Overlap phenotypes of the left ventricular noncompaction and hypertrophic cardiomyopathy with complex arrhythmias and heart failure induced by the novel truncated DSC2 mutation

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Abstract

Background: The left ventricular noncompaction cardiomyopathy (LVNC) is a rare subtype of cardiomyopathy associated with a high risk of heart failure (HF), thromboembolism, arrhythmia, and sudden cardiac death.

Methods: The proband with overlap phenotypes of LVNC and hypertrophic cardiomyopathy (HCM) complicates atrial fibrillation (AF), ventricular tachycardia (VT), and HF due to the diffuse myocardial lesion, which were diagnosed by electrocardiogram, echocardiogram and cardiac magnetic resonance imaging. Peripheral blood was collected from the proband and his relatives. DNA was extracted from the peripheral blood of proband for high-throughput target capture sequencing. The Sanger sequence verified the variants. The protein was extracted from the skin of the proband and healthy volunteer. The expression difference of desmocollin2 was detected by Western blot.

Results: The novel heterozygous truncated mutation (p.K47Rfs*2) of the DSC2 gene encoding an important component of desmosomes was detected by targeted capture sequencing. The western blots showed that the expressing level of functional desmocollin2 protein (~94kd) was lower in the proband than that in the healthy volunteer, indicating that DSC2 p.K47Rfs*2 obviously reduced the functional desmocollin2 protein expression in the proband.

Conclusion: The heterozygous DSC2 p.K47Rfs*2 remarkably and abnormally reduced the functional desmocollin2 expression, which may potentially induce the overlap phenotypes of LVNC and HCM, complicating AF, VT, and HF.

Keywords: Left ventricular noncompaction cardiomyopathy, Hypertrophic cardiomyopathy, Heart failure, desmocollin2, Desmosome

Introduction

The left ventricular noncompaction cardiomyopathy (LVNC) is a rare subtype of cardiomyopathy (CM) and is characterized by predominant left ventricular trabeculations with deep intertrabecular recesses and thinning of the compact epicardium [1]. LVNC can coexist with dilated (DCM), hypertrophic (HCM), restrictive (RCM), and arrhythmogenic cardiomyopathy (ACM)
LVNC diagnosis was based on the presence of an end-systolic ratio of the noncompacted layer to compacted layer above 2 (NC/C ≥ 2.0) on echocardiography [10] and/or an end-diastolic ratio of the noncompacted and compacted layer greater than 2.3/2.0 (NC/C ≥ 2.3/2.0) in the long/short-axis view of CMRI with specificity and negative predictive values of 99% [11]. The left ventricular systolic dysfunction was defined as systolic LVEF < 50% by echocardiogram [1]. The clinical assessment also included physical examination and 12-lead and Holter electrocardiograms (ECGs). The N-terminal of B-type natriuretic peptide precursor (NT-proBNP) assays was performed at a central independent laboratory using a commercially available kit (Roche Diagnostics, Mannheim, Germany). We obtained the skin and subcutaneous tissue of the upper left limb of the patient (II: 1) and healthy volunteer through small surgery and carried out molecular biological detection. The healthy volunteer was a 37-year-old male without cardiac diseases verified by ECG and echocardiogram.

CMRI Imaging was acquired using the 1.5 T MR imaging system (MAGNETOM Aera, Siemens Healthcare, Germany) by using a 6-channel phased-array coil. After scout and reference scans, functional and geometric assessments were achieved using ECG-gated, cine steady-state-free precession images in standard long- (2-, 3-, and 4-chamber views) and short-axis orientations with full ventricle coverage from basis to apex. Left and right ventricular outflow tract cine sequences were also obtained. Cine images with a temporal resolution of approximately 40 ms were obtained. Additional pulse sequences, including T1WI and T2WI of blood-suppressed double inversion recovery fast spin-echo, were acquired in a standard location before contrast administration. Then, the dynamic enhancement was performed during the administration of 0.2 mmol/kg contrast agent (Gadovist, Bayer Healthcare, Berlin, Germany) with 50 frames. Late gadolinium-enhanced imaging was performed with 20 min delay and phase-sensitive inversion recovery sequence to detect myocardial scarring or fibrosis. CMRI analyses were performed using SigoVia (Siemens). The functional and geometric left ventricular indices, including left and right ventricular end-diastolic volumes, LVEF and right ventricular ejection fraction, indexed left ventricular compacted mass with papillary muscles, indexed left ventricular noncompacted mass, and their ratio was determined. In addition, the end-diastolic extent of compacted and noncompacted myocardium and their ratio were measured in one long axis geometry.

Collection of human specimens and target capture sequencing Skin biopsies were collected from the upper left arm of the proband and healthy volunteer. Protein was extracted from tissues. Peripheral blood was collected from the proband and his relatives. DNA was extracted (using D3537-02#MagPure Buffy Coat DNA Midi KF Kit, Magen, Beijing, China) from the peripheral blood of proband for high-throughput target capture sequencing using Gene fragment capture chip (MGI BGI EXOME V4, Shenzhen, China) and MGIseq-2000 sequencer (MGI, Shenzhen, China). The panel of common risk

[2–4]. LVNC is an inherited cardiac disease, classified as primary genetic CM, and associated with high risks of syncope, chest pain, heart failure (HF), malignant arrhythmia, sudden cardiac death (SCD), and thromboembolism [5]. A recent systematic review illustrated that the risks of thromboembolism and ventricular arrhythmias in LVNC are similar to DCM. Additionally, LVNC has a higher incidence of HF hospitalization than DCM. The low left ventricular ejection fraction (LVEF) induced by LVNC is associated with a poor prognosis [6]. A previous genetic study indicated that the mutations of genes encoding sarcomeric proteins account for up to 30% of LVNC [7]. Other common mutations of genes encoding cytoskeletal, Z-line, and mitochondrial proteins include myosin heavy chain (MYH7), protein-binding protein C myosin (MYBP3), tropomyosin alfa (TPM1), myocardin actin (ACTC1), troponin T (TNNT2), and cardiac troponin I. The less common mutations of genes inducing LVNC include Z-band protein mutations, such as Cypher/ZASP cytoskeleton protein, alpha-distrobrevin (DTNA), calcium transport proteins, calsequestrin, phospholamban, membrane proteins (A/C lamina), parazinc-finger transcription factor [8], and mitochondrial enzymes. Our study identifies a proband with rare overlap phenotypes of LVNC and HCM from a Chinese Han family and explores the potential pathogenesis via genetic screening and molecular experiments.

Material and methods
Patients and clinical variables
All participants signed informed consent. All procedures performed in the study involving human participants were in accordance with the Declaration of Helsinki and ethical standards and were approved by the Medicine Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University (No. 2020K216-1).

In accordance with previous studies [1, 9], LVNC was diagnosed by cardiologists based on clinical presentation and interpretation of echocardiogram and cardiac magnetic resonance imaging (CMRI) results by using the Jenni and Petersen criteria, respectively [10, 11]. The LVNC diagnosis was based on the presence of an end-systolic ratio of the noncompacted layer to compacted layer above 2 (NC/C ≥ 2.0) on echocardiography [10] and/or an end-diastolic ratio of the noncompacted and compacted layer greater than 2.3/2.0 (NC/C ≥ 2.3/2.0) in the long/short-axis view of CMRI with specificity and negative predictive values of 99% [11]. The left ventricular systolic dysfunction was defined as systolic LVEF < 50% by echocardiogram [1]. The clinical assessment also included physical examination and 12-lead and Holter electrocardiograms (ECGs). The N-terminal of B-type natriuretic peptide precursor (NT-proBNP)
genes associated with CMs and arrhythmias (Table 1) was detected in the proband (II: 1). SNPs and Indels were annotated using a pipeline, in which all insertion and deletion variants occurring at coding regions were considered damaging. Nonsynonymous SNPs were predicted using the SIFT (http://sift.jcvi.org/www/), PolyPhen-2 (Polymorphism Phenotyping v2, http://genetics.bwh.harvard.edu/pph2/), and MetaSVM [12]. Variants were classified as “pathogenic (P)“, “likely pathogenic (LP)“, “uncertain significance (US or VUS)“, “likely benign (LB)“, or “benign (B)” by using the InterVar tool [13] following the 2015 ACMG/ACP guidelines [14]. Variants in predisposing genes associated with hereditary arrhythmias and CMs were screened, and the filtering criteria were as follows: (1) same variants in the WES data; (2) nonsense, nonsense, insertion, and deletion variants; and (3) SNPs with minor allele frequency < 0.01 according to the SNP database of National Center. Other familial members were validated using the Sanger sequencing for potential pathogenic genes. Details are shown in our previous research [15].

**ACMG classification**

According to ACMG standards and guidelines, all variants have been reclassified for interpreting sequence variants as P, LP, VUS, LB, or B [14]. The PM2 item in the ACMG classification is considered fulfilled if minor allele frequency (MAF) in relevant population databases is ≤ 0.1% [16]. The vast majority of reported pathogenic variants in arrhythmia and CM are extremely rare (MAF < 0.01%) [17]. The classification “high degree of pathogenicity” (item PVS1) should only be used for rare variants in genes where the loss of function is a well-established disease mechanism [18–20]. In the case of VUS, a rare variant classified as ambiguous does not provide molecular confirmation of a diagnosis. Still, it cannot be discarded as indicating a low risk of major arrhythmias for any patient, at least until additional data clarify its clinical role [21]. The VUS changed to LB due to a substantial increase of MAF seen with ongoing analysis of the global population, which notes the key role of global frequencies and its correlation with the prevalence of inherited arrhythmia and CM in the population [19]. Previous studies showed VUS rarely changed to P or LP variants [22].

**Sanger sequencing**

The variant of DSC2 p.I520T was screened again using Sanger sequencing (CX0020, TSINGKE Biological technology, Guangzhou, China) in the other members of the family. The mutation of DSC2 p.K47Rfs*2 was screened again using the TA cloning technique in the other familial members. The purified PCR product was directly linked with pClone007 Versatile Simple Vector (TSINGKE Biological technology, Guangzhou, China) by TA cloning technique and transformed into Escherichia coli (DH5α). The extracted plasmids were sequenced with ABI 3730XL (Applied Biosystem, USA). The primer of TA cloning sequencing was as follows: M13F: 5′- CGCCAGGTTTTTCCCCGTACGAC-3′; reverse primer 5′-ATATGACCCAGAAC AAGAA-3′.

**Western blot**

Tissues were homogenized on ice in the lysis buffer. After centrifugation and protein quantification, proteins were loaded onto SDS–PAGE gels and transferred onto nitrocellulose membranes. Membranes were incubated in 5% nonfat dry milk in TBST for 1 h at room temperature and incubated overnight at 4 °C with primary antibodies. Rabbit anti-DSC2 and mouse anti-β-actin antibody were purchased from Abcam Inc (Cambridge, MA). Antibodies were detected using 1:10,000 horseradish peroxidase-conjugated, donkey anti-rabbit, and donkey anti-mouse

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Table 1  Susceptible genes of inherited cardiomyopathy and arrhythmia detected in the proband II: 1

| Genes       | Arrhythmia | CM        |
|-------------|------------|-----------|
| TNNI2, TNNI3 | II: 1      |           |
| ZFPM2       | III: 2     |           |
| TMEM38B, TMEM43, TMEM70 |           |           |
| TNNC1, TNNT2, TNNT3 |           |           |
| TPM1, TPM2, TSC2, TSPY1, TTN |           |           |
| VCL, VKORC1, WNT1, YWHAE |           |           |

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IgG (Jackson ImmunoResearch, USA). The Western blot luminol reagent was used to visualize bands corresponding to each antibody.

