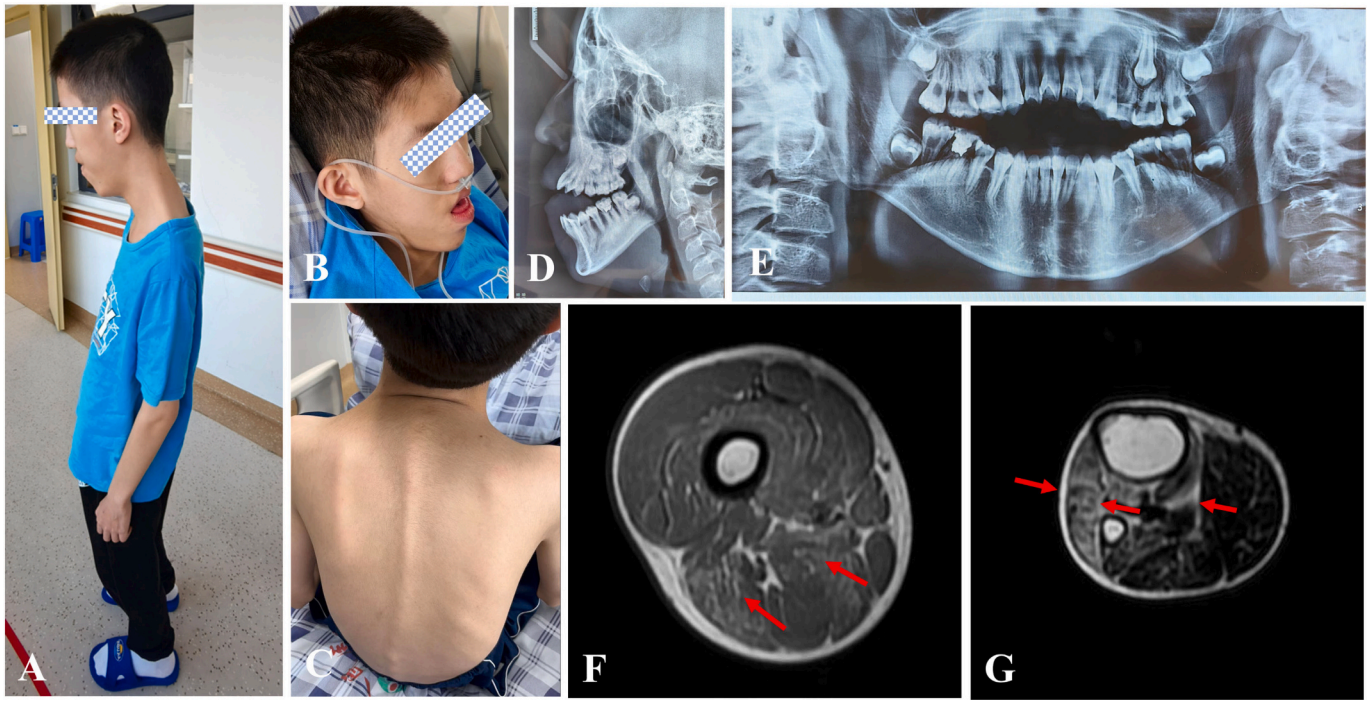

Fig. 1. Clinical presentation and imageology analysis. Lateral and posterior images of the proband (A, B and C). Physical examination findings, (D and E) X-ray images of teeth, (F) Right thigh MRI scans of the patient, fatty infiltration in the muscles and the muscle gaps (arrow), (G) Right calf MRI scans of the patient, fatty infiltration in the muscles and the muscle gaps (arrow).

Medical Research Council (MRC) scale. Symmetrical weakness was identified in the neck flexors (MRC grade 4), deltoid muscles (MRC grade 4), trapezius muscles (MRC grade 4/5), and foot extensor muscles (MRC grade 4). Additionally, the patient exhibited hypotonia, absent tendon reflexes in both knees, and no pathological findings on further examination. Further MRI of the right lower extremity showed fatty infiltration of muscles and muscle space (Fig. 1F-G).

