Co-Phenotype of Left Ventricular Non-Compaction Cardiomyopathy and Atypical Catecholaminergic Polymorphic Ventricular Tachycardia in Association With R169Q, a Ryanodine Receptor Type 2 Missense Mutation

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Background: Left ventricular non-compaction (LVNC) is a cardiomyopathy characterized by prominent trabeculae and intertrabecular recesses. We present the cases of 3 girls with the same ryanodine receptor type 2 (RYR2) mutation who had phenotypes of both catecholaminergic polymorphic ventricular tachycardia (CPVT) and LVNC.

Methods and Results: Clinical characteristics and genetic background of the 3 patients were analyzed retrospectively. Age at onset was 5, 6, and 7 years, respectively. Clinical presentation included syncope during exercise in all 3 patients and cardiac arrest in 2 patients. LVNC diagnosis was confirmed on echocardiography according to previously defined criteria. Exercise stress testing provoked ventricular arrhythmia in two of the patients. Beta-blockers (n=3) and flecainide (n=2) were given, and an implantable cardioverter defibrillator was used in 1 patient. Genotyping identified the same RYR2-R169Q missense mutation and no other CPVT- or LVNC-related gene mutations. Functional analysis of the mutation using HEK293 cells with single-cell Ca2+ imaging and [3H]ryanodine binding analysis, indicated a gain of function: a reduced threshold for overload-induced Ca2+ release from the sarcoplasmic reticulum and increased fractional Ca2+ release.

Conclusions: The rare association of LVNC and CPVT phenotypes with RYR2 mutations is less likely to be coincidental. Screening for life-threatening arrhythmias using exercise or pharmacologic stress tests is recommended in LVNC patients to prevent sudden cardiac death in those with preserved LV function.

Key Words: Catecholaminergic polymorphic ventricular tachycardia; Exercise-induced syncope; Left ventricular non-compaction; Ryanodine receptor type 2; Sudden cardiac death

Left ventricular non-compaction (LVNC) is a rare cardiomyopathy characterized by prominent trabeculae and intertrabecular recesses. The determinants of the clinical course and prognosis of LVNC include left ventricular (LV) dysfunction and thromboembolism as well as ventricular arrhythmias, which occur in 17% of children with LVNC, leading to sudden cardiac death. Mutations of the genes that encode mitochondria, the cell cytoskeleton, and calcium-binding proteins were identified in 29–41% of adult patients and in 17% of pediatric patients with LVNC who underwent genetic testing.

Although ryanodine receptor type 2 (RYR2) mutations are one of the typical causes of catecholaminergic polymorphic ventricular tachycardia (CPVT), RYR2 mutations have also been implicated in other fatal arrhythmias, including short-coupled torsades de pointes, and even in certain types of cardiomyopathies, such as arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), dilated cardiomyopathy (DCM), and hypertrophic cardiomyopathy (HCM). Previous reports rarely described the CPVT-LVNC overlap syndrome associated with RYR2 mutation with either exon 3 deletion, a gain-of-function mutation, or I4855M, a loss-of-function mutation. The role of RYR2 in the pathogenesis of structural heart
disease (SHD), however, remains unclear. In this report, we present the clinical features of 3 unrelated individuals with comorbid LVNC and atypical CPVT and carrying the same \textit{RYR2} mutation, R169Q (“atypical” here means positive for SHD, as opposed to typical CPVT, which occurs in a structurally normal heart). This mutation was previously reported as pathogenic in CPVT patients without SHD on the basis only of family history analysis. Although the mutation is located in a region that has been implicated in CPVT, its function has not been investigated. In this study, we performed functional analysis of the mutation using HEK293 cells and demonstrated that the activities of both spontaneous Ca²⁺ release via \textit{RYR2} and Ca²⁺-induced Ca²⁺ release (CICR) were increased.

