

Correspondence

Deadly emotional argument: Sudden cardiac death in catecholaminergic polymorphic ventricular tachycardia (CPVT)

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited channelopathy, characterized by severe polymorphic ventricular arrhythmias in a structurally normal heart induced by catecholaminergic rush following strong emotions, stressful events, or exercise.

CPVT primarily manifests at an early age (2–21 years) [1] and is part of the spectrum of etiologies of sudden cardiac death (SCD).

Diagnosis of CPVT remains challenging. Standard testing and cardiac electrophysiological studies are typically unrevealing. Consequently, testing for adrenergically triggered ventricular arrhythmias includes exercise stress testing (EST) or catecholamine provocation testing (CPT). However, EST was reported to have limited predictive value [2]. Therefore, inclusion of genetic testing in the diagnostic algorithm is required.

The goal of this case report is to raise awareness of signs and symptoms of CPVT and the importance of early diagnosis. Detection of red flags in a patient's history is critical to prevent major adverse cardiovascular events.

A 41-year-old woman was evaluated in the emergency room after having an unexplained out-of-hospital cardiac arrest following an accident. After an emotional argument with the other driver, she passed out trembling. A bystander started cardiopulmonary resuscitation.

The first rhythm detected was ventricular fibrillation. After 15 min of resuscitation and defibrillation, return of spontaneous circulation was achieved. The patient underwent implantation of a subcutaneous cardioverter defibrillator (sICD) for secondary prevention.

Our patient's pedigree is reported in Fig. 1.a.

Past medical history was relevant for an episode of syncope 20 years ago triggered by stress before giving a public lecture. The patient denied any prodrome, tongue bite, urinary or bowel incontinence accompanying that episode.

The differential diagnosis included:

- Congenital coronary abnormality
- Channelopathies, e.g. long QT syndrome (particularly type 1), CPVT
- Myocardial inflammation or other types of infiltrative cardiomyopathy
- Hypertrophic cardiomyopathy
- Idiopathic ventricular fibrillation (IVF)

Initial testing included resting ECG (Fig. 1.b), echocardiography and ajmaline testing, which was unrevealing. Computed tomography, coronary angiography and cardiac magnetic resonance imaging ruled out any underlying structural cardiomyopathy or myocardial inflammation. However, the history of syncope during a stressful event followed by the recent episode of ventricular fibrillation during an emotional dispute in the absence of any identifiable structural cardiovascular abnormalities raised a high suspicion for a genetic arrhythmogenic disease. Therefore, the patient underwent EST and genetic testing.

For EST, a modified Bruce protocol was used, in which the patient maintained a heart rate of 120–130/min for 10 min [3,4]. The EST revealed neither exercise-induced premature ventricular contractions (PVCs) nor ventricular tachycardia (VT).

Notably, genetic testing revealed a heterozygous missense-variant in the gene encoding the ryanodine receptor gene (RYR2) which is involved in intracellular calcium homeostasis, leading to a disproportionate or untimely calcium release from the sarcoplasmic reticulum causing delayed after-depolarizations (DADs). This variant leads to an exchange of the conserved, positively charged amino acid arginine for the polar amino acid cysteine [c.1240C > T, p. (Arg414Cys)] (Fig. 2.a). The phenotype associated with this gene variant is called catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT type 1 - an

Abbreviations: CPVT, Catecholaminergic polymorphic ventricular tachycardia; SCD, Sudden cardiac death; EST, Exercise stress testing; CPT, Catecholamine provocation testing; sICD, Subcutaneous cardioverter defibrillator; IVF, Idiopathic ventricular fibrillation; PVCs, Premature ventricular contractions; VT, Ventricular tachycardia; RYR2, Ryanodine receptor gene; DADs, Delayed after-depolarizations; ACMG, American College of Medical Genetics and Genomics; VUS, Variant of unclear significance; SCN5A, Sodium channel protein type 5 subunit α ; LTAE, Life-threatening arrhythmic events.