2.2. Muscle biopsy and electron microscopic findings

Hematoxylin and Eosin (H&E) staining showed a small number of inflammatory cells infiltrating the perimysium and endomysium, with scattered and grouped small round atrophic muscle fibers, and muscle fibers were heterogeneous in size and biphasic in distribution (Fig. 2A). Additionally, it is observed that inner nuclear muscle fibers and scattered muscle fibers contain a small number of fine vacuoles. Nicotinamide Adenine Dinucleotide Hydride (NADH) staining showed mild local grouping of homotypic muscle fibers (Fig. 2B). Neuron-Specific Enolase (NSE) staining showed scattered deep staining in the fasciculus and muscle fiber space, indicating atrophy of muscle fibers and inflammatory cell infiltration (Fig. 2C). Oil Red O (ORO) staining revealed slight lipid droplets deposited within scattered muscle fibers (Fig. 2D). Immunohistochemical staining of fast (MHC-f) and slow (MHC-s) myosin heavy chains (Fig. 2E, F) revealed local mild grouping of homotypic muscle fibers with a predominance of type I fibers with smaller diameters. Lymphocytes and mononuclear phagocytes are scattered in the perimysium and intermuscular spaces. (Fig. 2G-I). Under the electron microscope, we observed ultrastructural pathological changes, including the muscle cells exhibited uneven sizes, with significantly widened local spaces and edema (Fig. 2J). Disorganized myofibrillar arrangements in some muscle cells, the disappearance of focal sarcomeres, multiple tears of myofibrils, and local lamellar dissolution (Fig. 2K). Thus, the possibility of congenital myopathy was considered.

2.3. Genetic analysis

With parental consent, trio-based whole exome sequencing (trio-WES) was conducted, revealing that the patient carries a heterozygous missense variant in *TPM3* c.44A > G, (p.Asp15Gly) (NM_152263.4). This variant was confirmed to be a de novo mutation, as it was absent in both parents (PS2), and its presence was further validated by Sanger sequencing (Fig. 3A-D). The variant was absent in the ClinVar and HGMD databases, nor in the gnomAD and 1000 Genomes databases