### Methods

**Clinical Assessment**

This report presents the cases of 3 patients with the phenotypes of both atypical CPVT and LVNC with an \textit{RYR2} mutation, R169Q. The retrospective review includes the clinical presentation at diagnosis, clinical signs and symp-

toms, clinical course, family history, electrocardiography (ECG) findings at rest and on exercise, pharmacologic stress test, genetic analysis, echocardiography, pharmacologic and device treatments, and outcome. The diagnosis of LVNC was based on the criteria proposed by Jenni et al. and by Chin et al. The first set of criteria requires 3 echocardiography findings: (1) a thickened LV wall consisting of 2 layers (a thin compacted epicardial layer and a markedly thickened endocardial layer with numerous prominent trabeculations and deep recesses) with a maximum ratio of non-compacted to compacted myocardium >2:1 at end-systole in the parasternal short-axis view; and Y is the distance from the epicardial surface to the peak of trabeculation at end-diastole. An implantable cardioverter defibrillator was not applied, but an automated external defibrillator was available at home. Age, age at onset of CPVT; AVNRT, atrioventricular nodal reentrant tachycardia; bVT, bidirectional VT; CPVT, catecholaminergic polymorphic ventricular tachycardia; ICD, implantable cardioverter-defibrillator; ISP, isoproterenol; LVEF, left ventricular ejection fraction; NA, not applicable; ND, not done; pVPC, polymorphic VPC; pVT, polymorphic VT; VF, ventricular fibrillation; VPC, ventricular premature contraction; VT, ventricular tachycardia.

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td><strong>Exercise-related syncope</strong></td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Cardiac arrest</strong></td>
<td>(+)</td>
<td>(–)</td>
</tr>
<tr>
<td><strong>Family history of sudden death</strong></td>
<td>(–)</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Electrocardiogram</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Resting HR (beats/min)</strong></td>
<td>50</td>
<td>53</td>
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<tr>
<td><strong>QTc (s)</strong></td>
<td>0.461</td>
<td>0.400</td>
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<tr>
<td><strong>bVT</strong></td>
<td>(+)</td>
<td>(–)</td>
</tr>
<tr>
<td><strong>pVT</strong></td>
<td>(–)</td>
<td>(–)</td>
</tr>
<tr>
<td><strong>VF</strong></td>
<td>(+)</td>
<td>(–)</td>
</tr>
<tr>
<td><strong>Other arrhythmias</strong></td>
<td>Sinus bradycardia*</td>
<td>Sinus bradycardia*</td>
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<tr>
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<td>Epilepsy</td>
<td>CPVT</td>
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<td><strong>Exercise stress test</strong></td>
<td>pVPCs, bVT</td>
<td>pVT</td>
</tr>
<tr>
<td><strong>Pharmacologic stress test</strong></td>
<td>ND</td>
<td>AVNRT by ISP</td>
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<td><strong>Echocardiogram</strong></td>
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<tr>
<td><strong>LVEF</strong></td>
<td>76%</td>
<td>51%</td>
</tr>
<tr>
<td><strong>NC/C of Jenni’s criterion‡</strong></td>
<td>2.6</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>X/Y of Chin’s criterion§</strong></td>
<td>0.28</td>
<td>0.44</td>
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<td><strong>Gene analysis</strong></td>
<td></td>
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<td><strong>Nucleotide change</strong></td>
<td>c.506g&gt;a</td>
<td>c.506g&gt;a</td>
</tr>
<tr>
<td><strong>Protein change</strong></td>
<td>R169Q</td>
<td>R169Q</td>
</tr>
<tr>
<td><strong>Genotyped family members</strong></td>
<td>Trio</td>
<td>Only proband</td>
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<tr>
<td><strong>Inheritance</strong></td>
<td>De novo</td>
<td>NA</td>
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<tr>
<td><strong>Time from onset to diagnosis of CPVT</strong></td>
<td>3 months</td>
<td>2 weeks</td>
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<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Pharmacologic treatment</strong></td>
<td>Carvedilol, flecainide, enalapril</td>
<td>Propranolol</td>
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<tr>
<td><strong>Device treatment</strong></td>
<td>ICD</td>
<td>(–)</td>
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<tr>
<td><strong>Outcome</strong></td>
<td>Alive</td>
<td>Alive</td>
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</table>

