

Short Communication

Genetics and Mechanisms of Catecholaminergic Polymorphic Ventricular Tachycardia

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Abstract

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmia syndrome characterized by ventricular tachyarrhythmia induced by adrenergic stress in the absence of structural heart disease and high incidence of sudden cardiac death. Five causative genes of CPVT have been identified. There is a common mechanism by which mutations in these genes cause CPVT: Ca²⁺ leakage through the destabilized ryanodine channel complex in sarcoplasmic reticulum. Spontaneous Ca²⁺ release through ryanodine channel leads to delayed after depolarization, triggered activity, and bidirectional/polymorphic VT. Implantable cardioverter defibrillators (ICDs) are used for prevention of sudden death in patients with CPVT. However, because painful shocks can trigger further adrenergic stress and tachyarrhythmias, ICD shocks delivered to initiating triggered arrhythmias have nearly always failed and deaths have occurred despite appropriate ICD shocks. Treatment with β-adrenergic blockers reduces arrhythmia burden and mortality, but is not completely effective. The beneficial effects of Ca²⁺ channel blocker verapamil in combination with β-blocker have been reported, but the role of verapamil has not been well assessed. Flecainide directly inhibits ryanodine channels and prevent CPVT. Left cardiac sympathetic denervation may be an effective alternative treatment in combination with ICD, especially for patients whose arrhythmias are not controlled by drug therapies. Catheter ablation for premature ventricular beats triggering CPVT has recently been effective.

Keywords: Arrhythmias; Genetics; Mechanism; Ryanodine channel; Therapy

Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmia syndrome characterized by ventricular tachyarrhythmia induced by adrenergic stress in the absence of structural heart disease and high incidence of sudden cardiac death [1-4]. The age of CPVT onset is usually before 10 years, although the much later onset has been reported [4]. The diagnosis is made based on reproducible ventricular tachyarrhythmias including bidirectional VT, which is characterized by a beat-to-beat 180° rotation of the QRS axis and polymorphic VT during exercise testings and/or epinephrine administration. Five causative genes of CPVT have been identified (Table 1). There is a common mechanism by which mutations in these genes cause CPVT: Ca²⁺ leakage through the destabilized ryanodine channel complex in sarcoplasmic reticulum (Figure 1) [5]. Spontaneous Ca²⁺ release through ryanodine channel leads to delayed after depolarization, triggered activity, and bidirectional/polymorphic VT. Therefore, ryanodine channel block can be therapeutic for CPVT, and it has recently discovered that flecainide directly inhibits ryanodine channels and prevent CPVT [6-8].

RYR2, cardiac ryanodine receptor Ca²⁺ release channel

RYR2 is the first gene associated with the autosomal dominant form of CPVT [9]. Ryanodine channels open in response to Ca²⁺ entry from the outside of cardiomyocytes through L-type Ca²⁺ channel and release Ca²⁺ from the sarcoplasmic reticulum into the cytosol (Figure) [10]. Mutations in RYR2 are identified in ~60% of patients

with CPVT, and the vast majority of the genotype-positive CPVT patients have RYR2 mutations [4]. RyR2 channels open in response to Ca²⁺ entry from the outside of cardiomyocytes through L-type Ca²⁺ channel and release Ca²⁺ from the sarcoplasmic reticulum into the cytosol (Figure 1) [10]. There have been three proposed mechanisms underlying leaky RyR2 channels that cause spontaneous Ca²⁺ release

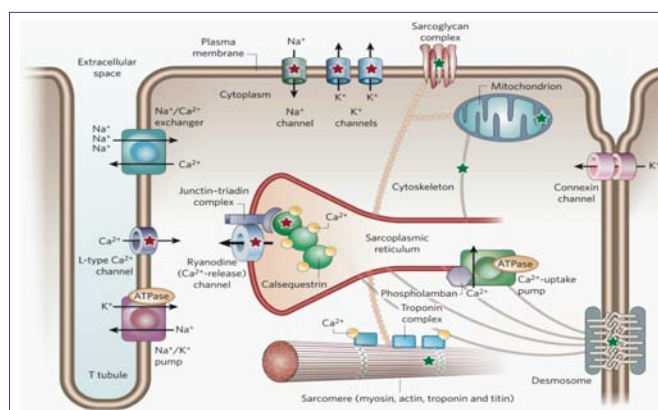


Figure 1: Protein complexes, cardiomyocyte architecture, and intracellular organelles involved in excitation–contraction coupling. Entry of Ca²⁺ into the cell triggers the release of Ca²⁺ from the sarcoplasmic reticulum through the ryanodine channel. Ca²⁺ then binds to the troponin complex and activates the contractile apparatus (the sarcomere, bottom). Relaxation occurs on removal of Ca²⁺ from the cytosol via Ca²⁺ uptake into the sarcoplasmic reticulum where Ca²⁺ binds to calsequestrin and via Ca²⁺ transport out the cell by the Na⁺ / Ca²⁺ exchanger. Modified from reference 5.

