RESEARCH NOTE

A novel *de novo* mutation of β-cardiac myosin heavy chain gene found in a twelve-year-old boy with hypertrophic cardiomyopathy

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Introduction

Hypertrophic cardiomyopathy (HCM) is characterized by thickening of left ventricle (LV), especially the interventricular septum (IVS), and diastolic ventricular failure (Maron 2002). It is one of the most important diseases causing a sudden death in young individuals (Maron 2002). Approximately 50% of the patients have a family history of HCM, and exhibit an autosomal dominant (AD) pattern of inheritance (Maron *et al*. 2012). Most of the causative genes for familial HCM encode contractile proteins such as β-cardiac myosin heavy chain, cardiac myosin-binding protein-C, and cardiac troponin T (Kimura 2010; Maron *et al*. 2012; Otsuka *et al*. 2012). Moreover, various mutations of HCM-causing genes exhibit a variety of phenotypes and prognoses (Towbin 2000; Franz *et al*. 2001; Towbin and Bowles 2002; Ho and Seidman 2006; Kimura 2010; Otsuka *et al*. 2012). The gene for β-cardiac myosin heavy chain, *MYH7*, is an important causative gene for HCM. In recent studies, ∼20% of HCM patients have been shown to carry a mutation in *MYH7* (Richard *et al*. 2003; Van Driest *et al*. 2004, 2005; Kimura 2010; Otsuka *et al*. 2012), and several types of *MYH7* mutations have been reported (Kubo *et al*. 2011). In the present report, we describe a case of a 12-year-old boy with HCM who is a carrier of a novel *de novo* point mutation in *MYH7* (p.Ala820Asp). Functional analysis of this mutation indicated that it may eventually lead to impairment of protein function, and therefore, we are carefully following up this patient.

Case history

A previously healthy 12-year-old boy was admitted to our hospital for an examination of thickened IVS. His condition had been incidentally detected on electrocardiography (ECG) that was performed during a routine physical examination at school. His parents were clinically normal, and there was no family history of HCM. On admission, he was asymptomatic, and his height and weight were 145.7 cm (−0.6 standard deviation, SD) and 40.1 kg (−0.3 SD), respectively. His blood pressure was 109/56 mm Hg and heart rate was 63 beats per min. Respiratory sounds were clear and no heart murmur was audible. A 12-lead ECG showed sinus rhythm and normal axial deviation, whereas increased voltages and marked T-wave inversion were noted in the lateral precordial leads (figure 1A). Chest radiography showed protrusion of left third and fourth arches and the cardio-thoracic ratio was 0.50. Two-dimensional echocardiogram showed asymmetrical hypertrophy of the LV (figure 1, B & C). The thickness of the IVS and left ventricular posterior wall (LVPW) was 22.5 mm (357% of the normal) and 8.2 mm, respectively, and the IVS/LVPW ratio was 2.74. The LV showed excessive contraction (ejection fraction, 88%) and mild diastolic dysfunction. No left ventricular outflow obstruction was noted. Laboratory examinations showed elevated serum levels of brain natriuretic peptide (347 pg/mL; normal range, 0–18.4 pg/mL) and atrial natriuretic peptide (118 pg/mL; normal range, 0–43 pg/mL). Cardiovascular magnetic resonance imaging revealed a markedly thickened IVS and decreased wall motion. The proportion of late gadolinium enhancement area (the scar area) was 26%. Nuclear imaging showed excessive accumulation of ^{201}Tl and impaired accumulation of ^{123}I-beta-methyliodophenyl-pentadecanoic acid in the

