# Unveiling catecholaminergic polymorphic ventricular tachycardia: A case of type 2 ryanodine receptor exon 3 deletion mimicking long QT syndrome type 1

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## Introduction

Catecholamine-induced polymorphic ventricular tachycardia (CPVT) denotes a cardiac disorder characterized by genetic variations affecting the intracellular $Ca^{2+}$ homeostasis within cardiomyocytes, thereby reducing the threshold for $Ca^{2+}$ release from the sarcoplasmic reticulum. This aberration precipitates potentially fatal ventricular arrhythmias via delayed depolarization, typically during exercise- or emotion-induced catecholamine overload. Although CPVT patients may not uniformly exhibit classical CPVT features, they frequently manifest a composite phenotype, characterized by QT interval prolongation and catecholamine-induced ventricular arrhythmias, resembling long QT syndrome (LQTS).[1] We present a clinical case in which initial suspicion of LQTS type 1 (LQT1) was dismissed because of the absence of pathogenic variants in LQTS-associated genes. Subsequent identification of type 2 ryanodine receptor gene (*RYR2*) exon 3 deletion led to the conclusive diagnosis of CPVT.

## Case presentation

A 40-year-old man was admitted to our medical facility with suspected Adams-Stokes syndrome after an initial evaluation at a local hospital for head trauma caused by exertional syncope. Electrocardiographic (ECG) assessment (Figure 1A) indicated Wenckebach-type second-degree atrioventricular block, QT interval prolongation (QTc 521 msec), and negative T waves evident in the precordial leads. Hereditary LQTS was initially suspected based on the family history of his mother's pacemaker implantation at age 40, followed by her sudden death at age 55, and the patient's own episode of cardiac arrest during swimming at age 15, with a post-resuscitation ECG revealing a junctional rhythm (Figure 1B). At that time, exercise stress test did not provoke any further bradyarrhythmia or tachyarrhythmias, thus limiting further investigation (detailed information was limited due to the age and partial loss of medical records). Other medical history included psoriasis and type 2 diabetes mellitus since age 35. Serum electrolyte levels remained within normal ranges. The follow-up ECG consistently demonstrated QTc prolongation (546 msec) and negative T waves (Figure 1C). Echocardiogram and cardiac magnetic resonance imaging indicated preserved left ventricular function without findings suggestive of structural heart diseases, including left ventricular noncompaction. Coronary angiography showed no abnormal findings. Frequent nonsustained ventricular tachycardia (NSVT) was detected on Holter recordings. However, polymorphic NSVT was triggered by R-on-T during an ergometer exercise stress test at 100 watts (Figure 2). Transient complete atrioventricular block was also documented during the initial hospitalization. The patient was discharged from the hospital after the insertion of an implantable cardioverter defibrillator (ICD) pacemaker. The modified Schwartz score[2] stood at 5.5, suggesting a high probability of LQTS, prompting genetic testing. Nonetheless, initial genetic screening for LQTS, including *KCNQ1*, *KCNH2*, and *SCN5A*, returned negative results. Five months after ICD implantation, the first appropriate ICD shock was documented for ventricular fibrillation

### KEY TEACHING POINTS

- The case highlights the challenge of distinguishing CPVT from LQTS, with a final diagnosis of CPVT confirmed by genetic testing.
- Conventional genetic tests may not identify all mutations, such as *RYR2* exon 3 deletions, necessitating advanced diagnostic techniques for accurate detection.
- Effective CPVT management required both beta-blockers and flecainide, emphasizing the need for personalized treatment based on specific genetic findings.

**KEYWORDS** $Ca^{2+}$ handling; Catecholaminergic polymorphic ventricular tachycardia; Genetic testing; Ryanodine receptor 2; Long QT syndrome

