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Case report: A new *de novo* mutation of the Troponin T2 gene in a Chinese patient with dilated cardiomyopathy

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Dilated cardiomyopathy (DCM) is a cardiovascular disease characterized by persistent ventricular dilatation and systolic dysfunction. DCM has a variety of causes, including myocarditis; exposure to narcotics, alcohol, or other toxins; and metabolic or endocrine disorders. Genetic factors play a dominant role in 30%–40% of DCM cases. Here, we report a case of DCM with very severe heart failure. Because of the severity of heart failure, the patient underwent heart transplantation. We speculated that the patient's DCM might be due to a mutation; hence, we performed whole-exome sequencing of the patient and their parents, which showed a *de novo* heterozygous mutation (NM_001001431.2c.769G>A:p.E257K) in *TNNT2*, which was considered pathogenic according to the ACMG pathogenicity assessment. This finding expands the genetic map of DCM and *TNNT2* and will be important for future studies on the genetic and disease relationships between DCM and *TNNT2*.

KEYWORDS

dilated cardiomyopathy, mutation, TNNT2, genome, whole-exome sequencing

1. Introduction

Dilated cardiomyopathy (DCM) is a cardiovascular disease characterized by continuous ventricular dilatation and systolic dysfunction, with an incidence of approximately 1 in every 2,500 individuals (1–3). Due to its high prevalence, morbidity, and mortality, as well as frequent hospitalizations, DCM is a significant public health concern among adults. DCM has numerous causes, including myocarditis; exposure to narcotics, alcohol, or other toxins; and metabolic or endocrine disorders. In 30%–40% of DCM cases, genetic mutations involving genes responsible for cytoskeleton, sarcomere, and nuclear envelope proteins are observed (4, 5). Due to the heterogeneity of DCM etiology, a thorough diagnostic evaluation is required to identify the specific underlying cause and exclude other diseases with overlapping phenotypes (6).

Currently, over 50 genes encoding cytoskeletal, nuclear skeleton, mitochondrial, and calcium-handling proteins are linked to hereditary DCM. Pathogenic variants of DCM have been reported with a heterogeneous group of genes encoding proteins with different functions, such as sarcomere integrity and force transmission, cytoskeletal architecture, cell–cell contact, nuclear organization, transcription, and ion channel activity. Although extensive genetic heterogeneity is present, titin (*TTN*) is the most common disease gene accounting for 20%–25% of the genetic causes (7). The second most prevalent gene is lamin A/C (*LMNA*), which accounts for about 6% of the

genetic causes, followed by beta-myosin heavy chain (MYH7) (8). Several other genes account for 1%–2% of familial cases, while many others are less frequent or even reported only once. Alterations, such as copy number variations (CNVs), have been infrequently reported in association with DCM (9). This disorder is therefore regarded as a complex of multiple genetic and structural disorders. Recently, whole-exome sequencing (WES) has been utilized more frequently to examine the genetic basis of the disease by sequencing the protein-coding exome. This method of genetic screening for extremely uncommon Mendelian disorders is accurate and cost-effective (6). In addition, unlike traditional sequencing methodologies, WES does not require *a priori* assumptions regarding the causes of disease (10). Troponin T (TNNT2) cardiomyopathy is an aggressive, early-onset disease accompanied by substantial morbidity and mortality. Elegant functional investigations have previously demonstrated distinctive changes in calcium sensitivity and contractility in DCM and hypertrophic cardiomyopathy (HCM) resulting from *TNNT2* mutations.

Here, we describe a rare case of *TNNT2* mutation resulting in dilated cardiomyopathy. The patient had to undergo a heart transplantation due to the severity of heart failure.

2. Case report

2.1. Clinical information

The patient was a 31-year-old man who experienced recurrent shortness of breath and poor appetite for 3 months, which worsened in the last 2 weeks. The patient was initially hospitalized, and echocardiography revealed the following values:

LVED 78 mm, LAS 58 mm, RVD 39 mm, FAS 78 mm, IVsd 8 mm, LVPWd 8 mm, and EF20%. The results of the color Doppler ultrasound suggested global enlargement of the heart and generally low and uncoordinated ventricular wall motion. Myocardial tissue at the apex of the left ventricle was mildly lax. The apices of the left and right ventricles were evaluated for thrombosis. We found mild aortic regurgitation, moderate-severe bicuspid valve regurgitation, and mild tricuspid valve regurgitation. The pulmonary artery was moderately dilated and had mild regurgitation. We estimated an increase in the pulmonary artery pressure. Moreover, his left ventricular function had deteriorated (Figures 1A, B). He was diagnosed with DCM, moderate-severe bicuspid regurgitation, left ventricular apical thrombosis, right ventricular apical thrombosis, occasional ventricular premature beats and paroxysmal ventricular tachycardia, right pleural effusion, chronic heart failure, acute heart failure, and heart function grade IV. 2163. The patient was discharged 1 week after receiving symptomatic and supportive interventions (cardiotonic, diuresis, ventricular rate control, and inhibition of myocardial remodeling). Post-discharge, the patient received anti-heart failure medication on a regular basis. Three months later, the patient was readmitted to the hospital due to recurrent shortness of breath and poor appetite for 7 months, which had worsened over 20 days. We speculated dilated cardiomyopathy. After hospitalization, the patient was administered cardiotonic, diuretic, anti-heart failure, transplantation of myocardial remodeling, and prognostic enhancement medication. The patient continued to be treated post-discharge with cardiotonic, diuretic, and other medications, but the symptoms of chest constriction and shortness of breath persisted. The patient sought admission to our department for surgical treatment.

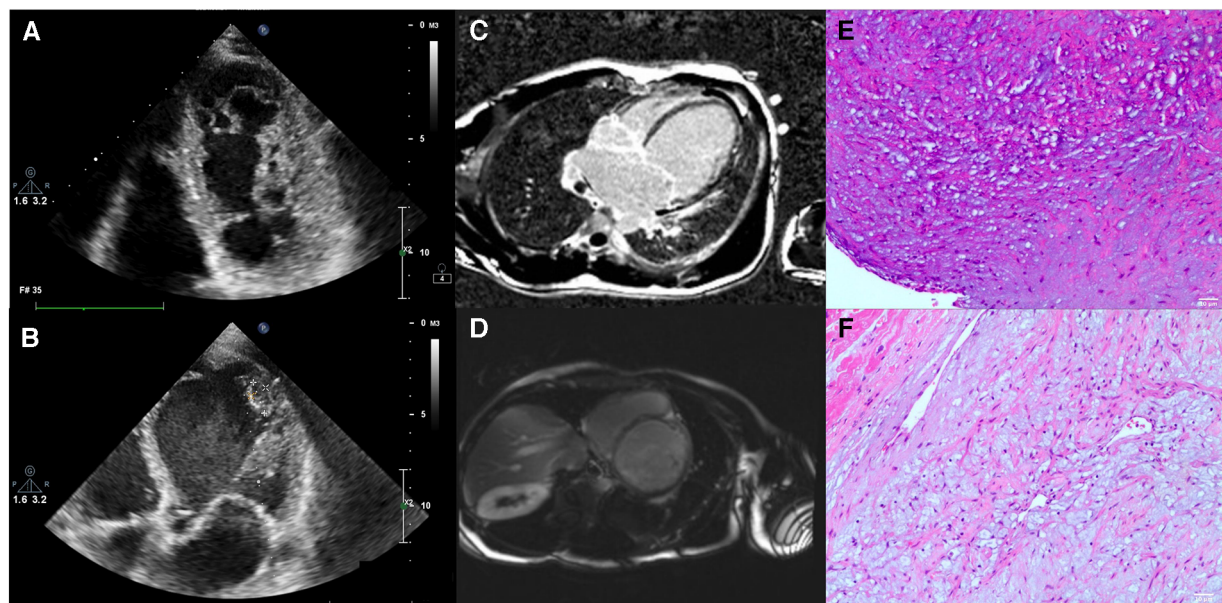
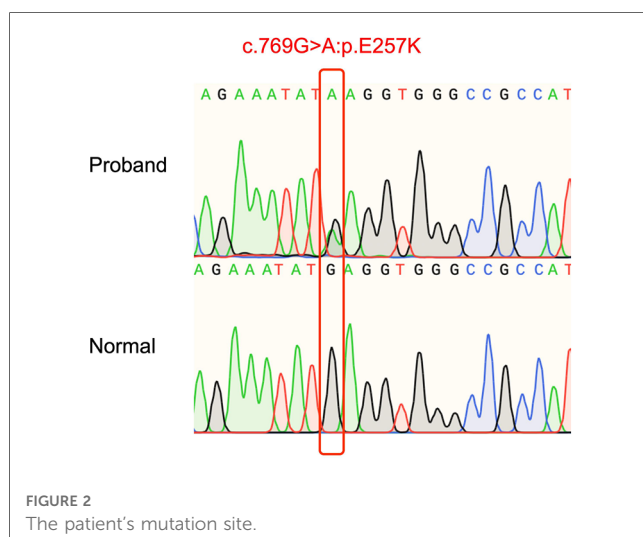


FIGURE 1
The patient's examination results. (A,B) Show the echocardiographic results of the patient's heart. (C,D) Show the images from a cardiac MRI examination. (E,F) show the pathological examination of recipient heart specimens from patients.

