Catecholaminergic Polymorphic Ventricular Tachycardia

Synonyms: Catecholamine-Induced Polymorphic Ventricular Tachycardia (CPVT), Familial Polymorphic Ventricular Tachycardia (FPVT)

Carlo Napolitano, MD, PhD
Molecular Cardiology Laboratories
IRCCS Fondazione Salvatore Maugeri
Pavia, Italy
carlo.napolitano@fsm.it

Silvia G Priori, MD, PhD
Associate Professor of Cardiology
Director, Molecular Cardiology Laboratories
IRCCS Fondazione Salvatore Maugeri University of Pavia
Pavia, Italy
silvia.priori@fsm.it

Raffaella Bloise, MD
Molecular Cardiology Laboratories
IRCCS Fondazione Salvatore Maugeri
Pavia, Italy
raffaella.bloise@fsm.it

Initial Posting: October 14, 2004; Last Update: March 6, 2014.

Summary

Clinical characteristics. Catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterized by episodic syncope occurring during exercise or acute emotion in individuals without structural cardiac abnormalities. Arrhythmias may be well tolerated, with only mild symptoms such as dizziness or lypothymia. The underlying cause of these episodes is the onset of fast ventricular tachycardia (bidirectional or polymorphic). Spontaneous recovery occurs when these arrhythmias self-terminate. In other instances, ventricular tachycardia may degenerate into ventricular fibrillation and cause sudden death if cardiopulmonary resuscitation is not readily available. The mean age of onset of symptoms (usually a syncopal episode) of CPVT is between age seven and twelve years; onset as late as the fourth decade of life has been reported. If untreated, CPVT is highly lethal, as approximately 30% of affected individuals experience at least one cardiac arrest and up to 80% one or more syncopal spells. Sudden death may be the first manifestation of the disease.

Diagnosis/testing. The resting electrocardiogram is usually normal. The most important diagnostic test is the exercise stress test, which can reproducibly evoke the typical ventricular tachycardia during acute adrenergic activation (e.g., exercise, acute emotion). The bidirectional tachycardia is defined as a ventricular arrhythmia with an alternating 180°-QRS axis on a beat-to-beat basis; some individuals may have polymorphic VT without a "stable" QRS
vector alternans. The onset of arrhythmias during exercise occurs at a heart rate threshold of 100-120 beats per minute and the arrhythmias tend to worsen with increasing workload. Mutation in four genes – *RYR2*, *CASQ2*, *TRDN*, and *CALM1* – is known to cause CPVT or related phenotypes of adrenergically induced life-threatening arrhythmias. The presence of other as-yet unidentified loci is postulated.

**Management.** *Treatment of manifestations:* The use of beta-blockers is the mainstay of CPVT therapy. Although there are no comparative studies, the majority of international referral centers use nadolol (1-2.5 mg/kg/day divided into two doses per day) or propranolol (2-4 mg/kg/day divided into 3-4 doses per day). Non-selective beta-blockers are recommended in all cases in the absence of contraindications (e.g., asthma). Reproducible induction of arrhythmia during exercise allows titration and monitoring of the dose of beta-blockers. When there is evidence of incomplete protection (recurrence of syncope or complex arrhythmias during exercise) with beta blockers, flecainide (100-300 mg/day) should be added. Beta-blockers and flecainide are also indicated for affected individuals who have experienced a previous aborted sudden death. An implantable cardioverter defibrillator (ICD) may be necessary for those with recurrent cardiac arrest while on beta-blocker therapy or for those unable to take beta-blockers. Pharmacologic therapy should be maintained/optimized even in individuals with an ICD in order to reduce the probability of ICD firing. Left cardiac sympathetic denervation (LCSD) can be considered in those who are refractory to other therapies or in those who are intolerant of or have contraindications to beta-blocking therapy; however, due to side effects and recurrence of cardiac events in those with LCSD, pharmacologic therapy should always be optimized prior to considering LCSD.

**Prevention of primary manifestations:** Beta-blockers are indicated for all clinically affected individuals and for individuals with a *RYR2* pathogenic variant with no history of cardiac events (syncope) or ventricular arrhythmias on exercise stress testing, since sudden death can be the first manifestation of the disease. Flecainide can be added for primary prevention of a cardiac arrest when beta-blockers alone cannot control the onset of arrhythmias during exercise stress test.

**Prevention of secondary complications:** To avoid exacerbation of allergic asthma, use of the cardiac-specific beta-blocker, metoprolol, may be used; the dose is based on the need of the affected individual (≤3 mg/kg). Anticoagulation may be necessary for some persons with an ICD.

**Surveillance:** Follow-up visits with a cardiologist every six to twelve months (depending on disease severity) to monitor the efficacy of therapy; the limit for any allowed physical activity can be defined on the basis of exercise stress test done in the hospital setting; the use of commercially available heart rate monitoring devices for sports participation can be helpful in keeping the heart rate in a safe range during physical activity but should not be considered as an alternative to medical follow-up visits.

**Agents/circumstances to avoid:** Competitive sports and other strenuous exercise; digitalis.

**Evaluation of relatives at risk:** Because treatments and surveillance are available to reduce morbidity and mortality in individuals known to have the disease-causing allelic variant(s), first-degree relatives of a proband should be offered molecular genetic testing if the family-specific pathogenic variant(s) are known; if the family-specific variant(s) are not known, all first-degree relatives of an affected individual should be evaluated with resting
ECG, Holter monitoring, and, most importantly, with exercise stress testing.

