Case Report

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A novel *TNNI3* gene mutation (c.235C>T/ p.Arg79Cys) found in a thirty-eight-year-old women with hypertrophic cardiomyopathy

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Abstract: We report the case of a thirty-eight-year-old woman admitted to our hospital due to palpitation and chest distress. ST-T segment change was found in her ECG. She was then diagnosed with hypertrophic cardiomyopathy by two-dimensional echocardiography. Physical examination showed no obvious abnormal signs and all laboratory examinations were within the normal range. Myocardial fibrosis was detected by cardiac magnetic resonance imaging (MRI). A novel heterozygous mutation (c.235C>T/ p.Arg79Cys) in *TNNI3* for cardiac troponin I was identified in her. Subsequently, her families were investigated. No one died suddenly in her family. Her father, one of her siblings and one of her daughters had the same genetic mutation but with different clinical manifestations while the others were healthy. Her father and brother were also diagnosed with hypertrophic cardiomyopathy with different clinical manifestation. However, the echocardiography of her daughter was absolutely normal. We hypothesized that the Arg79Cys mutation in *TNNI3* leads to a slow development of cardiac hypertrophy and the phenotype of this gene mutation is diverse.

Keywords: Hypertrophic cardiomyopathy; Gene test; TNNI3

1 Introduction

Characterized by idiopathic hypertrophy, especially the interventricular septum (IVS), hypertrophic cardiomyopathy (HCM) is one of the most commonly inherited cardiovascular diseases. Family history of about half of the patients are positive for HCM. Family HCM often presents an autosomal dominant (AD) pattern of inheritance, which is due to mutation of the genes encoding sarcomeric proteins. Until now, there are approximately 450 point mutations in 13 genes contributing to HCM, among which, beta-myosin heavy chain (*MYH7*), cardiac troponin I (*TNNI3*), myosin binding protein C (*MYBPC3*), cardiac troponin T (*TNNT2*) are most common [1]. Families with various mutations of HCM exhibit a variety of phenotypes and prognosis. Recent evidence showed that the mutations of responsible gene may not be related to the disease phenotype, or the gene mutation is not associated with clinical presentation [2, 3].

Investigation of genetic basis of HCM is contributable to deeply understand the pathogenesis of cardiac hypertrophy and may improve the prevention, diagnosis, treatment of the disease. Here we report a case of thirty-eight- year-old women with HCM who is a carrier of a novel point mutation in *TNNI3* and screen the gene of her family at the same time. We are carefully following up with this patient and her family to observe the prognosis of HCM caused by this mutation.

2 Case report

A thirty-eight- year-old woman was admitted to our hospital due to palpitation and chest distress. She was in good health before without high blood pressure or diabetes. The clinic twelve-lead electrocardiography (ECG) indicated sinus rhythm with ST-T segment change, PR interval was 160ms, QT interval was 447ms, QRS width was 100ms, and Sokolow index was 67mm. Therefore, it is recommended to further perform the echocardiogram. Transthoracic

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echocardiography demonstrated interventricular septal hypertrophy with thickness of about 19 mm, while the posterior wall of the left ventricle is approximately 8 mm. Global left ventricular systolic function was normal with an ejection fraction of 65% and no regional wall motion was abnormal. Based on the results of the examination, we initially diagnosed the patient with hypertrophic cardiomyopathy. Physical examination and laboratory examination were further performed. Her height and body weight were 155 cm and 51 kg, respectively. Her blood pressure and pulse rate were 122/75 mmHg and 74 beats/minute while Oxygen saturation was 99%. Physical examination showed no obvious abnormal signs and laboratory examinations were within the normal range. Myocardial fibrosis was detected by cardiac magnetic resonance imaging (MRI). Her risk of sudden cardiac death at 5 years was 2.03% by European Society of Cardiology calculator (http://doc2do.com/hcm/webHCM.html). Genomic DNA was extracted from peripheral venous blood, which was amplified by polymerase chain reaction (PCR). The PCR products were sequenced by terminating double deoxidization terminal (ABI company 3730XL automatic sequencing machine). The mutations in 4 HCM-associated genes *(MYH7*, *MYBPC3*, *TNNT2*, and *TNNI3)* were searched in the proband and a heterozygous mutation (c.235C>T/ p.Arg79Cys) in *TNNI3* for cardiac troponin I was identified. Up to now, only 5 mutations in *TNNI3* associated with HCM were reported, namely, c.37C>T/ p. Arg13Cys, c.422G>A/ p. Arg141Gln, c.433C>T / p. Arg145 Trp, c.434G>A / p. Arg145Gln, c.470C>T/ p.Ala157 Val [4]. We report a new mutation (Figure 1).

