JACC: CASE REPORTS VOL. 29, 2024

CASE REPORT

CLINICAL CASE

Novel Compound Heterozygous Variants in Trans-2,3-Enoyl-Coenzyme A Reductase-Like Gene Associated With Catecholaminergic Polymorphic Ventricular Tachycardia

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ABSTRACT

A 10-year-old female patient experienced syncope while swimming, and electrocardiography revealed polymorphic ventricular tachycardia, leading to a diagnosis of catecholaminergic polymorphic ventricular tachycardia. No pathogenic variant was identified in *RYR2*. Additional comprehensive genetic testing revealed novel compound heterozygous variants in trans-2,3-enoyl-coenzyme A reductase-like gene, which caused a recessive form of catecholaminergic polymorphic ventricular tachycardia. (J Am Coll Cardiol Case Rep 2024;29:102364) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 10-year-old female patient was brought to the emergency department after experiencing transient syncope while swimming. Upon arrival, her consciousness was clear, and her general condition was stable.

LEARNING OBJECTIVES

- To recognize *TECRL* gene as a cause of an autosomal-recessive form of CPVT, which can be controlled by combination therapy with a nonselective β-blocker and flecainide.
- To understand the efficacy of genetic testing in patients with CPVT and family members.

PAST MEDICAL HISTORY

The patient had previously experienced 2 similar episodes of unconsciousness lasting 10 to 15 minutes during swimming since the age of 7 years.

DIFFERENTIAL DIAGNOSIS

Syncope during exercise can arise from various heart, brain, and autonomic nerve disorders. In this patient, an anomalous coronary artery, exercise-induced advanced atrioventricular block, long-QT syndrome, and epilepsy were ruled out.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 15, 2024; revised manuscript received April 8, 2024, accepted April 11, 2024.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2024.102364

ABBREVIATIONS AND ACRONYMS

CALM = calmodulin

CASQ2 = calsequestrin 2

CPVT = catecholaminergic polymorphic ventricular tachycardia

RYR2 = ryanodine receptor 2

TECRL = trans-2,3-enoyl-coenzyme A reductase-like

VT = ventricular tachycardia

INVESTIGATIONS

Twelve-lead electrocardiography showed prolongation of the corrected QT interval at administration (Figure 1A), but it was normalized at 4 days after administration (Figure 1B). After that, exercise stress testing induced a polymorphic premature ventricular contraction and nonsustained ventricular tachycardia (VT) (Figure 2A). Incessant polymorphic VT was also recorded by Holter monitoring, although the patient reported only symptoms of dyspnea and palpitations (Figure 2B). Echocardiography revealed no obvious structural abnormalities. On the basis of these findings, the patient was clinically diagnosed with catecholaminergic polymorphic VT (CPVT).

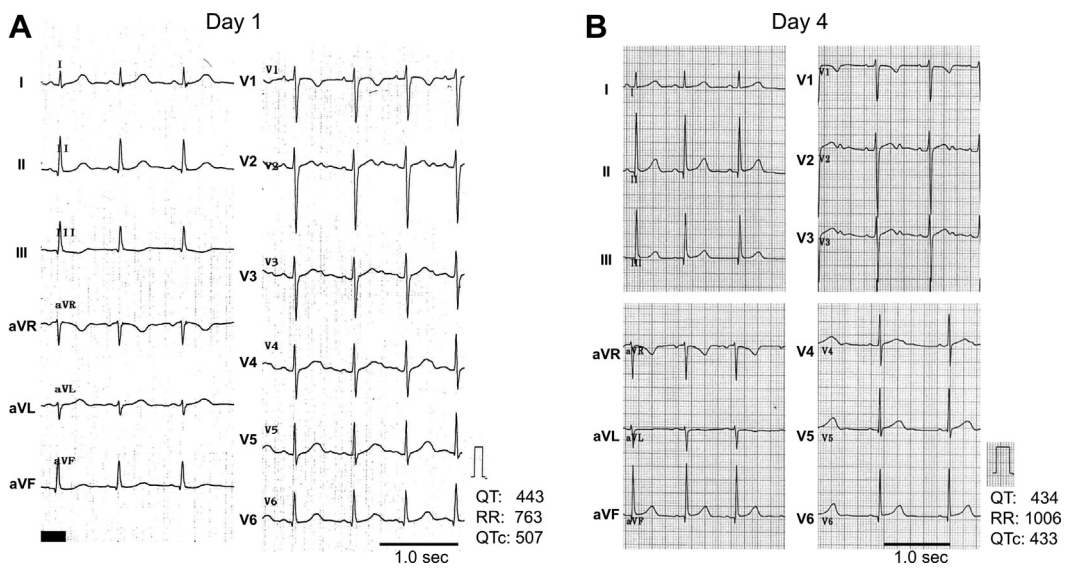
When the patient was 15 years of age, she underwent genetic testing using Sanger sequencing, targeting only the ryanodine receptor 2 (*RYR2*) gene, the most common causative gene for CPVT. However, no pathogenic (or likely pathogenic) variants were identified.