Results

Clinical presentation

The familial pedigree is shown in Fig. 1A. A male patient (proband, II: 1) aged 54 years was admitted to our hospital because of recurrent chest dullness and chest pain for three years and exacerbation for half a month. He suffered from poststernal chest distress and palm-sized chest pain, which were sometimes accompanied by palpitation. Symptoms usually occur during exhaustion and could be relieved after taking a break. The Holter of II: 1 (oral bisoprolol, 5 mg, once a day) showed persistent atrial fibrillation (AF) with a long RR interval of 3.95 seconds, low voltage in limb lead, and T wave inversion in leads of V1–V6 (Fig. 2A). The frequently paired premature ventricular extrasystoles (PVCs) originated from the left ventricular lateral wall (Fig. 2B), left ventricular apex (Fig. 2C), and left ventricular inflow tract (Fig. 2D). The episodes of ventricular tachycardia (VT) originated from the middle posterior septum (Fig. 2E) and lateral wall (Fig. 2F) of the left ventricle (LV). Coronary heart disease was excluded by coronary angiography. The level of NT-proBNP was 13,800.00 pg/ml (normal range: 0–125 pg/ml) during hospitalization and increased continuously among the trabeculae carneae, which communicated with the LV lumen, and this finding was consistent with the LVNC diagnosis. The basal segment, anterior wall, and anterolateral wall of LV were thickened with increased, rough, and disorderly arranged trabeculae carneae in the subendocardial layer. The interventricular septum was thickened with a diameter of 2.67. Deep recesses with slow blood flow could be seen during diastole. CMRI (Fig. 4) demonstrated the typical forward blood flowed from the ventricular cavity into the deep spaces between the prominent trabeculations during diastole. The genetic screening revealed that the proband (II: 1) carried 10 exonic variants (Table 2), including two variants of DSC2 p.K47Rfs*2 (NM_004949: EX2/CDS2: c.140_147delAAC  TTG TT) and p.I520T (NM_004949: EX11/CDS11: c.1559T>C), which were located in chromosome 18. The local and 1000 Genomes Project database frequency of DSC2 p.K47Rfs*2 and p.I520T was less than 0.001. DSC2 p.K47Rfs*2 was not detected in gnomAD exomes combined population. Desmocollin2 encoded by the DSC2 gene was an important component for desmosome assembly. Abnormal desmocollin2 caused the dysfunction of cell–cell adhesions and intercellular gap junctions, failing to hold together the cardiomyocytes, fibrofatty myocardial replacement, cardiac conduction delay, mechanically ventricular dysfunction and arrhythmias [23]. According to the protein reference sequence, DSC2 p.K47Rfs*2 converted the 47th amino acid (AA) from lysine to arginine and led to a premature termination codon at the 48th AA, which was therefore considered as frameshift and truncated mutation. This phenomenon caused the interrupting protein synthesis at the cadherin pro domain and loss of protein structure, including extracellular domains 1–4, extracellular anchor, a transmembrane domain, intracellular anchor, intracellular cadherin-like sequence, resulting in truncated protein without normal function (Fig. 1C). Based on the ACMG/AMP guidelines [14], the null variant (e.g., frameshift mutation) in a gene where the loss of function is a known disease mechanism was classified as PVS1, suggesting strong evidence of pathogenicity. Therefore, DSC2 p.K47Rfs*2, as a truncated and loss-of-function mutation, served as PVS1. DSC2
Fig. 1 The familial pedigree, Sanger sequencing and the change of desmocollin2 protein. A: The pedigree of the family. II: 1 (the proband) presented with LVNC and HCM, complicating AF, VT and HF. SCD: sudden cardiac death. B: Sanger sequencing of DSC2 variants in the family members. Sanger sequencing revealed that II: 1 carried two variants of DSC2 p.K47Rfs*2 and p.I520T, which were not detected in II: 2. II: 3 only carried with DSC2 p.I520T variant. C: the protein of desmocollin2 consists of several domains, including signaling peptide (S), proprotein (P), four extracellular cadherin domains (EC), extracellular anchor domain (EA), the transmembrane region (TM), the intracellular anchor (IA), as well as the intracellular cytoplasmic domain (ICS). X: the lost domains of desmocollin2 protein induced by DSC2 p.K47Rfs*2 mutation. D: conservative analysis of DSC2 p.I520T.
p.I520T (rs561310777) was demonstrated to be benign or likely benign by Clinvar database and the CHEO Genetics Diagnostic Laboratory in Children’s Hospital of Eastern Ontario (https://www.ncbi.nlm.nih.gov/clinvar/variation/155783/). The MAF of DSC2 p.I520T was 0.02% and not fulfilled with the criteria of the vast majority of reported pathogenic variants (MAF < 0.01%). Additionally, according to the analysis of the UCSC Genome Browser, the amino acid site of DSC2 p.I520 is not conserved in several species (Fig. 1D). Based on the genotype of II: 1, II: 2 did not carry heterozygous DSC2 p.K47Rfs*2 or p.I520T, whereas II: 3 with normal electrocardiogram and echocardiography only carried the heterozygous DSC2 p.I520T (Fig. 1A and B), indicating that these two variants were not linked on the same chromosome, but located on the homologous chromosomes, respectively. The variants of CACNA1C, COL5A1, GDF1, HTRA1, MEF2A, TSPYL1, and TTN were classified as benign or likely benign by Clinvar database and ACMG guideline algorithm. Recently, no study confirmed that ELN variants cause CMs. The variant of ELN p.T248S was predicted to be tolerated/benign by SIFT and MetaSVM algorithms.

**Literature review of LVNC**

We searched the NCBI database for studies with the theme of “left ventricle noncompaction” on June 13, 2021. We summarized the genes and their mutations associated with LVNC, which were predicted as likely pathogenic and pathogenic by ≥ 2 predicting algorithms, familial cosegregation validation, and molecular and/or animal/cell experiments, as shown in Table 3. Results showed that MYH7, MYBPC3, TPM1, TAZ, TTN, and NONO genes were the most common genes causing LVNC. LVNC caused by MYH7 and MYBPC3 mutations often complicated congenital heart diseases (CHD), such as atrial septal defect, ventricular septal defect, Ebstein, tetralogy of Fallot, patent ductus arteriosus, patent foramen ovale, and aortic hypoplasia. Some cases occurred with thromboembolism. Recently, LVNC induced by DES and DSP mutations was common and young-onset with HCM, DCM, ACM, myocarditis and HF, complicating ventricular and atrial tachycardias, and even needed therapy of heart transplantation in some cases. LVNC was associated with FBN1 mutation combined with DCM and Marfan syndrome. LVNC induced by HCN4 and EMD mutations complicated sick sinus syndrome.
(SSS), AF, atrial standstill, and interventricular block. Additionally, the LVNC induced by EMD mutation was combined with DCM. The LVNC caused by RYR2, KCNQ1, and KCNH2 mutations occurred with catecholamine-sensitive VT, long QT syndrome (LQTSs), torsade de pointes, and ventricular fibrillation. In contrast, the LVNC result from SCN5A mutation complicated SSS, AF, LQTSs, Wolff–Parkinson–White syndrome, VT, and atrioventricular block. Some genes led to LVNC and caused complex and critical clinical disease syndromes, such as Rubinstein–Taybi syndrome (i.e., ABCC9 gene), Ehlers–Danlos syndrome (i.e., COL3A1 gene), Emery–Dreifuss muscular dystrophy (i.e., EMD gene), Danon disease (i.e., LAMP2 gene), intellectual disability syndrome (i.e., NONO gene), Sotos syndrome (i.e., NSD1 gene), LEOPARD syndrome (i.e., PTPN11 gene), Coffin-Lowry syndrome (i.e., RPS6KA3 gene), Cornelia de Lange syndrome (i.e., SMC1A gene), Barth syndrome (i.e., TAZ gene), and Holt–Oram syndrome (i.e., TBX5 gene). Additionally, ARFGEF2, MIPEP, NONO, SH2B1, and TMEM70 led to LVNC complicating developmental delay. The deletion of one of these genes, including FKBP12, JARID2, NUMB, and PLZND1, induced LVNC by affecting the activity of the Notch signaling pathway in animal models, which had not been discovered in clinical cases until now. For these genes from Table 3, only ACTC1, ACTN2, DTNA, LDB3, MIB1, MYBPC3, MYH7, PRDM16, TNNT2, and TPM1 were reported to be associated with LVNC in the OMIM database (Table 4).

Expression of DSC2
The western blot (Fig. 5) showed that the expressing level of functional desmocollin2 protein (~94kd) was lower in the proband than that in the healthy volunteer, indicating that DSC2 p.K47Rfs*2 remarkably and abnormally reduced the functional desmocollin2 expression in the proband.

Discussion
In our study, we have first discovered that the truncated mutation (p.K47Rfs*2) of DSC2 remarkably and abnormally reduced the functional desmocollin2 expression, as
Fig. 4 The cardiac magnetic resonance of the proband II: 1. In the end-diastolic images of cine True-FISP sequence, the short axis view of middle segment (A), coronal view of the left ventricular outflow tract (B), and three-chamber view of the heart (C) showed that myocardial thickening of the subendocardial, basal and middle segment, anterior and anterior-lateral wall of LV. The cardiac trabeculae increased and disordered, showing a reticular/palisade shape (yellow arrow). The maximum thickness ratio of the noncompacted layer to compacted layer (N/C = D2/D1) was between 2.25 and 2.67 in different sections. Deep recess was found among the trabeculae, and the communication existed between trabecular recess and the left ventricular cavity. The interventricular septum was thickened (green arrow) about 18 mm, and the inferior wall of LV became thinner (red arrow). The short-axis view in the middle segment (D) of the T2W-TIRM sequence showed thickening of the anterior and anterior-lateral wall of LV, increased signal intensity in the subendocardial region due to slow blood flow in trabecular recess (yellow arrow), localized thinning of the lateral-inferior wall (red arrow), and general thickening of the ventricular septum (green arrow). The short axis (E) and four-chamber (G, H) views of the first-pass enhancement sequence showed that the early enhancement signal of trabecular recess in the anterior and anterior-lateral wall of LV was consistent with that of the heart cavity (yellow arrow), indicating that there were flowing blood component in it. The short axis (F) and four-chamber (I) views of PSIR-LGE showed extensive abnormal enhancement in the lateral wall of LV (yellow arrow) and abnormal enhancement in the interventricular septum (green arrow). T1W showed no abnormal fat depositing signal in left and right ventricles (blue arrow). Yellow arrow: thickened lateral-anterior wall. Red arrow: thinned lateral wall. Green arrow: thickened interventricular septum. Blue Arrow: normal right ventricular wall.
| Chr | Gene | Transcript | Zygosity | RS-ID | 1000G | Local Fre | GnomAD | SIFT | PolyPhen | MetaSVM | Clinvar | ACMG classification |
|-----|------|------------|----------|-------|-------|-----------|--------|------|----------|---------|---------|---------------------|
| chr12 | CACNA1C | NM_001129827, c.5753C>T, p.T1918M | Het | rs201777030 | 0 | A | 0.0011 | 0.17 (T) | 0.60 (P) | T | B | US |
| chr9 | COL5A1 | NM_000093, c.61C>T, p.P21S | Het | rs548525119 | 0 | A | 0.0011 | 0.43 (T) | 0.00 (B) | T | B | B |
| chr18 | DSC2 | NM_004949, c.1559T>C, p.I520T | Het | rs51310777 | 0 | A | 0.0002 | 0.00 (D) | 0.47 (P) | T | B | US |
| chr18 | DSC2 | NM_004949, c.140_147delACTTGT, p.K47Rfs*2 | Het | – | 0 | A | – | – | – | – | – | LP |
| chr7 | ELN | NM_000501, c.742A>T, p.E248S | Het | rs71387097 | 0 | A | 0.038 | – | – | – | – | B |
| chr10 | HERA1 | NM_002775, c.59C>T, p.A20V | Het | rs369149111 | 0 | A | 0.0207 | 0.53 (T) | 0.00 (B) | T | B | B |
| chr15 | MEF2A | NM_005587, c.1234_1236delCAG | Het | rs373652230 | 0 | A | 0.1518 | – | – | – | – | B |
| chr6 | TPSY1L | NM_003309, c.528_S299insGTG | Hom | rs397735194 | 0 | A | – | – | – | – | – | B |
| chr2 | TTN | NM_001267550, c.36655T>G, p.L12219V | Hom | rs139508281 | 0 | A | 0.0954 | – | 0.00 (U) | T | B | B |

Chr: chromosome. Fre: frequency. Het: heterozygosis. Hom: homogyzosis. GnomAD: frequency of existing variant in gnomAD exomes combined population. Local Fre: frequency information about this SNP in sequencing samples of over 200 normal people collected locally. Local frequency: 0–0.01 = A; 0.01–0.05 is B (including 0.01 and 0.05); 0.05–1 is C. P: possibly damaging; T: tolerated; U: unknown. 1000G: 1000 Genomes Project databases (2014 version). B: benign. D: deleterious. US: uncertain significance. LB: likely benign. LP: likely pathogenic. –, no report.
Table 3  The detailed mutations and their clinical characteristics associated with left ventricular noncompaction