*Resting heart rate was less than the second-decile percentile of established age- and sex-appropriate norms. Already bedridden when adrenergic VT was suspected. Maximum ratio of noncompacted to compacted myocardium at end-systole in the parasternal short-axis view. IX is the distance from the epicardial surface to the trough of the trabecular recess, and Y is the distance from the epicardial surface to the peak of trabeculation at end-diastole. An implantable cardioverter defibrillator was not applied, but an automated external defibrillator was available at home. Age, age at onset of CPVT; AVNRT, atrioventricular nodal reentrant tachycardia; bVT, bidirectional VT; CPVT, catecholaminergic polymorphic ventricular tachycardia; ICD, implantable cardioverter-defibrillator; ISP, isoproterenol; LVEF, left ventricular ejection fraction; NA, not applicable; ND, not done; pVPC, polymorphic VPC; pVT, polymorphic VT; VF, ventricular fibrillation; VPC, ventricular premature contraction; VT, ventricular tachycardia.
Genomic Analysis
Genomic DNA was isolated from peripheral white blood cells in each patient. Testing of 71 genes related to inherited arrhythmia and/or cardiomyopathy, including CPVT-associated genes (*RYR2*, *CASQ2*, *CALM1*, and *TRDN*) and LVNC-associated genes (*LDB3*, *ACTC1*, *MYH7*, *TNNT2*, *TPM1*, *MYBPC3*, and *TAZ*) was undertaken (Supplementary Table). All novel putative pathogenic variants were confirmed to be absent in the Genome Aggregation Database (http://gnomad.broadinstitute.org/about) and in the Human Genetic Variation Database, which includes more than 1,000 Japanese individuals.¹⁸

**Figure 1.** (A, B) Electrocardiogram (ECG). (C, D) Echocardiogram and (E, F) cardiac magnetic resonance imaging (MRI) in case 1. (A) Waveforms of bidirectional ventricular tachycardia followed by ventricular fibrillation were recorded with an automated external defibrillator. (B) Standard ECG at rest showed isolated sinus bradycardia with a heart rate disproportionate to the patient’s age. (C, D) On short-axis view on the echocardiogram, the thickness ratio of the non-compacted layer to the compacted layer met the Jenni et al criteria at (C) end-systole, and the proportion of the distances from the epicardial surface to the trough of the trabecular recess and to the peak of trabeculation met the Chin et al criteria at (D) end-diastole. (E, F) The 2-chamber and 4-chamber views on cardiac MRI showed typical findings of left ventricular non-compaction with a ratio of non-compacted to compacted myocardium of 5.2, which met the Petersen et al criteria.²⁴
was obtained from each patient (or from the parents if the patient was aged <15 years or incapable of communication) by a coordinator in charge at each institution before registration of the patient data.

Results

Clinical Features and Genetic Testing

Case 1 A 5-year-old girl fainted during exercise, but physical examination and ECG on arrival at hospital were normal. Two months after the episode, she had another syncopal episode. Clinical examination was again negative and epilepsy-related syncope was suspected, although electroencephalogram was normal (Table). One month later,

Figure 2. (A) Pedigree of patient 2. Two siblings of the proband died at age 7 years (sister) and 2 years (brother), and 2 cousins of the proband's mother both died at age 19 years. Two of the 3 cousins of the proband (IV-5, IV-6) underwent an exercise stress test, and no arrhythmia was induced in either case. (B-E) Two-dimensional and color Doppler echocardiograms of patient 2, showing (B) non-compacted layers and deep intertrabecular recesses characteristic of non-compaction cardiomyopathy, (C) filled with blood at the left ventricular (LV) apical portion. (D, E) The 2-D echocardiogram in the apical view showed non-compacted layers and deep trabecular recesses, which met the (D) Jenni et al criteria and (E) Chin et al criteria.17 (F) Cardiac magnetic resonance imaging, 4-chamber view, showed typical findings of LV non-compaction with a ratio of non-compacted to compacted myocardium of 3.1, which met the Petersen et al criteria.24 (G, H) Late gadolinium enhancement was observed at the mid-myocardial layer of the mid-apical anteroseptal segment.