Although there was no history of sudden death or CPVT in the family at that time, the patient's brother, who had experienced syncope at 13 years of age during exercise, died suddenly at 20 years of age (Figure 3A). When the patient was 29 years of age, comprehensive genetic screening using our customized next-generation sequencing panel (Supplemental Table 1) identified a nonsense variant (c.307C>T, p.Arg103Ter) and a frameshift variant (c.592delC, p.Leu198PhefsTer17) in the trans-2,3-enoyl-coenzyme A reductase-like (*TECRL*) gene (Figure 3B). Other mutations in known CPVT-causative genes were not found. Both parents, who were asymptomatic and had normal results on electrocardiography (Supplemental Figure 1), were carriers of 1 of each variant identified in the patient (Figure 3B), confirming that these 2 *TECRL* variants were located on different alleles and identified as compound heterozygous.

MANAGEMENT

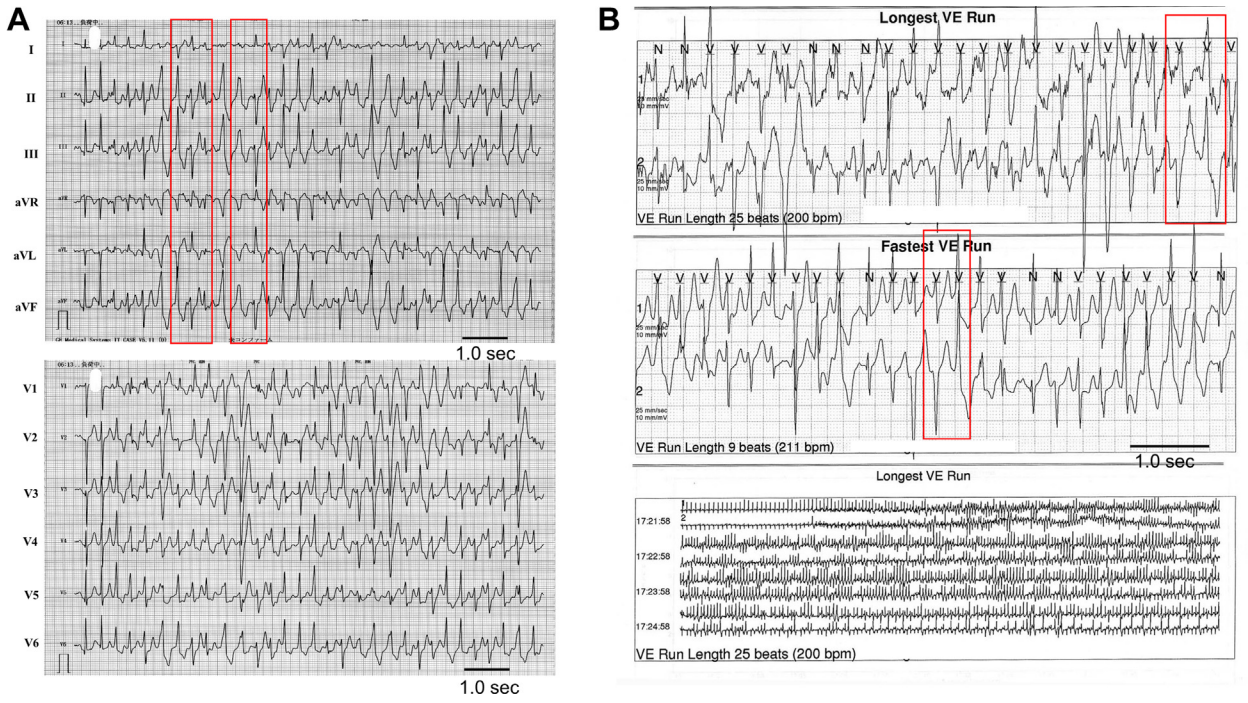
The patient started oral metoprolol (80 mg/d), and high-intensity exercise was restricted when she was diagnosed with CPVT at 10 years of age. However, despite the medication, polymorphic premature ventricular contraction or nonsustained VT occurred during exercise testing. Therefore, flecainide (100 mg/d) was introduced at 10 years of age, and increased (150 mg/d) at 16 years old in addition to metoprolol (120 mg/d), resulting in almost complete suppression of exercise-induced arrhythmias (Figures 4A to 4C). Subsequently, the patient

