ARTICLE

Update on genetics of catecholaminergic polymorphic ventricular tachycardia

Authors

Oscar Campuzano[1,2,3], Georgia Sarquella-Brugada[2,4], Sergi Cesar[4], Josep Brugada[3,4,5], Ramon Brugada[1,2,3,6]

AffiliationS

[1] Cardiovascular Genetics Centre, University of Girona-IDIBGI, Girona, Spain

[2] Medical Science Department, School of Medicine, University of Girona, Girona, Spain

[3] Centro Investigación Biomédica en Red. Enfermedades Cardiovasculares (CIBERCV), Spain

[4] Arrhythmia Unit, Hospital Sant Joan de Déu, University of Barcelona, Barcelona, Spain

[5] Arrhythmia Section, Hospital Clinic, University of Barcelona, Barcelona, Spain

[6] Familial Cardiomyopathies Unit, Hospital Josep Trueta de Girona, Girona, Spain

Correspondence

Oscar Campuzano, BSc, MSc, PhD

Cardiovascular Genetics Center, Institut d'Investigació Biomèdica Girona (IDIBGI)

C/ Dr Castany s/n, Parc Hospitalari Martí i Julià (M-2), 17190, Salt -Girona- (Catalonia, Spain)

oscar@brugada.org

Abstract

Catecholaminergic polymorphic ventricular tachycardia is a rare genetic cause of sudden cardiac death in the young population. It is characterized by adrenergic-induced bidirectional and polymorphic ventricular tachycardias in patients with structurally normal heart. This lethal arrhythmogenic syndrome is difficult to diagnose due to incomplete penetrance and variable expressivity. Recognition of the characteristic electrocardiogram findings and knowledge of the management of patients are crucial, given the risk of arrhythmia recurrence and cardiac arrest. Early identification of families at risk help to prevent lethal episodes. Currently, nine genes have been associated with the disease (*ANK2*, *CALM1*, *CALM2*, *CALM3*, *CASQ2*, *KCNJ2*, *RyR2*, *TECRL*, and *TRDN*), following an autosomal dominant or recessive pattern of inheritance. The main gene related to the disease is *RyR2*, which encodes the cardiac ryanodine receptor 2, and underlies 60% of all cases. A large part of current genetic variants reported remains classified as of uncertain significance, impeding a conclusive translation into clinical practice. In this review, we discuss the main clinical characteristics and current advances in genetic basis of catecholaminergic polymorphic ventricular tachycardia.

Keywords: **s**udden cardiac death, arrhythmias, catecholaminergic polymorphic ventricular tachycardia, genetics

1. Introduction

In 1975, a bidirectional tachycardia precipitated by effort and emotion was reported in a child.[1] However, the first cohort of patients diagnosed with catecholaminergic polymorphic ventricular tachycardia (CPVT) was published in 1995.[2] Several patients included presented with a family history of syncope or sudden cardiac death (SCD), suggesting a genetic origin of CPVT. In 2001, the first rare variant in the *RyR2* gene as cause of CPVT was identified.[3]

Currently, CPVT is classified (OMIM-ID#604772) as a pathological cardiac disorder characterized by adrenergic-induced ventricular tachycardias that typically are bidirectional or polymorphic, and can lead to dizziness, fainting (with syncope), and even SCD, usually as the first manifestation of the disease. Lethal arrhythmias are due to an abnormal calcium-release from the sarcoplasmic reticulum during diastole in response to adrenergic stimulation (intense physical exercise or acute emotional stress).[4] The prevalence of CPVT is estimated in 1:10000, and usually occurs in juvenile population without structural heart alterations.[5, 6] CPVT commonly manifests at an early age, being mean age of presentation before 10 years. Earlier onset of clinical symptoms and a significantly higher risk of cardiac events at a young age is observed in males.[7] The overall mortality rate is nearly 40% and about 30% of patients have a positive familial history of SCD.[8]