Functional Analysis of RYR2-R169Q

Using the Flp-In T-Rex system (Invitrogen), we generated stable HEK293 cells that can be induced to express mouse RyR2-wild type (WT) and R169Q.19,20 Cytoplasmic Ca2+ ([Ca2+]cyto) and endoplasmic reticulum (ER) luminal Ca2+ ([Ca2+]ER) signals were monitored with G-GECO1.11 and R-CEPIA1er,22 respectively.6,20 The [3H]ryanodine binding assay was carried out with microsomes isolated from the HEK293 cells.6,20 Details of these methods are described in Supplementary Material.

Ethics

The study protocol was approved by the University of Tsukuba Hospital ethics committee, and informed consent was obtained from each patient (or from the parents if the patient was aged <15 years or incapable of communication) by a coordinator in charge at each institution before registration of the patient data.
Co-Phenotype of Atypical CPVT and LVNC

their ECG findings were normal. On genetic testing the parents were negative for the RYR2 mutation.

**Case 2** A 6-year-old girl with a family history of sudden death (2 siblings of the proband and 2 cousins of the proband’s mother; Figure 2A) fainted during exercise. Electroencephalogram and brain MRI were normal. ECG at rest showed sinus bradycardia, monomorphic VPC, and normal corrected QT interval (QTc; 0.40 s). On the first cardiac event, LV function was normal on echocardiography and no cardiomyopathy was identified. Exercise stress test provoked polymorphic non-sustained VT, and a pharmacologic stress test using i.v. isoproterenol provoked atrioventricular nodal re-entrant tachycardia. Following treatment with oral propranolol, the patient did not have syncopal attacks and exercise stress testing did not induce VT. The generalized low-voltage T waves on ECG progressed gradually, and a non-compacted structure in the mid-to-apical portion of the LV was found on repeat echocardiography conducted at age 21. LVEF was slightly reduced, to 51% (Figure 2B–E). The previous echocardiograms did not focus on the LV apical portion, and whether LVNC was present could not be determined. Cardiac MRI at age 23 showed a thick non-compacted and a thin compacted myocardium layer (Figure 2F), with a ratio of the former to the latter of 3.1. LVEF was preserved (66%), and late gadolinium enhancement was not evident. The patient was treated with flecainide and carvedilol, and an implanted cardioverter defibrillator (ICD) with atrial pacing at 80 beats/min was subsequently implanted. Under this therapeutic regimen, exercise stress testing did not induce VT, and the ICD did not trigger appropriate or inappropriate shock. Gene testing identified the de novo RYR2-R169Q mutation. The parents of the patient underwent neither echocardiography nor exercise stress testing because they had had no symptoms from childhood and

**Figure 3.** (A–C) Electrocardiograms (ECG) and (D,E) echocardiograms in case 3. (A) ECG at rest showed a regular sinus rhythm (heart rate, 69 beats/min) with a corrected QT interval of 0.40 s. (B) Typical bidirectional ventricular tachycardia and (C) ventricular fibrillations occurred repeatedly. (D,E) Echocardiography showed (D) prominent recesses, (E) filled with blood at the left ventricle apex.
undergo echocardiography or exercise stress testing because they had been asymptomatic from childhood and ECG was normal. Although genetic analysis of the family members was not performed, 2 cousins of the proband underwent exercise stress tests, which were negative for ventricular arrhythmia (Figure 2A, IV-5, IV-6).

Case 3
A 7-year-old girl was diagnosed with epilepsy after 2 episodes of fainting, and valproic acid was started at a neighboring clinic. Diagnosis of attention-deficit hyperactivity disorder was also made later. At the age of 8 years, she had a cardiac arrest during exercise and received bystander CPR followed by defibrillation with an AED, which detected ventricular fibrillation (VF) and provided defibrillation shock. The family history was negative for life-threatening arrhythmia and sudden death. ECG at rest showed a regular sinus rhythm (HR, 69 beats/min) with a QTc of 0.40 s (Figure 3A). Typical bidirectional VT (Figure 3B) and VF (Figure 3C) were noted repeatedly after arrival at hospital. Echocardiography showed LVNC with preserved LVEF (67%; Figure 3D,E). Despite intensive care, the patient developed severe neurologic disabilities and became bedridden. ICD was not applied, but an AED was set up at home. After commencement of treatment with carvedilol and flecainide, 24-h Holter ECG monitoring showed no ventricular arrhythmias. Genetic testing identified a de novo RYR2-R169Q mutation. The parents of the patient had no symptoms. Both ECG and echocardiography were normal, although they did not undergo exercise stress testing. On genetic testing the parents were negative for the RYR2 mutation.