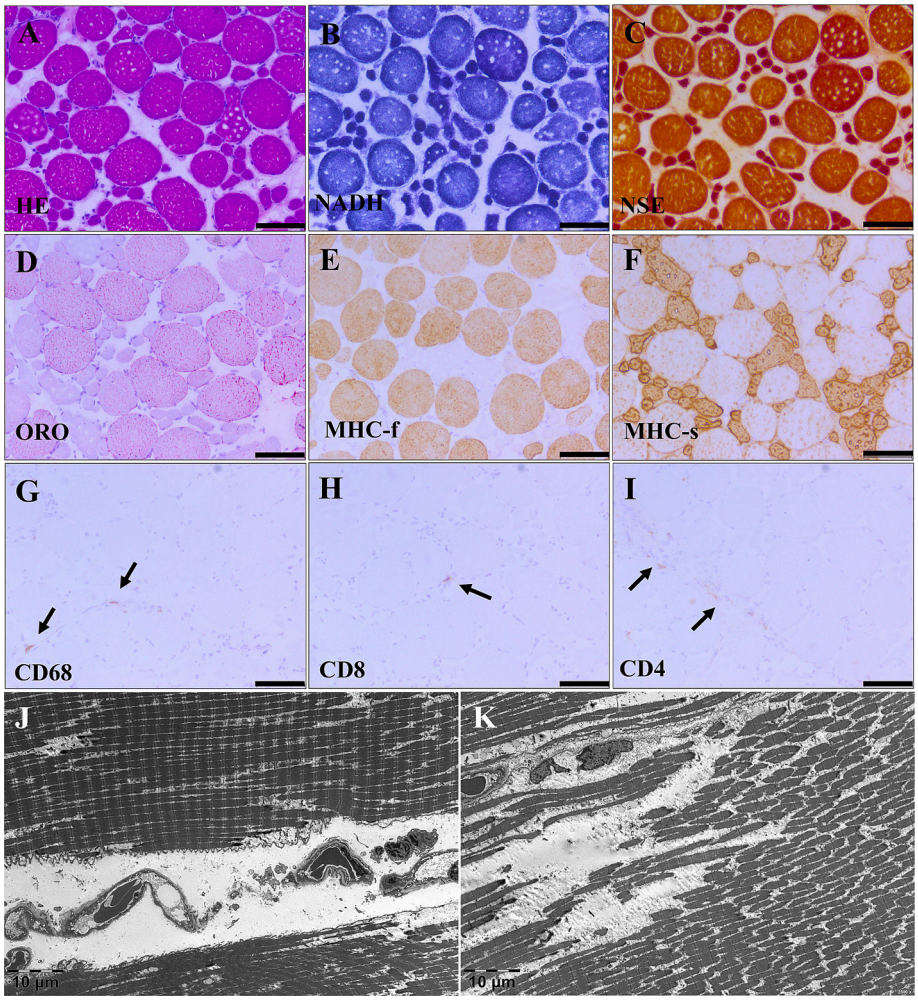

Fig. 2. Muscle biopsy of the left upper arm. (A) H&E staining, the muscle fibers exhibit uneven size with a bimodal distribution, ranging in diameter from 15 to 25 μm and 80-100 μm. (B) NADH staining, local mild grouping of homotypic muscle fibers. (C) NSE staining showed scattered deep staining in the fasciculus and muscle fiber space. (D) ORO staining, slight lipid deposition in scattered muscle fibers. (*E*-I) Immunohistochemical staining, (E) MHC-f and (F) MHC-s, mild homogenization of muscle fiber groups is observed in some areas. (G-I) shows sporadic positivity for CD68, CD8, and CD4 (arrows). (J-K). Ultrastructural examination revealed disorganized arrangement of myofibrils within muscle cells, focal disappearance of sarcomeres, multiple foci of myofibrillar fragmentation, and local patchy dissolution under an electron microscope. Scale bars: panels (A–I) 100 μm, panel (J-K) 10 μm.

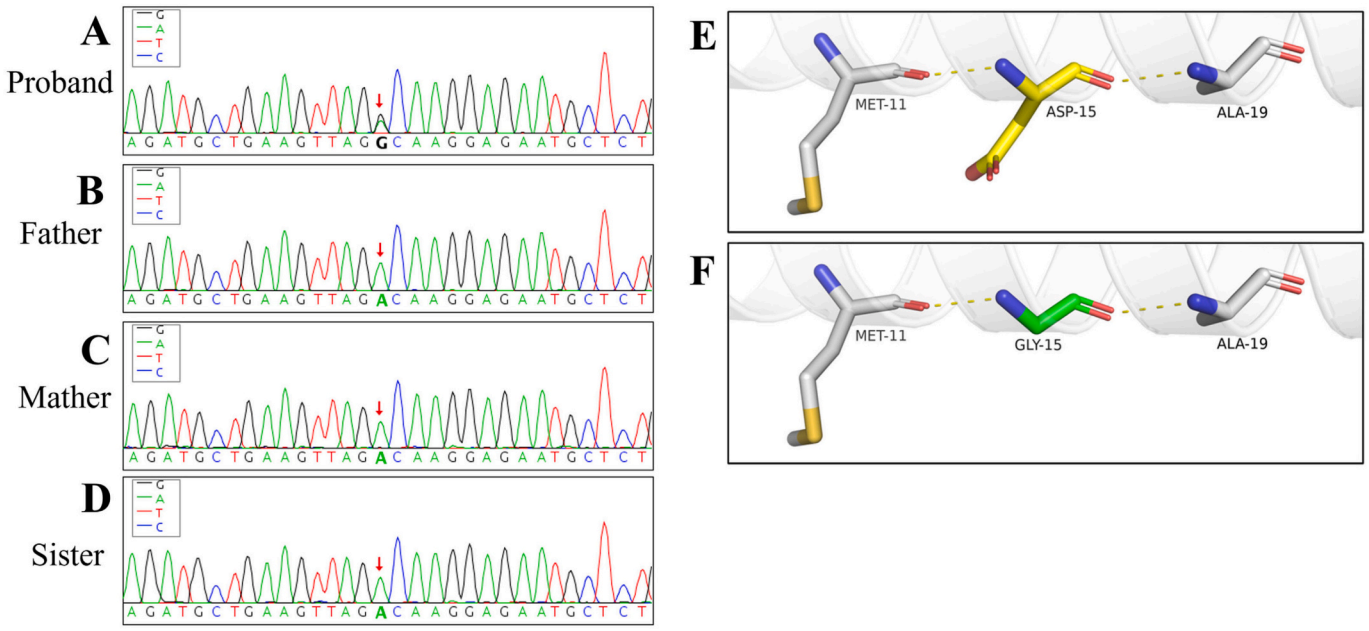

Fig. 3. (A-D) The exome gene sequencing and mapping results, especially for the mutation sites. (A) Proband, heterozygous mutation at chr1:154164451 c.44A > G, (p.Asp15Gly); (B, C and D) Father, mother and sister, wide-type at chr1:154164451. (*E*-F) Tertiary structure analysis of the mutation site in TPM3 protein. (E) Wild type, (F) Mutant c.44A > G, p.Asp15Gly.