**Genetic counseling.** Autosomal dominant CPVT: *RYR2*- and *CALM1*-related CPVT are inherited in an autosomal dominant manner. Each child of an individual with autosomal dominant CPVT has a 50% chance of inheriting the pathogenic variant.

Autosomal recessive CPVT: *CASQ2*- and *TRDN*-related CPVT are inherited in an autosomal recessive manner. The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele. Minor abnormalities (rare and benign arrhythmias) have been reported in heterozygotes in anecdotal cases. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

Prenatal testing for pregnancies at increased risk for some forms of CPVT is possible if the family-specific pathogenic variant(s) are known.

**Diagnosis**

**Clinical Diagnosis**

The diagnosis of catecholaminergic polymorphic ventricular tachycardia (CPVT) should be considered in individuals who have one or more of the following [Priori et al 2013a]:

- Exercise-induced polymorphic ventricular arrhythmias
  - ECG during a graded exercise (exercise stress test) allows ventricular arrhythmias to be reproducibly elicited in the majority of affected individuals. Typically, the onset of ventricular arrhythmias is 100-120 beats/min.
  - With increase in workload, the complexity of arrhythmias progressively increases from isolated premature beats to bigeminy and runs of non-sustained ventricular tachycardia (VT). If the affected individual continues exercising, the duration of the runs of VT progressively increases and VT may become sustained.
  - An alternating 180°-QRS axis on a beat-to-beat basis, so-called bidirectional VT, is often the distinguishing presentation of CPVT-related arrhythmias.
  - Some individuals with CPVT may also present with irregular polymorphic VT without a "stable" QRS vector alternans [Swan et al 1999, Priori et al 2002].
  - Exercise-induced supraventricular arrhythmias (supraventricular tachycardia and atrial fibrillation) are common [Leenhardt et al 1995, Fisher et al 1999].
• Syncope occurring during physical activity or acute emotion; mean onset age seven to twelve years. Less frequently, first manifestations may occur later in life; individuals with first event up to age 40 years are reported.

• Ventricular fibrillation occurring in the setting of acute stress.

• History of exercise or emotion-related palpitations and dizziness in some individuals

• Absence of structural cardiac abnormalities

• Sudden unexpected cardiac death triggered by acute emotional stress or exercise

Note: The resting ECG of individuals with CPVT is usually normal, although some authors have reported a lower-than-normal resting heart rate [Postma et al 2005] and others have observed a high incidence of prominent U waves [Leenhardt et al 1995, Aizawa et al 2006]. Overall these features are inconstant and not sufficiently specific to allow diagnosis. Therefore, in many instances, the origin of the syncope may be erroneously attributed to a neurologic disorder. The exercise stress test is the single most important diagnostic test. In the present authors’ series, the mean time interval to diagnosis after the first symptom was 2±0.8 years [Priori et al 2002].

**Molecular Genetic Testing**

**Genes.** The four genes in which mutation is known to cause CPVT are:

• *RYR2* (autosomal dominant), encoding the cardiac ryanodine receptor channel [Laitinen et al 2001, Priori et al 2001b];

• *CASQ2* (autosomal recessive), encoding calsequestrin, a calcium buffering protein of the sarcoplasmic reticulum (SR) [Lahat et al 2001];

• *TRDN* (autosomal recessive), encoding triadin, a CASQ2 and RyR2 partner protein that regulates sarcoplasmic reticulum calcium release [Roux-Buisson et al 2012];

• *CALM1* (autosomal dominant), encoding calmodulin [Nyegaard et al 2012].

**Evidence for further locus heterogeneity.** Because causative allelic variants are identified in only approximately 55%-65% of individuals with CPVT [Ackerman et al 2011], it is likely that other genes (loci) contribute to disease pathogenesis. A CPVT-like locus has been identified on chromosome 7p14-p22 but screening of candidate genes in the region has not revealed a disease-associated gene [Bhuiyan et al 2007].

• *ANKB*. A pathogenic variant in *ANKB*, the gene encoding ankyrin-B, was reported in a single individual with polymorphic ventricular tachycardia similar to CPVT [Mohler et al 2004]. The role of *ANKB* mutation in causing CPVT has yet to be elucidated.
- **KCNJ2.** Some authors have claimed that KCNJ2 variants responsible for Andersen-Tawil syndrome (ATS) may also cause CPVT; however, ATS is a distinct disorder (see Differential Diagnosis).

**Clinical testing**

**Table 1.**

Summary of Molecular Genetic Testing Used in Catecholaminergic Polymorphic Ventricular Tachycardia

<table>
<thead>
<tr>
<th>Gene</th>
<th>Proportion of All CPVT</th>
<th>Test Method</th>
<th>Allelic Variants Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>RYR2</td>
<td>50%-55% 4</td>
<td>Sequence analysis / mutation scanning 5 of select exons 6</td>
<td>Sequence variants in select exons 7, 8, 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sequence analysis of entire coding region 10</td>
<td>Sequence variants 7, 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion/duplication analysis 11</td>
<td>Unknown 12</td>
</tr>
<tr>
<td>TRDN</td>
<td>Unknown</td>
<td>Sequence analysis / mutation scanning of entire coding region</td>
<td>Sequence variants 7, 13</td>
</tr>
<tr>
<td>CASQ2</td>
<td>2%-5%</td>
<td>Sequence analysis</td>
<td>Sequence variants 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion/duplication analysis 11</td>
<td>Unknown; none detected 14</td>
</tr>
<tr>
<td>CALM1</td>
<td>&lt;1% 15</td>
<td>Sequence analysis</td>
<td>Sequence variants 7</td>
</tr>
</tbody>
</table>

