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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 socks 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 mechanisms by which mutations in these genes cause CPVT: Ca^{2+} leakage through the destabilized ryanodine channel complex in sarcoplasmic reticulum (Figure 1) [5]. Spontaneous Ca^{2+} 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 Ca^{2+} release channel

RYR2 is the first gene associated with the autosomal dominant form of CPVT [9]. Ryanodine channels open in response to Ca^{2+} entry from the outside of cardiomyocytes through L-type Ca^{2+} channel and release Ca^{2+} 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 Ca^{2+} entry from the outside of cardiomyocytes through L-type Ca^{2+} channel and release Ca^{2+} from the sarcoplasmic reticulum into the cytosol (Figure 1) [10]. There have been three proposed mechanisms underlying leaky RyR2 channels that cause spontaneous Ca^{2+} release

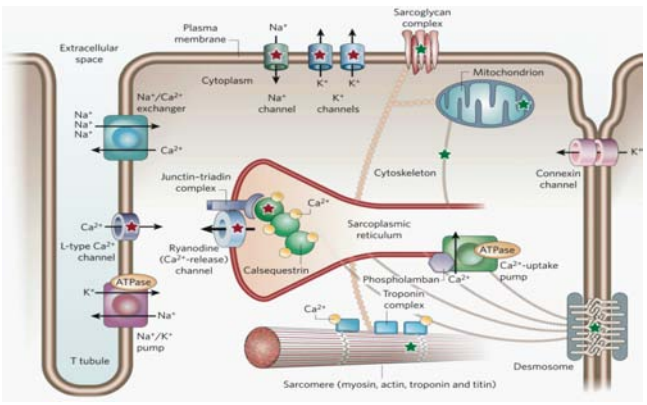

Figure 1: Protein complexes, cardiomyocyte architecture, and intracellular organelles involved in excitation–contraction coupling. Entry of Ca^{2+} into the cell triggers the release of Ca^{2+} from the sarcoplasmic reticulum through the ryanodine channel. Ca^{2+} then binds to the troponin complex and activates the contractile apparatus (the sarcomere, bottom). Relaxation occurs on removal of Ca^{2+} from the cytosol via Ca^{2+} uptake into the sarcoplasmic reticulum where Ca^{2+} binds to calsequestrin and via Ca^{2+} transport out the cell by the Na^+ / Ca^{2+} exchanger. Modified from reference 5.

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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 Ca^{2+} storage protein in the sarcoplasmic reticulum and plays an essential role in the regulation of Ca^{2+} 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 Ca^{2+} 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 Ca^{2+} leak from sarcoplasmic reticulum, premature spontaneous Ca^{2+} releases, and exercise- and catecholamine-induced VT [19]. The mechanisms by which mutations in *CASQ2* cause CPVT are various, including decreases Ca^{2+}-storing capacity in the sarcoplasmic reticulum, altered Ca^{2+} 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 Ca^{2+} overload, spontaneous Ca^{2+} 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

KNCJ2 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 Ca^{2+} 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].

References

1. Leenhardt A, Lucet V, Denjoy I, Grau F, Ngoc DD, Coumel P. Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients. Circulation. 1995; 91: 1512-1519.
2. Hayashi M, Denjoy I, Extramiana F, Maltret A, Buisson NR, Lupoglazoff JM, et al. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. Circulation. 2009; 119: 2426-2434.
3. Laitinen PJ, Brown KM, Piippo K, Swan H, Devaney JM, Brahmbhatt B, et al. Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. Circulation. 2001; 103: 485-490.
4. Cerrone M, Napolitano C, Priori SG. Catecholaminergic polymorphic ventricular tachycardia: A paradigm to understand mechanisms of arrhythmias associated to impaired ca(2+) regulation. Heart Rhythm. 2009; 6: 1652-1659.
5. Watanabe H, Knollmann BC. Mechanism underlying catecholaminergic polymorphic ventricular tachycardia and approaches to therapy. J Electrocardiol. 2011; 44: 650-655.
6. Watanabe H, Chopra N, Laver D, Hwang HS, Davies SS, Roach DE, Duff HJ, Roden DM, Wilde AA, Knollmann BC. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. Nat Med. 2009; 15: 380-383.
7. Watanabe H, van der Werf C, Roses-Noguer F, Adler A, Sumitomo N, Veltmann C, et al. Effects of flecainide on exercise-induced ventricular arrhythmias and recurrences in genotype-negative patients with catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm. 2013; 10: 542-547.