2. Clinical Presentation and Diagnosis

Current clinical guidelines report the diagnosis of CPVT (class I recommendation): (a) a structurally normal heart, normal electrocardiogram (ECG), and exercise- or emotion-induced bidirectional or polymorphic ventricular tachycardia; (b) patients who are carriers of a pathogenic genetic alterations in *RYR2* or *CASQ2*.[9] It is important to remark that other seven genes have been also suggested as potentially cause of CPVT despite no mention of any in current guidelines. CPVT typically occurs in patients younger than 40 years of age under physical or emotional stress. Syncope may be the first clinical manifestation of CPVT patients despite other signs and symptoms include dizziness or palpitations may also be present.[10] Presentation of most arrhythmic events occurs during childhood, between 7 and 11 years, and more than 60% of affected individuals have experienced a syncopal episode or cardiac arrest by age 20.[11] The baseline ECG is usually normal although some authors have reported lower-than-normal heart rates, and others have observed prominent U waves.[12] In addition, a moderate QTc prolongation associated with CPVT was reported,[2] and the overlap between CPVT and Long QT Syndrome (LQTS) type 7 was later confirmed.[13] Therefore, 30% of current CPVT cases can be misdiagnosed as "concealed LQTS" due to slight QTc prolongation.[14] Family history of SCD and/or stress-related syncope is present in approximately 30% of patients, especially young population[15] despite a recent study suggest that family history of SCD is an unreliable predictor.[16] CPVT exhibits incomplete penetrance, which has been reported to be around 78%,[17] and has variable expressivity. All these facts make difficult the assessment of the prevalence of the disease in the general population. If exercise testing is not possible, as it occurs in very young children, Holter ECG and event loop-recorders might be of additional help to detect the typical ECG patterns.[9]

Gene	ID	Inheritance	Locus	Protein	Incidence
ANK2	287	AD	4q25-q26	Ankyrin 2	<1%
CALM1	801	AD	14q32.11	Calmodulin 1	<1%
CALM2	805	AD	2p21	Calmodulin 2	<1%
CALM3	808	AD	19q13.32	Calmodulin 3	<1%
CASQ2	845	AD/AR	1p13.1	Calsequestrin 2	<5%
KCNJ2	3759	AD	17q24.3	Kv2.1 / Kir2.1	<1%
RYR2	6262	AD	1q43	Ryanodine Receptor 2	50-60%
TECRL	253017	AR	4q13.1	Trans-2,3-Enoyl-CoA Reductase Like	<1%
TRDN	10345	AR	6q22.31	Triadin	<1%

Table 1: Current genes associated with CPVT.

3. Treatment

The main current therapy is beta-blockers (recommended in all symptomatic patients –class I– and should be considered in asymptomatic carrying a pathogenic mutation –class IIa–). It should be combined with lifestyle modifications (disqualification of competitive sports or avoidance of strenuous exercise and stressful situations).[18, 19] A combination of beta-blockers, calcium-channels blockers and flecainide for patients resistant to conventional therapy has been proposed.[20, 21] If beta-blockers cannot be tolerated, flecainide has been used alone.[22] However, up to 45% of patients may still experience symptoms under pharmacological treatment. Hence, use of implantable cardiac defibrillator (ICD) in patients with a clear diagnosis of CPVT that remain symptomatic despite treatment, or after cardiac arrest, is warranted.[23] However, ICDs can be counter-productive in polymorphic VT due to CPVT; a shock may be ineffective, and the ensuing adrenergic output can worsen the VT storm.[24] Left cardiac sympathetic denervation (LCSD) has been postulated as an alternative in patients in whom ventricular arrhythmias were not controlled by pharmacological treatment.[25] Although the technique seems to show encouraging results, long-term follow-up data are needed to confirm clinical efficacy. Despite recent clinical advances on CPVT, no risk stratification indicators or biomarkers of outcome or severity exist, so far.

