Heterozygous desmin gene (DES) mutation contributes to familial dilated cardiomyopathy

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Abstract
Familial dilated cardiomyopathy (FDCM) is characterized by high genetic heterogeneity and an increased risk of heart failure or sudden cardiac death in adults. We report the case of a 62-year-old man with a 2-month history of shortness of breath during activity, without paroxysmal nocturnal dyspnea. The patient underwent a series of examinations including transthoracic echocardiography, coronary arteriography, transesophageal echocardiography, and myocardial perfusion imaging. After excluding secondary cardiac enlargement, he was diagnosed with dilated cardiomyopathy (DCM). His sister had also been diagnosed with DCM several years before. Genetic sequencing analysis revealed that the patient, his sister, and his son all had the same mutation in the desmin gene (DES) (chr2-220785662, c.1010C>T). Genetic testing confirmed a heterozygous DES mutation contributing to FDCM. In this case, the etiology of the patient’s whole-heart enlargement was determined as FDCM with DES gene mutation. This is the first report to describe DES c.1010C>T as a cause of FDCM.

Keywords
Familial dilated cardiomyopathy, dilated cardiomyopathy, desmin, case report, gene mutation, heterozygous

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Introduction

Dilated cardiomyopathy (DCM) is defined as left ventricular (LV) dilation and systolic dysfunction in the absence of coronary artery disease or abnormal loading conditions proportionate to the degree of LV impairment. DCM is one of the most common primary myocardial diseases and an important cause of heart failure and sudden cardiac death, with 30% to 50% of cases having a familial origin. Familial DCM (FDCM) is defined most conservatively as DCM meeting the criteria for idiopathic DCM in at least two closely related family members. A diagnosis of FDCM is made after excluding other etiologies, such as ischemic or hypertrophic cardiomyopathy. Some retrospective studies estimated that 2% to 10% of patients with DCM were eventually diagnosed with FDCM. In the 1990s, however, prospective cardiovascular screening of close relatives of patients with idiopathic dilated cardiomyopathy estimated that 20% to 48% of individuals had FDCM.

A genetic origin has been identified in 30% to 40% of cases of FDCM, and more than 50 disease-related genes, including desmin (DES), have been associated with FDCM. Desmin plays an important role in maintaining cytoskeletal architecture in skeletal, smooth, and cardiac muscle, and DES mutations are associated with various skeletal and/or cardiac myopathies. However, most DES mutations have been reported in patients with desmin-related myofibrillar myopathy, and DES mutation is an uncommon cause of FDCM.

Case Report

A 62-year-old man presented with a 2-year history of dyspnea and a feeling of chest compression during activity, and had also experienced shortness of breath with edema of the lower extremities for 2 months. He was receiving loop diuretic therapy. He had received a pacemaker implant 2 years earlier because of complete atrioventricular block, and the pacemaker had been replaced due to pacemaker pocket infection 2 months ago. He developed atrial fibrillation 1 month before pacemaker replacement surgery, which persisted to date. He had experienced hypertension for 3 years, with good blood pressure control, and had chronic bronchitis for over 10 years.

His vital signs were normal. Physical examination revealed signs of jugular venous engorgement, a small amount of bilateral lung rales and low breath sound in both sides, reflux heart murmur, and positive hepatic jugular venous reflux. His heart rate was 80 beats/minute and irregular. There was pulse deficit. Both lower extremities had pitting edema.

N-terminal-pro B-type natriuretic peptide serum levels were significantly above the normal range, fluctuating between 2000 to 4000 pg/mL. An electrocardiogram indicated atrial fibrillation with left bundle branch block (Figure 1). A chest radiograph showed bilateral pleural effusion. The echocardiogram revealed an enlarged four-chamber (LV end-systolic diameter 4.8 cm and end-diastolic diameter 6.0 cm, left atrial diameter 4.5 cm) with normal LV thickness (1.0 cm) and diffuse reduction of wall motion (LV ejection fraction 37% by Simpson’s method) (Figure 2a-c), color Doppler showed in-gravescence of mitral and tricuspid regurgitation. Transesophageal echocardiography showed patent foramen ovale. Coronary angiography showed no severe coronary artery stenosis. 99mTc-sestamibi myocardial perfusion imaging showed dilated cardiomyopathy with LV insufficiency (Figure 1b). Pulmonary function tests confirmed chronic obstructive pulmonary disease (COPD). A pulmonary ventilation perfusion scan showed a small pulmonary
embolism in the posterior basal segment of the lower lobe.