No one died suddenly in the family (Figure 2) and we suggest that her immediate relatives come to the hospital for relevant examinations. The same gene mutation was found in her father. He was sixty-five years old with hypertrophic cardiomyopathy diagnosed by echocardiogram while her mother was healthy. He had the symptoms of chest tightness and shortness of breath. His ECG showed sinus rhythm with ST-T segment change. No myocardial fibrosis was found in his cardiac MRI (Figure3).

She has four siblings, only one of which had been diagnosed with hypertrophic cardiomyopathy by echocardiogram. He was thirty-four years old and in good condition before with no symptoms of hypertrophic cardiomyopathy. The same heterozygous mutation was found in TNNI3. ST-T segment change was found in his ECG and his cardiac MRI showed myocardial fibrosis (Figure 4).

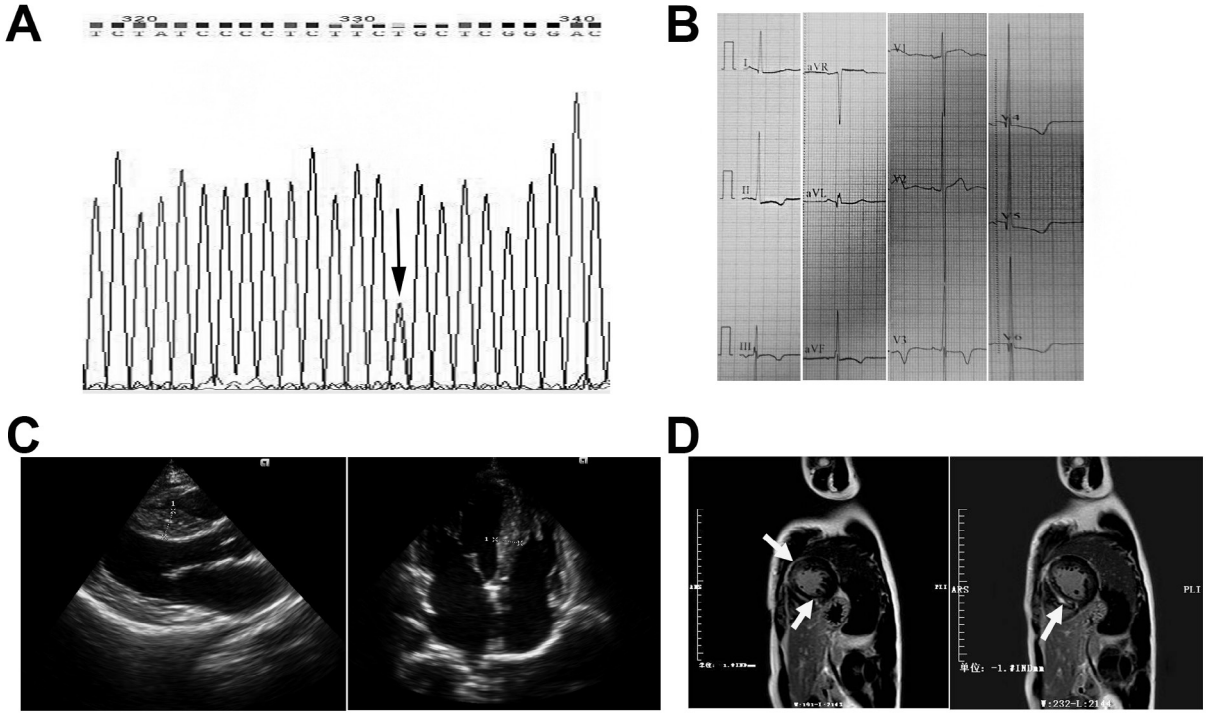

Figure1. Case 1: The proband. (A) Sequencing analysis of exon 8 in TNNI3. **(B)** The representative image of ECG. **(C)** The representative image of echocardiography. **(D)** The representative image of MRI.