FIGURE 1 Electrocardiogram at Administration and 4 Days Later



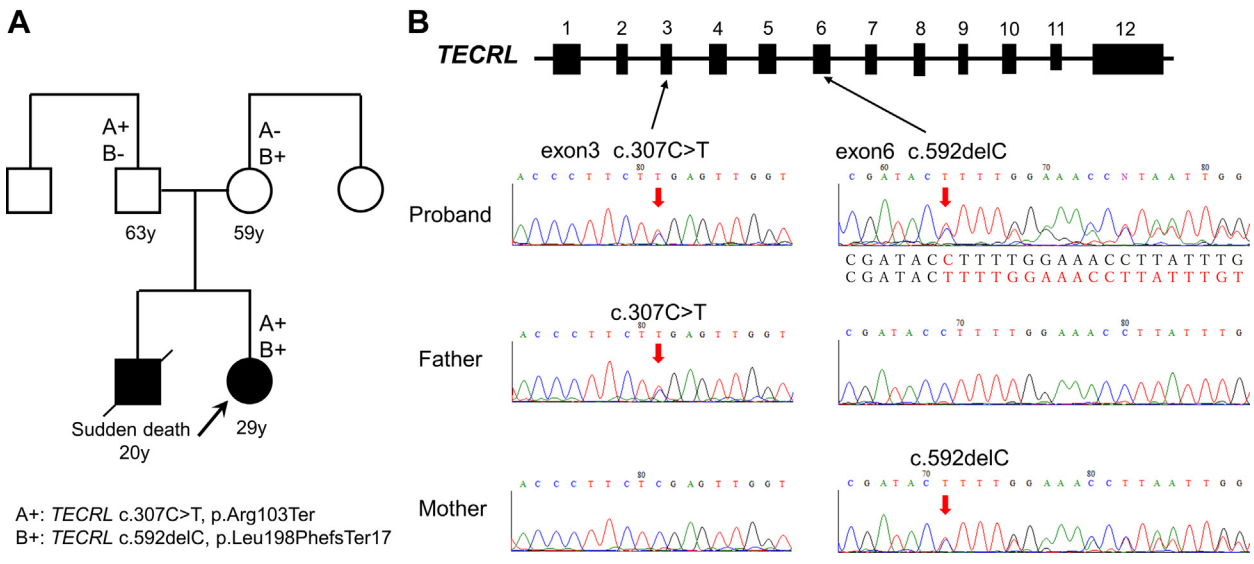
Patient's resting 12-lead electrocardiogram at administration (A) and 4 days after administration (B), when she was 10 years of age.
QTc = corrected QT interval (Bazett formula).