1. See Table A. Genes and Databases for chromosome locus and protein.
2. In individuals meeting diagnostic criteria (see Clinical Diagnosis)
3. See Molecular Genetics for information on allelic variants.
4. Priori et al [2002]
5. Sequence analysis and mutation scanning of the entire gene can have higher mutation detection frequencies; however, mutation detection rates for mutation scanning may vary considerably between laboratories depending on the specific protocol used.
6. Exons analyzed and detection rates may vary between laboratories.
7. Examples of pathogenic variants detected by sequence analysis may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
8. Sequence analysis of select exons has an average lower yield than does screening of the entire coding sequence.

9. Most RYR2 pathogenic variants seen in CPVT appear to cluster in specific regions of the gene: codons 2200-2500 (FKBP12.6 binding domain) or starting from codon 3700 (Ca\(^{2+}\) binding domain and transmembrane domain [C-terminus]). Therefore, some laboratories sequence only those exons encompassing these critical regions; however, a recent analysis showed that 24% of pathogenic variants occur outside such “canonical” clusters [Priori & Chen 2011].

10. Priori & Chen [2011]. Mutation detection frequency (i.e., the sensitivity of the test method to detect a pathogenic variant) is greater than 95%.

11. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.

12. Large genomic rearrangements have been reported [Marjamaa et al 2009, Medeiros-Domingo et al 2009].

13. Identified in two families: one 4-bp deletion, one nonsense variant and one missense variant.

14. No deletions or duplications of CASQ2 have been reported to cause isolated catecholaminergic polymorphic ventricular tachycardia. (Note: By definition, deletion/duplication analysis identifies rearrangements that are not identifiable by sequence analysis of genomic DNA.)

15. Estimated from the data provided in the only paper available [Nyegaard et al 2012]

**Interpretation of test results.** Typically, sequence analysis cannot detect exon/multiexon deletions, duplications, or splice variants resulting in (multi)exon skipping.

**Test characteristics.** See Clinical Utility Gene Card [Napolitano et al 2014] for information on test characteristics including sensitivity and specificity.

**Testing Strategy**

**To confirm/establish the diagnosis in a proband.** Molecular genetic testing is indicated in individuals with CPVT.

**Single gene testing.** In those without a family history strongly suggestive of an autosomal recessive pattern of transmission:

- Mutation of RYR2 is by far the most prevalent cause of CPVT and should be evaluated first EITHER:
  - By sequence analysis of select exons followed by sequence analysis of the entire coding region if an RYR2 pathogenic allelic variant is not identified (approximately 20%-25% of mutations occur outside the known mutation clusters [Priori & Chen 2011]).
  OR
By sequence analysis of the entire coding region.

- If a pathogenic variant in \textit{Ryr2} is not identified in an individual with CVPT who represents a simplex case (i.e., the only affected person in the family) sequence analysis of \textit{Casq2} can be performed.

- If no pathogenic variant is found in \textit{Ryr2} or \textit{Casq2}, sequence analysis of \textit{Trdn} and/or deletion/duplication analysis of \textit{Ryr2} can be considered.

- \textit{Calm1} has been associated with autosomal dominant stress-induced arrhythmias and sudden death (typical CPVT arrhythmias are not clearly reported in those with \textit{Calm1} pathogenic variants). Thus, \textit{Calm1} screening may be indicated in simplex cases and in families with CPVT in which no \textit{Ryr2} pathogenic variant has been identified.

In those with a family history that is consistent with autosomal recessive inheritance:

- Sequence analysis of \textit{Casq2} and \textit{Trdn} should be performed first.

- If only one pathogenic allelic variant in \textit{Casq2} is identified through sequencing, deletion/duplication analysis of \textit{Casq2} can be considered.

**Multi-gene panel.** Another strategy for molecular diagnosis of a proband suspected of having CPVT is use of a multi-gene panel. The genes included and the methods used in multi-gene panels vary by laboratory and over time; a panel may not include a specific gene of interest. See Differential Diagnosis.

**Molecular genetic testing** may be indicated in individuals who do not have CPVT but have findings (or have a relative with findings) that could be related to CPVT, including the following:

- Idiopathic ventricular fibrillation, which may be caused by CPVT

- Family members of individuals with sudden unexplained death occurring during acute stress [Priori & Chen 2011]. Note: The yield of the analysis in these cases is unknown (and probably low).

- SIDS (sudden infant death syndrome), which has been associated with mutation of \textit{Ryr2} [Tester et al 2007]. However, it is unclear whether systematic \textit{Ryr2} screening is indicated and cost effective for this population [Ackerman et al 2011].

It is important that genetic testing of first-degree relatives be offered when the pathogenic variant(s) are identified in a proband (see Evaluation of Relatives at Risk).

*Genetically Related (Allelic) Disorders*
Although some have suggested that arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) may be caused by \textit{RYR2} mutation in a few cases (designated ARVC2) that present with mild or "concealed" right ventricular myocardium abnormalities [Tiso et al 2001], these observations have not been confirmed by others. However, some \textit{RYR2} pathogenic allelic variants have been associated with cardiomyopathies and ventricular non-compaction and appear to have different pathophysiologic mechanisms [Tang et al 2012, Ohno et al 2014]. The lack of systematic assessments in large populations makes it difficult to quantify the clinical relevance of these findings.