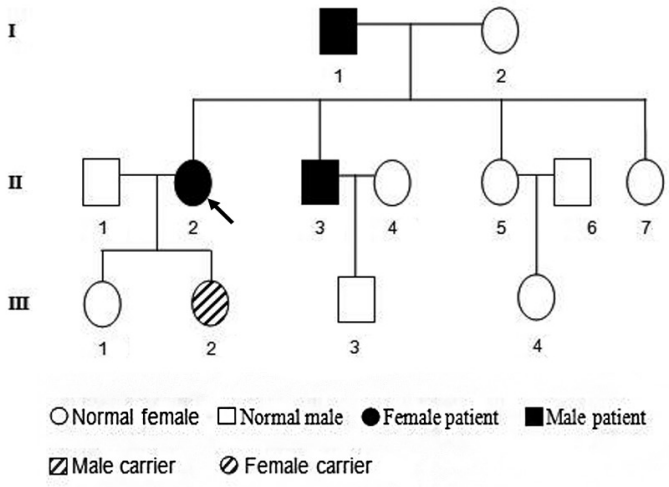

Figure2. Family pedigree of the present case

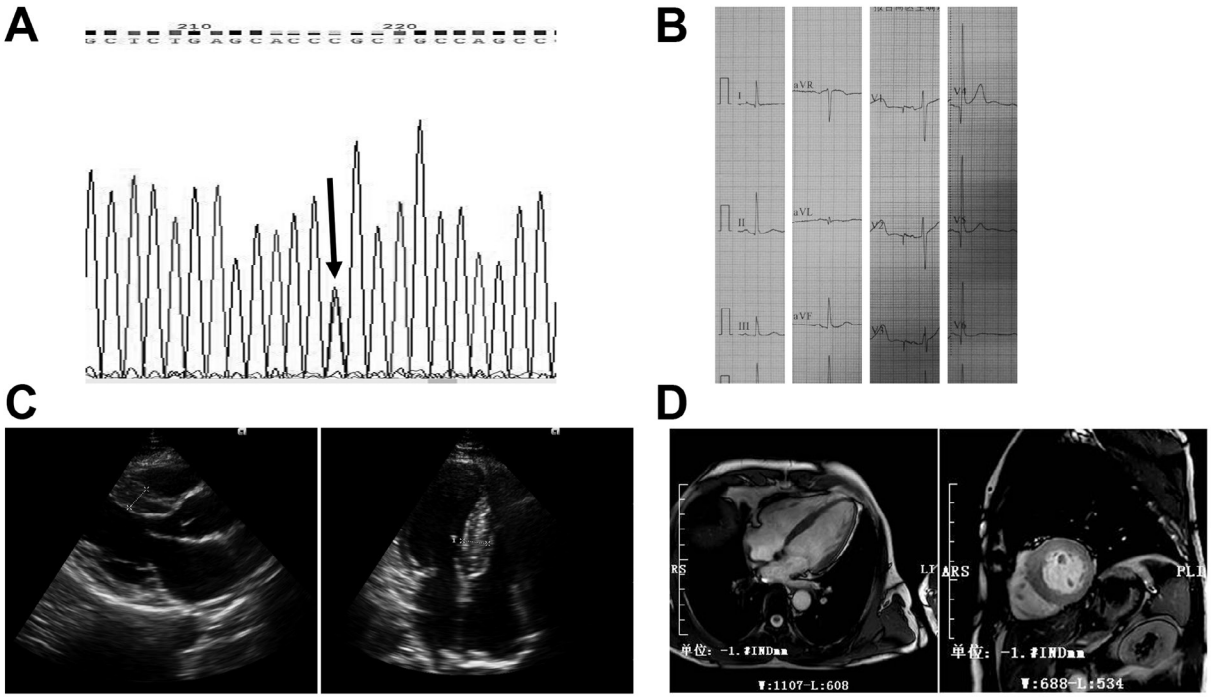

Figure3. Case 2: The father of the proband (A) Sequencing analysis of exon 8 in TNNI3. **(B)** The representative image of ECG. **(C)** The representative image of echocardiography. **(D)** The representative image of MRI.

