A novel ACTC1 mutation in a young boy with left ventricular noncompaction and arrhythmias

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Introduction

Left ventricular noncompaction (LVNC) is a heterogeneous myocardial disorder characterized by prominent left ventricular trabeculae and deep intertrabecular recesses with variable clinical features. The classical triad of complications is heart failure, thromboembolic events, and arrhythmias including sudden cardiac death. LVNC has been recognized as a primary cardiomyopathy of genetic origin.1 However, the genetic basis of the disease in a large proportion of patients with LVNC remains unresolved. The first genetic cause of isolated LVNC was described in the X-linked tafazzin gene,2 the gene also responsible for Barth syndrome,3 which encodes α-cardiac actin (ACTC1) as the causal gene.4

Sarcomere gene mutations are generally considered to be causative for hypertrophic cardiomyopathy and dilated cardiomyopathy.5 In 2007, Monserrat et al. first reported a sarcomeric mutation in Spanish LVNC families and identified ACTC1 (which encodes α-cardiac actin) as the causal gene.5

Here we describe clinical and molecular investigations in a rare case of young boy with LVNC and novel mutation of the ACTC1 (c.692C>G, p.T231R).

Case report

A 4-year-old boy was referred to our cardiac intensive care unit because of ventricular tachyarrhythmias causing hypotensive shock. The patient was of mixed heritage (half Japanese and half Chinese), with no family history of cardiac disease; he had experienced recurrent syncope beginning at age 3 years. Results of basic evaluations after each syncopal event were normal. He was initially diagnosed with epilepsy. Eight months after the onset of syncope, he experienced cardiopulmonary arrest after mild exercise. He was resuscitated and transferred to a local hospital for hypothermic therapy. On admission, the electrocardiogram (ECG) showed mild sinus bradycardia. The following day, the patient experienced the sudden onset of ventricular tachycardia that degenerated into fibrillation, without evidence of ischemia or electrolyte abnormalities. After resuscitation and electrical defibrillation, sinus rhythm was restored. The patient was started on a continuous amiodarone infusion and transported to our hospital for further evaluation and treatment.

On arrival, the patient was still bradycardic. Blood tests showed an elevated brain natriuretic peptide concentration of 550 pg/mL. A 12-lead ECG showed biventricular hypertrophy with normal QT/QTc intervals. A 2-dimensional echocardiogram revealed prominent trabeculations and deep intertrabecular recesses at the apical, anterolateral, and posterior regions of the left ventricle (Figure 1A). The left ventricular ejection fraction was mildly decreased at 49%.

A tiny trabecular muscular ventricular septal defect was also observed.

After the patient was extubated and regained consciousness, he underwent cardiac catheterization. The cardiac index was found to be slightly decreased, to 2.8 L/min/m². A coronary angiogram was normal. The programmed stimulation did not induce any arrhythmia with or without isoproterenol infusion. His signal-averaged ECG did not reveal delayed potentials.

After other types of secondary cardiomyopathies (infective, infiltrative, storage, autoimmune, and neuromuscular) were ruled out, the patient was diagnosed with LVNC. Barth syndrome was ruled out, owing to the lack of other characteristics such as neutropenia, hypotonia, muscle weakness, or undeveloped skeletal muscles.

KEYWORDS ACTC1; Child; Left ventricular noncompaction; Sarcomere protein genes; Ventricular arrhythmias

ABBREVIATIONS ACTC1 = actin, α-cardiac muscle 1 gene; ECG = electrocardiogram; LVNC = left ventricular noncompaction

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**KEY TEACHING POINTS**

- Left ventricular noncompaction (LVNC) has been recognized as a genetic primary cardiomyopathy; its causative genes are heterogeneous and include sarcomeric protein genes.
- Compared with adult patients with LVNC, pediatric patients with LVNC experience ventricular arrhythmias relatively rarely.
- A novel ACTC1 mutation (c.692C>G, p.T231R) was detected in a young boy with LVNC, repeated syncope, and resuscitated ventricular arrhythmias; this mutation could be related to potentially fatal arrhythmias in LVNC patients.

On hospital day 14, recurrent attacks of ventricular tachycardia at 170 beats per minute were observed on ECG monitoring (Figure 1B); the patient was treated with intravenous landiolol (an ultrashort-acting β1-blocker) in addition to the oral amiodarone. A secondary prevention epicardial implantable cardioverter defibrillator was placed (Figure 1C). The patient received standard heart-failure therapies (diuretics, angiotensin 1-converting enzyme inhibitor, and oral β-blocker) and anticoagulant therapy and was discharged on hospital day 51 without neurologic sequelae. He did not have any cardiac events with the prophylactic administration of oral amiodarone and β-blocker during 2 years’ follow-up.