(PM2). And, it has not been reported in the literature. *TPM3* c.44A > G (p. Asp15Gly) is a novel missense mutation occurring at the same amino acid position as other potentially pathogenic missense variants (e.g., p. Asp15Asn, p.Asp15Val, p.Asp15His) reported in ClinVar (PM5). Bioinformatics tools SIFT, PolyPhen, and Mutation Taster predicted this variant to be deleterious, probably damaging, and disease-causing, respectively (PP3). The variant also received a CADD score of 29.5, indicating a very high likelihood of causing disease. Conservation analysis using the GERP^{++} score yielded a value of 5.75, indicating a very conservative estimate (PP3). Analysis of the mutation site using PyMOL software revealed that the variant affected intermolecular interactions within the Tpm3.12, thus impacting its normal activity (Fig. 3E, F). Missense variant in *TMP3* that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease (PP2). In summary, the variant was classified as pathogenic (PS2, PM2, PM5, PP3, and PP2).

3. Discussion

CMYP4A, a rare autosomal dominant genetic disorder, presents with muscle weakness in infancy or childhood, varying in severity and pattern [13,17,18]. This study reports a novel missense variant c.44A > G in *TPM3* that results in p.Asp15Gly. According to the ACMG standards and the suggestions of pathogenicity prediction tools, the *TPM3* c.44A > G (p.Asp15Gly) variant is considered pathogenic. Moreover, PyMOL software analysis showed that the variant affected intermolecular interactions within the Tpm3.12. The patient's clinical phenotypes were largely consistent with CMYP4A. In summary, our research findings allow us to classify the *TPM3* c.44A > G (p.a sp15gly) variant as pathogenic, and this mutation leads to the patient's manifestation of CMYP4A.

TPM3, along with *TPM1*, *TPM2*, and *TPM4*, are the four known coding genes for vertebrate tropomyosin. These genes produce distinct mature transcripts and corresponding protein isoforms through alternative splicing in both skeletal and non-skeletal muscle tissues [19,20]. In skeletal muscle, tropomyosin isoforms serve as a component of the thin filaments in the sarcomere, playing a role in regulating the interaction between actin and myosin involving calcium ions, and controlling filament length through its interaction with tropomodulin. The two skeletal muscle isoforms of tropomyosin, Tpm1.1 and Tpm2.2, form α-helical dimers through interactions at their N-terminal and C-terminal regions. These dimers bind within the grooves of filamentous actin, stabilizing the actin filaments and playing a crucial role in the functional regulation of actin dynamics. In this study, the *TPM3* c.44A > G variant results in the substitution of aspartic acid with glycine at position 15 of the Tpm3.12. This variant causes an amino acid replacement in the N-terminal segment of Tpm3.12, potentially affecting the interaction between the N-terminal and C-terminal segments, thereby disrupting its binding to regulatory proteins such as tropomodulin. Such disruption may weaken the capping function at the filament ends, resulting in the loss of control over actin filament elongation or depolymerization, leading to abnormalities in filament stability and length regulation [8]. Furthermore, Tpm3.12 mutations may affect its regulation of the interaction between actin and myosin. In summary, the *TPM3* c.44A > G variant results in structural and functional abnormalities of the Tpm3.12 protein, leading to congenital myopathy.

CFTD is a key characteristic of CMYP4A and the most prevalent diagnosis in patients with TPM3 mutations. It is characterized by the selective atrophy of type I fibers [21]. In this study, the muscle biopsy revealed findings consistent with CFTD, including type I fiber hypotrophy and an elevated proportion of type II fibers. This imbalance likely contributes to reduced muscle strength and endurance, ultimately impairing motor function [21].