FIGURE 2 **Exercise Stress Electrocardiogram and Holter Monitoring**



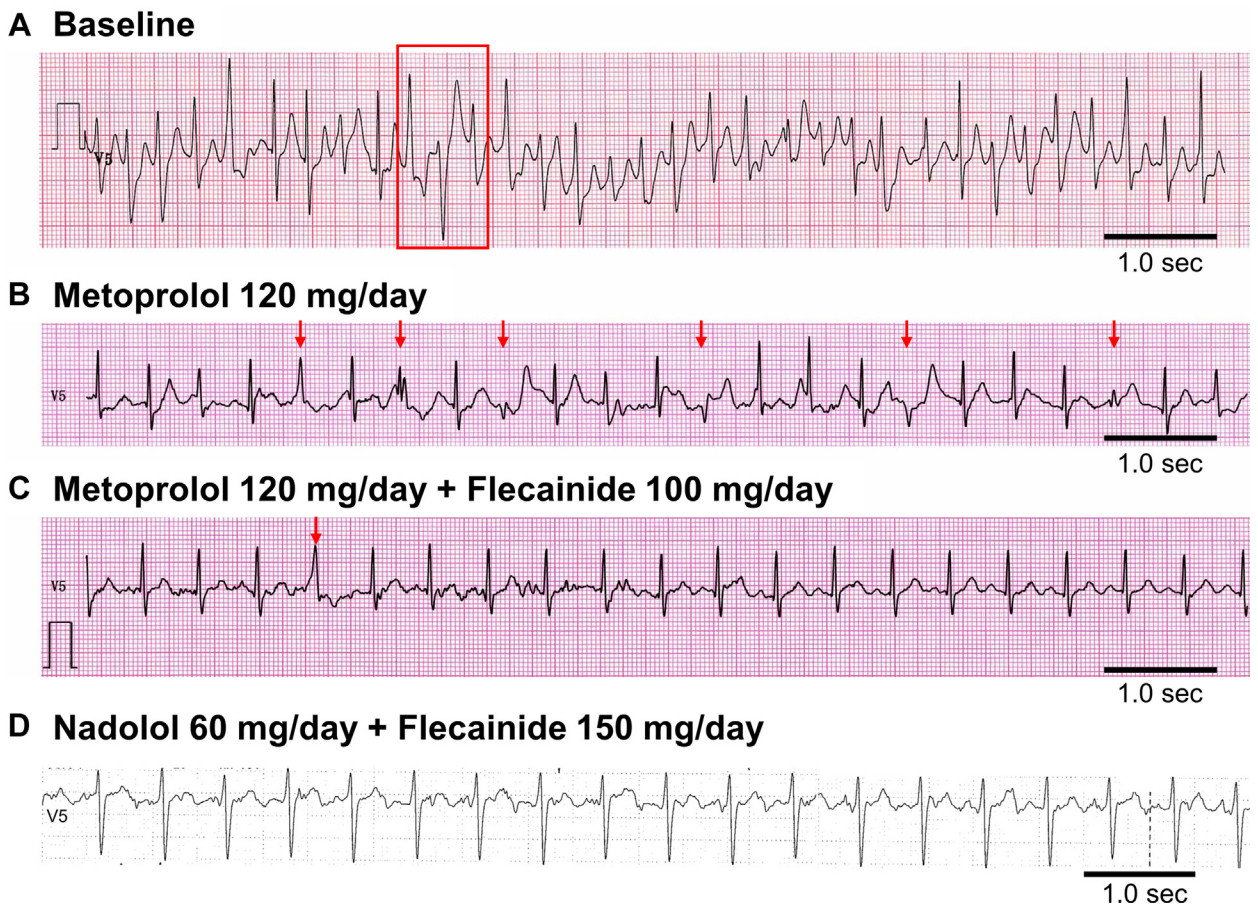
Patient's 12-lead electrocardiogram during exercise stress testing (A) and Holter monitoring (B) at 10 years of age. Polymorphic nonsustained ventricular tachycardia, including a short episode of bidirectional changed QRS axis (red box), was observed at peak exercise (A) and higher heart rate (B).

FIGURE 3 **Family Pedigree and Sequencing of *TECRL* Gene Exons 3 and 6**



(A) Family pedigree. (B) Sequencing of trans-2,3-enoyl-coenzyme A reductase-like (*TECRL*) gene exon 3 and exon 6 in patient (proband) and parents. Both nonsense (c.307C>T) and frameshift (c.592delC) variants were identified in the proband, while 1 of each was shown in the parents.