4. Genetics

Currently, CPVT is caused by impaired intracellular calcium handling due to pathogenic genetic variations in nine different genes (*ANK2*, *CALM1*, *CALM2*, *CALM3*, *CASQ2*, *KCNJ2*, *RyR2*, *TECRL*, and *TRDN*). Nearly 250 rare variants have been identified to date as pathogenic or potentially pathogenic. Most cases follow an autosomal dominant pattern of transmission, though a recessive form has also been documented in three genes (*CASQ2*, *TECRL*, and *TRDN*). A comprehensive genetic investigation may

unravel nearly 65% of all cases despite almost 60% of variants are usually located in the *RyR2* gene.[16] Therefore, more than 30% of families remain without genetic diagnoses after an exhaustive analysis.

Pathogenic variants in the *ANK2* gene has been associated with a normal ECG at rest and polymorphic ventricular tachycardias induced by exercise, thus mimicking the clinical phenotype of CPVT but with an overall better outcome.[26] To date, no further studies conclude a strong association between this gene and CPVT. Thus, these disorders have recently been proposed as a distinct clinical entity known as the Ankyrin B syndrome.[27]

The *CALM1* gene encodes the Calmodulin protein, a member of the EF-hand calcium-binding protein family. Calmodulin mediates the control of a large number of enzymes, ion channels and other proteins through calcium. Among the enzymes to be stimulated by the Calmodulin-calcium complex are a number of protein kinases and phosphatases. The first variant in this gene associated with CPVT was reported in 2012.[28] Alterations in *CALM1* disrupt the interaction between CaM and the ryanodine favoring the calcium leak. Up to now, few potentially pathogenic variants have been associated with CPVT. In 2014, a rare genetic variant in *CALM2* was reported associated with an overlapping clinical phenotype of LQTS and CPVT.[29] Alteration in *CALM2* do not disrupt the interaction but lower the CaM-Ca2+-binding affinity, prompting spontaneous calcium waves and spark activity, phenotype that mimics an increase in ryanodine function. To date, other genetic variants have been reported in this gene despite associted with cardiac arrhyhtmias not with a conclusive diagnosis of CPVT.[30] In 2016, a novel variant was identified in the *CALM3* gene as potentially associated with CPVT.[31] Alterations in *CALM3* do not disrupt the interaction but lower the CaM-Ca2+-binding affinity, prompting spontaneous calcium waves and spark activity, phenotype that mimics an increase in ryanodine function. To date, no more potentially pathogenic variants have been reported this gene in association with CPVT.

Concerning the *CASQ2* gene, encodes the cardiac muscle family member of the Calsequestrin family that acts as an internal calcium store in muscle cells. It is a high capacity, moderate affinity, calcium-binding protein localized to the sarcoplasmic reticulum in cardiac and slow skeletal muscle cells. The release of calcium bound to Calsequestrin through a calcium release channel triggers muscle contraction. However, the interactions between Calsequestrin and the other sarcoplasmic reticulum proteins regulating calcium release appear to be complex, and many questions on the pathophysiological mechanisms remain to be clarified.[32] Several genetic alterations in *CASQ2* have been associated with CPVT, present in 5% of all genetically diagnosed patients.[33, 34] These genetic alterations, inherited in a dominant or recessive manner, are associated to a higher rate of SCD.[35-37] In a recent report, a family diagnosed with CPVT was followed for more than 20 years. Patients carry homozygous and compound heterozygous *CASQ2* genetic alterations, associated with a severe phenotype but heterozygous carriers of these mutations can remain asymptomatic or have a much milder clinical course.[38]

The *KCNJ2* gene encodes potassium inwardly rectifying channel, subfamily J, member 2 protein. The protein encoded is an essential protein of the membrane, inward-rectifier type potassium channel that establish action potential waveform and excitability of muscle. It is the main gene associated with LQT type 7

also known as Andersen-Tawil syndrome. Regarding CPVT, few genetic variations have been associated with this disease so far.[39, 40] The phenotypes reported usually also show other alterations in the QT interval mimic CPVT.[41] However, distinction with true CPVT is important because patients with Andersen–Tawil syndrome show a much more benign course.[42] As also occurs with the *ANK2* gene, additional studies should be performed in CPVT cohorts to confirm the relationship between *KCNJ2* and CPVT.