Table 1: Causative genes of CPVT

Gene	Protein	Transmission mode	Frequency
RYR2	Ryanodine receptor	Autosomal dominant	60%
CASQ2	Calsequestrin	Autosomal recessive	1-2%
TRDN	Triadin	Autosomal recessive	Rare
KCNJ2	Inward rectifier K ⁺ channel, Kir 2.1	Autosomal dominant	Rare
CALM1	Calmodulin	Autosomal dominant	Unknown

leading to CPVT as a result of *RYR2* mutations: 1) enhanced basal activity of RyR2 channels [11-13]., 2) disruption of ryanodine channel-stabilizing protein FKBP12.6 (or calstabin2) binding, [14] and 3) defective inter-domain folding to ryanodine receptor [15,16].

CASQ2, cardiac calsequestrin

CASQ2 is associated with the autosomal recessive form of CPVT, and mutations in *CASQ2* are identified only in 1% to 2% of patients with CPVT patients [17]. Calsequestrin is the major Ca²⁺ storage protein in the sarcoplasmic reticulum and plays an essential role in the regulation of Ca²⁺ storage and release required for excitation-contraction coupling [18]. Calsequestrin forms a complex with the ryanodine channels and the junctional sarcoplasmic reticulum membrane proteins triadin 1 and junctin (Figure 1). Calsequestrin is also important as a regulator of ryanodine channels through the interaction with triadin and junctin, independent of its role for global Ca²⁺ buffering in the sarcoplasmic reticulum. Because *CASQ2* is linked to the recessive form of CPVT, *Casq2* null mice can be used in order to understand the mechanism underlying this form of CPVT. *Casq2* null mice show increase in Ca²⁺ leak from sarcoplasmic reticulum, premature spontaneous Ca²⁺ releases, and exercise- and catecholamine-induced VT [19]. The mechanisms by which mutations in *CASQ2* cause CPVT are various, including decreases Ca²⁺-storing capacity in the sarcoplasmic reticulum, altered Ca²⁺ sensitivity, reduced binding to triadin-1 and junctin, disrupted interaction with RyR2 channels, and decreased expression levels of calsequestrin [20-24].

TRDN, triadin

Triadin binds to both ryanodine channel and calsequestrin, and is important for anchoring calsequestrin at the junction in specialized areas where sarcoplasmic reticulum forms junctions with the sarcolemma. Triadin knock-out mice exhibit Ca²⁺ overload, spontaneous Ca²⁺ releases from sarcoplasmic reticulum, and CPVT [25]. Mutations in *TRDN* with a recessive mode of transmission have recently been identified in 2 of 97 families [26]. Two mutations are nonsense ones that result in complete absent of triadin and thus can cause CPVT by same mechanism to triadin knock-out mice. Another mutation in *TRDN* results in intracellular retention and lack of mutant triadin expression.

KCNJ2, inward rectifier K⁺ channel Kir2.1

KCNJ2 is a causative gene of Andersen-Tawil syndrome or long QT syndrome 7. However, some patients carrying a mutation in *KCNJ2* do not have Andersen-Tawil syndrome phenotypes including periodic paralysis nor dysmorphic features, but have CPVT [27]. Furthermore, a heterozygous mutation in *KCNJ2* has been identified in 1 of 50 proband with CPVT [28]. Interestingly, electrocardiograms

show abnormal U wave in *KCNJ2*-associated CPVT, similar to Andersen-Tawil syndrome, although electrocardiograms at rest are completely normal in other genetic CPVT forms [27,28]. Mutations in *KCNJ2* result in decreased inward rectifier K⁺ currents, but the precise mechanism by which *KCNJ2* mutations cause CPVT is unknown [27].

CALM1, calmodulin

Calmodulin is a ubiquitous, multifunctional calcium signaling protein, which is essential for myriad intracellular signaling. Calmodulin regulates activities of various ion channels and has a critical role for cardiac electrophysiology. Mutations in calmodulin genes have recently been associated with long QT syndrome, idiopathic ventricular fibrillation, and CPVT [29-31]. Mutant calmodulins associated with CPVT show enhanced binding to ryanodine channels and result in increased activity of ryanodine channel and high frequency of Ca²⁺ waves, possibly leading to CPVT, while mutant calmodulins associated with long QT syndrome do not show these abnormalities [32].

Mechanisms of bidirectional VT

Bidirectional VT is one of the unique characteristics in CPVT, and optical mappings in hearts of mice heterozygously carrying a *Ryr2* mutation showed the possible underlying mechanism of bidirectional VT [33]. There are alternating foci between the right and left ventricles during bidirectional VT and the foci are located at the site of insertion of the major Purkinje system branches. Evidence that the susceptibility to DADs and triggered activity are high in Purkinje cells in comparison to ventricular myocytes supports the arrhythmogenic role of Purkinje systems in CPVT [34]. Furthermore, the initial beats of polymorphic VT originate from the free-running Purkinje fibers in the mouse model, [33] and catheter ablation for premature beats triggering polymorphic VT has been effective in patients with CPVT [35].

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