| Gene   | Mutation                                      | Sex | Aged | LVNC | HCM | DCM | ACM | RCM | HF | SCD/VF | CTR | MA | Other                          | FV | FA |
|--------|-----------------------------------------------|-----|------|------|-----|-----|-----|-----|-----|--------|-----|----|--------------------------------|----|----|
| ABC9   | NM_005691, c.3594G>A, p.M1198I, rs199900459   | M   | 32   | +    | −   | −   | −   | −   | −   | −      | −   | −  | Rubinstein–Taybi syndrome    | −  | −  |
| ACTC1  | NM_005159.4, c.62C>T, p.A21V                  | M   | 10 y | +    | +   | −   | −   | −   | −   | −      | +   | −  | Transmural crypts            | +  | −  |
| ACTC1  | NM_005159.4, c.301G>A, p.E99K                | M   | 11 y | +    | +   | −   | −   | −   | +   | −      | −   | +  | +                              | +  | −  |
| ACTC1  | NM_005159.4, c.478G>A, p.E101K               | M   | 15 y | +    | +   | −   | −   | −   | +   | +      | +   | −  | −                              | +  | −  |
| ACTC1  | NM_005159.4, c.659A>C, p.Y220S                | M   | 3 y  | +    | −   | −   | −   | +   | −   | −      | −   | +  | −                              | −  | +  |
| ACTC1  | NM_005159.4, c.692C>G, p.T231R                | F   | 9 m  | +    | −   | −   | −   | +   | −   | −      | −   | +  | ASD                           | +  | −  |
| ACTC1  | NM_005159.4, c.886T>C, p.Y296H                | F   | 13 y | +    | +   | −   | −   | −   | −   | −      | −   | −  | −                              | +  | −  |
| ACTC1  | NM_005159.4, c.986T>C, p.I329T                | F   | 48 y | +    | −   | −   | −   | +   | −   | −      | −   | +  | AF, AVB, esophageal atresia, tracheal fistula, ASD | +  | −  |
| ACTC1  | NM_005159.4, p.I289T                          | F   | 9 m  | +    | −   | −   | −   | +   | −   | −      | −   | +  | Developmental delay and microcephaly | −  | +  |
| ACTN2  | NM_001103.2, c.683T>C, p.M228T                | M   | 30 y | +    | +   | −   | −   | −   | −   | −      | −   | +  | AF, AVB, esophageal atresia, tracheal fistula, ASD | +  | −  |
| ACTN2  | chr1: 236881238:CCT>–NM_001278343, p.L70del  | F   | 9 y  | +    | +   | −   | −   | −   | −   | −      | −   | +  | −                              | +  | −  |
| ACTN2  | NM_001103.3, c.668T>C, p.L223P                | M   | 15 y | +    | +   | −   | −   | −   | −   | −      | −   | +  | −                              | −  | +  |
| ANK2   | NM_001148.4, c.11150T>A, p.I3717N             | M   | 15 y | +    | +   | −   | −   | −   | −   | −      | −   | +  |−                              | −  | +  |
| ANK2   | NM_001148.4, c.9145C>T, p.R3049W              | M   | 15 y | +    | +   | −   | −   | −   | −   | −      | −   | +  | −                              | −  | +  |
| ALPK3  | NM_002778, c.639G>G, p.W213X                   | M   | 34 w | +    | +   | −   | −   | −   | −   | −      | −   | +  | −                              | −  | +  |
| ARFGF2 | NM_006420.2, c.5126G>G, p.W709X                | F   | 10 y | +    | +   | −   | −   | −   | −   | −      | −   | +  | Movement disorder, development delay and microcephaly | −  | +  |
| BAG3   | NM_004281.3, c.465_466insGCC, p.A156dup        | M   | 32   | +    | +   | −   | −   | −   | −   | −      | −   | +  | −                              | −  | +  |
| BRAF   | chr1:140477829->A, NM_004333, p.Q493H; MYH6:chr1:23858233:G>A, NM_002471, p.S1337L, rs758922922 | F   | 9 y | +    | +   | −   | −   | −   | −   | −      | −   | +  | −                              | −  | +  |
| BMP10  | NM_014482.3, c.1219G>G, p.V407I                | M   | 32   | +    | −   | −   | −   | −   | −   | −      | −   | +  | −                              | −  | +  |
| BMP10  | deletion                                      | M   | 32   | +    | −   | −   | −   | −   | −   | −      | −   | +  | −                              | −  | +  |
| CACNA2D1| g.81603880_81603881delAA, NM_1, NP(-), p.R652R; R6X3 and RANGRF, NM(-), NP(-), p.P155S | F   | 1 m  | +    | +   | −   | −   | −   | −   | −      | −   | +  | Histiocytoid cardiomyopathy, WPW, arrhythmia storms | −  | +  |
| CASQ2  | NM_001232.4, p.H244R                          | M   | 53 y | +    | −   | −   | −   | −   | −   | −      | −   | +  | −                              | −  | +  |
| Gene    | Mutation                                                                 | Sex | Aged | LVNC | HCM | DCM | ACM | RCM | HF | SCD/VF | CTR | MA | Other                  | FV | FA |
|---------|--------------------------------------------------------------------------|-----|------|------|-----|-----|-----|-----|-----|-------|-----|----|------------------------|----|----|
| CASZ1   | NM(1), NP(-), c.2443_2459del, p.V1815PfsX14                              | M   | 11 m | +    | +   | −   | +   | −   | +   | −     | +   | −  | −                      | −  | −  |
| CDK10   | NM_052988.4, c.452T>C, p.L151P Chromosome 16q24.3 deletion encompassing 9 genes: CDK10, CPNE7, DPEP1, CHMWP1A, SPATA3, SPATA2L, VPS9D1, ZNF276 and FANCA | M   | 3 m  | +    | +   | −   | +   | −   | +   | −     | +   | −  | Partial agenesis of the corpus callosum, unilateral multicystic dysplastic kidney, a single central incisor with pyriform aperture stenosis | +  | −  |
| COL3A1  | NM_000090.4, c.2959G>A, p.G987S                                          | M   | 32 y | +    | +   | −   | +   | −   | +   | −     | +   | −  | Vascular Ehlers-Danlos Syndrome, AF | −  | −  |
| DES     | NM(1), NP(-), p.L69P                                                      | −   | −    | +    | −   | −   | −   | −   | −   | −     | −   | −  | −                      | −  | −  |
| DES     | NM_001927.3, NP(1), c.336_344del, p.Q113_L115del Chromosome 16q24.3 deletion encompassing 9 genes: CDK10, CPNE7, DPEP1, CHMWP1A, SPATA3, SPATA2L, VPS9D1, ZNF276 and FANCA | M   | 13 y | +    | +   | +   | −   | +   | +   | −     | +   | +  | VT, AVB                | +  | +  |
| DES     | NM(1), NP(-), p.R212Q                                                    | −   | −    | +    | −   | −   | −   | −   | −   | −     | −   | −  | −                      | −  | −  |
| DES     | NM(1), NP(-), p.A360S                                                    | −   | −    | +    | −   | −   | −   | −   | −   | −     | −   | −  | −                      | −  | −  |
| DES     | NM(1), NP(-), c.C1360T, p.R454W                                           | F   | 11 y | +    | +   | +   | −   | −   | −   | +     | +   | −  | Coronary artery dissection, AVB, AFL | +  | −  |
| DSC2    | NM_004949, c.140_147del, p.K47Rfs*2                                       | M   | 54 y | +    | +   | −   | −   | +   | −   | −     | +   | −  | AF, VT                  | +  | −  |
| DSC2    | NM_024422.3, c.1448A>T, p.N483I                                          | −   | −    | +    | −   | −   | −   | −   | −   | −     | −   | −  | −                      | −  | −  |
| DSP     | NM(1), NC_00006.11, c.1339C>T                                            | M   | 37 y | +    | −   | +   | −   | +   | −   | +     | −   | −  | VT, myocarditis         | +  | −  |
| DSP     | NM_00415.2, c.3035delA, p.D1012fs                                        | −   | −    | +    | −   | −   | −   | −   | −   | −     | −   | −  | −                      | −  | −  |
| DSP     | NM(1), NP(-), c.5208del1AG, p.G1737fs*2                                   | M   | 5 y  | +    | +   | −   | +   | −   | −   | +     | +   | −  | Palmo plantar keratoderma | +  | −  |
| DTPA    | NM(1), NP(-), c.146A>G, p.A49S                                           | M   | 39 y | +    | −   | +   | −   | −   | +   | −     | −   | −  | −                      | +  | +  |
| DTNA    | NM(1), NP(-), c.362C>T, p.P121L                                          | F   | 2 d  | +    | −   | +   | −   | −   | +   | −     | −   | −  | −                      | +  | −  |
| EMD     | NM(1), NP(-), c.226-2A>C                                                | M   | 16 y | +    | −   | +   | −   | −   | −   | −     | −   | −  | −                      | +  | −  |
| EMD     | NM(1), NP(-), c.1A>G, p.M14V                                              | M   | 53 y | +    | −   | +   | −   | −   | +   | −     | −   | −  | −                      | +  | −  |
| EMD     | NM(1), NP(-), c.23C>T, p.S80L                                            | M   | 65 y | +    | −   | +   | −   | −   | +   | −     | −   | −  | −                      | +  | −  |
| EMD     | NM(1), NP(-), c.415delIC, p.L396fsX98                                     | M   | 13 y | +    | −   | +   | −   | −   | −   | −     | −   | −  | −                      | +  | −  |
| FBN1    | NM(1), NP(-), c.1633C>T                                                 | F   | 14 y | +    | −   | +   | −   | −   | +   | −     | −   | −  | −                      | −  | −  |
| FBN1    | NM(1), NP(-), c.3173G>T                                                 | F   | 20 y | +    | −   | +   | −   | −   | +   | −     | −   | −  | −                      | −  | −  |
| FBN1    | NM(1), NP(-), c.6832C>T                                                 | M   | 2 y  | +    | −   | +   | −   | −   | +   | −     | −   | −  | −                      | −  | −  |
| FKBP12  | deletion                                                                  | −   | −    | +    | −   | +   | −   | −   | −   | −     | −   | −  | −                      | −  | −  |
| FKTN    | NM(1), NP(-), c.536G>C, p.R179T                                           | M   | 26 y | +    | −   | +   | −   | −   | −   | −     | −   | −  | −                      | −  | −  |
| Gene  | Mutation                                           | Sex   | Aged | LVNC | HCM | DCM | ACM | RCM | HF   | SCD/VF | CTR | MA  | Other                                      | FV | FA |
|-------|----------------------------------------------------|-------|------|------|-----|-----|-----|-----|-----|-------|-----|-----|--------------------------------------------|----|----|
| FLNC  | NM_001458.4, c.1933_1935del, p.645del              | −     | −    | +    | −   | −   | −   | −   | −   | −     | −   | −   | −                                                          | −  | −  |
| FLNC  | NM(-), NP(-), c.4997T>C, p.I1666T                   | M     | 37   | +    | −   | −   | −   | −   | −   | −     | −   | −   | − AF                                                      | −  | −  |
| GATA4 | NM(-), NP(-), c.778 C>T, p.A242V and PTEN: NM(-), NP(-), c.517C>T, p.R173C | M     | 19 y | +    | −   | −   | −   | −   | −   | −     | −   | −   | −                                                          | +  | +  |
| HADHB | NM(-), NP(-), c.1109+243_1438-703del                | −     | Fetus| +    | −   | −   | −   | −   | −   | −     | −   | −   | − TFP deficiency, lactic acidosis, hypoketotic hypoglycemia, and neonatal death | +  | −  |
| HCN4  | NM_005477.2, c.1123C>T, p.R375C                     | F     | 16 y | +    | −   | −   | −   | −   | −   | −     | −   | −   | − SSS, left atrial dilatation                        | +  | +  |
| HCN4  | NM_005477.2, c.1231C>G, p.L411V                     | −     | −    | +    | −   | −   | −   | −   | −   | −     | −   | −   | −                                                          | −  | −  |
| HCN4  | NM(-), NP(-), c.1241C>G, p.A414G                    | M     | 74 y | +    | −   | −   | −   | −   | −   | −     | −   | −   | − SSS, AF                                              | +  | +  |
| HCN4  | NM_005477.2, c.1403C>T, p.A468V                     | −     | −    | +    | −   | −   | −   | −   | −   | −     | −   | −   | −                                                          | −  | −  |
| HCN4  | NM_005477.2, c.1438G>T, p.G480C                     | M     | −    | +    | −   | −   | −   | −   | −   | −     | −   | −   | − SSS                                              | +  | −  |
| HCN4  | g.73620206 G>A, NM_005477.2, c.1444G>A, p.G482R    | M     | 23 y | +    | −   | −   | −   | −   | −   | −     | −   | −   | − SSS, AF                                      | +  | +  |
| HCN4  | NM(-), NP(-), p.R483_V487del                        | F     | 47 y | +    | −   | −   | −   | −   | −   | −     | −   | −   | − SSS, AETThoracic aortic aneurysms                   | +  | −  |
| HCN4  | NM_005477.2, c.2432G>A, p.G811E                      | F     | 6 m  | +    | −   | −   | −   | +   | −   | −     | −   | −   | − VSD, IVB                                            | +  | +  |
| HEY2  | NM_012259, c.683G>T, p.T228M                         | −     | −    | +    | −   | −   | −   | −   | −   | −     | −   | −   | −                                                          | −  | −  |
| Jarid2 | deletion                                            | −     | −    | −    | +   | −   | −   | −   | −   | −     | −   | −   | −                                                          | −  | −  |
| KCNH2 | NM_001204798, c.818 C>T, p.T273M                      | F     | 22 y | +    | −   | −   | −   | −   | +   | −     | −   | −   | − LQTs, Tdp, VT, VF                                   | +  | +  |
| KCNQ1 | NM(-), NP(-), c.817C>T, p.L273F                      | M     | 48 y | +    | −   | −   | −   | −   | +   | −     | −   | −   | − LQTs, VSD                                           | −  | −  |
| KCNQ1 | NM(-), NP(-), c.1831G>T, p.D611T                      | F     | 5 y  | +    | −   | −   | −   | +   | −   | −     | −   | −   | − LQTs, VT, VF, epilepsy                          | +  | −  |
| LAMP2 | NM(-), NP(-), c.644_2T>A                             | F     | 23 y | +    | −   | +   | −   | −   | −   | −     | −   | −   | − VSD                                         | −  | +  |
| LAMP2 | NM_002294.2, c.987G>T, p.Y329X                        | M     | 21 y | +    | −   | −   | −   | −   | −   | −     | −   | −   | − Electrical myotonia, Danon disease              | +  | −  |
| LDB3  | NM_007078.2, c.608C>T, p.S203L                        | −     | −    | +    | −   | −   | −   | −   | −   | −     | −   | −   | − Congenital muscular dystrophy                     | −  | −  |
| LDB3  | NM_007078.2, c.608C>G, p.E209Q                        | −     | −    | +    | −   | −   | −   | −   | −   | −     | −   | −   | −                                                          | −  | −  |
| LDB3  | NM(-), NP(-), c.163G>A, p.V55I                       | F     | 14 y | +    | −   | +   | −   | −   | −   | −     | −   | −   | −                                                          | −  | −  |
| LDB3  | NM(-), NP(-), c.349G>A, p.D1117N                      | M     | 33 y | +    | +   | −   | −   | −   | −   | −     | −   | −   | − IVB                                               | −  | +  |