No phenotypes other than those discussed in this \textit{GeneReview} are known to be associated with mutation of \textit{TRDN} or \textit{CASQ2}.

\textbf{CALM1}

- \textit{CALM1} promoter variants have been associated with osteoarthritis in the Japanese population [Mototani et al 2005].
- A \textit{CALM1} pathogenic variant was also reported in a case of ventricular arrhythmias associated with QT prolongation, epilepsy, and neurodevelopmental disorders [Crotti et al 2013]. This phenotype is compatible with the wide expression pattern of \textit{CALM1} and the finding suggests that mutation of \textit{CALM1} causes an atypical form of CPVT.

\textbf{Clinical Characteristics}

\textbf{Clinical Description}

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmogenic disease characterized by cardiac electrical instability exacerbated by acute activation of the adrenergic nervous system. If untreated the disease is highly lethal, as approximately 30% of those affected experience at least one cardiac arrest and up to 80% one or more syncopal spells. Two clinical studies [Leenhardt et al 1995, Priori et al 2002] have contributed to the understanding of the natural history of CPVT. The main clinical manifestation of CPVT is episodic syncope occurring during exercise or acute emotion. The underlying cause of these episodes is the onset of fast ventricular tachycardia (bidirectional or polymorphic). Spontaneous recovery occurs when these arrhythmias self-terminate. In other instances, ventricular tachycardia may degenerate into ventricular fibrillation and cause sudden death if cardiopulmonary resuscitation is not readily available. Sudden death may be the first manifestation of the disease. Of note: As there is no structural abnormality of the myocardium, several individuals have tolerated the arrhythmias rather well, with only mild symptoms such as dizziness or lypothymia. If such symptoms reproducibly recur during exercise, further clinical investigations for CPVT may be indicated.

CPVT is a cause of "idiopathic" ventricular fibrillation in previously asymptomatic individuals (no history of syncope or dizziness) who die suddenly during exercise or while experiencing acute emotions. Growing evidence shows that sudden cardiac death can be the first manifestation of CPVT caused by mutation of \textit{RYR2} [Priori et al 2002, Krahn et al 2005].
The mean age of onset of CPVT symptoms (usually a syncopal episode) is between age seven and twelve years [Leenhardt et al 1995, Priori et al 2002, Postma et al 2005]; onset as late as the fourth decade of life has been reported.

Instances of SIDS (sudden infant death syndrome) have been associated with mutation of RYR2 [Tester et al 2007]. Others have suggested that mutation of RYR2 may underlie near-drowning or drowning, especially after the exclusion of the diagnosis of long QT syndrome type 1 [Choi et al 2004]. Family history of sudden death in relatives under age 40 years is present in approximately 30% of probands with CPVT [Priori et al 2002].

**Genotype-Phenotype Correlations**

Available evidence suggests that the clinical features of CASQ2- and RYR2-related CPVT are virtually identical. Lahat et al [2001] reported a mild QT interval prolongation in their initial paper; however, this was not confirmed in subsequent reports [Postma et al 2002].

At present no data support a role for genotype in risk stratification and management. Usually CASQ2 pathogenic variants appear more severe and more resistant to beta-blockers. Individuals with polymorphic VT without a "stable" QRS vector alternans are more likely to have pathogenic variants in CASQ2.

Priori et al [2002] and Lehnart et al [2004] reported genotype-phenotype correlations by comparing the clinical characteristics of affected individuals with and without RYR2 pathogenic variants. These data show the following:

- The natural history of the disease does not appear to differ when affected individuals with and without RYR2 pathogenic variants are compared.
- The average age of onset of the disease in both study groups (i.e., age of the first syncope) is seven to twelve years

The mutation-specific clinical course of CPVT was analyzed by Lehnart et al [2004], who did not find a significant difference in mortality rates or pattern of arrhythmias among a small cohort of individuals with the RYR2 pathogenic variants p.Pro2328Ser, p.Gln4201Arg, and p.Val4653Phe.

Only two CALM1 pathogenic variants have been described: in a large family with stress-induced sudden death and arrhythmias and in a simplex case with suspected CPVT, arrhythmias, and RYR2 screening that did not identify a pathogenic variant [Nyegaard et al 2012]. No clear bi-directional pattern of ventricular arrhythmias as described in typical CPVT [Leenhardt et al 1995] was shown; thus, the clinical phenotype of individuals with CALM1 pathogenic variants may be slightly different from that of typical CPVT (see Genetically Related Disorders). This observation awaits confirmation.

**Penetrance**

The mean penetrance of RYR2 pathogenic variants is 83% [Author, unpublished data]. Therefore, asymptomatic individuals with RYR2-related CPVT are
a minority.

**Anticipation**

Anticipation has not been reported.

**Prevalence**

The true prevalence of CPVT in the population is not known. An estimate of CPVT prevalence is 1:10,000.

The high prevalence of simplex cases (i.e., single occurrences in a family) and lethality at a young age suggest that the overall prevalence of CPVT is significantly lower than that of other inherited arrhythmogenic disorders such as long QT syndrome (1:7,000-1:5,000).

