Genetics of Catecholaminergic Polymorphic Ventricular Tachycardia

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Abstract

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a rare cardiac channelopathy characterized by the development of complex ventricular arrhythmias in patients with structurally normal heart. Ventricular tachycardia can be induced by adrenergic stimulation or by exercise, leading to syncope, and/or Sudden Cardiac Death (SCD), usually in young individuals. Early detection of CPVT is crucial to prevent SCD. CPVT can be inherited in an autosomal-dominant (RyR2, KCNJ2, CALM1) or recessive pattern (CASQ2, TRDN). All currently known genes together are responsible for nearly 85% of clinically diagnosed cases. The main responsible gene for CPVT is RyR2, which encodes the cardiac ryanodine receptor 2, and underlies 60% of all cases. Genetic screening is recommended in all diagnosed CPVT patients and all first degree relatives for early detection of asymptomatic carriers, also at risk of SCD. However, a large part of genetic variants identified after a comprehensive genetic screening remain classified as of uncertain significance, difficulting a useful translation into clinical practice. In this review we focus on genetic basis of CPVT and current challenges in clinical interpretation of ambiguous genetic variants.

Keywords: Arrhythmias; Genetics; Catecholaminergic polymorphic ventricular tachycardia; Sudden death

Introduction

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT, MIM-ID # 604772) is a cardiac disorder characterized by adrenergic-induced bi-directional and polymorphic ventricular arrhythmias leading to Sudden Cardiac Death (SCD). Its prevalence is estimated in 1:10000, and usually occurs in juvenile population without structural heart alterations [1]. The first case was reported by Reid et al., [2]. The mean age of presentation is before 10 years of age, with syncopal events associated with emotional stress or exercise. Unfortunately, the first presentation can also be SCD. The overall mortality rate is nearly 40% and about 30% of patients have a positive familial history of SCD [3].

Clinical diagnosis is based on the detection of bidirectional VT (Figure 1), polymorphic ventricular premature beats or VT during exercise stress test or catecholamine infusion, especially in patients younger than 40 years of age. The baseline Electrocardiogram (ECG) is usually normal; however, occasionally a subtle, non-diagnostic bradycardia and U waves can be present. In 1995, Leenhardt et al., also reported moderate QTc prolongation associated with CPVT [4], and the overlap between CPVT and Long QT Syndrome (LQTS) was later confirmed [5]. Currently, 30% of CPVT cases can be misdiagnosed as “concealed LQTS” due to slight QTc prolongation [6]. This makes 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 recorders might be of additional help to detect the typical ECG patterns [7].

Regarding CPVT treatment, beta-blockers are the most recommended anti-arrhythmic drugs despite their limited effectiveness [4,8,9]. A combination of beta-blockers, calcium-channels blockers and flecainide for patients resistant to conventional therapy has recently been proposed [10,11]. ICD implantation in patients with a clear diagnosis of CPVT that remain symptomatic despite treatment, or after cardiac arrest, is warranted [7,12]. Despite short series have been published reporting significant results of the Left Cardiac Sympathetic Denervation (LCSD) [13] it has been postulated as an alternative in patients in whom ventricular arrhythmias were not controlled by beta-blocker therapy.

Figure 1: ECG showing biventricular tachycardia associated with CPVT.
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.

### Genetics

At the molecular level, CPVT is caused by impaired intracellular calcium handling due to Pathogenic Genetic Variations (PGV) in 5 different genes (RyR2, CASQ2, KCNJ2, CALM1 and TRDN).
Currently clinical guidelines recommend classic and genetic assessment of relatives in order to identify asymptomatic patients who could be at risk of SCD. Furthermore, relatives who carry a PGV should receive pharmacological treatment despite being asymptomatic and/or showing a negative exercise test [7]. In the field of cardiac genetics, the biggest challenge at present is the clinical interpretation of Genetic Variants of Unknown Significance (GVUS), hence distinguishing common variants in the general population from rare genetic variations with a potential pathogenic role. In fact, in recent years almost 15% of the variants previously associated with CPVT have been identified in the Exome Sequencing Project (ESP) [15], classifying these potential pathogenic variants as potentially common variants in the global population, discarding their pathogenic role and remaining as GVUS.