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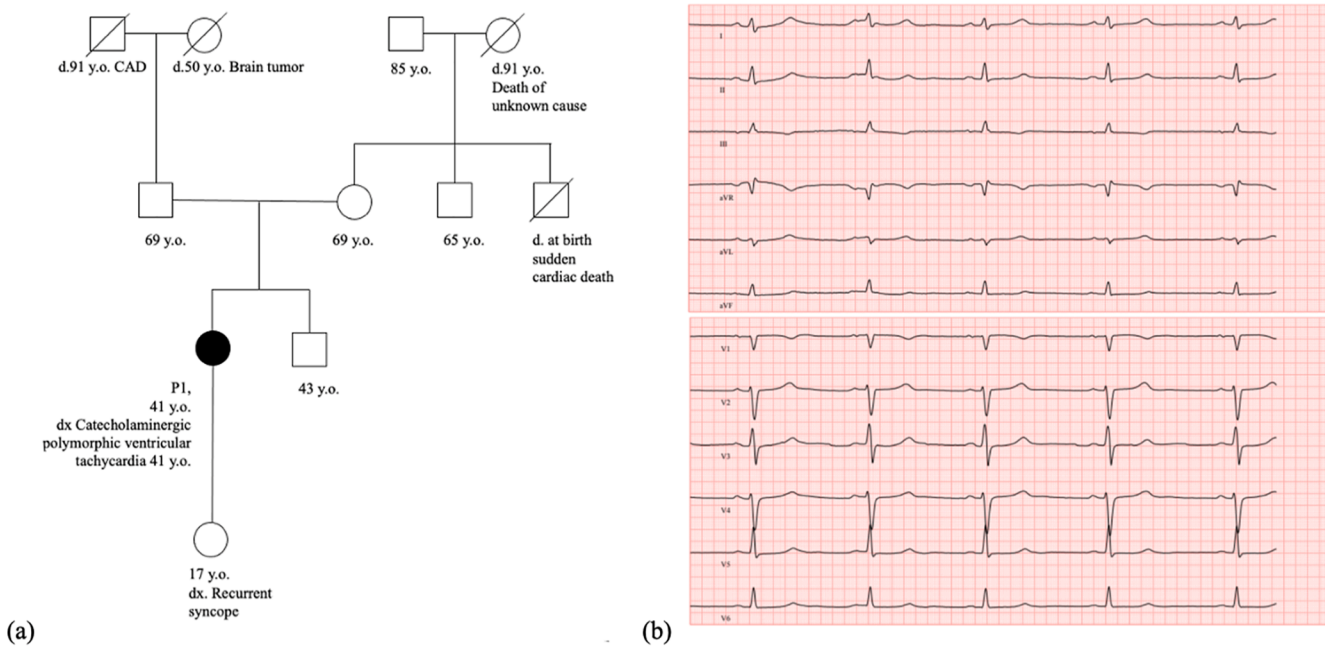


Fig. 1. Pedigree of index patient and resting ECG at the initial testing. (a) The index patient is marked by a black circle. Deceased individuals are marked by a slash. (b) This resting ECG doesn't show any abnormalities. In patients with CPVT, the resting ECG doesn't show any significant suspicious findings, but may show mild, non-diagnostic sinus bradycardia.

autosomal dominant inherited channelopathy).

The patient's variant was categorized as *potentially pathogenic* according to the American College of Medical Genetics and Genomics (ACMG).

Additionally, a *variant of unclear significance* (VUS, ACMG class III) in the gene affecting the sodium channel protein type 5 subunit α (*SCN5A*) in a heterozygous state was detected, leading to an exchange of the highly conserved, non-polar amino acids alanine for the likewise non-polar amino acid valine within the protein ion-transdomain (Fig. 2.b). However, this VUS may not have any clinical effect on the patient's phenotype [5].

Once the diagnosis of CPVT was established, a therapy with the nonselective betablocker propranolol (4 mg/kg/day in three divided doses) was initiated [6].

Six months after starting therapy with betablocking agents, the patient was asymptomatic and none of the subsequent follow-up examinations showed recurrence of arrhythmias.