**Differential Diagnosis**

Given the absence of structural cardiac abnormalities, individuals presenting with cardiac arrest could be misclassified as having "idiopathic ventricular fibrillation" [Priori et al 2001a]. Therefore, if a careful analysis of the factors triggering ventricular fibrillation in an otherwise healthy individual indicates a possible causative role for adrenergic stimuli (e.g., cardiac arrest occurring in the setting of acute stresses such as fear or anger), catecholaminergic polymorphic ventricular tachycardia (CPVT) should be considered in the differential diagnosis (see Testing Strategy).

Cardiac evaluation (including an exercise stress test to unmask CPVT arrhythmias) of relatives of persons dying a sudden cardiac death may reveal the underlying disease and identify asymptomatic family members at risk for cardiac events [Tan et al 2005]. The yield of genetic testing in relatives is yet to be established. However, it is justified to consider the diagnosis of CPVT (and to consider genetic testing) in cases of sudden cardiac death or aborted cardiac arrest occurring during acute stress (see Testing Strategy).

The presence/absence of structural abnormalities of the right ventricle (right ventricle enlargement, fibro-fatty infiltrations) must be evaluated in all individuals with *RYR2* pathogenic variants in order to exclude the presence of a rare variant and “atypical” form of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVDC2) allelic to *RYR2*-related CPVT (see Genetically Related Disorders). Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC) presents with structural abnormalities (dilatation, increased fibrosis/fat, micro-aneurysms) of the right ventricle. Typical ARVC is caused by mutation of genes that code for desmosomal proteins. *RYR2* pathogenic variants have been found in few (<5) families labeled as ARVC. However, in all cases the structural abnormalities were atypical and very mild. This raises the unresolved question of whether *RYR2*-ARVC is a real clinical entity or an incorrect classification of some families with CPVT who have unspecific abnormalities of the right ventricle.

Short-coupled ventricular tachycardia (SC-TdP) is a clinical entity presenting with life-threatening polymorphic ventricular arrhythmias resembling in part the pattern of arrhythmias observed in individuals with CPVT. SC-TdP presents with polymorphic VT occurring in the setting of a structurally normal heart and in the absence of any overt baseline electrocardiographic abnormality. However, the onset of SC-TdP is not clearly related to
adrenergic stimuli (exercise or emotion) and is not associated with the typical bidirectional pattern of CPVT-related tachycardia. Distinguishing between the two disorders is important as there is no known effective therapy for SC-TdP, whereas CPVT usually responds to beta-blocking agents.

Exercise-related syncope is also typically found in the LQT1 variant of long QT syndrome. Since incomplete penetrance is possible in LQT1, some individuals may have a normal QT interval and may therefore appear to have the typical CPVT clinical presentation (exercise-related syncope and normal ECG). However, individuals with LQT1 do not usually show any inducible arrhythmia during graded exercise (exercise stress test). The initial description of CPVT by Philippe Coumel included cases with borderline or mildly prolonged QT interval. For this reason it has been suggested that an overlap phenotype (LQTS-CPVT) is possible. This hypothesis has not been thoroughly investigated.

A possible parallelism between CPVT and Andersen-Tawil syndrome (ATS), an inherited arrhythmogenic disorder caused by mutation of KCNJ2, has been reported. ATS is characterized by cardiac (QT prolongation, prominent U waves) and extra-cardiac features (distinctive facial features, periodic paralysis). The present authors and others [Postma et al 2006, Tester et al 2006] have observed that some individuals with ATS may develop bidirectional VT similar to that of CPVT. However, ATS is to be considered as a distinct disorder with manifestations that may overlap with CVPT in rare instances. In ATS the presence of extracardiac manifestations, the low or absent risk of sudden death, and the lack of a direct relationship of arrhythmias to adrenergic activation distinguish it from CPVT.

### Management

#### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with catecholaminergic polymorphic ventricular tachycardia (CPVT), the following evaluations are recommended:

- Resting ECG
- Holter monitoring, as arrhythmias develop when heart rate increases
- Exercise stress test both for diagnosis and monitoring of therapy
- Echocardiogram to evaluate for structural defects
- Medical genetics consultation

Note: Although the association between RYR2 pathogenic variants and arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) has not been conclusively established, cardiac echo and/or nuclear magnetic resonance may be indicated to assess structural abnormalities in the right ventricle.
Treatment of Manifestations

Management of CPVT is summarized in a recent consensus document from the Heart Rhythm Association (HRS) and the European Heart Rhythm Association (EHRA) [Priori et al 2013b] (full text).

**Beta-blockers** are the first therapeutic choice of proven efficacy for about 60% of individuals with CPVT [Leenhardt et al 1995, Priori et al 2002]. Beta-blockers antagonize the effect of catecholamines by reducing heart rate and by a direct electrophysiologic effect at the myocyte level. The proposed mechanism of action on an individual with CPVT is inhibition of adrenergic-dependent triggered activity. This effect can be due to both heart rate reduction and direct effect on calcium release from the sarcoplasmic reticulum. Chronic treatment with full-dose beta-blocking agents prevents recurrence of syncope in the majority of affected individuals.

The reproducible induction of arrhythmia during exercise allows effective dose titration and monitoring. Recommended drugs are nadolol (1-2.5 mg/kg/day divided into two doses per day) or propranolol (2-4 mg/kg/day divided into 3-4 doses per day), because of long-standing experience with their use in inherited arrhythmogenic diseases. Non-selective beta-blockers are recommended in all cases in the absence of contraindications (e.g. asthma), although no comparative clinical trials are available. The above-mentioned doses are those most widely used; however, the dose of beta-blockers should always be individualized, if possible, until arrhythmias are not inducible on exercise stress testing.