FIGURE 4 Electrocardiogram at Baseline and With Pharmacologic Therapy



Patient's electrocardiogram (lead V_5) during exercise stress test at baseline (A), after metoprolol 120 mg/d (B), after additional flecainide 100 mg/d with metoprolol 120 mg/d (C), and finally replaced by nadolol (60 mg/d) (D) with flecainide 150 mg/d. Repetitive premature ventricular contractions (PVCs) and nonsustained ventricular tachycardia with bidirectional changed QRS axis (red box) were induced during exercise at baseline (A), and those were decreased under metoprolol, but some PVCs (red arrow) were still induced (B). Additional flecainide with metoprolol almost suppressed the exercise-induced PVCs (C). Finally, nadolol and flecainide completely suppressed PVCs during exercise (D).

continued taking flecainide, but metoprolol was replaced by propranolol (50 mg/d) and finally by nadolol (60 mg/d) (**Figure 4D**) because nonselective β-blockers are preferred for *TECRL*-CPVT.[1]

DISCUSSION

CPVT is clinically characterized by adrenergic-induced bidirectional and polymorphic VT, often leading to sudden cardiac death, particularly in young patients without structural heart diseases.[2] Although the most common CPVT-causative gene is *RYR2*, other genes such as calsequestrin 2 (*CASQ2*), calmodulin 1-3 (*CALM1-3*), and triadin, related to intracellular calcium handling, have been identified as CPVT-susceptibility genes.[3] Loss-of-function variants of *TECRL* were initially reported as a plausible cause for autosomal-recessive CPVT.[4] Most previously reported *TECRL*-CPVT cases have homozygous variants,[1,5] probably because of consanguineous marriage, although there are a few cases with compound heterozygous variants.[6,7] This case is the first instance of Japanese CPVT caused by novel compound heterozygous variants in *TECRL* gene.

TECRL is an endoplasmic reticulum protein expressed in the heart, and impaired intracellular calcium dynamics have been demonstrated. Using human induced pluripotent stem cell-derived

cardiomyocytes from an affected patient, Devalla et al[8] demonstrated that smaller $[Ca^{2+}]i$ transient amplitude and elevated diastolic $[Ca^{2+}]i$ in *TECRL*-homozygous variant increased action potential duration and susceptibility of triggered activity in response to norepinephrine. Recent RNA sequencing from the heart tissues of *TECRL*-knockout mice has shown a synergistic relationship between *TECRL* deficiency and cardiometabolic and calcium regulation.[9]

The previous European Society of Cardiology guideline (2015) defined only *RYR2* and *CASQ2* as the causative genes for CPVT. However, a recent expert consensus statement[3] recommends molecular genetic testing for established CPVT-susceptibility genes, including *RYR2*, *CASQ2*, *CALM1-3*, *Triadin*, and *TECRL*. Although *TECRL* is not a major cause of CPVT, constituting approximately 1% of CPVT cases, the prognosis appears to be poor compared with that of *RYR2*-CPVT. Therefore, even if genetic testing for *RYR2* is negative, additional genetic screening using a next-generation sequencing panel targeting genes including *TECRL* should be considered, especially when patients exhibit typical CPVT or atypical polymorphic VT with symptoms.

In addition, once CPVT-causative variants are identified, cascade screening for family members, regardless of symptoms, is recommended to screen candidates requiring preventive therapy. If cascade screening had been performed for the patient's deceased brother, he could have avoided sudden death with optimal medications.

FOLLOW-UP

The patient has been free of symptoms since starting combination therapy with a β-blocker and flecainide, which is consistent with those previously reported cases.[5,10]

CONCLUSIONS

We report a case of CPVT caused by novel compound heterozygous *TECRL* variants, effectively managed using β-blocker and flecainide combination therapy. Comprehensive genetic testing, including the *TECRL* gene, can aid in diagnosis and therapeutic strategies for CPVT for both affected patients and unaffected family members.

ACKNOWLEDGMENTS The authors thank Kaori Kugo and Madoka Tanimoto for technical assistance with the genetic analysis.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was supported by a grant from the Japan Agency for Medical Research and Development (23ek0109681h0001 to Dr Aiba). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS CPVT, electrocardiogram, genetics, pharmacology, TECRL

APPENDIX For supplemental methods, a table, references, and a figure, please see the online version of this paper.