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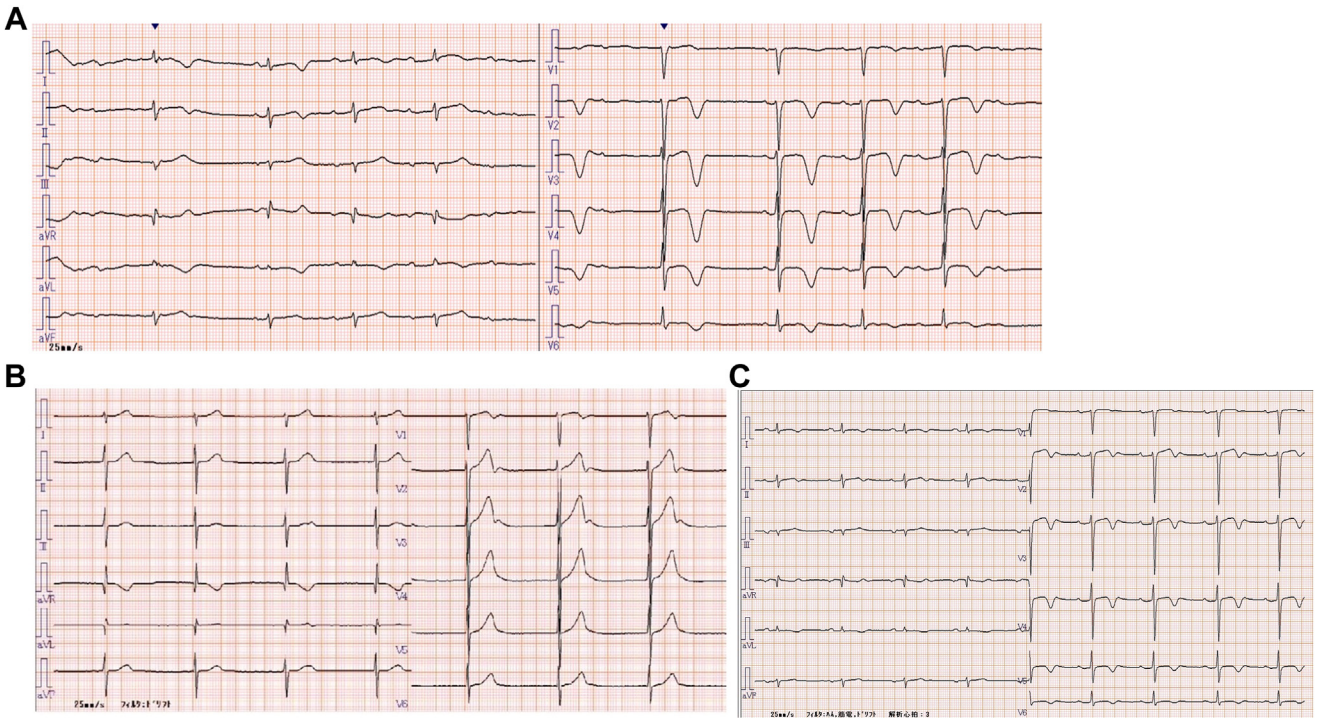


**Figure 1** **A:** ECG on first admission showed Wenckebach-type second-degree atrioventricular block, QT interval prolongation (QTc 521 msec), and negative T waves evident in the precordial leads. **B:** ECG post-resuscitation at age 15 showed junctional rhythm. **C:** Follow-up ECG consistently demonstrated QTc prolongation (546 msec) and negative T waves.

(VF). Beta-blocker therapy was initiated, with subsequent uptitration to 10 mg/day of carvedilol. Further genetic testing was undertaken,[3] revealing the presence of *RYR2* exon 3 deletion, thereby confirming the diagnosis of CPVT. Five months after the first ICD shock, the patient experienced incessant polymorphic VT (Figure 3A) and VF storm (Figure 3B), despite being on the maximum tolerated dose of beta-blocker therapy (20 mg/day of carvedilol). Given the confirmed CPVT diagnosis, 200 mg/day flecainide commenced. The patient's subsequent clinical course remained stable, with occasional episodes of NSVT, and free of ICD intervention for over a year.

## Discussion

We present a case initially suggestive of LQT1, indicated by a history of cardiopulmonary arrest during swimming, QT prolongation on presentation, and the induction of polymorphic VT during exercise stress test. Complicating factors included nonspecific abnormalities such as sinoatrial dysfunction and complete atrioventricular block. Initial genetic testing yielded negative results for LQTS-associated gene variants, prompting a further investigation that showed *RYR2* Exon3 deletion, which allowed a definitive diagnosis of CPVT. In addition to ICD pacemaker insertion, the administration of beta-blockers and flecainide therapy effectively suppressed ventricular arrhythmias.

The number of genes encoding proteins affecting intracellular $Ca^{2+}$ homeostasis, such as *RYR2*, calsequestrin, calmodulin, and triazine, has been recognized in association with CPVT.[1] Nevertheless, patients presenting with CVPT may not uniformly exhibit classical CPVT features, often manifesting a composite phenotype characterized by QT interval prolongation and catecholamine-induced ventricular arrhythmias, posing challenges in clinical differentiation from LQTS. Our patient experienced cardiopulmonary arrest while swimming, a relatively genotype-specific arrhythmogenic trigger for LQT1. However, a reported 9 of 43 patients who experienced swimming-triggered cardiac events harbored CPVT-causing *RYR2* gene variations.[4] Initially, our suspicion leaned toward LQTS; however, examinations targeting major LQTS-related genes yielded negative results. Intriguingly, in a retrospective analysis involving 269 patients referred for LQTS genetic testing and subsequently testing negative for LQTS-associated genetic variants, CPVT-1-causing variants in the *RYR2* gene were identified in 6% of these patients. Hence, when faced with atypical presentations suggestive of LQTS, it is imperative to entertain the possibility of CPVT and consider *RYR2* analysis, especially in cases in which initial genetic screening for LQTS returns negative results.[5]