It is important to note that efficacy needs to be periodically retested [Heidbuchel et al 2006] (see Surveillance).

**Flecainide.** Clinical [van der Werf et al 2011] and experimental [Liu et al 2011] data show that to improve arrhythmia control, flecainide (100-300 mg/day) can be given along with beta-blockers to persons who are not responsive to beta-blockers alone (i.e., persons who have recurrence of syncope or complex arrhythmias during exercise). Although controlled clinical trials are lacking, the evidence for effectiveness of flecainide is sufficient to indicate the use of this drug whenever beta-blockers are not sufficient to control arrhythmias. Beta-blockers and flecainide are also indicated for affected individuals who have experienced a previous aborted sudden death.

**Implantable cardioverter defibrillator (ICD).** Although beta-blockers have been reported to be highly effective [Postma et al 2005], an implantable cardioverter defibrillator (ICD) may become necessary for secondary prevention of recurrent cardiac arrest. Furthermore, in those individuals in whom the highest tolerated dose of beta-blockers fails to adequately control arrhythmias [Priori et al 2002, Sumitomo et al 2003], an ICD can be considered for primary prevention of cardiac arrest/sudden death [Zipes et al 2006]. Whenever possible pharmacologic therapy should be maintained/optimized even in individuals with ICD in order to reduce the probability of ICD firing.

**Left cardiac sympathetic denervation (LCSD)** may be considered in those with a diagnosis of CPVT who experience recurrent syncope, polymorphic/bidirectional VT, or several appropriate ICD shocks while on beta-blocking agents and in those who are intolerant of or with contraindication to beta-blocker therapy [Priori et al 2013a, Priori et al 2013b]. However, LCSD is not without side effects, including palpebral ptosis, elevation of the left hemidiaphragm, and lack of sweating from the left arm and face. Recurrences of cardiac events have been also reported in those with
LCSD. Therefore, pharmacologic therapy should be always optimized prior to considering LCSD.

**Prevention of Primary Manifestations**

Beta-blockers are indicated for primary prevention in all clinically affected individuals (see Treatment of Manifestations). Although no quantitative data on actual risk for cardiac arrest as the first manifestation of the disease are available, this treatment is probably also indicated for individuals with an RYR2 pathogenic variant and no history of cardiac events (syncope) or no ventricular arrhythmias on exercise stress testing. Recommended drugs are nadolol (1-2.5 mg/kg/day) or propranolol (2-4 mg/kg/day). For symptomatic individuals with CPVT, the maximum tolerated dosage should be maintained. Flecainide can be added for primary prevention of a cardiac arrest when beta-blockers alone cannot control the onset of arrhythmias during exercise stress test.

**Prevention of Secondary Complications**

Secondary complications are mainly related to therapy.

Beta-blockers could worsen allergic asthma. Therefore, the cardiac-specific beta-blocker, metoprolol, could be indicated in some individuals with CPVT who have a history of asthma. The dose of metoprolol is based on the need of the affected individual (≤3 mg/kg). Note: It is important to keep in mind that metoprolol and newer beta-blockers (e.g., bisoprolol) may not have the same efficacy as nadolol and/or propranolol; the reasons for this are under investigation.

For persons with an ICD, anticoagulation to prevent formation of thrombi may be necessary (particularly in children who require looping of the right ventricular catheter).

**Surveillance**

Regular follow-up visits every six to 12 months (depending on the severity of clinical manifestations) are required in order to monitor therapy efficacy. These visits should include the following:

- Resting ECG
- Exercise stress test, performed at the maximal age-predicted heart rate. For individuals on beta-blocker therapy (in whom maximal heart rate cannot be reached), the test should be performed at least at the highest tolerated workload.
- Holter monitoring

The limit for any allowed physical activity can be defined on the basis of exercise stress test done in the hospital setting; the use of commercially
available heart rate monitoring devices for sports participation can be helpful in keeping the heart rate in a safe range during physical activity but should not be considered as an alternative to medical follow-up visits.

**Agents/Circumstances to Avoid**

Competitive sports and other strenuous exercise are always contraindicated. All individuals showing exercise-induced arrhythmias should avoid physical activity, with the exception of light training for those individuals showing good suppression of arrhythmias on exercise stress testing while on therapy. It is important to note that efficacy needs to be periodically retested [Heidbuchel et al 2006].

A single case report highlighted the possible proarrhythmic effect of an insulin tolerance test (ITT), driven by severe hypokalemia and adrenergic activation secondary to the metabolic imbalance induced by the test [Binder et al 2004].

Digitalis favors the onset of cardiac arrhythmias due to delayed afterdepolarization (DAD) and triggered activity; therefore digitalis should be avoided in all individuals with CPVT.

**Evaluation of Relatives at Risk**

Because treatment and surveillance are available to reduce morbidity and mortality, first-degree relatives should be offered clinical work up and molecular genetic testing if the family-specific pathogenic allelic variant(s) are known. Indeed the availability of effective preventive therapies can reduce the number of fatal arrhythmic events if individuals with pathogenic variants are diagnosed early.