The proband has two daughters and the same mutation in TNNI3 was detected in one of them. She was three years old and showed no cardiac hypertrophy by echocardiography. No abnormalities were found in her ECG. She is too young for complete a MRI examination. (Figure 5).

Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

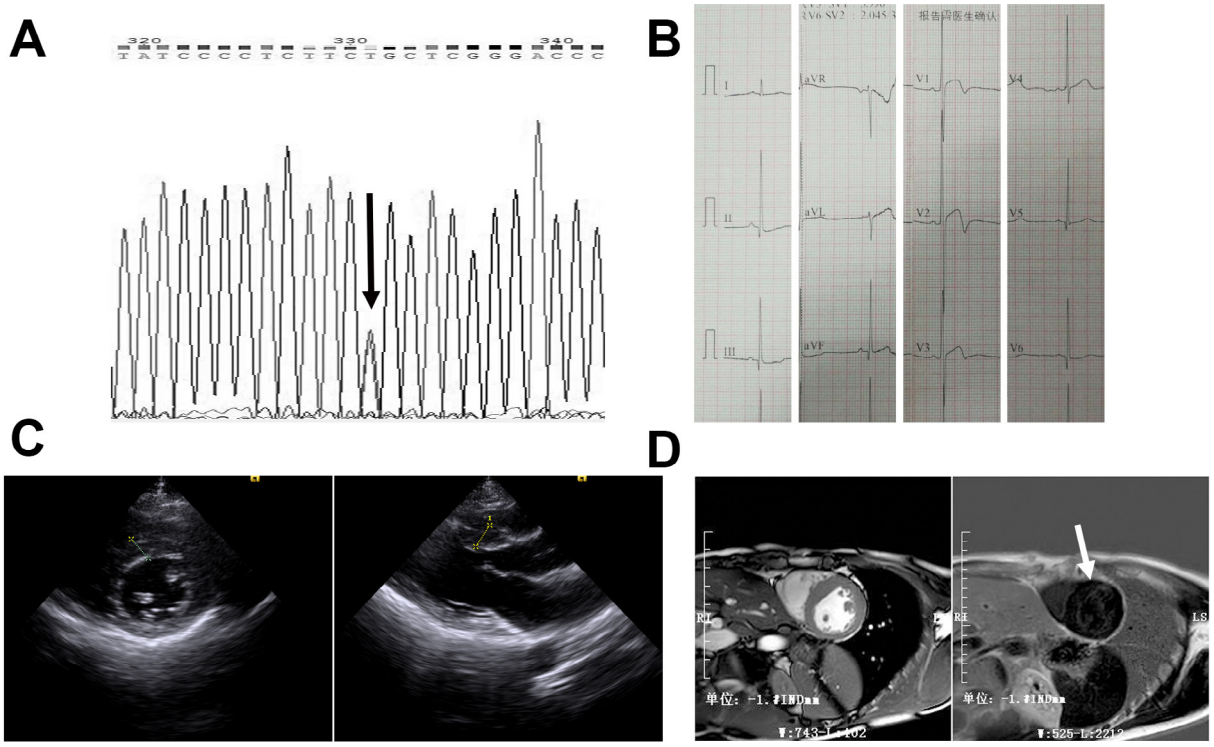

Figure4. Case 3: The brother of the proband (A) Sequencing analysis of exon 8 in TNNI3. **(B)** The representative image of ECG. **(C)** The representative image of echocardiography. **(D)** The representative image of MRI.