Cardiac magnetic resonance imaging (MRI) revealed a small amount of delayed enhancement in the left ventricular septal wall, consistent with dilated cardiomyopathy and tricuspid insufficiency (Figures 1D, E). A coronary computed tomography angiography (CTA) was also performed, and the coronary arteries were found to be unproblematic. After matching with a donor, we promptly performed a heart transplantation using the dual-chamber method. The patient was discharged from the hospital 3 weeks after surgery. Hematoxylin and eosin (HE) staining revealed focal interstitial fibrous hyperplasia with vitreous change, mucinous degeneration, angiogenesis, and dilated muscle red tissue (Figures 1E, F).

2.2. Genetic analysis

DNA from the patient and his parents was extracted from peripheral venous blood. Genomic DNA was prepared using the DNeasy Blood & Tissue Kit (Qiagen, Valencia, CA, USA). The majority of WES and CNV sequencing (Beijing, China) was completed by the Berry Genomics Bioinformatics Institute. Exons were extracted using the Agilent SureSelect Human All Exon V6 reagent, and high-throughput sequencing was performed using the Illumina HiSeq X-10. The Berry Genomics Bioinformatics Institute also performed fundamental bioinformatics analyses, including reads, mapping, variant detection, filtering, and annotation. We then filtered the data as follows: (1) we ranked genes using Polyphen-2, SIFT, MutationTaster, and CADD; (2) we excluded non-coding regions and synonymous variants that had no effect on splicing; and (3) we examined variants in the 1,000 g, Exome Aggregation Consortium, and gnomAD databases. Sanger sequencing was used to identify a unique non-synonymous variant. WES revealed a *de novo* heterozygous mutation *TNNT2* (NM_001001431.2:c.769G>A:p.E257K) in the patient, which was absent in the patient's parents (Figure 2). Based on the ACMG pathogenicity assessment, we chose PM1 + PM2 + PM6 + PP3 + PP4 to evaluate this mutation as likely pathogenic. Consequently, this patient's DCM may have been caused by a mutation in this gene.



3. Discussion

DCM is a prevalent primary myocardial disease characterized by left ventricular or biventricular systolic dysfunction, which frequently leads to heart failure, arrhythmia, thromboembolism, and sudden mortality. DCM is associated with the dysfunction of diverse pathways, including Z discs, nuclear lamins, intermediate filaments, and dystrophin-associated glycoprotein complexes (11), in contrast to hypertrophic cardiomyopathy (HCM), which is strongly associated with myosin mutations. Idiopathic DCM is diagnosed when detectable causes of DCM are ruled out (12). These include hypothyroidism, chemotherapy medications, alcoholism, ischemia, and known pathogenic mutations. Studies on DCM have determined that 20% to 50% of DCM cases are due to familial inheritance (13, 14), which is associated with rare mutations in more than 40 genes (15). In 90% of cases, inheritance is autosomal dominant, while autosomal recessive and X-linked inheritance are uncommon (4). The majority of these mutations are single-nucleotide variants that alter the amino acid sequence of the encoded protein. Rare mutations consist of minor in-frame insertions or deletions, but rarely large deletions (16).