**RyR2**

The RyR2 gene (ID: 6262) is located in chromosome 1, 1q43 (Start 237,205,505 bp / End 237,997,288 bp), and encodes the ryanodine receptor found in the cardiac muscle sarcoplasmic reticulum (4967 aminoacids; 564567 Da). 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 receptors. Calcium channel mediates the release of calcium from the sarcoplasmic reticulum into the cytoplasm, being crucial in triggering heart muscle contraction. Mouse models harbouring similar PGV have demonstrated that calcium leaks in the cytoplasm of cardiac cells may trigger arrhythmias [16,17].

PGVs in the RyR2 gene have been associated with several diseases [18] (Figure 3). Regarding CPVT, only 4 variations have been associated with ventricular tachycardia (missense variations p.C101R / c.303T>C (CM045295) [24], p.R82W / c.244C>T (CM066888 / rs199473373) [25], and p.V227F / c.679G>T (CM066889 / rs199473657) [25]. In addition, there is one more missense variation, p.R260P / c.779G>C (CM111211 / rs199473385) [26], reported in a patient showing Andersen-Tawil syndrome and CPVT mimicry. These PGVs display a loss of function of phenotype modulated by PKA-dependent Kir2.1 phosphorylation which correlates with adrenergic conditions underlying the clinical arrhythmia in CPVT.

**CALM1**

The CALM1 gene (ID: 801) is located in chromosome 14, 14q32.11 (Start 90,862,846 bp / End 90,874,619 bp), and encodes the Calmodulin protein (149 aminoacids; 16838 Da), 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.

Up to now, 6 PGVs have been reported that have been associated with CPVT, osteoarthritides, and idiopathic ventricular fibrillation, among others (Figure 3). Regarding CPVT, only two have been linked with CPVT: missense variations p.153N / c.458>T-A (CM128791) [27], and p.N98S / c.293A>G (CM128792 / rs267607277) [27]. Recently, Makita et al., reported a potential association of CALM2 (chromosome 2, 2p21), and overlapping clinical features of LQTS and CPVT [28]. Further studies should be performed to elucidate the molecular mechanisms supporting its pathogenic role in CPVT.

<table>
<thead>
<tr>
<th>Type</th>
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**Table 1:** Main genes associated with CPVT.


Nearly 200 PGVs have been identified to date (supplementary table) (Figures 2&3). Most cases follow an autosomal dominant pattern of transmission, though a recessive form has also been documented in two genes (CASQ2 and TRDN). All genes together are responsible of nearly 65% of all clinically diagnosed cases, with PGV in RyR2 underlying 60% of cases [14]. This means that a large percentage of CPVT patients remain without an identified genetic cause.
TRDN

The TRDN gene (ID: 10345) is located in chromosome 6, 6q22.31 (Start 123,537,483 bp / End 123,958,238 bp), and encodes the Triadin protein -TRDN- (729 aminoacids / 81595 Da). Triadin is an integral membrane protein that contains a single transmembrane domain, involved in anchoring CASQ2 to the junctional sarcoplasmic reticulum and allowing its functional coupling with the RyR2 that regulates sarcoplasmic reticulum calcium release.

This gene has been associated mainly with CPVT, nephritis, familial dilated cardiomyopathy, muscular dystrophy and myopathy (Figure 3). Focusing on CPVT, to date, 3 PGV have been reported: missense variation p.T59R/c.176C>G (CM124195) [29], nonsense variation p.Q205* / c.613C>T (CM124194), which induces a truncation of the TRDN protein [29], and c.53_56delACAG (CD124196), a small deletion of 4 nucleotides that induces a frameshift [29]. As aforementioned, further studies should be performed to explain the molecular mechanisms supporting their pathogenic role.