**Molecular studies**

After obtaining informed consent from the parents of the patient, DNA was isolated from a peripheral blood sample of the patient and was screened for mutations by direct sequencing. A novel heterozygous missense variant in ACTC1 (c.692C>G, p.T231R) was identified (Figure 2A), and it was considered to be possibly pathogenic on in silico analysis. His parents refused genetic testing of themselves because they were healthy and asymptomatic.

The ACTC1 variant was considered to be a likely pathogenic mutation based on the following criteria: (1) it was de novo and present in blood; (2) it was not detected in 400 unrelated chromosomes of ethnicity-/race-matched control subjects; (3) it was not reported in public databases such as the National Center for Biotechnology Information’s dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/) or the National Heart, Lung, and Blood Institute’s Grand Opportunity Exome Sequencing Project Exome Variant Server (http://evs.gs.washington.edu/EVS/); (4) it affected evolutionarily conserved residues (nucleotide and amino acid: Figure 2B); and (5) it was predicted to be deleterious/pathogenic by multiple in silico algorithms (Polyphen2, PANTHER, Align GVGD, SIFT, and Mutation Taster). No mutation was identified in the TAZ, LMNA/C, LDB3, DTNA, MIB1, PRDM16, YWHAE, MYBPC3, TNNT2, TNNI3, ACTC, or TPM1 gene. In addition, no mutation was identified in RYR2 or CASQ2, where several mutations have been identified in patients with catecholaminergic polymorphic ventricular tachycardia.

**Discussion**

We present a rare case of LVNC associated with a likely pathogenic novel mutation of the ACTC1 gene (c.692C>G, p.T231R). A young boy was diagnosed with LVNC after cardiopulmonary arrest that was probably caused by a potentially fatal ventricular arrhythmia. The ventricular arrhythmia and recurrent syncope associated with LVNC are highlighted in the present case.

More than 100 mutations within the α-skeletal muscle actin gene (ACTA1) are known and are responsible for 20% of congenital myopathies, whereas only 12 mutations within ACTC1 have been identified and are correlated with diseases such as cardiomyopathies and atrial septal defects.4-11 (Figure 2C). A phenotypic variation was reported in LVNC families with sarcomeric mutations.4

As a cytoskeletal protein, actin is ubiquitously expressed in eukaryotic cells and is involved in an extraordinary array of cellular functions. Besides its classic role in muscle contraction, actin also plays important roles in cellular processes such as gene transcription, chromosome morphology, cell cycle control, modulation of a variety of membrane responses, translation of several messenger RNA species, modulation of enzyme activity and intracellular localization, and cellular apoptosis.12,13 Several studies have shown that these roles could be affected by mutations in genes that affect actin.14 In the present case, a T231R mutation may lie within the TPM1-binding domain because of an A232V mutation located in the TPM1-binding domain identified in hypertrophic patients, and it may result in mutation-specific disturbances in the actin–actin and actomyosin interactions, which could subsequently lead to LVNC.

In LVNC patients with reduced systolic left ventricular function, the major clinical manifestations include heart failure symptoms, arrhythmias, and embolic events. Various patterns of arrhythmia can be observed in LVNC patients. Compared with adult patients with LVNC, pediatric patients experience ventricular arrhythmias relatively rarely.8-10 Patients with LVNC have a significantly increased risk of sudden death, and LVNC is the cause of death in 6-18% of patients with congenital heart disease.11,12 The risk of sudden death in LVNC is 8 to 24 times that of non-LVNC patients.13,14 Multiple clinical presentations of arrhythmias in LVNC patients were reported.15-17
Figure 1  A: A 2-dimensional echocardiogram recorded on admission. Bidirectional arrows indicate a noncompaction layer, and solid lines indicate a compaction layer in the left ventricle. Note the prominent trabeculations and deep intertrabecular recesses in the left ventricle. B: Lead II monitor electrocardiogram recorded on hospital day 14 showing sustained ventricular tachycardia with a heart rate of 150–170 bpm. C: The images shows the epicardial bipolar electrodes placed on the right atrium and ventricle, the shock coil placed on posterior of the left atrium through transverse sinus, and the implantable cardioverter defibrillator placed in the intraperitoneal space.
Figure 2  A: Sequence analysis of exon 5 in ACTC1 of the proband showing results for the DNA sample isolated from a blood sample. The electropherograms show the heterozygous C>G substitution resulting in the threonine-to-arginine missense mutation. The putative amino acid sequence is shown above the nucleotide sequence. B: Alignment of the regions flanking the novel mutation in ACTC1 showing evolutionary conservation of the mutated residue across species (boxed). Dots indicate amino acids identical to the one in the human sequence. C: Structure of the ACTC1 indicating the position of the mutations previously described (black) and our novel variant (red), which are all highly conserved across species. ASD = atrial septal defect; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LVNC = left ventricular noncompaction; RCM = restrictive cardiomyopathy.
do not predict a clinical phenotype in LVNC, the phenotype–
genotype relationship may exist among LVNC patients with
ACTC1 mutations.