The purpose of this report is to raise awareness of the importance of thorough history taking and early diagnostic testing for CPVT in stress-induced syncope. EST and genetic screening are critical elements in the diagnostic workup [2].

While EST is a valuable technique, it has low sensitivity based on studies in genetically confirmed CPVT. Similarly to EST, CPT has low sensitivity in diagnosing CPVT [7] as demonstrated in a study by Marjamaa et al. [8], in which EST was superior to CPT in diagnosing genetically confirmed CPVT.

Therefore, genetic testing is critical to avoid underdiagnosis of the disease. The coding region of the *RYR2* gene counts 105 exons. Next generation sequencing enables a broad analysis of all coding exons of *RYR2*, leading to comprehensive detection of variants associated with classic symptoms. Previous guidelines for the use of genetic counseling in channelopathies [9] do not recommend a "shotgun" genetic testing approach in survivors of an unexplained out-of-hospital cardiac arrest due to the high prevalence of polymorphisms in *RYR2*. Although this gene is not considered a polymorphic gene, Medeiros-Domingo et al. [10] found missense variants of *RYR2* in up to 10.5% of their control subjects. Thus, large-scale genetic testing could lead to overdiagnosis and overtreatment in patients, who may not have an arrhythmic

phenotype. Lately, an association of loss-of-function mutations of *RYR2* with IVF has been reported in the literature [11]. The variant of our patient was not described as a loss-of-function mutation in that study but had a similar caffeine response as *RyR2* wildtype. A potential influence of polymorphisms of additional ion channels on clinical phenotype has been previously reported for *SCN5A*. One may speculate that a similar phenomenon could occur in *RYR2* [12].

The mortality rate of CPVT reaches up to 50%. Results from post-mortem genetic testing identified cardiac channelopathies as the etiology in up to 35% of sudden unexpected death [13].

Current recommendations for patients with CPVT experiencing syncope during exertion include avoidance of strenuous activity and betablocker at the highest tolerated dose. Complementary therapeutic approaches include flecainide or verapamil in the case of intolerance or lack of response to betablockers. Regarding the most appropriate β -blockers to prescribe, no significant difference in the occurrence of life-threatening arrhythmic events (LTAE) between propranolol and nadolol has been shown [14]. Propranolol has been suggested as first line therapy in patients presenting with electrical storm independently of the underlying mechanism [15]. In select cases, left cardiac sympathetic denervation may be required if medical therapy fails. In patients with initial abnormal EST, follow-up EST is recommended after initiation of medical therapy to adjust medications if ectopy persists.

Due to the 50% chance for siblings or children to be carriers of the variant and clinical penetrance ranging from 25 to 100%, cascade genetic screening for first degree relatives is recommended, even in the presence of a negative clinical phenotype.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