**Table 3 (continued)**
Table 3 (continued)

| Gene   | Mutation                                      | Sex | Aged  | LVNC | HCM  | DCM  | ACM  | RCM  | HF   | SCD/VF | CTR  | MA       | Other |   | FV | FA |
|--------|-----------------------------------------------|-----|-------|------|------|------|------|------|------|--------|------|----------|-------|---|---|---|
| LDB3   | NM(-), NP(-), c.587C>T, p.S196L               | M   | 40 y  | +    | +    | +    | −    | −    | +    | +      | −    | −        | −     |   |   |   |
| LDB3   | NM(-), NP(-), c.1876G>A, p.D626N              | M   | 13 y  | +    | −    | −    | −    | −    | −    | +      | +    | −        | WPW   |   |   |   |
| LMNA   | NM(-), NP(-), c.1608+5G>C and LDB3: NM(-), NP(-), p.D117N | M   | 30 y  | +    | +    | +    | −    | −    | −    | +      | −    | −        | −     |   |   |   |
| LMNA   | NM(-), NP(-), c.1968+26A>G and TAZ: NM(-), NP(-), p.F128S | M   | 57 y  | +    | −    | −    | −    | −    | −    | +      | −    | −        | −     |   |   |   |
| LMNA   | NM_170707.2, c.738delG, p.Q246fs              | −   | −     | −    | −    | −    | −    | −    | −    | −      | −    | −        | −     |   |   |   |
| LMNA   | NC_000001, c.T1334A, p.V445E                   | M   | 23 y  | +    | −    | −    | −    | −    | −    | +      | −    | −        | −     |   |   |   |
| LMNA   | NM(-), NP(-), c.1930C>T, p.R644C              | F   | 2 y   | −    | +    | −    | −    | −    | −    | −      | −    | −        | −     |   |   |   |
| MEF2A  | NM(-), NP(-), p.R17X                         | −   | −     | −    | +    | −    | −    | −    | −    | −      | −    | −        | −     |   |   |   |
| MIB1   | NM(-), NP(-), c.1587C>T, p.R530X              | −   | −     | −    | +    | −    | −    | −    | −    | −      | −    | −        | −     |   |   |   |
| MIB2   | NM(-), NP(-), c.2827G>T, p.V943F              | −   | −     | −    | +    | −    | −    | −    | −    | −      | −    | −        | −     |   |   |   |
| MIB2   | NM_080875, c.2225G>A, p.V742G                  | F/M | −     | −    | +    | −    | −    | −    | −    | −      | −    | −        | −     |   |   |   |
| MIBP   | NM_005932, c.1745G>A, p.L582R and c.2172T>A, p.L71Q | M   | 5.5 m | +    | −    | −    | −    | −    | −    | −      | −    | −        | −     |   |   |   |
| MIBP   | NM_005932, c.916C>T, p.L306F and c.1804G>T, p.T602X | F   | 11 m  | +    | −    | +    | −    | −    | −    | −      | +    | +        | −     |   |   |   |
| MMACHC | NM(-), NP(-), c.271dupA                       | F   | 35 w  | +    | −    | −    | −    | −    | −    | −      | +    | −        | −     |   |   |   |
| MYBPC3 | NM(-), NP(-), c.68G>A, p.G5R                   | M   | 20 y  | +    | −    | −    | −    | −    | −    | −      | −    | −        | −     |   |   |   |
| MYBPC3 | NM(-), NP(-), p.G148R                         | M   | 30 y  | +    | +    | +    | −    | −    | −    | +      | −    | −        | −     |   |   |   |
| MYBPC3 | NM_000256.3, c.532G>A, p.V718M                 | −   | −     | +    | −    | −    | −    | −    | −    | −      | −    | −        | −     |   |   |   |
| MYBPC3 | NM(-), NP(-), p.A2167T and ACTC1: NM(-), NP(-), p.A2167T | M   | 50 y  | +    | −    | −    | −    | −    | −    | −      | −    | −        | −     |   |   |   |
| MYBPC3 | NM(-), NP(-), c.1523G>A, p.G490R              | M   | 32 y  | +    | −    | −    | −    | −    | −    | −      | −    | −        | −     |   |   |   |
| MYBPC3 | NM_000256.3, c.1504C>T, p.R502W               | F   | 19 y  | +    | +    | −    | −    | −    | −    | −      | −    | −        | −     |   |   |   |
| MYBPC3 | NM(-), NP(-), p.R502Q and p.R943X             | M   | −     | +    | −    | −    | −    | −    | −    | +      | −    | −        | −     |   |   |   |

**Note:** Some mutations are associated with additional clinical features or specific disease presentations. For example, mutations in MIB1 are associated with Menetrier-like gastropathy, while mutations in MMACHC are associated with intracellular vitamin B12 disorder.
| Gene   | Mutation                                                                 | Sex | Aged | LVNC | HCM | DCM | ACM | RCM | HF | SCD/VF | CTR | MA | Other                          | FV | FA |
|--------|---------------------------------------------------------------------------|-----|------|------|-----|-----|-----|-----|-----|--------|-----|----|--------------------------------|----|----|
| MYBPC3 | NM(-), NP(-), c.2373dup, p.W792fs                                       | F   | 7 w  | +    | +   | +   | −   | −   | −   | +      | −   | −  | PFO and mitral valve insufficiency | +  | −  |
| MYBPC3 | NM(-), NP(-), c.2460C>T, p.R820W                                         | F   | 43 y | +    | +   | +   | −   | −   | −   | +      | −   | −  | AF                                          | +  | −  |
| MYBPC3 | NM_000256, NP_000247, c.2572A>C, p.S858R                                 | F   | 2 m  | +    | −   | +   | −   | −   | +   | −      | −   | +  | +                                            | +  | +  |
| MYBPC3 | NM(-), NP(-), c.2673C>T, p.P873L                                         | M   | 37   | +    | −   | −   | −   | +   | +   | −      | −   | −  | Pulmonary hypertension                   | −  | −  |
| MYBPC3 | NM(-), NP(-), c.2827C>T, p.R943X                                         | M   | 5 w  | +    | +   | +   | −   | −   | +   | −      | −   | −  | ASD                                          | +  | −  |
| MYBPC3 | NM(-), NP(-), c.2919-2920delCT, p.P95R6X95                               | F   | 28   | +    | −   | −   | −   | −   | −   | −      | −   | +  | VT                                          | −  | −  |
| MYBPC3 | NM(-), NP(-), c.2864_2865del, p.P95fs and c.1513_1515del, p.K9fsdel    | F   | 5 m  | +    | +   | +   | −   | −   | +   | −      | −   | −  | −                                            | +  | −  |
| MYBPC3 | NM(-), NP(-), c.2909G>A, p.R970Q                                        | M   | −    | +    | −   | −   | −   | −   | +   | −      | −   | −  | −                                            | +  | −  |
| MYBPC3 | NM(-), NP(-), c.3408C>A, p.Y1136X and c.2373dupG                          | M   | 36 w | +    | +   | −   | −   | +   | +   | −      | −   | −  | −                                            | +  | −  |
| MYBPC3 | NM(-), NP(-), c.377delA, p.Q1259fs and c.35997T>C, p.L1200P              | M   | 11 d | +    | −   | −   | −   | +   | +   | +      | −   | +  | −                                            | +  | −  |
| MLC1   | c.393_400del8                                                             | F   | 10 m | +    | −   | +   | −   | +   | −   | −      | −   | −  | Malonyl coenzyme A decarboxylase deficiency  | −  | −  |
| MLC1   | c.50G>T, p.R17L                                                            | −   | −    | +    | −   | −   | −   | −   | −   | −      | −   | −  | CHD                                          | −  | −  |
| MLC1   | c.1793dupA, p.N598fs                                                      | −   | −    | +    | −   | −   | −   | −   | −   | −      | −   | −  | −                                            | −  | −  |
| MLC1   | c.4828C>T, p.R610C                                                         | −   | −    | +    | −   | −   | −   | −   | −   | −      | −   | −  | −                                            | −  | −  |
| MYH6   | NM_002471.3, c.50G>T, p.R17L, p.R17L, p.R17L, p.R17L, p.R17L, p.R17L, p.R17L | −   | −    | +    | −   | −   | −   | −   | −   | −      | −   | −  | −                                            | −  | −  |
| MYH6   | NM_002471.3, c.1793dupA, p.N598fs                                         | −   | −    | +    | −   | −   | −   | −   | −   | −      | −   | −  | −                                            | −  | −  |
| MYH6   | NM_002471.3, c.4828C>T, p.R610C                                            | −   | −    | +    | −   | −   | −   | −   | −   | −      | −   | −  | −                                            | −  | −  |
| MYH7   | NM_000257, c.130C>T, p.Q44X and c.5029C>T, p.R1677C                       | M   | 32 y | +    | −   | −   | −   | −   | −   | −      | −   | −  | Ebstein                                     | +  | −  |
| MYH7   | NM_000257, c.379G>A, p.P127T                                              | −   | −    | +    | −   | −   | −   | −   | −   | −      | −   | −  | −                                            | −  | −  |
| MYH7   | NM_000257, c.464_476del, p.delF155                                       | M   | 8 y  | +    | −   | −   | −   | −   | −   | −      | −   | −  | ASD, Ebstein                                | −  | −  |
| MYH7   | g.23901862T>G, NM_000257, p.Q163P                                        | −   | −    | +    | −   | −   | −   | −   | −   | −      | −   | −  | −                                            | +  | −  |
| MYH7   | NM_000257, c.801_803delGAC, p.D233del                                     | M   | 65 y | +    | −   | −   | −   | −   | +   | −      | −   | −  | −                                            | −  | −  |
| MYH7   | NM_000257, c.814G>A, p.R243H                                             | M   | 25 y | +    | −   | −   | −   | −   | −   | −      | −   | −  | −                                            | −  | −  |
| MYH7   | NM_000257, c.745C>G, p.R249G                                              | F   | 35 y | +    | −   | −   | −   | −   | −   | −      | −   | −  | −                                            | −  | −  |
| MYH7   | NM_000257, c.847T>C, p.F252L                                              | M   | 58 y | +    | −   | −   | −   | −   | −   | −      | −   | −  | −                                            | −  | −  |
| MYH7   | NM_000257, p.R281T                                                        | −   | −    | +    | −   | −   | −   | −   | −   | −      | −   | −  | EBstein, CHD                                 | +  | −  |
| MYH7   | NM_000257, p.Y283D                                                        | F   | 49 y | +    | −   | −   | −   | −   | −   | −      | −   | −  | −                                            | −  | −  |