If the family-specific pathogenic variant(s) are not known, all first-degree relatives of an affected individual should be evaluated with resting ECG, Holter monitoring, and – most importantly – exercise stress testing.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

**Pregnancy Management**

Beta-blockers (preferentially nadolol or propranolol) should be administered throughout pregnancy in affected women.

**Therapies Under Investigation**

A clinical trial is ongoing to evaluate the effectiveness and safety of flecainide in CPVT (NCT01117454). However, clinical experience with flecainide is sufficient to allow for its use in a clinical setting.

**Additional pharmacologic treatments.** Additional pharmacologic treatment has been proposed for CPVT, but in the past failures with sodium channel blockers [Leenhardt et al 1995, Sumitomo et al 2003] and amiodarone [Leenhardt et al 1995] have been reported. Other authors have reported partial
effectiveness with verapamil [Sumitomo et al 2003, Swan et al 2005]. However, these reports remain anecdotal and have not been independently confirmed. Furthermore, the effect of chronic treatment with high doses of beta-blockers and calcium antagonists on cardiac contractility in children is not known. At present, calcium antagonists cannot be considered an alternative for persons unresponsive to ICDs.

JTV519 (also known as K201) is an experimental drug that stabilizes the ryanodine receptor and has proven to be effective in vitro in counteracting the RyR2 channel instability caused by some CPVT-causing variants [Lehnart et al 2004]. However, experimental data obtained in a CPVT mouse model do not support a significant antiarrhythmic effect with this drug [Liu et al 2006].

Adeno-associated (AAV9) viral gene transfer of wild type CASQ2 has been shown to be effective in completely abolishing CPVT arrhythmias up to one year after infection in a recessive CPVT mouse model. Since this vector is already available for human use, gene therapy of recessive CPVT may become available in the future [Denegri et al 2012, Liu et al 2013].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

**Genetic Counseling**

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

**Mode of Inheritance**

*RYR2*- and *CALM1*-related catecholaminergic polymorphic ventricular tachycardia (CPVT) are inherited in an autosomal dominant manner.

*CASQ2*-related CPVT and *TRDN*-related CPVT are inherited in an autosomal recessive manner.

One or more additional CPVT-related genes probably exist, pathogenic variants in which may be inherited in an autosomal recessive or an autosomal dominant manner.

**Risk to Family Members — Autosomal Dominant CPVT**

**Parents of a proband**

- Approximately 50% of individuals with autosomal dominant CPVT have an affected parent.
- A proband with autosomal dominant CPVT may have the disorder as the result of *de novo* mutation. Accurate data on the prevalence of *de novo*
*RYR2* pathogenic variants are not available but they are estimated at approximately 40%. This finding suggests that some probands with *RYR2*-related CPVT do not reach reproductive age.

- Recommendations for the evaluation of parents of a proband with an apparent de novo pathogenic variant include a maximal exercise stress test and molecular genetic testing if the variant has been identified in the proband.

Note: Although approximately 50% of individuals diagnosed with autosomal dominant CPVT have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or reduced penetrance.

**Sibs of a proband**

- The risk to the sibs of a proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- If a pathogenic variant cannot be detected in the DNA extracted from the leukocytes of either parent, two possible explanations are germline mosaicism in a parent or de novo mutation in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.

**Offspring of a proband.** Each child of an individual with autosomal dominant CPVT has a 50% chance of inheriting the pathogenic variant.

**Other family members of a proband.** The risk to other family members depends on the genetic status of the proband's parents. If a parent is affected, his or her family members are at risk.

**Risk to Family Members — Autosomal Recessive CPVT**

**Parents of a proband**

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic. Minor abnormalities (rare and benign arrhythmias) have been reported in anecdotal cases.
- It is possible (although likely rare) that one or both parents of a proband is actually themselves affected. Therefore, a maximal exercise stress test and molecular genetic testing can be considered for the parents of a proband with autosomal recessive CPVT.

**Sibs of a proband**
At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being neither affected nor a carrier.

Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.

Heterozygotes (carriers) are usually asymptomatic. Minor abnormalities (rare and benign arrhythmias) have been reported in anecdotal cases.

**Offspring of a proband.** The offspring of an individual with autosomal recessive CPVT are obligate heterozygotes (carriers) for a pathogenic variant in *CASQ2* or *TRDN*.

**Other family members of a proband.** Each sib of the proband's parents is at a 50% risk of being a carrier.

**Carrier Detection**

Carrier testing for at-risk family members is possible if the pathogenic variants in the family are known.

**Related Genetic Counseling Issues**

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

**Considerations in families with an apparent de novo pathogenic variant.** When neither parent of a proband with an autosomal dominant condition has the pathogenic variant or clinical evidence of the disorder, it is likely that the proband has a de novo pathogenic variant or less likely that a parent has germline mosaicism. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

**Testing of asymptomatic at-risk family members.** Testing of asymptomatic at-risk family members for CPVT is possible using the techniques described in Molecular Genetic Testing. Although this testing is not useful in predicting age of onset, severity, or specific symptoms that may occur in asymptomatic individuals, it does allow for initiation of treatment and surveillance. When testing at-risk individuals for CPVT, an affected family member should be tested first to identify the specific pathogenic variant(s).

**Family planning**

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.
DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing

If the pathogenic variant(s) have been identified in an affected family member, prenatal testing for pregnancies at increased risk may be available from a clinical laboratory that offers either testing for this disease/gene or custom prenatal testing.