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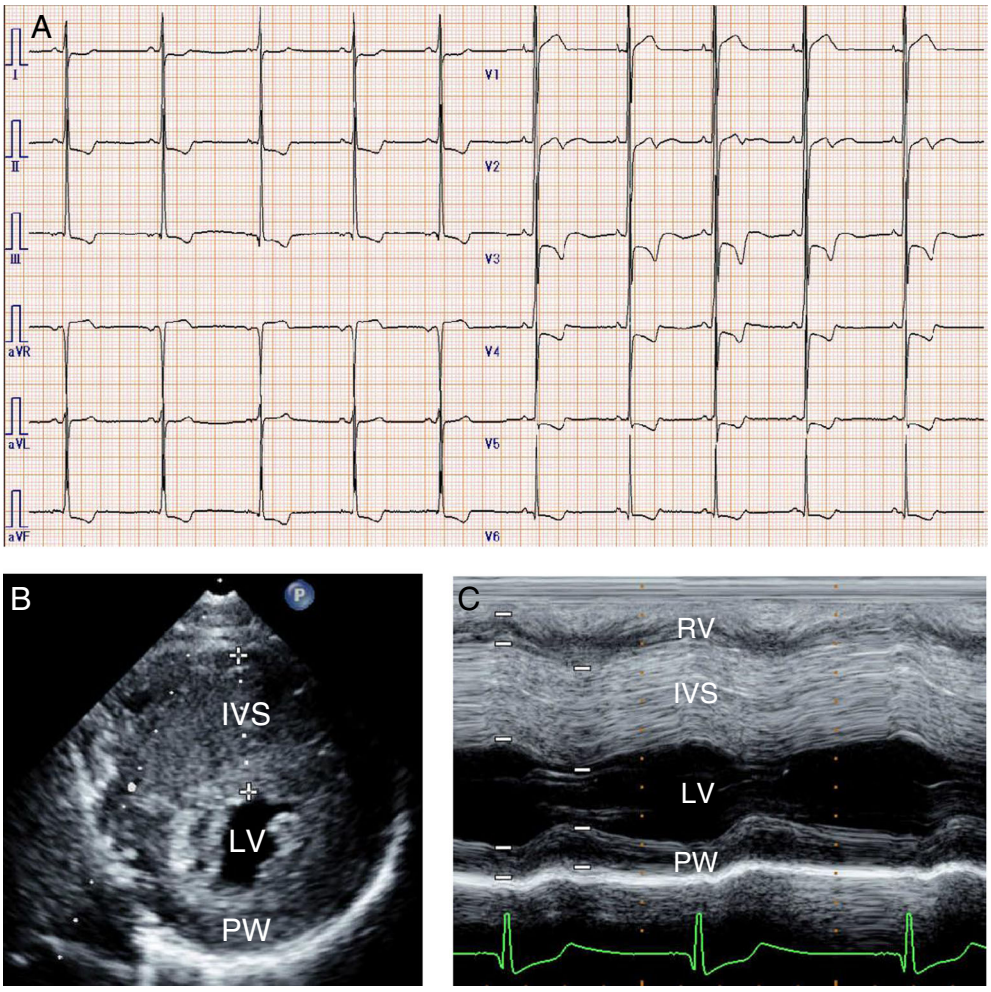

Figure 1. A 12-lead electrocardiogram and two-dimensional echocardiograms of the patient. Increased voltages and marked T-wave inversion in the lateral precordial leads (A). Asymmetrical hypertrophy of the left ventricle from the parasternal short-axis (B) and in M mode (C). IVS, interventricular septum; LV, left ventricle; PW, posterior wall; RV, right ventricle.

IVS. During cardiac catheterization, the left ventricular end-diastolic pressure was found to be elevated (26 mm Hg), whereas left ventricular outflow gradient was within normal limits (3 mm Hg). Treatment with a moderated dose of propranolol (15 mg/day) was initiated during hospitalization. After seven months of propranolol administration, the patient remained asymptomatic and his clinical findings remained almost unchanged.

Materials and methods

DNA samples were extracted from the peripheral blood of the patient and his parents for use as templates to identify mutations in the genes for sarcomeric proteins, as described previously (Otsuka *et al*. 2012). All PCR products were analysed for sequence variations by direct DNA sequencing of both strands using Big Dye Terminator chemistry (ver. 3.1) and ABI3100 DNA Analyzer (Applied Biosystems, Foster City, USA). The sequence variations detected in the patient were considered to be a mutation on the basis of following criteria: (i) absence from a public polymorphism database, the dbSNP database (http://www.ncbi.nlm.nih.gov/projects/SNP/); (ii) mutations at the evolutionarily conserved residues; and/or (iii) identification of the variation as an HCM-causing mutation in previous reports. Direct sequencing of coding exons of *MYH7* revealed a novel heterozygous C to A transition at nucleotide 2459 (p.Ala820Asp) (figure 2). The PolyPhen-2 program was used to predict the possibility of damage by the Ala820Asp mutation (http://genetics.bwh.harvard.edu/pph2/), and the protein function score was 0.947 (benign: 0.00–0.20, possibly damaging: 0.20–0.85, probably damaging: 0.85–1.00). This mutation was absent in his parents and in 200 unrelated control subjects. Kinship between the patient and his parents was confirmed by genotyping six microsatellite