**Table 3 (continued)**
# Table 3 (continued)

| Gene | Mutation | Sex | Aged | LVNC | HCM | DCM | ACM | RCM | HF | SCD/VF | CTR | MA | Other | FV | FA |
|------|----------|-----|------|------|-----|-----|-----|-----|----|--------|-----|----|--------|----|----|
| MYH7 | NM_000257, c.847T>C, p.Y283H | M | − | + | − | − | − | − | − | − | − | − | + | − | [65] |
| MYH7 | NM_000257, p.L301Q | M | 12 y | − | + | − | − | − | − | − | − | − | − | − | − | [76, 130] |
| MYH7 | NM_000257, p.Y350N | F | 26 y | − | + | − | − | − | − | − | − | − | − | − | − | [131] |
| MYH7 | NM_000257, p.E1350del | F | 32 y | − | + | − | − | − | − | − | − | − | − | − | − | [76] |
| MYH7 | NM_000257, c.1207C>T, p.R403W and c.1000–1G>A | M | 14 y | + | + | − | − | − | − | − | − | − | − | − | − | [124] |
| MYH7 | g.23895236T>C, NM_000257, p.E700G | M | 11 y | + | + | − | − | − | − | − | − | − | − | − | − | [129] |
| MYH7 | NM_000257, c.2785G>A, p.E929K | M | 42 y | − | + | − | − | − | − | − | − | − | − | − | − | [33] |
| MYH7 | g.2389779G>C, NM_000257, c.1492C>G, p.Q498E | M | 19 y | − | + | − | − | − | − | − | − | − | − | − | − | [134] |
| MYH7 | NM_000257, c.1678T>G, p.R563C | F | 14 y | − | + | − | − | − | − | − | − | − | − | − | − | [135, 136] |
| MYH7 | NM_000257, c.3830G>C, p.R1277P | M | 55 y | − | + | − | − | − | − | − | − | − | − | − | − | [131, 130] |
| MYH7 | g.23894642G>A, NM_000257, p.S648L | M | 61 y | + | + | − | − | − | − | − | − | − | − | − | − | [76] |
| MYH7 | NM_000257, c.2155C>T, p.R719W | M | 29 y | − | + | − | − | − | − | − | − | − | − | − | − | [138] |
| MYH7 | NM_000257, c.2107C>T, p.R703S | M | 14 y | + | + | − | − | − | − | − | − | − | − | − | − | [124] |
| MYH7 | NM_000257, c.3748C>T, R1250W | M | 55 y | − | + | − | − | − | − | − | − | − | − | − | − | [127] |
| Gene   | Mutation                                  | Sex | Aged | LVNC | HCM | DCM | ACM | RCM | HF | SCD/VF | CTR | MA | Other      | FV | FA |
|--------|-------------------------------------------|-----|------|------|-----|-----|-----|-----|-----|-------|-----|----|------------|----|----|
| MYH7   | NM_000257, p.R723G and p.S1335L           | M   | 22 y | +    | +   | −   | −   | −   | +   | +     | +   | −  | −          | +  | −  |
| MYH7   | NM_000257, c.4161C>T, p.R1359C            | M   | 29 y | +    | −   | −   | −   | −   | +   | −     | +   | −  | −          | −  | +  |
| MYH7   | NM_000257, c.4090G>C, p.A1364F            | M   | −    | +    | −   | −   | −   | −   | −   | −     | +   | −  | −          | −  | +  |
| MYH7   | NM_000257, p.K1459N                       | F   | 58 y | +    | −   | −   | −   | −   | −   | −     | −   | −  | −          | +  | −  |
| MYH7   | NM_000257, p.Y1488C                       | M   | 41 y | +    | −   | −   | −   | −   | −   | +     | −   | −  | −          | +  | −  |
| MYH7   | NM_000257, c.4588C>T, p.R1530X            | −   | −    | +    | −   | −   | −   | −   | −   | −     | −   | −  | −          | −  | +  |
| MYH7   | NM_000257, c.5030G>A, p.R1677H            | M   | −    | +    | −   | −   | −   | −   | −   | −     | +   | −  | −          | −  | +  |
| MYH7   | NM_000257, c.5382G>A, p.A1766T            | M   | 20 y | +    | −   | −   | −   | −   | −   | −     | −   | −  | −          | −  | +  |
| MYH7   | NM_000257, c.5401G>A, p.E1801K            | M   | 25 y | +    | −   | −   | −   | −   | −   | −     | −   | −  | −          | −  | +  |
| MYH7   | NM_000257, c.5566G>A, p.E1856K            | F   | 37 y | +    | −   | +    | −   | −   | +   | −     | −   | −  | −          | −  | +  |
| MYH7   | NM_000257, p.N1918K                       | M   | 5 y  | +    | −   | −   | −   | −   | −   | −     | −   | −  | −          | +  | −  |
| MYH7   | NM_000257, p.R1925G                       | F   | 50 y | +    | −   | −   | −   | −   | −   | −     | −   | −  | −          | +  | −  |
| MYH7   | NM_000257, c.8183T>G, p.R1694X            | M   | 14 y | +    | −   | −   | −   | −   | −   | −     | −   | −  | −          | −  | +  |
| MYL2   | NM_0331183, c.1754T>A, p.I585N             | −   | −    | +    | −   | −   | −   | −   | −   | −     | −   | −  | −          | −  | +  |
| MYL2   | NM_0331183, c.1658G>A, p.R533H             | −   | −    | +    | −   | −   | −   | −   | −   | −     | −   | −  | −          | −  | +  |
| MYOT   | NM_000257, c.1791C>T, p.1701X              | M   | 72 y | +    | −   | −   | −   | −   | −   | −     | −   | −  | −          | −  | +  |
| MYOT   | NM_032578.2, c.3457G>A, p.G1153R           | −   | −    | +    | −   | −   | −   | −   | −   | −     | −   | −  | −          | −  | +  |
| NELK1  | NM_006393.2, c.2747C>T, p.P916L            | M   | 37 y | +    | −   | −   | −   | −   | −   | −     | −   | −  | −          | −  | +  |
| NEXN   | NM_000257, c.3457G>A, p.R1359C            | M   | 29 y | +    | −   | −   | −   | −   | +   | −     | +   | −  | −          | −  | +  |
| NEXN   | NM_000257, c.3457G>A, p.R1359C            | M   | 29 y | +    | −   | −   | −   | −   | +   | −     | +   | −  | −          | −  | +  |
| NEXN   | NM_000257, c.3457G>A, p.R1359C            | M   | 29 y | +    | −   | −   | −   | −   | +   | −     | +   | −  | −          | −  | +  |
| Gene   | Mutation                                                                 | Sex | Aged | LVNC | HCM  | DCM  | ACM  | RCM  | HF   | SCD/VF | CTR  | MA    | Other                                                                 | FV | FA  |
|--------|--------------------------------------------------------------------------|-----|------|------|------|------|------|------|------|--------|------|-------|------------------------------------------------------------------------|----|-----|
| NNT    | NM_012343, c.638_639insT, p.R213fs                                      |     | −    | +    | −    | +    | −    | −    | +    | −      | −    | +     | Mitral valve dysplasia, and aorta hypoplasia                          |    | [129]|
| NONO   | NM_001145408:1, c.154+9A>G, MYH6: NM_0024713, c.718G>A, p.D240N         | Fetus| −    | +    | −    | −    | −    | −    | −    | −      | −    | +     |                                                                         |    |     |
| NONO   | NM_001145408, c.1171+1G>T                                              | M    | 17 y | +    | −    | −    | −    | −    | −    | −      | −    | +     | Intellectual disability syndrome                                      |    | [148]|
| NONO   | NM_001145408, c.1171+1G>A                                              | M    | 4 y  | +    | +    | −    | −    | −    | −    | −      | −    | +     | Intellectual disability syndrome                                      |    | [149, 150]|
| NONO   | NM_001145408, the first three coding exons and 19 kb of sequence upstream of the transcriptional start site | M    | 1 m  | +    | −    | −    | −    | +    | +    | +      | −    | +     | PFO, Ebstein, developmental delay, encephalopathy, seizures and dysautonomia, cerebellum dysplasia |    | [151]|
| NONO   | NM_001145408, c.246_249del, p.P93TfsX7                                 | M    | 2 y  | +    | −    | +    | −    | −    | −    | −      | −    | +     | Ebstein, PS, VSD, VSD, PLSVA, cardiovascular hypoplasia or transposition | +  | [153]|
| NONO   | NM_001145408, c.550C>T, p.R184X                                         | M    | 2 y  | +    | −    | +    | −    | −    | −    | −      | −    | +     | ASD, VSD, PDA, aortic dilatation, intellectual disability syndrome     |    | [149, 150]|
| NONO   | NM_001145408, c.1093C>T, p.R365X                                         | M    | 10 y | +    | +    | +    | −    | −    | −    | −      | −    | +     | RVH, ASD, VSD, PDA, Intellectual disability syndrome                  |    | [151]|
| NONO   | NM_001145408, c.1394dupC, p.N466KfsX13                                   | M    | 5 y  | +    | +    | −    | −    | −    | −    | −      | −    | +     | ASD, VSD, PDA, intellectual disability syndrome                        |    | [151]|
| NONO   | NM_001145408, c.471del, p.T57HfsX18                                      | M    | fetus| +    | −    | −    | −    | +    | −    | −      | −    | +     | Ebstein, PS, ASD, VSD, aortic arch variation, endocardial fibroelastosis, PFO, corpus callosum hypoplasia |    | [153]|
| NRG1   | NM(-), NP(-), c.661G>A, p.W143X                                         | M    | −    | +    | −    | −    | −    | −    | −    | −      | −    | +     |                                                                         |    | [73]|
| NSD1   | NM(-), NP(-), c.6218_6219insG                                           | M    | 11 y | +    | −    | +    | −    | −    | −    | −      | +    | +     | Sotos syndrome                                                        |    |     |
| NSD1   | NM(-), NP(-), c.2604_2605dupTT                                          | F    | 6 y  | +    | +    | −    | −    | −    | −    | −      | −    | +     | Sotos syndrome                                                        |    | [1]|
| NUMB   | deletion                                                                  | −    | −    | +    | −    | −    | −    | −    | −    | −      | −    | +     | VSD                                                                    | −  | [154]|
| OBSCN  | g.228552765_228552767delinsG, NM(-), NP(-), p.T2766RfsX53                | M    | 56 y | +    | +    | −    | −    | −    | −    | −      | −    | −     |                                                                         | −  | [155]|
| OBSCN  | g.228559442delC, NM(-), NP(-), p.S7947PfsX82, rs71180793                  | F    | 30 y | +    | +    | −    | −    | −    | −    | −      | −    | −     |                                                                         | −  | [155]|
| OBSCN  | g.22862285G>C, NM(-), NP(-), c.25367-1G>C, rs55883237                    | M    | 39 y | +    | +    | −    | −    | −    | −    | −      | −    | −     |                                                                         | −  | [155]|
| PDLIM3 | NM_014476.4, c.742C>T, p.R248C                                          | −    | −    | +    | −    | −    | −    | −    | −    | −      | −    | −     |                                                                         | −  | [33]|
| PKP2   | deletion                                                                  | F    | 12 d | +    | −    | −    | −    | +    | −    | −      | −    | +     |                                                                         |    | [50]|

**Table 3** (continued)
| Gene      | Mutation                                                                 | Sex | Aged | LVNC | HCM | DCM | ACM | RCM | HF | SCD/VF | CTR | MA | Other | FV | FA |
|-----------|---------------------------------------------------------------------------|-----|------|------|-----|-----|-----|-----|-----|------|-----|----|-------|----|----|
| PKP2      | NM_004572.3, c.2018G>A, p.G673D                                           |     |      | +    | −   | −   | +   | −   | −   | −    | −   | −  |       | −  | −  |
| PLEC2M2   | NM(1), NF(1), c.2156_2157delAG, p.K645ASX12                               | M   | 7 y  | +    | −   | −   | +   | −   | +   | +    | −   | −  | VT    | +  | +  |
| PKD1      | deletion                                                                  |     |      | −    | −   | −   | −   | −   | −   | −    | −   | −  | VSD, aortic arch anomalies, persistent truncus arteriosus | −  | +  |
| PLN       | NM(1), NP(1), p.R14del                                                   | F   | 48 y | +    | −   | −   | −   | −   | −   | −    | −   | −  | MVT, thrombus | +  | −  |
| PRDM16    | NM_022114.3, c.1047dupC, p.S350fsX48                                      | M   | 4 m  | +    | −   | −   | +   | −   | −   | −    | +   | −  |       | −  | −  |
| PRDM16    | g.3322083C>T, NC_000001.10, c.1057C>T, p.Q353X                            |     | 31 w fetus | +    | −   | −   | −   | −   | −   | −    | +   | −  |       | −  | −  |
| PTPN11    | NM(1), NP(1), p.W279C                                                    | M   | 40 y | +    | −   | −   | −   | −   | −   | −    | −   | −  | AF, LEOPARD syndrome | −  | −  |
| RBM20     | NM_001134363, c.1901G>T, p.R634L                                         | F   | 39 y | +    | −   | −   | −   | −   | −   | +    | +   | −  | TOF   | +  | +  |
| RBM20     | NM_001134363, c.1907G>A, p.R636H                                          | F   | 11 y | +    | −   | −   | −   | −   | −   | +    | −   | −  |       | +  | −  |
| RBM20     | NM_001134363, c.1909A>G, p.S637G                                          | M   | 13 y | +    | −   | −   | −   | −   | −   | −    | +   | −  |       | −  | −  |
| Rac1      | deletion                                                                  |     |      | −    | −   | −   | −   | −   | −   | −    | −   | −  | VSD, CHD | −  | +  |
| RPS6KA3   | NM(1), NP(1), c.1000-2A>G                                                | M   | 1 y  | +    | −   | −   | −   | −   | −   | −    | −   | −  | Coffin–Lowry syndrome | +  | −  |
| RYR2      | deletion                                                                  |     |      | −    | −   | −   | −   | −   | −   | −    | −   | −  | AF, VF | +  | −  |
| RYR2      | NM(1), NP(1), p.506G>A, p.R169Q                                          | F   | 20 y | +    | −   | −   | −   | −   | −   | −    | −   | −  |       | +  | −  |
| RYR2      | NM_001035.2, c.169-7_c.273+7del                                          | M   | 13 y | +    | −   | −   | −   | −   | −   | −    | −   | −  |       | −  | −  |
| RYR2      | NM_001035.2, c.878A>C, p.Q293P                                            |     |      | +    | −   | −   | −   | −   | −   | −    | −   | −  |       | −  | −  |
| RYR2      | NM_001035.2, c.6180G>T, p.Q2060H                                          |     |      | +    | −   | −   | −   | −   | −   | −    | −   | −  |       | −  | −  |
| RYR2      | NM_001035.2, c.13936G>C, p.D4646H                                         |     |      | +    | −   | −   | −   | −   | −   | −    | −   | −  |       | −  | −  |
| RYR2      | NM(1), NP(1), p.I4855M                                                    | F   | 10 y | +    | −   | −   | −   | −   | −   | −    | −   | −  | CPVT, ASD | +  | +  |
| SCN5A     | NM_198056.1, c.1141-3C>A                                                  | M   | 13 y | +    | −   | −   | −   | −   | −   | −    | −   | −  | PVC, WPW | +  | −  |
| SCN5A     | NM_198056.1, c.87G>A, rs6599230                                           | M   | 43 y | +    | −   | −   | −   | −   | −   | −    | −   | −  | PVC, LQTs | +  | −  |
| SCN5A     | NM_198056.1, c.453C>T                                                    | F   | 1 y  | +    | −   | −   | −   | −   | −   | −    | −   | −  | PVC    | +  | −  |
| SCN5A     | NM_198056.1, c.1673A>G, p.H558R, rs1805124                                | M   | 13 y | +    | −   | −   | −   | −   | −   | −    | −   | −  | PVC, WPW | +  | −  |
| SCN5A     | NM_198056.1, c.3269C>T, p.T1090IL, rs1805125                              | M   | 4 y  | +    | −   | −   | −   | −   | −   | −    | −   | −  | AE, SSS, PVC | +  | −  |
Table 3 (continued)