The *RyR2* gene encodes the ryanodine receptor found in the cardiac muscle sarcoplasmic reticulum. It is a component of a calcium channel, composed of a tetramer of the ryanodine receptor proteins and a tetramer of FK506 binding protein 1B proteins. Calcium channel mediates the release of calcium from the sarcoplasmic reticulum into the cytoplasm, being crucial in triggering heart muscle contraction.[43] In some cases, CPVT has been often misdiagnosed as LQT syndrome, which phenotypically mimics CPVT but has a relatively better prognosis. The presence of a *RyR2* genetic alteration and a recent modification of Schwartz score facilitated the differential diagnosis.[44] Regarding CPVT, near 200 rare potentially pathogenic variants have been associated with CPVT despite large part remains classified as ambiguous significance.[45] Many of these variants are located in three hot spots regions: the N-terminal domain, the Central region -calstabin-2 binding domain-, and the C-terminal domain -including the channel region-. It is important to remark that almost 50% of variants are *de novo* and this fact should be taken into account in genetic counseling for families. In addition to punctual alterations, Copy Number Variations (CNVs) have been also related to CPVT.[46, 47]

In 2016, a potentially pathogenic variant was located in the *TECRL* gene following a recessive pattern of inheritance in a family suffering of CPVT.[48] This gene encodes for the trans-2,3-enoyl-CoA reductase-like protein, strongly expressed in the heart and localized in the sarcoplasmic reticulum, is thought to participate in the synthesis of fatty acids. Mutations in this gene correlated with a reduction in ryanodine and calsequestrin-2 protein levels and a consequent impairment in calcium handling. No more genetic variants have been reported in this gene associated with CPVT, so far.

The *TRDN* gene encodes Triadin, an integral membrane protein that contains a single transmembrane domain, involved in anchoring calsequestrin to the junctional sarcoplasmic reticulum and allowing its functional coupling with the ryanodine that regulates sarcoplasmic reticulum calcium release.[49] Focusing on CPVT, few pathogenic alterations have been associated with the disease and following an autosomal recessive pattern of inheritance.[50-52] The same genetic alterations were implicated in a particularly malignant autosomal recessive LQT syndrome, named "*triadin knockout syndrome*".[53] As aforementioned, further studies should be performed to explain the molecular mechanisms supporting their pathogenic role.

Finally, concerning families, current guidelines recommend clinical and genetic assessment of relatives in order to identify asymptomatic patients who could be at risk of SCD. Furthermore, relatives who carry a pathogenic variant should receive pharmacological treatment despite being asymptomatic and/or showing a normal exercise test.[9] The biggest current challenge is the clinical interpretation of genetic variants of ambiguous significance, hence distinguishing rare genetic variations

without clinical effect and variants with a potential pathogenic role in CPVT. In fact, in recent years almost 15% of the variants previously associated with CPVT have been identified in global population, supporting an unknown deleterious role.[45] Therefore, a group of experts, including cardiologist and geneticist, should perform a comprehensive interpretation of each variant in each relative before translation into clinical practice.

