Update on genetics of catecholaminergic polymorphic ventricular tachycardia

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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 (\textit{ANK2}, \textit{CALM1}, \textit{CALM2}, \textit{CALM3}, \textit{CASQ2}, \textit{KCNJ2}, \textit{RyR2}, \textit{TECRL}, and \textit{TRDN}), following an autosomal dominant or recessive pattern of inheritance. The main gene related to the disease is \textit{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: sudden 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. However, the first cohort of patients diagnosed with catecholaminergic polymorphic ventricular tachycardia (CPVT) was published in 1995. 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. 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). The prevalence of CPVT is estimated in 1:10000, and usually occurs in juvenile population without structural heart alterations. 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. The overall mortality rate is nearly 40% and about 30% of patients have a positive familial history of SCD.

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. 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. 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. The baseline ECG is usually normal although some authors have reported lower-than-normal heart rates, and others have observed prominent U waves. In addition, a moderate QTc prolongation associated with CPVT was reported, and the overlap between CPVT and Long QT Syndrome (LQTS) type 7 was later confirmed. Therefore, 30% of current CPVT cases can be misdiagnosed as “concealed LQTS” due to slight QTc prolongation. Family history of SCD and/or stress-related syncope is present in approximately 30% of patients, especially young population despite a recent study suggest that family history of SCD is an unreliable predictor. CPVT exhibits incomplete penetrance, which has been reported to be around 78%, 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.
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). A combination of beta-blockers, calcium-channels blockers and flecainide for patients resistant to conventional therapy has been proposed. If beta-blockers cannot be tolerated, flecainide has been used alone. 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. 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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, 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.\textsuperscript{32} Several genetic alterations in CASQ2 have been associated with CPVT, present in 5% of all genetically diagnosed patients.\textsuperscript{33}, \textsuperscript{34} These genetic alterations, inherited in a dominant or recessive manner, are associated to a higher rate of SCD.\textsuperscript{35}-\textsuperscript{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.\textsuperscript{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.\textsuperscript{39, 40} The phenotypes reported usually also show other alterations in the QT interval mimic CPVT.\textsuperscript{41} However, distinction with true CPVT is important because patients with Andersen–Tawil syndrome show a much more benign course.\textsuperscript{42} As also occurs with the ANK2 gene, additional studies should be performed in CPVT cohorts to confirm the relationship between \textit{KCNJ2} and CPVT.

The \textit{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.\textsuperscript{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 \textit{RyR2} genetic alteration and a recent modification of Schwartz score facilitated the differential diagnosis.\textsuperscript{44} Regarding CPVT, near 200 rare potentially pathogenic variants have been associated with CPVT despite large part remains classified as ambiguous significance.\textsuperscript{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 \textit{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.\textsuperscript{46, 47} In 2016, a potentially pathogenic variant was located in the \textit{TECRL} gene following a recessive pattern of inheritance in a family suffering of CPVT.\textsuperscript{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 \textit{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.\textsuperscript{49} Focusing on CPVT, few pathogenic alterations have been associated with the disease and following an autosomal recessive pattern of inheritance.\textsuperscript{50-52} The same genetic alterations were implicated in a particularly malignant autosomal recessive LQT syndrome, named “\textit{triadin knockout syndrome}”.\textsuperscript{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.\textsuperscript{9} The biggest current challenge is the clinical interpretation of genetic variants of ambiguous significance, hence distinguishing rare genetic variations

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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.\textsuperscript{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 effective 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.

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