| Gene | Mutation | Sex | Aged | LVNC | HCM | DCM | ACM | RCM | HF | SCD/VF | CTR | MA | Other | FV | FA |
|------|----------|-----|------|------|-----|-----|-----|-----|----|--------|-----|----|-------|----|----|
| SCN5A | NM_198056.1, c.3996G>A | M | 0 y | + | − | − | − | − | + | − | − | − | − | − | − |
| SCN5A | NM_198056.1, c.5457T>C, rs1805126 | F | 5 y | + | − | − | − | − | − | − | − | − | − | − | − |
| SDHD | NM(-), NP(-), c.275A>G, p.D92G | M | neonate | + | + | − | − | − | − | − | − | − | − | − | − |
| SH2B1 | Deletion | M | 18 d | + | − | − | − | − | − | − | − | − | − | − | − |
| SLC39A8 | Deletion | — | — | + | − | − | − | − | − | − | − | − | − | − | − |
| SMCTA | NM(-), NP(-), c.1636_1638delATT | F | 21 m | + | + | − | − | − | − | − | − | − | − | − | − |
| STRA6 | NM_022369.4, c.113+3_113+4del | — | Fetus (22 w) | + | − | − | − | − | − | − | − | − | − | − | − |
| TAZ | NM_000116.3, p.R94H | M | 12 h | + | − | − | − | − | + | − | − | − | − | + | − |
| TAZ | NM_000116.3, intron1+9G>C | M | 4 m | + | − | − | − | − | − | + | − | − | − | − | − |
| TAZ | NM_000116.3, c.MS8-1G>C | M | 3 m | + | − | − | − | − | − | − | − | − | − | − | − |
| TAZ | NM_000116.3, N510+2T>A | M | 8 m | + | − | − | − | − | − | − | − | − | − | − | − |
| TAZ | NM_000116.3, c.109+1G>C | M | 4 m | + | − | − | − | − | − | − | − | − | − | − | − |
| TAZ | NM_000116.3, c.177+2T>A | M | infant | + | − | − | − | − | − | − | − | − | − | − | − |
| TAZ | NM_000116.3, c.134_136delinsCC, p.H45PfsX38 | M | 1.0 | + | − | − | − | − | − | − | − | − | − | − | − |
| TAZ | NM_000116.3, 158insC, p.L53Pfs80X | M | 19 y | + | − | − | − | − | − | − | − | − | − | − | − |
| TAZ | chrX:153641550:T>C, NM_000116, p.L82P | M | 1 m | + | − | − | − | − | − | − | − | − | − | − | − |
| TAZ | NM_000116.3, p.C118R and p.T352C | M | 5 m | + | − | − | − | − | − | − | − | − | − | − | − |
| TAZ | NM_000116.3, c.367C>T, p.R123X | M | 20 y | + | − | − | − | − | − | − | − | − | − | − | − |
| TAZ | NM_000116.3, c.527A>G, p.H176R | M | 3.0 y | + | − | − | − | − | − | − | − | − | − | − | − |
| TAZ | NM_000116.3, c.583G>T, p.G195X | M | 45 y | + | − | − | − | − | − | − | − | − | − | − | − |
| TAZ | NM_000116.3, c.777_778delATT | M | 3.0 y | + | − | − | − | − | − | − | − | − | − | − | − |
| TAZ | chrX:153648583:A>insAA, NM_000116, p.Y227_F228delinsX | M | 19 y | + | − | − | − | − | − | − | − | − | − | − | − |
| TAZ | NM_000116.3, c.710_711delTG, p.V237AfsX73 | M | 6.5 y | + | − | − | − | − | − | − | − | − | − | − | − | − |

Note: LVNC = LVNC; HCM = HCM; DCM = DCM; ACM = ACM; RCM = RCM; HF = HF; SCD/VF = SCD/VF; CTR = CTR; MA = MA; Other = Other; FV = FV; FA = FA.
Table 3 (continued)

| Gene        | Mutation                                                                 | Sex | Aged | LVNC | HCM | DCM | ACM | RCM | HF | SCD/VF | CTR | MA | Other                  | FV | FA |
|-------------|--------------------------------------------------------------------------|-----|------|------|-----|-----|-----|-----|-----|--------|-----|----|------------------------|----|----|
| TAZ         | chrX: 153649305G>., NM_000116, p.A281QfsX58                             | M   | 1 y  | +    | +   | +   | −   | −   | +   | −      | −   | −  | [9]                     |    |    |
| TBX5        | NM_000192.3, c.153649305G>T, NM_000116, p.A281QfsX58                   | F   | 34 y | −    | −   | −   | −   | −   | −   | −      | +   | −  | SSS, AF, ASD, Holt-Oram syndrome |    |    |
| TBX5        | NM_000192.3, p.363H5fs*25                                               | M/F | 49 y | +    | +   | +   | −   | −   | −   | −      | +   | −  | SSS, Holt-Oram syndrome |    |    |
| TBX5        | NM(-), NP(-), c.791G>A, p.R264K                                         | M/F | 3 m  | +    | +   | +   | +   | +   | +   | −      | −   | −  | Embolism, VSD |    |    |
| TBX20       | NM(-), NP(-), c.785G>T, p.T262M                                         | F   | −    | −    | −   | −   | −   | −   | −   | −      | −   | −  | −          |    |    |
| TBX20       | NM(-), NP(-), c.951C>A, p.Y311X                                          | M/F | −    | −    | +   | +   | +   | −   | −   | −      | −   | −  | +          |    |    |
| TMEM43      | NM_024334.2, c.317A>G, p.Y106C                                          | −   | −    | −    | −   | −   | −   | −   | −   | −      | −   | −  | +          |    |    |
| THEM70      | NM_017866.5, c.141delG, p.48RS*2, and c.316+1G>A                        | M   | 36 w | +    | +   | +   | −   | −   | −   | −      | −   | −  | Developmental delay, undescended testicle |    |    |
| TNNT1       | NM(-), NP(-), c.249G>C, p.M811                                          | F   | 5 m  | +    | +   | +   | −   | −   | −   | −      | −   | −  | +          |    |    |
| TNNT1       | NM(-), NP(-), c.281A>G, p.E94A                                          | F   | 4 m  | +    | +   | +   | +   | −   | −   | −      | +   | −  | −          |    |    |
| TNNT1       | NM(-), NP(-), c.304C>T, p.R102C                                         | F   | 12 y | +    | +   | +   | −   | −   | −   | −      | −   | −  | +          |    |    |
| TNNT1       | NM_000363.4, c.575C>A, p.R192H                                          | F   | 13 y | +    | +   | +   | +   | +   | +   | −      | −   | −  | −          |    |    |
| TNNT2       | NM_001001430.1, c.7GAG>AAG, p.E96K                                       | F   | 5 m  | +    | +   | +   | −   | −   | −   | −      | +   | −  | +          |    |    |
| TNNT2       | NM_0003643, c.305G>A, p.R102Q                                           | F   | 44 y | +    | +   | +   | −   | −   | −   | −      | −   | −  | AF, IVB |    |    |
| TNNT2       | NM(-), NP(-), p.D117N                                                   | F   | 36 w | +    | +   | +   | −   | −   | −   | −      | −   | −  | +          |    |    |
| TNNT2       | NM_001001431, c.450C>T, p.R131W                                          | M   | 14 y | +    | +   | +   | −   | −   | −   | −      | −   | −  | SVT |    |    |
| TNNT2       | NM(-), NP(-), p.K210del                                                 | F   | 20 d | +    | +   | +   | −   | −   | −   | −      | −   | −  | +          |    |    |
| TPM1        | NM(-), NP(-), c.109A>G, p.K37E                                          | M   | 8 y  | +    | +   | +   | −   | −   | −   | −      | −   | −  | +          |    |    |
| TPM1        | NM_00108007, c.377C>G, p.L113V                                          | F   | 22 w | +    | +   | +   | −   | +   | +   | +      | +   | −  | Mitral valve insufficiency, pulmonary hypertension |    |    |
| TPM1        | NM_00108007, c.475G>A, p.D159A                                          | F   | 2 y  | +    | +   | +   | −   | +   | +   | +      | +   | −  | Ebstein |    |    |
| TPM1        | NM_00108007, c.475G>A, p.T178H                                          | F   | 13 d | +    | +   | +   | −   | +   | +   | +      | +   | −  | −          |    |    |
| TPM1        | NM(-), NP(-), c.765G>A, p.E192K                                         | M   | 55 y | +    | +   | +   | −   | −   | −   | −      | −   | −  | −          |    |    |
| TPM1        | NM_00108201, c.725C>T, p.A242V                                          | M   | 45 y | +    | +   | +   | −   | −   | −   | −      | −   | −  | VT, AF, IVB |    |    |
| TPM1        | NM(-), NP(-), c.933A>G, p.K248E                                         | M   | 63 y | +    | +   | +   | −   | −   | −   | −      | −   | −  | +          |    |    |
| Gene | Mutation | Sex | Aged | LVNC | HCM | DCM | ACM | RCM | HF | SCD/VF | CTR | MA | Other | FV | FA |
|------|----------|-----|------|------|-----|-----|-----|-----|-----|-------|-----|-----|--------|----|----|
| TPM1 | g.23857430C>C, NM(-), NP(-), p.D275H | − − | + − | + − | − − | − − | − − | − − | − − | − − | − − | − − | + − | [129] |
| TTN  | NM(-), NP(-), c.533C>A, p.A178D | M | 20 y | + | + | + | − | − | + | − | − | − | + | [191] |
| TTN  | NM(-), NP(-), c.885B_8859del, p.F2953fs | M | 17 y | + | − | − | + | − | − | − | − | − | ＋ | [34] |
| TTN  | NM_001256850.1, c.4330C>T, p.R14454X | − − | + | − | − | − | − | − | − | − | + | − | ＋ | [33] |
| TTN  | NM_001256850.1, c.44248C>T, p.R14750X | − − | + | − | − | − | − | − | − | − | − | − | ＋ | [33] |
| TTN  | NM_001256850.1, c.53947C>T, p.R17983X | − − | + | − | − | − | − | − | − | − | − | − | ＋ | [33] |
| TTN  | NM(-), NP(-), c.54668G>A, p.G18223D | F | 30 y | + | − | − | − | − | − | − | − | − | ＋ | [34] |
| TTN  | NM_001256850.1, c.61961G>A, p.W20654X | − − | + | − | − | − | − | − | − | − | − | − | ＋ | [33] |
| TTN  | NM_001256850.1, c.64100_64101insTTGA, p.D21368X | − − | + | − | − | − | − | − | − | − | − | − | ＋ | [33] |
| TTN  | NM_001256850.1, c.68845C>T, p.R31126fs | M | 16 y | + | − | − | − | − | + | + | − | − | ＋ | [34] |
| TTN  | NM(-), NP(-), c.61961G>A, p.W20654X | − − | + | − | − | − | − | − | − | − | − | − | ＋ | [33] |
| TTN  | NM(-), NP(-), c.64100_64101insTTGA, p.D21368X | − − | + | − | − | − | − | − | − | − | − | − | ＋ | [33] |
| TTN  | NM_001256850.1, c.81307_81310del, p.i27103fs | M | 16 y | + | − | − | − | − | + | + | − | − | ＋ | [34] |
| TTN  | NM_001256850.1, c.82724delA, p.N72757fs | − − | + | − | − | − | − | − | − | − | − | − | ＋ | [33] |
| TTN  | NM(-), NP(-), c.83889_83909del, p.Y27963fs | M | 52 y | + | − | − | − | − | + | + | − | − | ＋ | [34] |
| TTN  | chr2: 179425207: GGA ACT GTA AAT G>-, NM_001267550, p.28547QfsX12, rs762286447 | M | 1 y | + | − | − | − | − | + | + | − | − | ＋ | [9] |
| TTN  | NM_001256850.1, c.93376delA, p.R31126fs | − − | + | − | − | − | − | − | − | − | − | − | ＋ | [33] |
| TTN  | NM_001256850.1, c.98039_98040insTCAA, p.N32680fs | − − | + | − | − | − | − | − | − | − | − | − | ＋ | [33] |
| TTN  | NM(-), NP(-), c.98039_98040insTCAA, p.N32680fs | − − | + | − | − | − | − | − | − | − | − | − | ＋ | [33] |
| TTN  | NM(-), NP(-), c.93888+1G>C, p.E2989fsX4 and c.102439T>C, p.W34072R | F | 38 y | + | − | − | − | − | + | − | − | − | ＋ | [192] |
| YWHAE | NM(-), NP(-), c.<458G>T | M | 2 w | + | − | − | − | − | + | − | − | − | ＋ | [193] |
Table 3 (continued)

| Gene     | Mutation       | Sex | Aged | LVNC | HCM | DCM | ACM | RCM | HF | SCD/VF | CTR | MA | Other | FV | FA    |
|----------|----------------|-----|------|------|-----|-----|-----|-----|----|--------|-----|-----|-------|----|-------|
| **Mitochondrial DNA** |               |     |      |      |     |     |     |     |    |        |     |     |       |    |       |
| *Met31*  | m. 3397A>G     |     |      | +    |    |    |    |    |    |        |    |    |       |    | [194] |
| *Met31*  | m. 3398T>C     | M   | 35 y | +    |    |    |    |    |    |        |    |    |       |    | [194] |
| *ND1*    | m. 3308T>C     | F   | 6 y  | +    |    |    |    |    |    |        |    |    |       |    | [195, 196] |