Figures

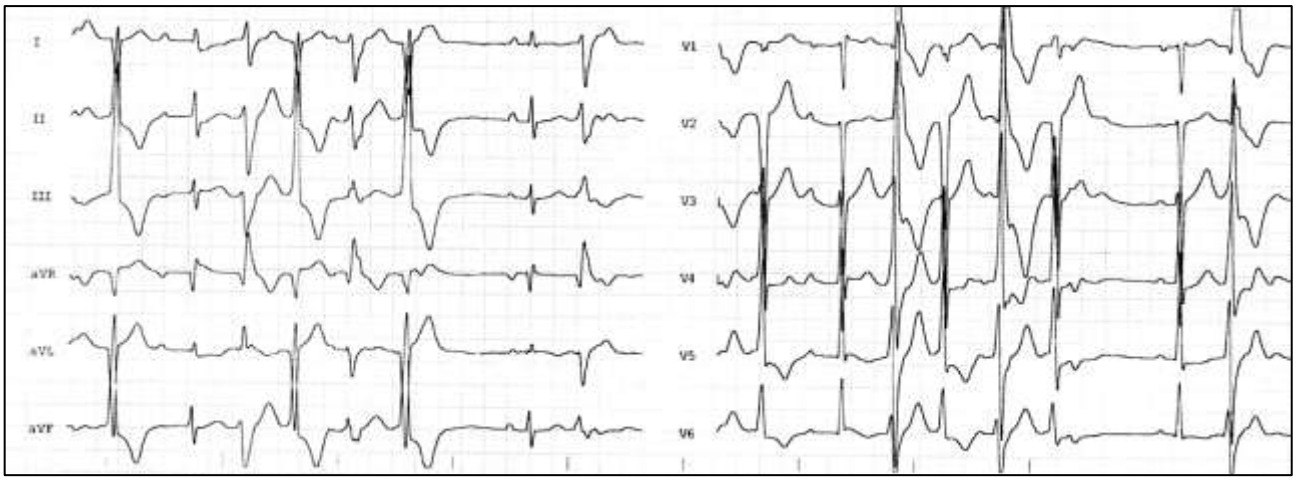

Figure 1: ECG showing ventricular tachycardia associated with CPVT.

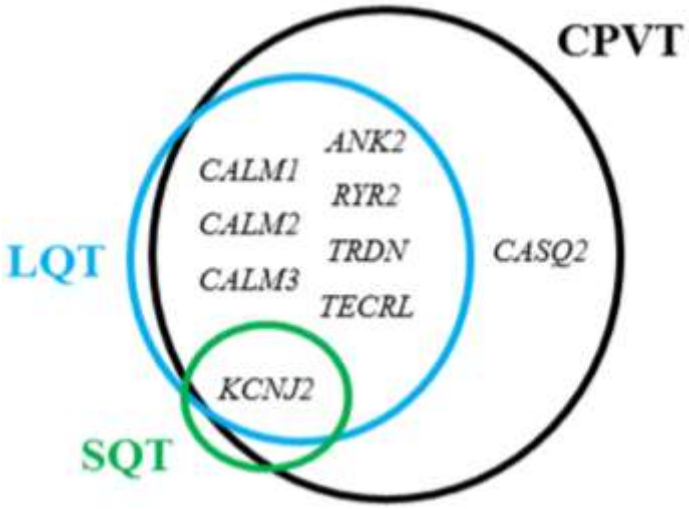

Figure 2: Interaction between current genes associated with CPVT and other arrhythmogenic cardiac syndromes. SQT, Short QT syndrome; LQT, Long QT syndrome; CPVT, Catecholaminergic Polymorphic Ventricular Tachycardia.

5. Conclusions

Catecholaminergic polymorphic ventricular tachycardia is a rare genetic ion channelopathy characterized by polymorphic ventricular tachycardia in adrenergic conditions due to calcium-release alterations. It can lead to syncope and sudden cardiac death, frequently as the first manifestation of the disease in untreated patients. Incomplete penetrance and variable expressivity difficult the diagnosis, thus early identification of families at risk is to prevent malignant arrhythmias. Extreme sport activities are forbidden and beta-blockers are the main current treatment despite flecainide, ICD implantation and LCSD have being considered as effectives alternatives. Currently, nine genes have been associated with the disease and a comprehensive genetic analysis unravel the cause of the disease in nearly 65% of families. Only one gene, *RyR2*, is responsible for 60% of them. Despite recent advances in clinical and pathophysiological basis, further research should be performed to improve early diagnosis, risk stratification, and personalized treatments.