*RYR2* exon 3 deletion observed in our case was initially described as an "atypical CPVT phenotype' by Bhuiyan et al,[6] exhibiting various clinical manifestations beyond VT/VF, including atrial arrhythmias, sinoatrial node dysfunction, atrioventricular nodal conduction defects, and dilated cardiomyopathy in 16 members from 2 separate families.[6] *RYR2* exon 3 deletion, which occurs

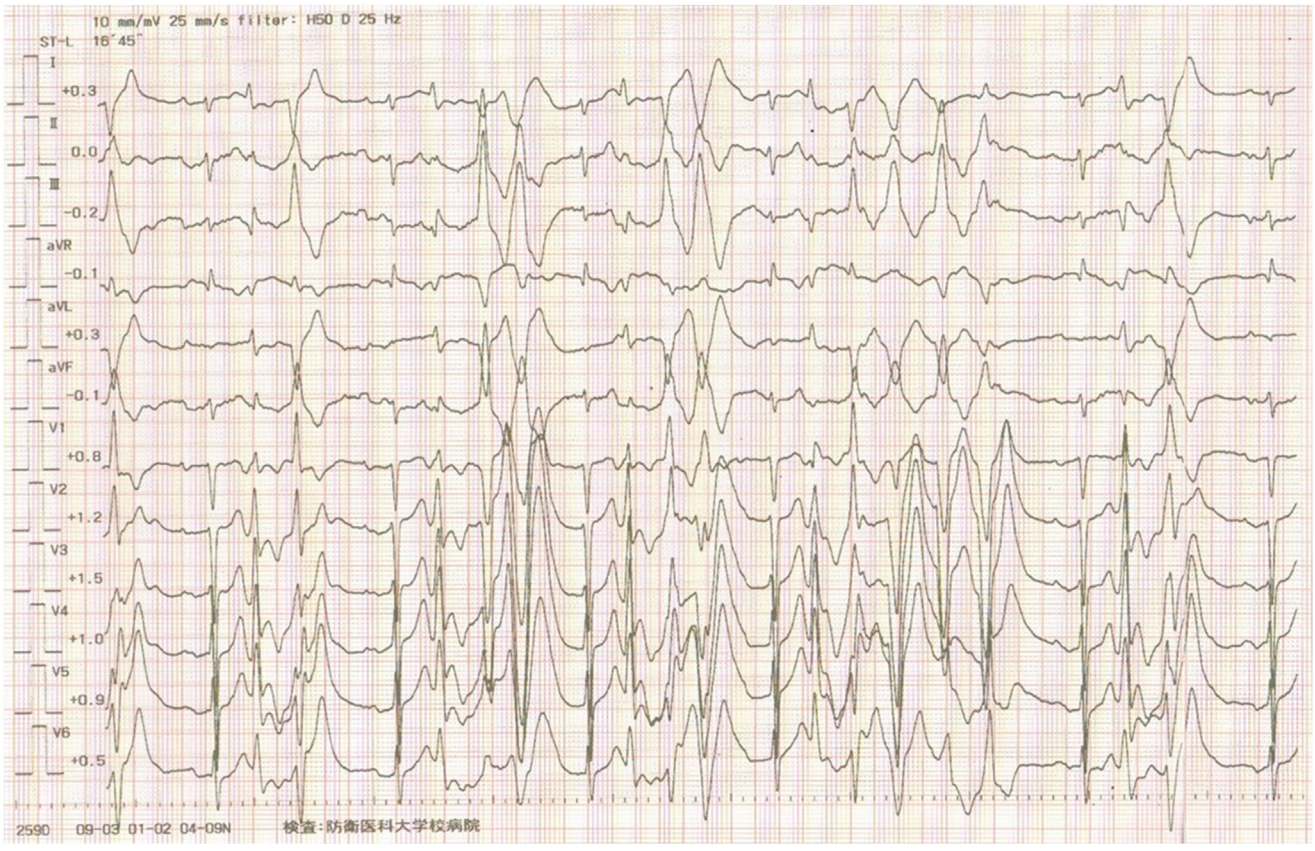


**Figure 2** ECG during ergometer stress testing showed polymorphic NSVT triggered by R on T.

heterozygously, may evade detection in conventional genetic testing because of the presence of normal alleles. Thus, assessment through multiple ligation-dependent probe amplification and other complementary methodologies becomes imperative for accurate diagnosis. Ohno et al[7] reported that they identified 2 CPVT families with *RYR2* exon 3 deletions within a cohort of 24 CPVT families.[7] Notably, conventional polymerase chain reaction methods failed to detect mutations in any exons of *RYR2* in these cases, underscoring potential issues of underdiagnosis in approximately 10% of patients presenting with suspected CPVT. This is of particular concern, considering that patients with *RYR2* exon 3 deletion may exhibit atypical manifestations beyond ventricular arrhythmias, such as sinoatrial dysfunction, atrioventricular block, and atrial arrhythmias, mirroring the presentation in our case.

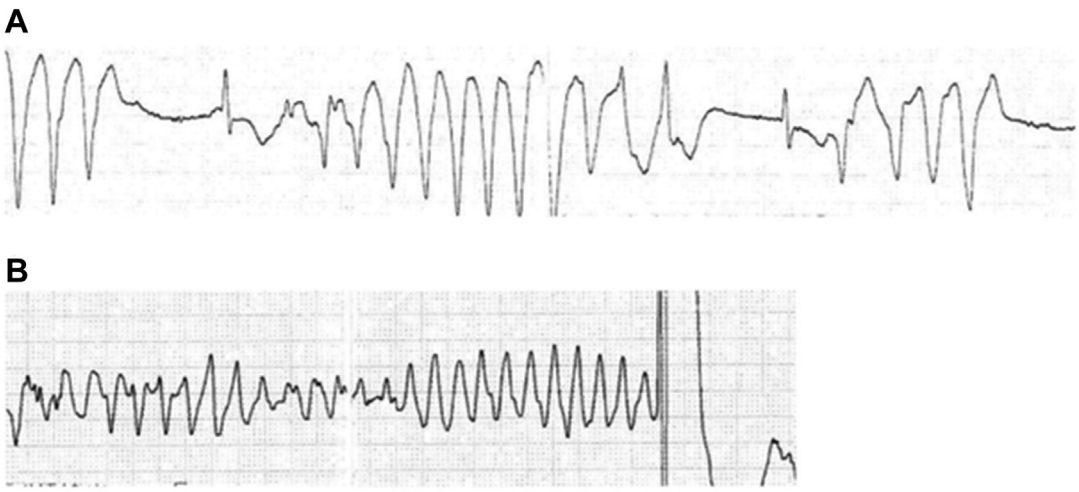


**Figure 3** **A:** Incessant polymorphic ventricular tachycardia. **B:** Ventricular fibrillation terminated by ICD shock.

Beta-blockers are the first-line therapy for both LQTS and CPVT. Given the initial suspicion of LQT1, and despite the presence of bradyarrhythmia in this patient, beta-blocker therapy should have been initiated promptly after ICD pacemaker implantation, even in the absence of genetic confirmation. Symptomatic LQTS patients treated with the beta-1 selective blocker metoprolol are 4 times more likely to experience LQTS-related cardiac events compared with those treated with nonselective beta-blockers such as nadolol or propranolol.