The patient’s symptoms of edema and dyspnea improved after treatment with an angiotensin-converting enzyme inhibitor (perindopril), beta-blocker (metoprolol tartrate), aldosterone antagonist (spironolactone), and loop diuretic (torasemide). The patient also received anticoagulation with dabigatran for atrial fibrillation and pulmonary embolism.

The patient’s sister (67 years old) had been diagnosed with DCM several years earlier and had undergone pacemaker implantation because of complete atrioventricular block. The current patient was accordingly diagnosed with FDCM because both he and his sister met the criteria of idiopathic DCM in at least two closely related family members. Both patients both showed III atrioventricular block, probably because cardiomyopathy involves the conduction system. The patient, his sister (both with confirmed DCM), and his son (aged 34 years; healthy, with no record of dilated heart) all received genetic testing, which revealed the same heterozygous DES mutation. None of the three individuals showed any abnormal skeletal muscle symptoms. Mutation analysis (see below) identified a c.1010C>T mutation in the DES gene, causing an alanine to

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Figure 1. Electrocardiogram (ECG) and 99mTc-sestamibi (MIBI) myocardial perfusion imaging of the patient. (a) ECG revealed atrial fibrillation with complete left bundle branch block. (b) 99mTc-MIBI myocardial perfusion imaging suggested dilated cardiomyopathy with left ventricular dysfunction.

Figure 2. Transthoracic echocardiography of the patient. (a) Long-axis view of left ventricle by ultrasound cardiography (UCG), showing left ventricular end-systolic diameter of 4.80 cm and end-diastolic diameter of 5.96 cm. (b) Four-chamber view by UCG, showing enlarged left atrium. (c) Left ventricular ejection fraction was 37% by Simpson’s method.
valine substitution at position 337 in the desmin protein in all three individuals (Figure 3a–c), which confirmed the FDCM diagnosis. The pedigree is shown in Figure 3d.

Gene sequencing was carried out as follows. Peripheral blood was collected from the patient and his family members and DNA was extracted using a blood DNA extraction kit (Tiangen, Beijing, China), according to the manufacturer’s instructions. Targeted gene capture sequencing was performed by MyGenostics (Beijing, China). Genomic DNA samples were fragmented and prepared for standard Illumina library construction. Biotinylated capture probes were designed for the exons of 94 genes related to cardiomyopathy and sequenced using an Illumina HiSeq 2000 Next-Generation Sequencing platform (Illumina, San Diego, CA, USA) and bioinformatics analyses (MyGenostics). Data analysis was performed according to MyGenostics protocols. Clinically relevant variants from the patient, his sister, and his son were confirmed by Sanger sequencing.

Informed written consent was obtained from the patient prior to publication of this report and ethical approval was provided by the Biomedical Ethics Committee of Beijing Friendship Hospital, Capital Medical University (No. 2019-P2-211-01).

Discussion

We present a patient who showed enlargement of all four chambers of the heart, with symptoms of heart failure including dyspnea and edema. The patient had a 2-year history of hypertension, but his blood
pressure was well-controlled. Before making a diagnosis of DCM, other etiologies that could cause enlargement of the heart should be excluded. Considering the patient's examination results, differential diagnoses accounting for left- and right-side heart dysfunction were thus considered. Hypertensive heart disease, ischemic cardiomyopathy, and pacemaker syndrome can cause left-side heart enlargement, while COPD, pulmonary embolism, and pulmonary arterial hypertension can cause right-side heart enlargement. This patient had a relatively complex history including hypertension, patent foramen ovale, and COPD, and the secondary etiology of cardiac dilation thus needed to be considered and differentiated carefully. However, none of these alternative etiologies could explain the extent of chamber enlargement, and after thorough examination, a diagnosis of DCM was confirmed. Hemodynamic disorders induced by atrial fibrillation and VVI pacemaker implantation may have contributed to the deterioration in cardiac function in this case.

DCM can be considered as familial (FDCM) when two or more affected relatives meet the major criteria of DCM, or when a first-degree relative dies suddenly before the age of 35. The onset age of FDCM is typically between year 20 and 50 years, and FDCM is rarely diagnosed in the elderly.

Desmin-related myofibrillar myopathy is a cardiac and skeletal muscle disease caused by mutations in the DES gene. DES mutations have an extremely low incidence rate in the population, accounting for only 2% of variants among 639 patients with familial DCM, whereas others reported a frequency of DES gene mutation of <1% in patients with FDCM.