Acknowledgements:

This work was supported by Obra Social "La Caixa", Fondo Investigacion Sanitaria PI17/01690 from the Instituto de Salud Carlos III, and Fundació Daniel Bravo Andreu. The CIBERCV is an initiative of the ISCIII, Spanish Ministry of Economy and Competitiveness (Fondos FEDER).

Disclosures:

All authors declare no conflicts of interest to disclose

References

1. Reid DS, Tynan M, Braidwood L, Fitzgerald GR. Bidirectional tachycardia in a child. A study using his bundle electrography. *Br Heart J*. 1975;37:339-344
2. 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
3. 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
4. Sumitomo N. Current topics in catecholaminergic polymorphic ventricular tachycardia. *Journal of arrhythmia*. 2016;32:344-351
5. Lieve KV, van der Werf C, Wilde AA. Catecholaminergic polymorphic ventricular tachycardia. *Circ J*. 2016;80:1285-1291
6. Lieve KV, Wilde AA, van der Werf C. The role of flecainide in the management of catecholaminergic polymorphic ventricular tachycardia. *Arrhythmia & electrophysiology review*. 2016;5:45-49
7. Lehnart SE, Wehrens XH, Laitinen PJ, Reiken SR, Deng SX, Cheng Z, et al. Sudden death in familial polymorphic ventricular tachycardia associated with calcium release channel (ryanodine receptor) leak. *Circulation*. 2004;109:3208-3214
8. van der Werf C, Wilde AA. Catecholaminergic polymorphic ventricular tachycardia: From bench to bedside. *Heart*. 2013;99:497-504
9. Priori SG, Blomstrom-Lundqvist C. 2015 european society of cardiology guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death summarized by co-chairs. *Eur Heart J*. 2015;36:2757-2759
10. Refaat MM, Hassanieh S, Scheinman M. Catecholaminergic polymorphic ventricular tachycardia. *Cardiac electrophysiology clinics*. 2016;8:233-237
11. 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
12. Aizawa Y, Komura S, Okada S, Chinushi M, Aizawa Y, Morita H, et al. Distinct u wave changes in patients with catecholaminergic polymorphic ventricular tachycardia (cpvt). *International heart journal*. 2006;47:381-389
13. Tester DJ, Ackerman MJ. Sudden infant death syndrome: How significant are the cardiac channelopathies? *Cardiovasc Res*. 2005;67:388-396
14. Kapplinger JD, Tester DJ, Salisbury BA, Carr JL, Harris-Kerr C, Pollevick GD, et al. Spectrum and prevalence of mutations from the first 2,500 consecutive unrelated patients referred for the familion long qt syndrome genetic test. *Heart Rhythm*. 2009;6:1297-1303
15. Priori SG, Napolitano C. Cardiac and skeletal muscle disorders caused by mutations in the intracellular ca2+ release channels. *J Clin Invest*. 2005;115:2033-2038