Functional Analysis
Single cell Ca²⁺ imaging in HEK cells expressing WT or R169Q was carried out 24–28 h after induction with doxycycline (Figure 4). Functional properties of wild type (WT) and R169Q Ryanodine receptor type 2 (RyR2) characterized by single-cell Ca²⁺ imaging and a Ca²⁺-dependent [³H]ryanodine binding assay (A-C) Single-cell Ca²⁺ imaging in WT- and R169Q-expressing HEK cells. (A) Representative traces of (Top) cytoplasmic Ca²⁺ ([Ca²⁺]cyto) and (Bottom) endoplasmic reticulum (ER) luminal Ca²⁺ ([Ca²⁺]ER) signals determined with G-GECO1.1 and R-CEPIA1er, respectively. (B) Average oscillation frequency in normal Krebs solution in WT and R169 cells. (C) Average threshold and nadir [Ca²⁺]ER in WT and R169Q cells. Data are presented as mean±SEM (n=47–80). ***P<0.001, compared with WT. (D) Ca²⁺-dependent [³H]ryanodine binding of WT (black) and R169Q (red) RyR2. Data are presented as mean±SD (n=4). *P<0.05, compared with WT. (E) Calculated Ca²⁺-induced Ca²⁺ release (CICR) activity of R169Q at resting Ca²⁺(100 nmol/L) (Supplementary Figure). Data are presented as mean±SD (n=4). *P<0.05, compared with WT.
cyclocine. Figure 4A shows representative [Ca\textsuperscript{2+}]\textsubscript{cyto} and [Ca\textsuperscript{2+}]\textsubscript{ER} measurements using G-GECO1.1 and R-CEPIA1er, respectively. WT cells showed spontaneous Ca\textsuperscript{2+} oscillations with corresponding periodic decrease in [Ca\textsuperscript{2+}]\textsubscript{ER} in normal Krebs solution (Figure 4A Left), as reported previously. Application of 10 mmol/L caffeine induced transient Ca\textsuperscript{2+} oscillations with amplitude similar to spontaneous oscillations (Figure 4A). The R169Q cells showed very small and more frequent Ca\textsuperscript{2+} oscillations in normal Krebs solution (Figure 4A Right). Both the threshold and nadir [Ca\textsuperscript{2+}]\textsubscript{ER} in the R169Q cells were markedly reduced compared with the WT cells (Figure 4A Right C). The Ca\textsuperscript{2+}-induced Ca\textsuperscript{2+} release (CICR) activity was assessed on Ca\textsuperscript{2+}-dependent [H\textsuperscript{3}]ryanodine binding. WT RYR2 exhibited biphasic Ca\textsuperscript{2+}-dependent [H\textsuperscript{3}]ryanodine binding and R169Q showed greater activity than WT at all Ca\textsuperscript{2+} concentrations tested (Figure 4D). On the basis of our calculation (Supplementary Figure), the estimated CICR activity of R169Q at resting Ca\textsuperscript{2+} (100 mmol/L) was 13-fold greater than that of WT at resting (100 mmol/L) Ca\textsuperscript{2+} (Figure 4E). This indicates that the R169Q mutation greatly enhanced CICR activity to facilitate spontaneous Ca\textsuperscript{2+} oscillation and to reduce [Ca\textsuperscript{2+}]\textsubscript{ER} in HEK cells.

Discussion

We have here presented 3 unrelated cases of phenotypes of both atypical CPVT and LVNC involving the same gene mutation, RYR2-R169Q. All 3 patients had clinical features of CPVT, including exercise/emotion-related syncopal attacks and bidirectional or polymorphic VT in the R169Q cells were markedly reduced compared with the WT cells (Figure 4A Right C).