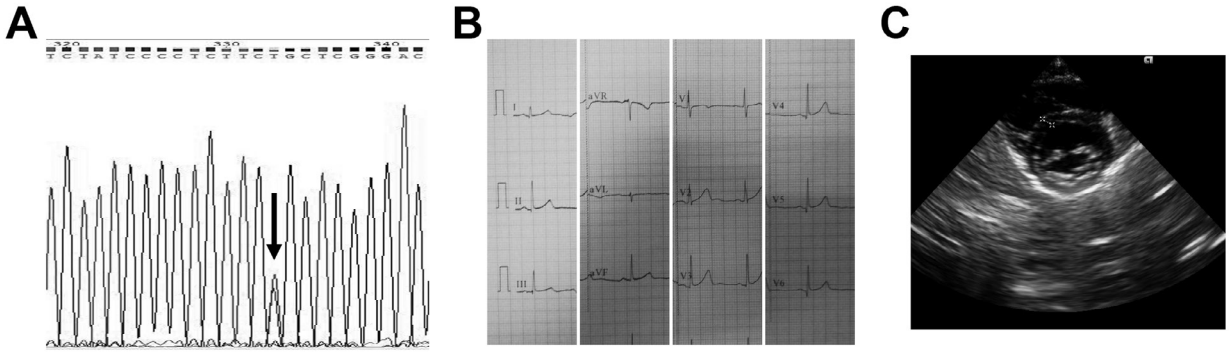

Figure5. Case 4: The daughter of the proband (A) Sequencing analysis of exon 8 in TNNI3. **(B)** The representative image of ECG. **(C)** The representative image of echocardiography.

3 Discussion

The *MYH7, MYBPC3, TNNT2* and *TNNI3* are the predominant genes causing HCM in Chinese population [4, 5]. In this case, we screened the four genes of the proband and her families and found a novel mutation in TNNI3. The present study is the first case with HCM who had a p. Arg79Cys mutation in TNNI3, which has never been reported before as a gene mutation responsible for HCM. The mutation of TNNI3 accounts for about 1-5% of patients with definitely genotyped HCM, but different phenotypes may be present [6]. It is estimated that mutation of TNNI3 is responsible for HCM. Most mutations in TNNI3 described up till now are found in exon 7 and 8, with some of these mutations found more frequently than others [7]. Concordantly, we also identified the mutation in exon 8.

It is reported in previous studies that TNNI3 mutations in single patients or small numbers of HCM families with few affected individuals and limited clinical information. The clinical expression of TNNI3 mutations was very heterogeneous and varied both within and between families with no apparent mutation- or gene-specific disease pattern. The fact that different types of cardiomyopathies can be manifested by the same sarcomere protein gene mutation in a single family is well known [8, 9]. The Mogensen's group considered that the mutation has some common TNNI3 mutations, namely the prevalence of different people between the great phenotypic differences, carrying the mutation phenotype varied from double ventricular hypertrophy mild thickening, apical hypertrophy and ventricular septal to end-stage heart enlargement can be observed [7]. In this case, we observed that every carrier of the novel mutation had diverse clinical features with each other. It seemed that the proband was the most serious with symptoms of palpitation and chest distress, changes in ST-T segment in ECG and myocardial fibrosis in cardiac MRI. Her father had symptoms of chest tightness and shortness of breath as well as ST-T segment changes in ECG, but no myocardial fibrosis was found in his cardiac MRI. Her brother had no symptom but with ST-T segment changes in ECG and his cardiac MRI showed myocardial fibrosis. The data suggest that genetic diagnosis of TNNI3 is valuable in identifying clinically unaffected mutation carriers at risk of disease development and facilitates accurate management and counseling.

The mechanism of TNNI3 induced mutation of HCM is unknown, Kimura studies suggest that mutation generated abnormal troponin I resulted in increased sensitivity of myocardial fibers in Ca2 +, mutation of sarcomere contraction caused by hyperthyroidism, whole myocardial contractile regulation disorder, leading to myocardial cell disorder induced HCM [10]. In addition, environmental factors are likely to influence the phenotypic expression of HCM, making it difficult to predict disease development and prognosis of individual patients with diverse genetic backgrounds [11, 12]. In this study, we found that the echocardiography of the proband's daughter was absolutely normal even though she carried the mutation in TNNI3. This is an indication that the Arg79Cys mutation in TNNI3 leads to a slow development of cardiac hypertrophy.

In conclusion, we hypothesized that the Arg79Cys mutation in TNNI3 leads to a slow development of cardiac hypertrophy and the phenotype of this gene mutation is diverse.

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Conflict of interest: Authors state no conflict of interest.

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