In conclusion, these observations suggest that some
LVNC patients with mutations in the ACTC1 gene could have potentially fatal arrhythmias and should be evaluated to
determine their risk of sudden cardiac death.

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Table 1 Clinical characteristics of patients with left ventricular noncompaction and ACTC1 mutations

| Age(y)/sex | Exon | Coding DNA change | Protein change | Mutation type | NYHA | LVEF/FS % | ECG findings | Cardiovascular complications | Reference |
|-----------|------|------------------|---------------|--------------|------|-----------|-------------|-----------------------------|-----------|
| 15/F      | 3    | c.478G>A         | p.E101K      | missense I   | 60/32 | syncpe,PM |             |                 |           |
| 58/M      | 3    | c.478G>A         | p.E101K      | missense III | 30/22 | syncpe,CHF,PH |             |                 |           |
| 38/F      | 3    | c.478G>A         | p.E101K      | missense III | 68/33 | AF,ST depression | CHF,PH |                 |           |
| 73/M      | 3    | c.478G>A         | p.E101K      | missense II  | 40/17 |             |             |                 |           |
| 56/F      | 3    | c.478G>A         | p.E101K      | missense I   | 53/31 | LVH       |             |                 |           |
| 54/F      | 3    | c.478G>A         | p.E101K      | missense I   | 50/29 |             |             |                 |           |
| 52/M      | 3    | c.478G>A         | p.E101K      | missense I   | 61/37 |             |             |                 |           |
| 31/F      | 3    | c.478G>A         | p.E101K      | missense I   | 69/43 |             |             |                 |           |
| 26/F      | 3    | c.478G>A         | p.E101K      | missense I   | 68/43 |             |             |                 |           |
| 20/F      | 3    | c.478G>A         | p.E101K      | missense I   | 66/41 |             |             |                 |           |
| 15/F      | 3    | c.478G>A         | p.E101K      | missense I   | 71/45 |             |             |                 |           |
| 16/M      | 3    | c.478G>A         | p.E101K      | missense I   | 67/42 | LVH       | ASD         |                 |           |
| 15/M      | 3    | c.478G>A         | p.E101K      | missense I   | 70/45 | LVH,abnQ  | syncpe      |                 |           |
| 13/F      | 3    | c.478G>A         | p.E101K      | missense I   | 71/45 | LVH       | MR          |                 |           |
| 10/M      | 3    | c.478G>A         | p.E101K      | missense I   | 65/40 | LVH,abnQ  |             |                 |           |
| 7/M       | 3    | c.478G>A         | p.E101K      | missense I   | 83/57 | LVH       |             |                 |           |
| 5/F       | 3    | c.478G>A         | p.E101K      | missense I   | 66/41 | LVH,abnQ  |             |                 |           |
| 26/F      | 3    | c.478G>A         | p.E101K      | missense I   | 54/32 | LVH,abnQ  |             |                 |           |
| 62/M      | 3    | c.478G>A         | p.E101K      | missense I   | 59/35 | LVH       | VSD         |                 |           |
| 35/M      | 3    | c.478G>A         | p.E101K      | missense III | 62/32 | LVH       |             |                 |           |
| 35/M      | 3    | c.478G>A         | p.E101K      | missense I   | 53/31 | LVH,abnQ  |             |                 |           |
| 28/F      | 3    | c.478G>A         | p.E101K      | missense I   | 61/37 | LVH       |             |                 |           |
| 29/F      | 3    | c.478G>A         | p.E101K      | missense I   | 61/37 | LVH       |             |                 |           |
| 5/M       | 3    | c.478G>A         | p.E101K      | missense I   | 61/37 | LVH       |             |                 |           |
| 55/F      | 3    | c.478G>A         | p.E101K      | missense II  | 65/40 |             |             |                 |           |
| 15/F      | 3    | c.478G>A         | p.E101K      | missense I   | 53/31 | LVH,abnQ  |             |                 |           |
| 4/M       | 5    | c.692C>G         | p.T231R      | missense I   | 54/32 | LVH,abnQ  |             |                 |           |
| 48/F      | 6    | c.986>T          | p.I329T      | missense I   | 48/27 | LVH,abnQ  |             |                 |           |
| 265.     |      |                  |              |              |       |           | VSD         |                 |           |

abnQ = abnormal Q wave; AF = atrial fibrillation; ASD = atrial septal defect; CHF = chronic heart failure; CPA = cavopulmonary arrest; FS = fraction
shortening; LBBB = left branch bundle block; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NYHA = New York Heart Association;
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