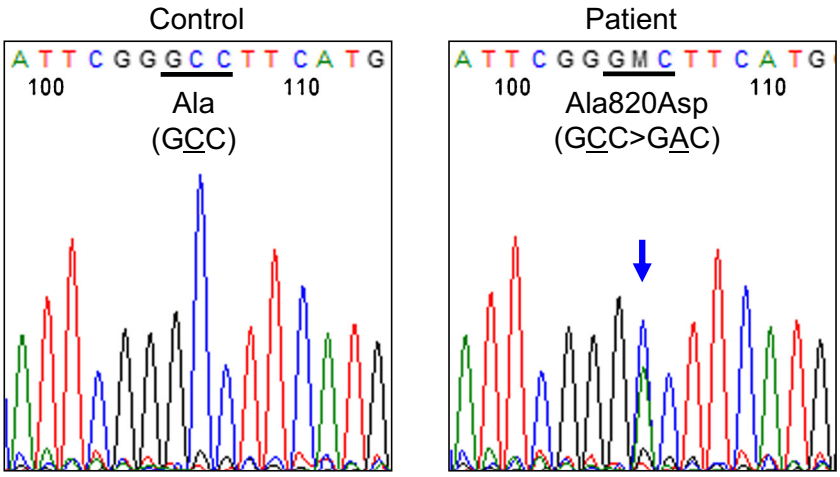

Figure 2. Mutation of *MYH7* found in the patient. Electropherogram demonstrates the sequence encompassing the heterozygous C to A transition at nucleotide 2459 (Ala820Asp).

markers on different chromosomes, D14S1426 (on chromosome 14), D22S280 (on chromosome 22), D17S792 (on chromosome 17), D13S1238 (on chromosome 13), 205xf12 (on chromosome 2), and TNFRSF1B (on chromosome 1).

Results and discussion

The present study is the first reported instance of heterozygous C to A transition at nucleotide 2459 (p.Ala820Asp) of *MYH7*. We believe our patient carries a *de novo* mutation, because his parents did not have the same mutation. Approximately 50% of HCM patients have a family history of HCM, and exhibit an autosomal dominant (AD) pattern of inheritance (Maron *et al*. 2012). In some cases, HCM occurs as a consequence of a *de novo* mutation. In a previous report, three patients (3.5%) were found to have *MYH7* mutations among 85 HCM patients without a family history of the condition (García-Castro *et al*. 2009). HCM has a wide variety of morphologies and clinical manifestations. In addition, the survival rate varies considerably depending on the nature of the mutation in each HCM-causing gene (Watkins *et al*. 1992; Fananapazir and Epstein 1994). HCM caused by *MYH7* mutations is associated with younger age and more severe hypertrophy, compared with HCM due to the mutations in other genes (Van Driest *et al*. 2004; Choi *et al*. 2010; Kimura *et al*. 2010). In addition, patients with *MYH7* mutations carry a higher risk of sudden death than those with other mutations (Wang *et al*. 2008; Choi *et al*. 2010); thus, a strategy for timely diagnoses, intervention, tighter exercise limitation, and implantation of cardioverter-defibrillator is recommended (Maron *et al*. 1994; Maron *et al*. 2003; Melacini *et al*. 2007). In cases of HCM, genetic testing of the patient is controversial (Maron *et al*. 2012), but detecting the gene responsible for this condition may help in the early prediction of prognosis and facilitates early intervention (Watkins *et al*. 1992; Fananapazir and Epstein 1994; Maron *et al*. 2012). Thus, we recommend that genetic screening should be performed in patients with HCM but without a family history of HCM, although the detection rate may be low among such patients.

However, this study has a limitation. To completely evaluate the condition of the patient's heart, it would be ideal to screen further for mutations in the nonsarcomeric protein genes or mitochondrial mutations; however, in the present case, we only screened for mutations of the sarcomeric proteins. Although it is technically feasible to screen further for additional mutations, it would not be realistic due to the considerable costs and time required.

In conclusion, the prognosis of HCM caused by this mutation in our patient is still unknown, and thus, we are carefully following up this patient.

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