[8] Additionally, nadolol has been shown to reduce the incidence and severity of ventricular arrhythmias during exercise stress testing in CPVT patients with *RyR2* variants, compared with metoprolol.[9] Based on these clinical data, nonselective beta-blockers nadolol or propranolol (depending on availability) are recommended to reduce ventricular arrhythmias in patients with LQTS and CPVT, as outlined in the Japanese and European guidelines on the pharmacotherapy of cardiac arrhythmias.[10,11] Because of the limited availability of nadolol in our region and the inconvenient dosing schedule of propranolol, we selected carvedilol as an alternative nonselective beta-blocker. Although carvedilol has been reported to directly suppress *RyR2*,[12] no clinical evidence demonstrates its superiority over other beta-blockers. In addition to beta-blockers, flecainide demonstrates efficacy against *RYR2* variants.[13] In vitro studies employing induced pluripotent stem cells suggest that *RYR2* exon 3 deletion confers a heightened anti-arrhythmic response to β-blockers/flecainide therapy compared with other variants.[14] Variations in $Ca^{2+}$-signaling abnormalities and drug sensitivities may arise based on the specific mutation site, emphasizing the importance of comprehensive genetic testing for precise diagnosis and optimal treatment outcomes.

## Conclusions

We present a case of atypical CPVT attributed to *RYR2* exon 3 deletion, mimicking LQTS, successfully diagnosed and managed with β-blocker and flecainide.

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## Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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