Clinical Interpretation of Genetic Data

The current Expert Consensus Statement of Heart Rhythm Society/European Heart Rhythm Association recommends clinical and genetic assessment of CPVT relatives following identification of a PGV in the index patient [7]. Genetic testing may help confirm the clinical diagnosis in CPVT patient, and may also identify asymptomatic genetic carriers that could be at risk of SCD. Moreover, family members who carry a PGV should receive pharmacological treatment despite being asymptomatic and/or showing a negative exercise test [7].

While controversial in the field of genetics, genetic testing should be performed as soon as possible, even at birth, because of the association between CPVT and the Sudden Infant Death Syndrome (SIDS) and the young age of presentation of this disease [30]. Relatives non-carriers can be released from further cardiologic follow-up. On the contrary, if positive, it enables prophylactic β-blocker therapy to be initiated at a young age [31]. Without the genotype, potentially at-risk family members would only be revealed after they are old enough to undergo a provocative stress test or if they manifest a concerning symptom.

Recent development of Next Generation Sequencing -NGS- technology has allowed analyzing more genes in shorter time and in a cost-effective manner, identifying more genetic alterations that could be responsible for CPVT cases. It also helps to further analyze CPVT candidate genes in families without genetic alterations in currently known genes. Nowadays, NGS is also being applied for post-mortem genetic testing of samples showing no cause of death after complete autopsy. In these cases, up to 30% of sudden unexplained death cases carry at least one PGV in genes associated with arrhythmogenic disease, being RyR2 one of the most important genes [32]. Additionally, NGS also allows us to discern common variants in population and rare genetic variations [15].

The pathogenicity of rare variants classified as GVUS remains to be clarified before the appropriate translation of genetic information into clinical practice. For that purpose, several items should be taken into account: kind of variation, frequency in the population, evolutionary conservation between species, reported in vitro studies, reported in vivo studies, in silico prediction, and familial segregation [33]. But even after exhaustive analysis, each GVUS should be interpreted with caution because some of these items can produce erroneous conclusions regarding pathogenicity, as recently reported by our group in a LQTS cohort [34]. Family segregation appears to be the most important point to clarify the role of a GVUS but not the only one. Accordingly, guidelines recommend genetic test in minimum 3 generations of the same family [35].

Currently, the main goal of CPVT genetic analysis is to perform a diagnosis, confirm a clinically suspected case of CPVT and establish the genotype [36]. Complex genetic studies in combination with bioinformatics analyses performed in CPVT families focus on elucidating the mechanisms that could explain phenotype variability and risk stratification. However, both incomplete penetrance and variable expressivity are still hallmarks of CPVT [37]. Regarding potential genetic alterations that could help to clarify these facts, in families diagnosed of CPVT, compound forms (more than one PGV in one gene) have been reported in RyR2 and CASQ2 [38,39], but these forms do not seem to be associated with a more severe CPVT phenotype. To our knowledge, no digenic (more than one PGV in two or more different genes) forms have been reported to date in any of genes associated with the disease. In addition, CNV have also been associated with CPVT but only in the RyR2 gene [19,20]. So far, no risk stratification has been established in CPVT patients regarding genetics. Preliminary data suggest that patients carrying a RYR2 PGV in the C-terminal channel-forming
domain may be at greater arrhythmic risk and, in consequence of SCD, than those carrying a RYR2 PGV in the N-terminal domain [40].

Conclusion

CPVT is a lethal cardiac arrhythmia, being sudden death the first manifestation of the disease relatively frequent. Early diagnosis is crucial considering the very high risk of death in untreated patients. To date, genetic analysis of 5 genes associated with CPVT identifies the cause of the arrhythmia in nearly 65% of families. Despite recent advances in genetics, pathophysiology, and clinical characteristics of CPVT, further research in unraveling molecular basis and clinical translation should be performed.

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References