TPM3 is primarily expressed in type I muscle fibers. Studies have demonstrated that this gene, like many others, exhibits phenotypic heterogeneity, meaning that the same mutation can give rise to different phenotypes, and there is no clear correlation between genotype and the severity of the phenotype [22]. Additionally, the results of muscle biopsies vary across different age groups [23,24]. Therefore, the type and severity of the disease cannot be solely determined by the type of gene mutation. Currently, muscle biopsy and muscle magnetic resonance imaging remain essential diagnostic tools for myopathy. Based on trio-WES, muscle biopsy, MRI results, and the patient's clinical phenotype, the study determined that the patient's pathogenic type is CMYP4A.

In addition, the patient presented with mild cardiac abnormalities. Considering the patient's difficulty in breathing and diffuse lung

inflammation in both lungs, we speculate that lung inflammation may have led to pulmonary hypertension, which can cause right heart enlargement and subsequently tricuspid insufficiency. Additionally, since *TPM3* is also expressed in cardiomyocytes, we cannot rule out the possibility that the *TPM3* c.44A > G variant contributes to cardiac dysfunction. In previous reports, a small number of patients with mutations in *TPM3* have shown similar clinical manifestations, mild, unspecific cardiac abnormalities, including valve insufficiency, aortic dilatation or mildly reduced cardiac function [25]. Therefore, we emphasize the importance of cardiac examination in patients with *TPM3* mutations.

Interestingly, some unreported phenotypes were also observed, the patient was breathing with his mouth open, along with a skeletal open bite and poor tooth alignment, which prevented him from completely closing the mouth. Currently, there are few reports on tooth anomalies caused by mutations in the *TPM3*. The tooth anomalies observed in this case represent a new phenotype. However, the potential mechanisms underlying these anomalies remain unclear. Existing studies have reported that mutations in the *TPM3* may lead to conditions such as myasthenia, hypertrophy of the masticatory muscles, and craniofacial skeletal abnormalities (e.g., long face and small mandible) [25]. We speculate that mutations in the *TPM3* may impair the function of the jaw musculature, subsequently resulting in craniofacial skeletal anomalies, including structural abnormalities of the maxilla and mandible. These abnormalities may ultimately cause the upper and lower teeth to fail to make proper contact or achieve normal occlusion, which could lead to the children developing skeletal open bite and tooth developmental anomalies. Furthermore, the patient's mouth breathing may be related to skeletal open bite.

Treatment for myopathies often involves respiratory muscles support, with respiratory muscles and lung function training being effective [26]. Non-invasive ventilators are also beneficial [27]. The patient, with respiratory muscle weakness, requires nighttime non-invasive ventilator support and may benefit from improved respiratory function and extended lifespan through training. Despite the potential of gene therapy for neuromuscular diseases and ongoing research, there is currently no reliable treatment for congenital myopathies caused by genetic mutations, due to their low incidence and complex pathogenesis [28,29].

4. Conclusion

This study presents a case of CMYP4A with a novel missense variant c.44A > G (p. Asp15Gly) in *TPM3*. In addition to having classical clinical features, it exhibits novel clinical phenotypes that have never been reported before. This enriches the mutation spectrum of the *TPM3*, provides a reference for clinical diagnosis and genetic counseling of children with CMYP4A, and contributes to enhancing clinicians' understanding of this condition.

Funding

This work was supported by grants from the Zhanjiang Science and Technology Plan Project (2021A05136, 2021A05116 and 2022A01079), and the Hospital-Level Research Initiation Project at Central People's Hospital of Zhanjiang (2022A04 and 2022A05).

Ethics approval and consent to participate

The study was approved by the Ethics Review Committee of Central People's Hospital of Zhanjiang (ethics number: YJ[IIT-2022-023-02]). Informed written consent was obtained from all participants and the parents of the proband.

CRediT authorship contribution statement

Shanshan Fan: Writing – review & editing, Funding acquisition, Formal analysis. **Guangpu Su:** Writing – original draft, Data curation. **Mingfeng Li:** Writing – review & editing. **Yunmiao Guo:** Writing – review & editing. **Lei Wang:** Writing – review & editing, Supervision. **Jinliang Li:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare no conflict of interests.

Acknowledgements

We are grateful to the patient and his family in our research study.

Data availability

All the data generated or analyzed during this study are included in this published article.

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