8. van der Werf C, Kannankeril PJ, Sacher F, Krahn AD, Viskin S, Leenhardt A, et al. Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. J Am Coll Cardiol. 2011; 57: 2244-2254.

9. Priori SG, Napolitano C, Tiso N, Memmi M, Vignati G, Bloise R, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. Circulation. 2001; 103: 196-200.

10. Blayney LM, Lai FA. Ryanodine receptor-mediated arrhythmias and sudden cardiac death. Pharmacol Ther. 2009; 123: 151-177.

11. Jiang D, Xiao B, Zhang L, Chen SR. Enhanced basal activity of a cardiac Ca2+ release channel (ryanodine receptor) mutant associated with ventricular tachycardia and sudden death. Circ Res. 2002; 91: 218-225.

12. Jiang D, Xiao B, Yang D, Wang R, Choi P, Zhang L, et al. RyR2 mutations linked to ventricular tachycardia and sudden death reduce the threshold for store-overload-induced Ca2+ release (SOICR). Proc Natl Acad Sci U S A. 2004; 101: 13062-13067.

13. Jiang D, Wang R, Xiao B, Kong H, Hunt DJ, Choi P, et al. Enhanced store overload-induced Ca2+ release and channel sensitivity to luminal Ca2+ activation are common defects of RyR2 mutations linked to ventricular tachycardia and sudden death. Circ Res. 2005; 97: 1173-1181.

14. Wehrens XH, Lehnart SE, Huang F, Vest JA, Reiken SR, Mohler PJ, et al. FKBP12.6 deficiency and defective calcium release channel (ryanodine receptor) function linked to exercise-induced sudden cardiac death. Cell. 2003; 113: 829-840.

15. Ikemoto N, Yamamoto T. Regulation of calcium release by interdomain interaction within ryanodine receptors. Front Biosci. 2002; 7: d671-683.

16. Uchinoumi H, Yano M, Suetomi T, Ono M, Xu X, Tateishi H, et al. Catecholaminergic polymorphic ventricular tachycardia is caused by mutation-linked defective conformational regulation of the ryanodine receptor. Circ Res. 2010; 106: 1413-1424.

17. Lahat H, Pras E, Olender T, Avidan N, Ben-Asher E, Man O, et al. A missense mutation in a highly conserved region of casq2 is associated with autosomal recessive catecholamine-induced polymorphic ventricular tachycardia in bedouin families from israel. Am J Hum Genet. 2001; 69: 1378-1384.

18. Knollmann BC. New roles of calsequestrin and triadin in cardiac muscle. J Physiol. 2009; 587: 3081-3087.

19. Knollmann BC, Chopra N, Hlaing T, Akin B, Yang T, Ettensohn K, et al. Casq2 deletion causes sarcoplasmic reticulum volume increase, premature Ca2+ release, and catecholaminergic polymorphic ventricular tachycardia. J Clin Invest. 2006; 116: 2510-2520.

20. di Barletta MR, Viatchenko-Karpinski S, Nori A, Memmi M, Terentyev D, Turcato F, et al. Clinical phenotype and functional characterization of casq2 mutations associated with catecholaminergic polymorphic ventricular tachycardia. Circulation. 2006; 114: 1012-1019.

21. Valle G, Galla D, Nori A, Priori SG, Gyorke S, de Filippis V, et al. Catecholaminergic polymorphic ventricular tachycardia-related mutations R33Q and L167H alter calcium sensitivity of human cardiac calsequestrin. Biochem J. 2008; 413: 291-303.