M: male. F: female. y: years. w: weeks. m: months. d: days. LVNC: left ventricular noncompaction. HCM: hypertrophic cardiomyopathy. DCM: dilated cardiomyopathy. ACM: arrhythmogenic cardiomyopathy. RCM: restricted cardiomyopathy. HF: heart failure. SCD: sudden cardiac death. FV: family verification. MA: mechanical assist. fs: frame-shift mutation. X: truncated mutation. VT: ventricular tachycardia. VF: ventricular fibrillation. MVT: ventricular tachycardia needed resuscitation. AVB: atrio-ventricular block. AF: atrial fibrillation. AS: atrial standstill. IVB: intra-ventricular block. ASD: atrial septal defect. CHD: congenital heart disease. VSD: ventricular septal defect. SVT: supraventricular tachycardia. PFO: patent foramen ovale. TOF: fallot tetralogy. PVC: premature ventricular contraction. LQT: long QT syndrome. SSS: sick sinus syndrome. WPW: Wolff–Parkinson–White syndrome. TdP: torsade de pointes. CPVT: Catecholamine sensitive ventricular tachycardia. PDA: patent ductus arteriosus. PLSVA: persistent left superior vena cava. PS: pulmonary stenosis. RVH: right ventricular hypertrophy. +, not mentioned in the previous reports. +, mentioned/occurred in previous reports.
Table 4  The phenotypes of genes associated with left ventricular noncompaction in OMIM database

| Location | Genes | Full name | Gene/locus MIM number | Phenotypes in OMIM |
|----------|-------|-----------|-----------------------|--------------------|
| 12p12.1  | ABC9  | ATP binding cassette subfamily C member 9 | 601439 | AF; DCM; hypertrichotic osteochondrodysplasia |
| 15q14    | ACTC1 | Actin alpha cardiac muscle 1 | 102540 | ASD; DCM; HCM; LVNC |
| 1q43     | ACTN2 | Actinin alpha 2 | 102573 | DCM; HCM; LVNC; myopathy |
| 4q25-q26 | ANK2  | Ankyrin 2 | 106410 | Cardiac arrhythmia; LQTS |
| 15q25.3  | ALPK3 | Alpha kinase 3 | 617608 | HCM |
| 20q13.13 | ARFGEF2| ADP ribosylation factor guanine nucleotide exchange factor 2 | 605371 | Periventricular heterotopia with microcephaly |
| 1q26.11  | BAG3  | BAG cocherpore 3 | 603883 | DCM; myofibrillar myopathy |
| 7q34     | BRAF  | B-Raf proto-oncogene, serine/threonine kinase | 164757 | Adenocarcioma of lung, somatic; cardiofaciocutaneous syndrome; colorectal cancer, somatic; LEOPARD syndrome; melanoma, malignant, somatic; nonsmall cell lung cancer, somatic; Noonan syndrome |
| 2p13.3   | BMP10 | Bone morphogenetic protein 10 | 608748 | – |
| 7q21.11  | CACNA2D1 | Calcium voltage-gated channel auxiliary subunit alpha2delta 1 | – | CPVT |
| 1p13.1   | CASQ2 | Calsequestrin 2 | 114251 | – |
| 1p36.22  | CASZ1 | Castor zinc finger 1 | 609895 | – |
| 2q32.2   | COL3A1 | Collagen type III alpha 1 Chain | 120180 | Ehlers–Danlos syndrome, vascular type; polymicrogyria with or without vascular type Ehlers–Danlos syndrome |
| 2q35     | DES   | Desmin | 125660 | DCM; myofibrillar myopathy; Scapuloperoneal syndrome; neurogenic, kaezer type |
| 18q12.1  | DSC2  | Desmocollin2 | 125645 | ACM; mild palmoplantar keratoderma and woolly hair |
| 6p24.3   | DSP   | Desmoplakin | 125647 | ACM; DCM; woolly hair and keratoderma; keratoderma and tooth agenesis; epidermolysis bullosa, lethal acantholytic; keratosis palmoplantis striata II; Skin fragility-woolly hair syndrome |
| 18q12.1  | DTNA  | Dystrobrevin alpha | 601239 | LVCN; CHD |
| Xq28     | EMD   | Emerin | 300384 | Emery-Dreifuss muscular dystrophy |
| 15q21.1  | FBNI  | Fibrin 1 | 134797 | Acromicic dysplasia; ectopia lentis, familial; geleophysic dysplasia; marfan lipodystrophy syndrome; Marfan syndrome; MASS syndrome; Stiff skin syndrome; Weill–Marchesani syndrome |
| 20p13    | FKBP12 | FKBP prolyl isomerase 1A | 186945 | – |
| 9q31.2   | FKTN  | Fukutin | 607440 | DCM; muscular dystrophy-dystroglycanopathy |
| 7q21.2   | FLNC  | Filamin C | 102565 | HCM; RCM; distal myopathy; myofibrillar myopathy |
| 2p23.3   | HADHB | Hydroxacyl-CoA dehydrogenase trifunctional multienzyme complex subunit beta | 143450 | Trifunctional protein deficiency |
| 15q24.1  | HCN4  | Hyperpolarization activated cyclic nucleotide gated potassium channel 4 | 605206 | Brugada syndrome; SSS |
| 6q22.31  | HEY2  | Hes related family bHLH transcription factor with YRPW motif 2 | 604674 | – |
| 6p22.3   | JARID2 | Junmonji and AT-rich interaction domain containing 2 | – | – |
| 8p23.1   | GATA4 | GATA binding protein 4 | 600576 | Testicular anomalies with or without congenital heart disease; ASD; VSD; TOF |
| Location | Genes | Full name | Gene/locus MIM number | Phenotypes in OMIM |
|----------|-------|-----------|-----------------------|--------------------|
| 11p15.5-p15.4 | KCNQ1 | Potassium voltage-gated channel subfamily Q member 1 | 607542/604115 | LQTs; SQTs; AF; Jervell and Lange–Nielsen syndrome; Beckwith–Wiedemann syndrome |
| 7q36.1 | KCNH2 | Potassium voltage-gated channel subfamily H member 2 | 152427 | LQTs |
| Xq24 | LAMP2 | Lysosomal associated membrane protein 2 | 309060 | Danon disease |
| 10q23.2 | LDB3 | LIM domain binding 3 | 605906 | DCM; HCM; LVNC; myofibrillar myopathy |
| 1q22 | LMNA | lamin A/C | 150330 | DCM; RCM; Charcot-Marie-Tooth disease; Emery-Dreifuss muscular dystrophy; Heart-hand syndrome; Hutchinson-Gilford progeria; lipodystrophy; Malouf syndrome; mandibuloacral dysplasia; muscular dystrophy |
| 15q26.3 | MEF2A | Myocyte enhancer factor 2A | 600660 | Coronary artery disease |
| 1p34.1 | MMACHC | Metabolism of cobalamin associated C | 609831 | Methylmalonic aciduria and homocystinuria |
| 18q11.2 | MIB1 | MIB E3 ubiquitin protein ligase 1 | 608677 | LVNC |
| 1p36.33 | MIB2 | MIB E3 ubiquitin protein ligase 2 | 611141 | – |
| 13q12.12 | MIPEP | Mitochondrial intermediate peptidase | 602241 | Combined oxidative phosphorylation deficiency |
| 11p11.2 | MYBPC3 | Myosin binding protein C3 | 600958 | DCM; HCM; LVNC |
| 16q23.3 | MLYCD | Malonyl-CoA decarboxylase | 606761 | Malonyl-CoA decarboxylase deficiency |
| 14q11.2 | MYH7 | Myosin heavy chain 7 | 160760 | DCM; HCM; LVNC; laing distal myopathy; myopathy, myosin storage; Scapulopeloneal syndrome |
| 20q11.21 | MYLK2 | Myosin light chain kinase 2 | 605666 | HCM |
| 5q31.2 | MYOT | Myotilin | 604103 | Myofibrillar myopathy; myopathy, spheroid body |
| 10p12.31 | NBL | Nebulette | 605491 | – |
| 5q35.1 | NKK2 | NK2 homeobox 5 | 600584 | ASD; AVB; conotruncal heart malformations; Hypoplastic left heart syndrome; hypothyroidism, congenital nongoitrous; TOF; VSD |
| 1p31.1 | NEXN | Nexilin F-actin binding protein | 613121 | DCM; HCM |
| 5p12 | NNT | Nicotinamide nucleotide transhydrogenase | 607878 | Glucocorticoid deficiency with or without mineralocorticoid deficiency |
| Xq13.1 | NONO | Non-POU domain containing octamer binding | 300084 | Mental retardation |
| 8p12 | NRG1 | Neuregulin 1 | 142445 | Schizophrenia |
| 5q35.3 | NSD1 | Nuclear receptor binding SET domain protein 1 | 606681 | Sotos syndrome |
| 1q42.13 | OBSCN | Obscurin, cytoskeletal calmodulin and titin-interacting RhoGEF | – | – |
| 4q35.1 | PDUM3 | PDZ and LIM domain 3 | – | – |
| 12p11.21 | PKP2 | Plakophilin 2 | 602861 | ACM |
| 1p36.21 | PLKHM2 | Pleckstrin homology and RUN domain containing M2 | 609613 | – |
| 3q22.1 | PLXND1 | Plexin D1 | 604282 | – |
| 5q22.31 | PLN | Phospholamban | 172405 | HCM; DCM |
| 1p36.32 | PRDM16 | PR/SET domain 16 | 605557 | DCM; LVNC |
| Location | Genes | Full name | Gene/locus MIM number | Phenotypes in OMIM |
|----------|-------|-----------|-----------------------|-------------------|
| 12q24.13 | PTPN11 | Protein tyrosine phosphatase non-receptor type 11 | 176876 | LEOPARD syndrome; leukemia, juvenile myelomonocytic, somatic; metachondromatosis; Noonan syndrome |
| 10q25.2  | RBM20 | RNA binding motif protein 20 | 613171 | DCM |
| Xp22.12  | RPS6KA3 | Ribosomal protein S6 kinase A3 | 300075 | Coffin–Lowry syndrome; mental retardation |
| 1q43     | RYR2  | Ryanodine receptor 2 | 180902 | ACM; CPVT |
| 3p22.2   | SCN5A | Sodium voltage-gated channel alpha subunit 5 | 600163 | Sudden infant death syndrome; AF; Brugada syndrome; DCM; LQTs; SSS; VF |
| 11q23.1  | SDHD  | Succinate dehydrogenase complex subunit D | 602690 | Mitochondrial complex II deficiency; araganglioma and gastric stromal sarcoma; paragangliomas with or without deafness |
| 16p11.2  | SH2B1 | SH2B adaptor protein 1 | 608937 | – |
| 4q24     | SLC39A8 | Solute carrier family 39 member 8 | 608732 | Congenital disorder of glycosylation |
| Xp11.22  | SMCTA | Structural maintenance of chromosomes 1A | 300040 | Cornelia de Lange syndrome; developmental and epileptic encephalopathy, with or without midline brain defects |
| 15q24.1  | STRA6 | Signaling receptor and transporter of retinol STRA6 | 610745 | Microphthalmia with coloboma; Microphthalmia, syndromic |
| X A7.3; X 37.95 cM | TAZ | Tafazzin | 300394 | Barth syndrome |
| 12q24.21 | TBX5  | T-box transcription factor 5 | 601620 | Holt–Oram syndrome |
| 7p14.2   | TBX20 | T-box transcription factor 20 | 606061 | ASD |
| 3p25.1   | TMEM43 | Transmembrane protein 43 | 612048 | ACM; Emery-Dreifuss muscular dystrophy |
| 8q21.11  | TMEM70 | Transmembrane protein 70 | 612418 | Mitochondrial complex V (ATP synthase) deficiency, nuclear type |
| 3p21.1   | TNWC1 | Troponin C1, slow skeletal and cardiac type | 191040 | DCM; HCM |
| 19q13.42 | TNNT3 | Troponin I3, cardiac type | 191044 | DCM; ROM; HCM |
| 1q32.1   | TNNT2 | Troponin T2, cardiac type | 191045 | DCM; ROM; HCM; LVNC |
| 15q22.2  | TPM1  | tropomyosin 1 | 191010 | DCM; HCM; LVNC |
| 2q31.2   | TTN   | Titin | 188840 | DCM; HCM; muscular dystrophy, limb-girdle; myofibrillar myopathy with early respiratory failure; salih myopathy; tibial muscular dystrophy, tardive; – |