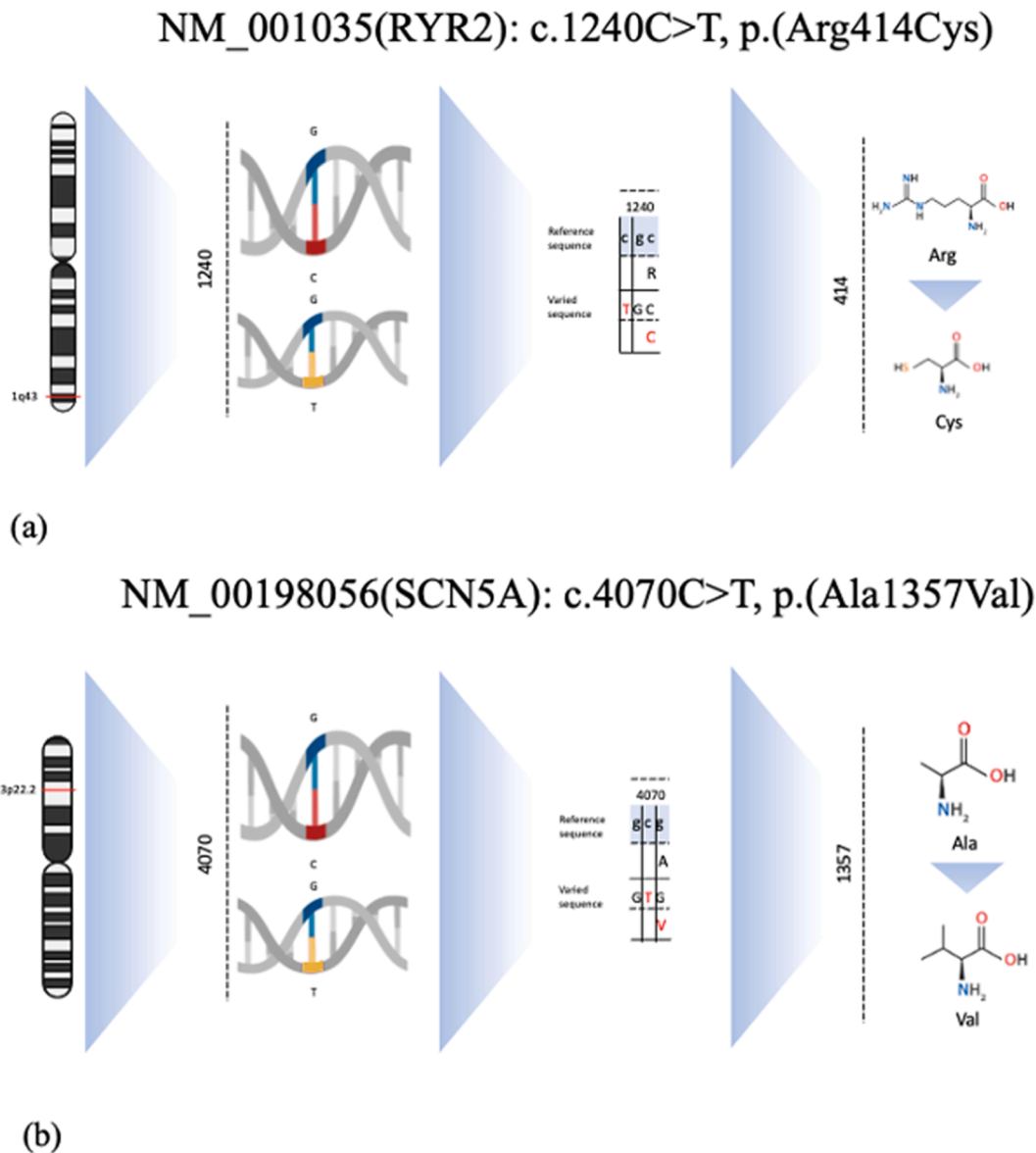


Fig. 2. Graphical representation of the RYR2 and SCN5A variants of our patient. (a) Missense RYR2 variant NM_001035(RYR2): c.1240C > T, p.(Arg414Cys). c.1240C > T corresponds to the replacement of a cytosine with a thymine base in the codon in position 1240 of the coding DNA. p.(Arg414Cys) represents the resulting protein, with the replacement of arginine with cysteine in position 414 of the RYR2 protein. (b) The missense SCN5A variant NM_00198056(SCN5A): c.4070C > T, p.(Ala1357Val). c.4070C > T corresponds to the exchange of a cytosine with a thymine base in the codon based in position 1240 of the coding DNA. p.(Ala1357Val) indicates the replacement in position 1357 of the amino acid sequence of an alanine with valine in the SCN5A protein. [Source: National Center for Biotechnology Information (NCBI), division of the National Library of Medicine (NLM) at the U.S. National Institutes of Health (NIH)].

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Michele Violano^a, Wolfgang Poller^a, Maria Roselle Abraham^b,
Martin Huemer^a, Melvin Scheinman^b, Ulf Landmesser^a,
Bettina Heidecker^{a,*}

^a Department of Cardiology, Charité Universitätsmedizin Berlin, Berlin,
Germany
^b Department of Cardiology, University of California, San Francisco, CA,
USA

* Corresponding author at: Department of Cardiology, Charité
Universitätsmedizin Berlin, Hindenburgdamm 30, 12203 Berlin,
Germany.
E-mail address: bettina.heidecker@charite.de (B. Heidecker).