The association between RYR2 mutations and LVNC has also been described in previous reports. Kanemoto et al reported an infant with LVNC and extracardiac manifestations, including facial dysmorphism and psychomotor delay. On chromosome analysis the infant had a karyotype of 46,XX.del (1)(q43q43), with the deleted region containing RYR2, although VT was not described in that patient. Furthermore, Szentpali et al described a case of LVNC with the same R169Q mutation as an unrelated patient with Wolff-Parkinson-White syndrome and LVNC. The precise mechanisms underlying the association of Ca\textsuperscript{2+} dynamics with cardiac morphology, however, remain unclear.

On the basis of structural analysis, R169Q is considered to diminish the size of the side chains and reduces the positive charge and stacking interaction. Thus, the mutation could affect allosteric regulation without induction of a conformational change or structural instability of RYR2. It is worth noting that the same mechanism, impaired allosteric regulation, has been proposed in patients with exon 3 deletion of RYR2, in which possible association of LVNC with CPVT has been postulated. Further studies are needed to elucidate how such mutations contribute to the combined phenotypes of CPVT and LVNC.

Sinus bradycardia, atrial fibrillation, and tachycardia-bradycardia syndrome are uncommon in children with LVNC, whereas resting ECG in childhood CPVT tends to show sinus bradycardia, and in 12% of children with the RYR2 mutation, the resting HR was often lower than the second percentile of age- and sex-adjusted normal values. In the afore-cited publications, patients with LVNC combined with RYR2 exon 3 deletion developed various types of arrhythmias, including atrial arrhythmias, sinoatrial dysfunction, and VT. It is noteworthy that 2 of the present 3 patients had bradycardia disproportionate to age and VT.

The diagnosis of CPVT remains challenging. Syncope triggered by exertion or emotion is a characteristic symptom, but there are no specific symptoms of CPVT that may be present during daily activity, while sitting quietly, or even during sleep. A family history of syncope or sudden cardiac death can provide a clue to diagnose in some cases. De novo mutations, however, were identified in 60–70% of genetically confirmed CPVT patients. In the present study, only 1 patient had an apparent family history of CPVT.
to the difficulty in the diagnosis of CPVT in early childhood. It is also possible that routine echocardiography might overlook the apical site of the LV, the most common site of non-compaction.39 In case 2 of the present study, the diagnosis of LVNC was established 16 years after the diagnosis of CPVT, which was in turn based on the syncopal episodes and on a positive family history. To clarify the association between CPVT and LVNC, follow-up echocardiography is needed, with special reference to the apical lesion of LV in CPVT populations.

Study Limitations

Although several cases of LVNC–CPVT overlap syndrome caused by either gain-of-function mutation or loss-of-function mutation of \( RYR2 \) have been reported, how \( RYR2 \) is associated with SHD or how Ca\(^{2+} \) handling in myocardial cells affects the cardiac structure remains to be investigated. Given that the present sample size was very small, it is also essential to study a large number of patients to elucidate whether development of LVNC occurs only in the case of some specific \( RYR2 \) mutations. Furthermore, we had limited clinical data for the deceased relatives of the probands.

Conclusions

In 3 unrelated patients with coexistent phenotypes of atypical CPVT and LVNC, the same \( RYR2\)-R169Q mutation was identified. Functional analysis demonstrated a prominent gain-of-function property of the channel, suggesting that this mutation could be the cause of the malignant tachyarrhythmia observed in the present 3 cases. Given that the coexistence of atypical CPVT and LVNC may not be coincidental, patients with LVNC, especially those with arrhythmia-related symptoms, should undergo screening for adrenergic ventricular arrhythmias, including CPVT, and other arrhythmias using exercise or pharmacologic stress testing to prevent sudden cardiac death, even when the standard ECG is completely normal. Conversely, echocardiography screening for cardiomyopathy is mandatory for patients with CPVT.

Acknowledgments

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Disclosures

This study was conducted in the capacity of our normal salaried positions as employees of each institution. Patient costs were covered by the Japanese National Health Insurance scheme. The authors declare no conflicts of interest.

References


Supplementary Files

Please find supplementary file(s); http://dx.doi.org/10.1253/circj.CJ-19-0720