LVNC: left ventricular noncompaction. HCM: hypertrophic cardiomyopathy. DCM: dilated cardiomyopathy. ACM: arrhythmogenic cardiomyopathy. ROM: restricted cardiomyopathy. AF: atrial fibrillation. ASD: atrial septal defect. CHD: congenital heart disease. VSD: ventricular septal defect. PFO: patent foramen ovale. TOF: fallot tetralogy. LQTs: long QT syndrome. SQTs: short QT syndrome. SSS: sick sinus syndrome. WPW: Wolff–Parkinson–White syndrome. CPVT: catecholamine sensitive ventricular tachycardia. VF: ventricular fibrillation. PDA: patent ductus arteriosus. –, not mentioned in OMIM database.
LVNC is a rare primary CM and serves as a global cardiac disease induced by the arrest of normal embryogenesis of the endocardium and mesocardium that leads to prominent trabeculations and deep intertrabecular recesses within the LV wall communicating with the cavity, a thin compacted epicardial layer, and acquired ventricular wall remodeling [24]. The inferior and lateral walls of LV from the midcavity to the apex are the most commonly involved [10]. The Jenni and Petersen diagnosis criteria of LVNC are generally accepted and rely on imaging modalities, including echocardiography and CMRI, e.g., (1) bilayer myocardium with multiple, prominent trabeculations in the end-systole; (2) NC/C ratio of >2:1 in echocardiography or >2.3 in CMRI measured in the end-systole or end-diastole, respectively; and (3) communication with the intertrabecular space and deep intertrabecular recesses in the noncompaction layer [10, 11]. Based on previous studies [25] and our literature review, the LVNC prevalence is 0.05%–0.3% in an adult population undergoing echocardiography. LVNC may occur with congenital heart malformations, myopathies, neuromuscular and metabolic diseases, complicating developmental delay and intellectual disability. LVNC with HF, ventricular arrhythmias, and thromboembolic events show poor prognosis with an overall mortality rate of 5–12% per year [26]. As shown in the literature review in our study, once the cases occur with LVNC and malignant clinical syndromes, the prognosis is poor with high mortality in the fetus or infant. Some LVNC patients have a family history of LVNC and/or sudden death and recurrent VT despite therapy with multiple antiarrhythmic drugs. The ventricular arrhythmia ordinarily originates from bilateral ventricles. The substrate of ventricular arrhythmia in LVNC typically involves the mid-apical segment, septum, and lateral wall of LV. In contrast, focal PVCs commonly arise from LV basal-septal regions and/or papillary muscles, reflecting the distribution of non-compaction myocardial segments [27]. LVNC mostly affects the left ventricular muscle and serves as a primary and genetically heterogeneous CM, which the American Heart Association exists in sporadic and hereditary forms. Previous research showed that among LVNC cases, 52% are sporadic, 32% have a genetic cause, and an additional 16% have affected family members with negative genetic testing. Not all family members present with the same LVNC phenotype as some proband occurs with DCM, HCM, or SCD [28]. Potentially causative gene mutations responsible for LVNC are involved in the sarcomere, cytoskeleton, mitochondria, desmosome, and storage and ion channels implicated in other cardiac diseases [29–31]. According to previous studies and our literature review, MYH7, MYBPC3, TPM1, TAZ, TTN, and NONO genes are the most common pathogenic mutations in LVNC [28, 32, 33], which are not demonstrated in the proband of our study. LVNC or an element of other CMs may be isolated due to sharing common genetic risk [34]. These common genetic backgrounds are phenotypically expressed as overlap CMs, fulfilling the criteria for LVNC and HCM (or DCM, RCM, or ACM). The LV hypertrabeculation and HCM may present as acquired conditions due to the adaptation of the ventricular myocardium to pressure or volume overload [35]. Some LVNCs also involve the right ventricle, exhibiting high values of right ventricular noncompaction and trabeculated area [36]. Therefore, the subtypes of LVNC include benign LVNC, LVNC with arrhythmias, dilated LVNC, hypertrophic LVNC, hypertrophic dilated LVNC, restrictive LVNC, right ventricular or biventricular LVNC, and LVNC with CHD [25]. Actually, some pathogenic mutations are associated with various complex rare diseases involving more than one organ. For example, the 11-16th exon deletion of KCNQ1 induced mild Beckwith-Wiedemann and severe LQTSs [37]. Notably, in light of our literature review, LVNC with complex clinical syndromes, poor prognosis, and high mortality that may occur in the fetus or infant should be classified as another new subtype of LVNC. These syndromes may include Rubinstein–Taybi syndrome, Ehlers–Danlos syndrome, Emery–DeFuss muscular dystrophy, Danon disease, intellectual disability syndrome, Soto’s syndrome, LEOPARD syndrome, Coffin-Lowry syndrome, Cornelia de Lange syndrome, Barth syndrome, and Holt–Oram syndrome.

Two independent biological events leading to abnormal trabeculations and compaction, including hypertrabeculation and noncompaction, are demonstrated by the FKBP12-deficient mouse model for LVNC [38, 39]. Hypertrabeculation refers to the phenotype with...
increased number and thickness of the trabeculae at the embryonic stage. In contrast, noncompaction refers to the lack of trabecular remodeling toward the compact wall during and after trabeculations [40]. The enhanced Notch signaling induces abnormal cardiomyocyte proliferation and hypertrabeculation/noncompaction via Neuregulin1, EphrinB2, FKBPI2, BMP10, TBX20 and its upstream of Sema3E/PlexinD1 signaling pathway, which potentially contributes to LVNC [41, 42]. The inhibition of Notch signaling partly normalizes the abnormal hypertrabeculation phenotype in FKBPI2-deficient hearts. The planar cell polarity (PCP) signaling is also an essential molecular mechanism of polarity establishment for epithelial cells in planes orthogonal to the apical-basal axis. The noncanonical Wnt signaling, which is independent of β-catenin, is critical for PCP signaling. Together, they serve as the Wnt/PCP signaling pathway, which is composed of core components (i.e., Frizzled, Disheveled, Prickle, Vangl, and Celsr1), PCP regulator (i.e., casein kinase 1ε) and a large number of PCP effectors (i.e., Daam1, Rac1, and PhoA) [43, 44]. These molecules of Wnt/PCP signaling induced by their genetic mutations result in abnormal polarization, organization of cardiomyocyte in ventricular and outflow myocardia, and subsequent LVNC pathogenesis [40].

In this study, the proband (II: 1) carried DSC2 p.K47Rfs*2 and p.I520T variants. According to the ACMG classification criteria, the DSC2 p.K47Rfs*2 is a truncated and loss-of-function mutation, likely to cause LVNC and HCM. Compared to the MAF (<0.01%) of inherited arrhythmia and CMs in the population, the MAF of DSC2 p.I520T (0.02%) is relatively high. Moreover, DSC2 p.I520T is not conservative in multiple species. In addition, the ECG is the main tool to judge the early changes of CMs. Especially, the abnormal changes of ECG caused by CMs are often earlier than that of the cardiac structure illustrated by echocardiography [45]. Whereas II: 3 only carrying DSC2 p.I520T and without cardiac event showed normal ECG and echocardiography. Therefore, we speculated that DSC2 p.I520T might not be pathogenic. In fact, as an important component of the cardiac desmosome, desmocollin2 maintains the normal electromechanical connection among cardiomyocytes. The desmocollin2 abnormality would lead to various CMs (such as DCM and HCM), HF, complex arrhythmia and even SCD. Recent research and our literature review showed that the abnormal components of the cardiac desmosome, including DES and DSP genes, are associated with LVNC. Desmosome is the intracellular structure that anchors intermediate filament to the plasma membrane. Desmosome, adherent junction, and gap junction are the major components of the intercalated disc, which is vital for the cell–cell adhesion and electronic coupling of cardiomyocytes [46]. Desmocollin2 and desmoglein2 (encoded by DSG2) are the important familial members of cadherin. Desmocollin2 and desmoglein2 form the adhesive heterodimer, which provides a structural framework for desmosome assembly together with armadillo proteins (plakoglobin and plakophilin, which are encoded by PG and PKP2, respectively) and the plakin family (desmplakin, which DSP encodes) [47, 48]. The desmin filament (encoded by DES), also expressed in cardiac desmosomes, connects Z-bands, costameres, and nuclei with the cytoskeleton. The pathogenic mutations associated with desmosome proteins may cause desmosome dysfunction and remodel intercalated disc, leading to the disturbance of the mechanical–electrical coupling of cell–cell adhesion and further alteration of signaling pathways.

Previous studies show that the homozygous deletion mutation of PKP2 lead to LVNC and rapid HF, whereas the heterozygous DES p.A337P (NM_001927.3, c.1009G>C) induces LVNC and skeletal myopathy [49, 50]. A report indicates a DSC2 variant (NM_024422.3, c.1448A>T, p.N483I) in a patient with sporadic LVNC, but whether the variant is the cause of LVNC remains unclear [32]. A previous study shows that the DSC2 deletion in zebrafish induces the reduction of the desmosome plaque area, deficiency of desmosome extracellular electron-dense midlines, and disturbance of myocardial contractility [51]. Additionally, DSC2 p.Q554X (c.1660C>T) participates in the pathogenicity of familial ACM [52]. DSC2 p.A897fs*900 shows an obvious reduction in desmosome binding to plakoglobin and plakophilin [53]. The truncated mutation of DSC2 (c.2553delA) decreases the connexin 43 expression and lost plakoglobin signal [54]. Furthermore, the loss of DSC2 activates the AKT/β-catenin pathway. AKT inhibition suppresses β-catenin-dependent transcription and proliferation, which are caused by DSC2 knockout [55]. In the present study, the 47th AA lysine of the DSC2 protein sequence at the cadherin pro is replaced by arginine, leading to premature codon termination. Consequently, DSC2 p.K47Rfs*2 remarkably and abnormally reduced the functional desmocollin2 expression, which may interfere with desmosome formation and the stability of the intermediated disc, and disturb the mechanical stress and electrical signal propagation of cardiomyocytes. Notably, the pathological and imaging changes induced by DSC2 p.K47Rfs*2 are observed in LV, resulting in the subendocardial thickening of the anterior lateral wall and interventricular septum, and thinning in part of the left ventricular wall. The ECG of the proband showed low voltage in the limb leads but no typical ST-T change, commonly suggesting diffuse myocardial lesion. The VT arises from the middle-posterior septum and lateral wall of LV. PVCs originate from
the lateral wall and apex of LV and the left ventricular inflow tract, and this finding is consistent with the cardiac lesion extent. Additionally, trabeculae are observed with serious dysplasia and distributed in a rough and disordered pattern. An apparent slow blood flow is observed in the recess of trabeculae, which may increase the risk of thrombus. However, the mechanism of DSC2 p.K47Rfs*2 that induces overlap phenotypes of LVNC and HCM remains unknown. There is no research about the relationship among DSC2, Notch, and Wnt/PCP signaling pathways.

Limitation
The limitations of the present study are as follows. First, the molecular mechanism of DSC2 p.K47Rfs*2 leading to abnormalities of the desmosome structure and function should be further explored. Second, DSC2 p.K47Rfs*2 is the main cause of LVNC and HCM but still cannot rule out DSC2 p.I520T, or other variants may increase the risk of LVNC and HCM phenotype penetrance. Third, the mechanism of how the DSC2 p.K47Rfs*2 induces overlap phenotypes needs further research. Fourth, the parents and grandparents of the patient (II: 1) could not be tracked because of death. The II: 1, II: 2 and II: 3 members declined to to carry out clinical examinations and genetic testing for their offspring. Therefore, long-term follow-up is needed in the future.

Conclusion
The desmocollin2 was an important component of cardiac desmosome assembly, of which abnormality caused the dysfunction of cell–cell adhesions and intercellular gap junctions. The novel heterozygous DSC2 p.K47Rfs*2 mutation remarkably and abnormally reduced the functional desmocollin2 expression, which may consequently induce the overlap phenotypes of LVNC and HCM, complicating AF, VT, and HF. The LVNC may be one of the important phenotypes for DSC2 pathogenic mutations.

Abbreviations
CM: Cardiomyopathy; LVNC: Left ventricular noncompaction cardiomyopathy; HCM: Hypertrophic cardiomyopathy; DCM: Dilated cardiomyopathy; RCM: Restrictive cardiomyopathy; ACM: Arrhythogenic cardiomyopathy; AF: Atrial fibrillation; VT: Ventricular tachycardia; HF: Heart failure; SCD: Sudden cardiac death; LVEF: Left ventricular ejection fraction; MYH7: Myosin heavy chain; MYBPC3: Protein-binding protein C myosin; TPM1: Tropomyosin alfa; ACTC1: Myocardial actin; TNN2: Troponin T; DTNA: Alpha-distrobrevin; CMRI: Cardiac magnetic resonance imaging; ECGs: Electrocardiograms; NT-proBNP: The N-terminal of B-type natriuretic peptide precursor; LV: Left ventricle.

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Authors’ contributions
Statistical analysis and manuscript drafting, Y.B.L. and J.N.H.; clinical data, family information and follow-up, Z.L.Z. and X.F.L.; designed the study and critical manuscript revision, Z.Y.H. and G.Y.X.; radiography analysis, Z.Q.Z.; echocardiogram analysis, J.Z.X.; western-blot and PCR experiments, T.F.Q, L.X.C. and J.M.H.; electrocardiogram analysis, Q.I.W and Y.H. All authors read and approved the final manuscript.

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Availability of data and materials
The data used in this study is not publicly available, but it might be available from the corresponding author upon reasonable request and permission from relevant Chinese Authorities.

Declarations

Ethics approval
All procedures performed in studies involving human participants were following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Medicine Ethics Committee approved the protocol of the Fifth Affiliated Hospital of Sun Yat-sen University (No. 2020K216-1).

Consent to participate
Informed consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable.

Competing interests
The authors of this study declare that they each have no conflict of interest.

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