22. Houle TD, Ram ML, Cala SE. Calsequestrin mutant D307H exhibits depressed binding to its protein targets and a depressed response to calcium. Cardiovasc Res. 2004; 64: 227-233.

23. Terentyev D, Nori A, Santoro M, Viatchenko-Karpinski S, Kubalova Z, Gyorke I, et al. Abnormal interactions of calsequestrin with the ryanodine receptor calcium release channel complex linked to exercise-induced sudden cardiac death. Circ Res. 2006; 98: 1151-1158.

24. Katz G, Shainberg A, Hochhauser E, Kurtzwald-Josefson E, Issac A, El-Ani D, et al. The role of mutant protein level in autosomal recessive catecholamine dependent polymorphic ventricular tachycardia (cpvt2). Biochemical pharmacology. 2013; 86: 1576-1583.

25. Chopra N, Yang T, Asghari P, Moore ED, Huke S, Akin B, et al. Ablation of triadin causes loss of cardiac Ca^2+ release units, impaired excitation-contraction coupling, and cardiac arrhythmias. Proc Natl Acad Sci U S A. 2009; 106: 7636-7641.

26. Roux-Buisson N, Cacheux M, Fourest-Lieuvin A, Fauconnier J, Brocard J, Denjoy I, et al. Absence of triadin, a protein of the calcium release complex, is responsible for cardiac arrhythmia with sudden death in human. Human molecular genetics. 2012; 21: 2759-2767.

27. Kimura H, Zhou J, Kawamura M, Itoh H, Mizusawa Y, Ding WG, et al. Phenotype variability in patients carrying KCNJ2 mutations. Circ Cardiovasc Genet. 2012; 5: 344-353.

28. Kawamura M, Ohno S, Naiki N, Nagaoka I, Dochi K, Wang Q, et al. Genetic background of catecholaminergic polymorphic ventricular tachycardia in japan. Circ J. 2013; 77: 1705-1713.

29. Crotti L, Johnson CN, Graf E, De Ferrari GM, Cuneo BF, Ovadia M. Calmodulin mutations associated with recurrent cardiac arrest in infants. Circulation. 2013; 127: 1009-1017.

30. Marsman RF1, Barc J2, Beekman L1, Alders M3, Dooijes D4, van den Wijngaard A5, et al. A Mutation in CALM1 Encoding Calmodulin in Familial Idiopathic Ventricular Fibrillation in Childhood and Adolescence. J Am Coll Cardiol. 2014; 63: 259-266.

31. Nyegaard M, Overgaard MT, Søndergaard MT, Vranas M, Behr ER, Hildebrandt LL, et al. Mutations in calmodulin cause ventricular tachycardia and sudden cardiac death. Am J Hum Genet. 2012; 91: 703-712.

32. Hwang H, Nitu R, Yang Y, Johnson C, Faggioni M, Chazin W, et al. Calmodulin mutations in human genetic arrhythmia disorders exhibit divergent functional effects on ryanodine receptor ca release channels. Circulation. 2013; 128: A14157.

33. Cerrone M, Noujaim SF, Tolkacheva EG, Talkachou A, O'Connell R, Berenfeld O, et al. Arrhythmogenic mechanisms in a mouse model of catecholaminergic polymorphic ventricular tachycardia. Circ Res. 2007; 101: 1039-1048.

34. Kang G, Giovannone SF, Liu N, Liu FY, Zhang J, Priori SG, et al. Purkinje cells from RyR2 mutant mice are highly arrhythmogenic but responsive to targeted therapy. Circ Res. 2010; 107: 512-519.

35. Kaneshiro T, Naruse Y, Nogami A, Tada H, Yoshida K, Sekiguchi Y, et al. Successful catheter ablation of bidirectional ventricular premature contractions triggering ventricular fibrillation in catecholaminergic polymorphic ventricular tachycardia with ryr2 mutation. Circ Arrhythm Electrophysiol. 2012; 5: e14-17.

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