16. Roston TM, Yuchi Z, Kannankeril PJ, Hathaway J, Vinocur JM, Etheridge SP, et al. The clinical and genetic spectrum of catecholaminergic polymorphic ventricular tachycardia: Findings from an international multicentre registry. *Europace*. 2018;20:541-547
17. Postma AV, Denjoy I, Kamblock J, Alders M, Lupoglazoff JM, Vaksmann G, et al. Catecholaminergic polymorphic ventricular tachycardia: Ryr2 mutations, bradycardia, and follow up of the patients. *J Med Genet*. 2005;42:863-870
18. Biernacka EK, Hoffman P. Efficacy of flecainide in a patient with catecholaminergic polymorphic ventricular tachycardia. *Europace*. 2011;13:129-130
19. Pott C, Dechering DG, Reinke F, Muszynski A, Zellerhoff S, Bittner A, et al. Successful treatment of catecholaminergic polymorphic ventricular tachycardia with flecainide: A case report and review of the current literature. *Europace*. 2011;13:897-901
20. Rosso R, Kalman JM, Rogowski O, Diamant S, Birger A, Biner S, et al. Calcium channel blockers and beta-blockers versus beta-blockers alone for preventing exercise-induced arrhythmias in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm*. 2007;4:1149-1154
21. 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
22. Padfield GJ, AlAhmari L, Lieve KV, AlAhmari T, Roston TM, Wilde AA, et al. Flecainide monotherapy is an option for selected patients with catecholaminergic polymorphic ventricular tachycardia intolerant of beta-blockade. *Heart Rhythm*. 2016;13:609-613
23. Epstein AE. Benefits of the implantable cardioverter-defibrillator. *J Am Coll Cardiol*. 2008;52:1122-1127
24. Roses-Noguer F, Jarman JW, Clague JR, Till J. Outcomes of defibrillator therapy in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm*. 2014;11:58-66
25. Wilde AA, Bhuiyan ZA, Crotti L, Facchini M, De Ferrari GM, Paul T, et al. Left cardiac sympathetic denervation for catecholaminergic polymorphic ventricular tachycardia. *N Engl J Med*. 2008;358:2024-2029
26. Mohler PJ, Splawski I, Napolitano C, Bottelli G, Sharpe L, Timothy K, et al. A cardiac arrhythmia syndrome caused by loss of ankyrin-b function. *Proc Natl Acad Sci U S A*. 2004;101:9137-9142
27. El Refaey MM, Mohler PJ. Ankyrins and spectrins in cardiovascular biology and disease. *Front Physiol*. 2017;8:852
28. Nyegaard M, Overgaard MT, Sondergaard 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
29. Makita N, Yagihara N, Crotti L, Johnson CN, Beckmann BM, Roh MS, et al. Novel calmodulin mutations associated with congenital arrhythmia susceptibility. *Circ Cardiovasc Genet*. 2014;7:466-474
30. Jimenez-Jaimez J, Palomino Doza J, Ortega A, Macias-Ruiz R, Perin F, Rodriguez-Vazquez del Rey MM, et al. Calmodulin 2 mutation n98s is associated with unexplained cardiac arrest in infants due to low clinical penetrance electrical disorders. *PloS one*. 2016;11:e0153851

31. Gomez-Hurtado N, Boczek NJ, Kryshtal DO, Johnson CN, Sun J, Nitu FR, et al. Novel cpvt-associated calmodulin mutation in calm3 (calm3-a103v) activates arrhythmogenic ca waves and sparks. *Circ Arrhythm Electrophysiol*. 2016;9
32. Chen H, Valle G, Furlan S, Nani A, Gyorke S, Fill M, et al. Mechanism of calsequestrin regulation of single cardiac ryanodine receptor in normal and pathological conditions. *The Journal of general physiology*. 2013;142:127-136
33. Faggioni M, Knollmann BC. Calsequestrin 2 and arrhythmias. *Am J Physiol Heart Circ Physiol*. 2012;302:H1250-1260
34. Faggioni M, Kryshtal DO, Knollmann BC. Calsequestrin mutations and catecholaminergic polymorphic ventricular tachycardia. *Pediatric cardiology*. 2012;33:959-967
35. Gray B, Bagnall RD, Lam L, Ingles J, Turner C, Haan E, et al. A novel heterozygous mutation in cardiac calsequestrin causes autosomal dominant catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm*. 2016;13:1652-1660
36. Eldar M, Pras E, Lahat H. 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. *Cold Spring Harbor symposia on quantitative biology*. 2002;67:333-337
37. 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
38. Josephs K, Patel K, Janson CM, Montagna C, McDonald TV. Compound heterozygous casq2 mutations and long-term course of catecholaminergic polymorphic ventricular tachycardia. *Molecular genetics & genomic medicine*. 2017;5:788-794
39. Tester DJ, Arya P, Will M, Haglund CM, Farley AL, Makielski JC, et al. Genotypic heterogeneity and phenotypic mimicry among unrelated patients referred for catecholaminergic polymorphic ventricular tachycardia genetic testing. *Heart Rhythm*. 2006;3:800-805
40. Barajas-Martinez H, Hu D, Ontiveros G, Caceres G, Desai M, Burashnikov E, et al. Biophysical and molecular characterization of a novel de novo kcnj2 mutation associated with andersen-tawil syndrome and catecholaminergic polymorphic ventricular tachycardia mimicry. *Circ Cardiovasc Genet*. 2011;4:51-57
41. Tully I, Atherton J, Hunt L, Ingles J, Semsarian C, McGaughran J. Rarity and phenotypic heterogeneity provide challenges in the diagnosis of andersen-tawil syndrome: Two cases presenting with ecgs mimicking catecholaminergic polymorphic ventricular tachycardia (cpvt). *Int J Cardiol*. 2015;201:473-475
42. Inoue YY, Aiba T, Kawata H, Sakaguchi T, Mitsuma W, Morita H, et al. Different responses to exercise between andersen-tawil syndrome and catecholaminergic polymorphic ventricular tachycardia. *Europace*. 2018;20:1675-1682
43. Lanner JT. Ryanodine receptor physiology and its role in disease. *Advances in experimental medicine and biology*. 2012;740:217-234
44. Ozawa J, Ohno S, Fujii Y, Makiyama T, Suzuki H, Saitoh A, et al. Differential