DES encodes the protein desmin, which plays an important role in the function of cardiomyocytes in terms of mechanical stabilization and linkage of the cell structures. Desmin functions as part of the dystrophin-associated glycoprotein complex, and mainly affects the cytoskeleton. DES variants are associated with desminopathy, and affected patients are mainly characterized by muscle weakness, conduction block, and DCM.

Analysis of the current patient and his relatives revealed a heterozygous missense mutation in the DES gene: c.1010C>T, resulting in a single amino acid change (alanine to valine substitution at position 337). This mutation did not occur at a polymorphic locus, and occurs very rarely in the population, with no reports in the Human Gene Mutation Database (HGMD; http://www.biobase-international.com/product/hgmd).

In the current patient, a novel missense mutation, c.1010C>T (p.A337V, NM_001927), was identified within exon 5 of the DES gene. This mutation site was not present in the 1000 Genome Project (http://www.1000genomes.org/), ESP6500 (NHLBI Exome Sequencing Project; http://evs.gs.washington.edu/EVS), ExAC_ALL (Exome Aggregation Consortium) and ExAC_EAS (Exome Aggregation Consortium East Asian) (http://exac.broadinstitute.org/), and MyGenostics Inhouse databases. SIFT (http://sift.jcvi.org/) and MutationTaster tools (http://www.mutationtaster.org/) both predicted deleterious mutations, the Genomic Evolutionary Rate Profiling (+++) prediction (http://mendel.stanford.edu/SidowLab/downloads/gerp/index.html) was located in conservative regions, and the same 337 position p.A337P (c.1010C>G, NM_001927) has previously been reported in a patient with myofibrillar myopathy. The difference in DES mutation-associated cardioskeletal myopathy in the current compared with this previous patient may be because the patient with skeletal myopathy had an
A360P mutation in addition to the A337P substitution. Notably, the American College of Medical Genetics and Genomics classifies this variant as “likely pathogenic.”

Mutations in the central 2B domain of desmin cause skeletal muscle disease that typically precedes cardiac involvement. However, the prevalence of DES mutations in cases of DCM without skeletal muscle disease is not known.\textsuperscript{10} 

DES p.Q113_L115del has been associated with DCM with prominent LV hypertrobracleulation.\textsuperscript{14} DES p.L136P was confirmed as a likely pathogenic mutation in another family with FDCM,\textsuperscript{15} and a novel mutation (c.679 C>T/p.R227C) in exon 3 of DES was identified in a Chinese family with isolated DCM phenotypes, leading to a substitution of arginine by cysteine.\textsuperscript{16} The DES mutations 38C>T and 1360C>T, resulting in Ser13Phe and Arg454Trp changes, respectively, were reported in a large DCM cohort.\textsuperscript{17} DES mutation screening in 116 families with DCM detected four novel variants in patients with DCM (Glu108Lys: c.408.G3A; Ser298Leu: c.979.C3T; Asp312Asn: c.1020.G3A; Arg350Trp: c.1134.C3T), and another two DES mutations (Val459Ile: c.1461.G3A and Ala213Val: c.730.T3C).\textsuperscript{10} Of these six DES mutations, none of the patients showed muscle disease, and three showed conduction system disease (left anterior fascicular block; left bundle-branch block, and I atrioventricular block).

To the best of our knowledge, the DES mutation in the current case has not been reported previously, and this thus represents the first report of the DES: c.1010C>T mutation as a cause of FDCM.

The current patient and his sister both showed complete atrioventricular block, suggesting that DES: c.1010C>T might contribute to DCM with conduction system disease as a pathogenic mutation. None of the patients with FDCM in this report showed muscle weakness or skeletal muscle myopathy, indicating that this mutation may not affect the cytoskeleton in skeletal muscle. The heterozygous mutation in the patient’s older sister and son were likely to have been inherited in an autosomal dominant manner. Although the patient’s son showed no symptoms of cardiac dysfunction and no evidence of chamber enlargement on transthoracic echocardiography, probably related to penetrance insufficiency, the penetrance rate is expected to increase gradually with age, suggesting that he will have an increased probability of developing DCM and atrioventricular block in future decades. The patient’s son should thus undergo regular follow-up and echocardiography examinations.

These cases highlight that, if the causal mutation is known, asymptomatic family members should receive genetic screening and periodic examinations to facilitate early diagnosis and therapy.\textsuperscript{12} In conclusion, clinical and genetic analysis of the current case revealed a rare mutation within the DES gene, c.1010C>T, which may mainly affect the cardiac conduction system, causing FDCM without skeletal muscle myopathy.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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