At present, the main pathogenic genes of DCM include *TTN*, *LMNA*, *RBM20*, and *DES*. The discovery of the role of *TTN* truncating variants in DCM has been a major advance (17). *TTN* encodes the giant protein titin, the largest known protein expressed in the heart. Titin acts as a spring, providing the drive for and regulating sarcomere contraction and signaling (18). Missense variants in *TTN* have a high prevalence, both rare and common (7). Missense and truncating mutations in *LMNA* account for 5%–8% of inherited DCM cases (19). As with *TTN*, *LMNA* mutations are inherited in an autosomal dominant manner. A single *LMNA* gene encodes laminin A and C, and differential splicing of the 3' termini results in the two proteins being identical for their first 566 amino acids. *LMNA* mutations result in various diseases, from premature aging to myopathy and DCM (20, 21). RNA-binding motif 20 (*RBM20*) is an RNA-binding protein that is highly expressed in the atrium and ventricle. Dominant mutations in the *RBM20* gene were first described in DCM, accounting for 1%–5% of DCM cases (22). ipSC-derived cardiomyocytes with the *RBM20* R636S mutation generate gene expression and splicing profiles consistent with cardiomyopathy, affecting not only *TTN* but also *CAMK2D* and *CACNA1C* (23, 24). *DES* encodes the protein desmin, a functional structure in cardiac myocytes in terms of cellular mechanical stability and connectivity. Desmin functions as part of the dystrophin-associated glycoprotein complex and primarily affects the cytoskeleton (25). The *DES* variant is associated with hopelessness and affected patients mainly present with muscle weakness, conduction block, and DCM (26, 27).

TNNT2 (OMIM: 191045) encodes the thin filament contractile protein cardiac troponin T, a troponin complex that binds to tropomyosin in sarcomeres (28). The 25 kb genome of *TNNT2* contains 16 exons and is located on chromosome 1q32. Cardiac troponin (cTn) consists of three distinct subunits,

each of which is named for its function: cardiac troponin I (cTnI) inhibits actin ATPase activity independently of other Tn subunits; cardiac troponin C (cTnC) binds Ca^{2+} to low-affinity Ca^{2+} -specific binding sites to alleviate cTnI inhibition (29, 30); and cardiac troponin T (cTnT) attaches tropomyosin (Tm) to the entire cTn complex. Recent investigations have revealed that cardiac TnT is essential not only for the structural integrity of the troponin complex but also for sarcomere assembly and cardiac contractility (31). The troponin complex is a calcium sensor that regulates striated muscle contraction and modifies the activity and force of actin ATPase (32). *TNNT2* gene mutations have been linked to familial HCM and DCM over the past decade (33–35). Numerous studies on recombination systems have provided valuable information on the functional impact of TnT disease-related mutations (36, 37).

We described a DCM patient with a mutated *TNNT2* gene. DCM was confirmed following a comprehensive examination of this patient. WES was then conducted, and sequencing revealed a *de novo* mutation that had not been previously reported. According to the ACMG pathogenicity assessment, we determined that this mutation was likely pathogenic. This patient most likely experienced a condition associated with this mutation. According to reports, truncating troponin T may result in a significant decrease in force production during cardiac contraction (38). It is possible that troponin T deficiency stimulates cardiac enlargement by increasing myocardial power and energy burden and decreasing force production during cardiac contraction. In addition, cTnT, composed of troponin C, troponin I, and troponin T, regulates myocardial contraction and relaxation by controlling calcium concentration-dependent interactions of 2+ actin (39). *TNNT2* gene mutations may affect the complex stability and/or interaction between myosin and troponin T, which may alter the actin interaction. Furthermore, *TNNT2* gene mutations can reduce the sensitivity of the complex to Ca^{2+} , thereby reducing the contractility of the myocardium. In contrast, mutations in genes encoding sarcomere proteins associated with HCM can increase Ca^{2+} sensitivity, thereby increasing cardiac contractility (40). Thus, mutations in different proteins may be associated with common cardiac phenotypes, DCM or HCM, depending on the ultimate effect of the mutation on the strength of myocardial contraction. The mutation in *TNNT2* results in a disease with an early onset and a poor prognosis. Therefore, DCM patients with a *TNNT2* mutation should receive early intervention, routine follow-ups, and surgical treatment for heart failure.

In summary, we report a novel mutation in *TNNT2* in a patient with DCM, which expands the genetic map of DCM and *TNNT2*.

Data availability statement

The data presented in the study are deposited in the dbSNP repository, accession number rs1131691898.

Ethics statement

The studies involving humans were approved by Ethics Committee, Second Xiangya Hospital, Central South University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

HY: Conceptualization, Writing – original draft, Writing – review & editing. KG: Conceptualization, Writing – original draft, Writing – review & editing. YL: Conceptualization, Writing – review & editing. LW: Conceptualization, Writing – review & editing. ZT: Conceptualization, Writing – review & editing. YY: Conceptualization, Writing – review & editing. LX: Conceptualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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