diagnosis between catecholaminergic polymorphic ventricular tachycardia and long qt syndrome type 1- modified schwartz score. *Circ J*. 2018;82:2269-2276

45. Jabbari J, Jabbari R, Nielsen MW, Holst AG, Nielsen JB, Haunso S, et al. New exome data question the pathogenicity of genetic variants previously associated with catecholaminergic polymorphic ventricular tachycardia. *Circ Cardiovasc Genet*. 2013;6:481-489
46. Medeiros-Domingo A, Bhuiyan ZA, Tester DJ, Hofman N, Bikker H, van Tintelen JP, et al. The ryr2-encoded ryanodine receptor/calcium release channel in patients diagnosed previously with either catecholaminergic polymorphic ventricular tachycardia or genotype negative, exercise-induced long qt syndrome: A comprehensive open reading frame mutational analysis. *J Am Coll Cardiol*. 2009;54:2065-2074
47. Marjamaa A, Laitinen-Forsblom P, Lahtinen AM, Viitasalo M, Toivonen L, Kontula K, et al. Search for cardiac calcium cycling gene mutations in familial ventricular arrhythmias resembling catecholaminergic polymorphic ventricular tachycardia. *BMC Med Genet*. 2009;10:12
48. Devalla HD, Gelinas R, Aburawi EH, Beqqali A, Goyette P, Freund C, et al. Tecrl, a new life-threatening inherited arrhythmia gene associated with overlapping clinical features of both lqts and cpvt. *EMBO molecular medicine*. 2016;8:1390-1408
49. Gyorke I, Hester N, Jones LR, Gyorke S. The role of calsequestrin, triadin, and junctin in conferring cardiac ryanodine receptor responsiveness to luminal calcium. *Biophys J*. 2004;86:2121-2128
50. 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. *Hum Mol Genet*. 2012;21:2759-2767
51. Rooryck C, Kyndt F, Bozon D, Roux-Buisson N, Sacher F, Probst V, et al. New family with catecholaminergic polymorphic ventricular tachycardia linked to the triadin gene. *J Cardiovasc Electrophysiol*. 2015;26:1146-1150
52. Walsh MA, Stuart AG, Schlecht HB, James AF, Hancox JC, Newbury-Ecob RA. Compound heterozygous triadin mutation causing cardiac arrest in two siblings. *Pacing Clin Electrophysiol*. 2016;39:497-501
53. Altmann HM, Tester DJ, Will ML, Middha S, Evans JM, Eckloff BW, et al. Homozygous/compound heterozygous triadin mutations associated with autosomal-recessive long-qt syndrome and pediatric sudden cardiac arrest: Elucidation of the triadin knockout syndrome. *Circulation*. 2015;131:2051-2060