Requests for prenatal testing for conditions such as CPVT are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be an option for families in which the pathogenic variant(s) have been identified.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Heart Association (AHA)**
  
  7272 Greenville Avenue  
  Dallas TX 75231  
  **Phone:** 800-242-8721 (toll-free)  
  **Email:** review.personal.info@heart.org  
  Ventricular Tachycardia

- **Canadian SADS Foundation**
  
  9-6975 Meadowvale Town Centre Circle  
  Suite 314  
  Mississauga Ontario L5N 2V7  
  **Phone:** 877-525-5995 (toll-free); 905-826-6303
Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A.

Catecholaminergic Polymorphic Ventricular Tachycardia: Genes and Databases

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome Locus</th>
<th>Protein</th>
<th>Locus Specific</th>
<th>HGMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>RYR2</td>
<td>1q43</td>
<td>Ryanodine receptor 2</td>
<td>Gene Connection for the Heart - Ryanodyne receptor mutation database RYR2 database</td>
<td>RYR2</td>
</tr>
<tr>
<td>CASQ2</td>
<td>1p13.1</td>
<td>Calsequestrin-2</td>
<td>CASQ2 database</td>
<td>CASQ2</td>
</tr>
<tr>
<td>TRDN</td>
<td>6q22.31</td>
<td>Triadin</td>
<td>TRDN homepage - Leiden Muscular Dystrophy pages</td>
<td>TRDN</td>
</tr>
</tbody>
</table>
**Molecular Genetic Pathogenesis**

*Ryr2, Casq2, Trdn, and Calm1* are involved in the control of intracellular calcium fluxes, sarcoplasmic reticulum calcium release, and the cytosolic free Ca\(^{2+}\) concentration.

The *Ryr2* pathogenic variants found in individuals with catecholaminergic polymorphic ventricular tachycardia (CPVT) have been shown to cause Ca\(^{2+}\) “leakage” from the sarcoplasmic reticulum (SR) in conditions of sympathetic (catecholamine) activation [Jiang et al 2002, George et al 2003, Wehrens et al 2003]. The consequent abnormal increase of the cytosolic free Ca\(^{2+}\) concentration creates an electrically unstable substrate. In a CPVT knock-in mouse model [Cerrone et al 2005, Liu et al 2006], it has been clearly shown that the pathogenesis of arrhythmias in CPVT is related to the onset of delayed afterdepolarizations (DADs) and triggered activity. Furthermore, cardiac cells isolated from mice with a pathogenic variant orthologous to the human p.Arg4497Cys (a typical and relatively common CPVT-causing allelic variant) present DAD also at baseline, suggesting that RyR2 function is also altered in the unstimulated setting.
In vitro expression of CASQ2 pathogenic variants has consistently shown an enhanced responsiveness of RyR2s to luminal Ca\(^{2+}\), which in turn leads to the generation of extrasystolic spontaneous Ca\(^{2+}\) transients, fragmented calcium waves DADs, and arrhythmogenic action potentials. This effect may be the result of altered Ca\(^{2+}\) buffering capacity of the calsequestrin polymer or impaired CASQ2-RyR2 interaction [Viatchenko-Karpinski et al 2004, di Barletta et al 2006].

Expression of the human TRDN p.Thr59Arg in COS-7 cells resulted in intracellular retention and degradation of the mutant protein. This was confirmed by in vivo expression of the mutant in triadin knock-out mice by viral transduction. The loss of triadin protein is likely to lead to the loss of control of RyR2 opening by CASQ2 (luminal calcium sensor). However, direct functional studies are lacking.

Only one study has assessed the effects of CALM1 pathogenic variants [Nyegaard et al 2012]; thus, the pathophysiology of CALM1-CPVT is largely unknown. Available data suggest that mutant CALM1 has reduced calcium binding affinity and impaired calmodulin-ryanodine receptor interaction at low calcium concentration. These effects may lead to RyR2 channel instability and “leakage” similar to that observed for RyR2 pathogenic variants.

**RYR2**

**Gene structure.** The RYR2 coding region encompasses 14901 nucleotides on 104 exons. For a detailed summary of gene and protein information, see Table A, Gene.

**Pathogenic allelic variants.** To date more than 150 RYR2 pathogenic variants causing CPVT have been reported [Priori & Chen 2011].

The majority of pathogenic variants appear to cluster in three regions of the predicted RyR2 protein topology: an FKBP12.6 (an RyR regulatory protein) -binding region (mid portion, intracytoplasmatic loop), a calcium-binding domain, and the transmembrane domain (C-terminus). However, a recent analysis showed that 24% of mutations occur outside such “canonical” clusters. Thus, complete sequencing of the coding region and flanking intronic regions is often needed [Priori & Chen 2011]. No mutation hot spots have been reported to date. See Table 2.

Table 2.

Selected RYR2 Pathogenic Variants

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Protein Amino Acid Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.6982C&gt;T</td>
<td>p.Pro2328Ser</td>
<td>NM_001035.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NP_001026.2</td>
</tr>
<tr>
<td>c.12602A&gt;G</td>
<td>p.Gln4201Arg</td>
<td></td>
</tr>
<tr>
<td>c.13489C&gt;T</td>
<td>p.Arg4497Cys</td>
<td></td>
</tr>
<tr>
<td>DNA Nucleotide Change</td>
<td>Protein Amino Acid Change</td>
<td>Reference Sequences</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>c.13957G&gt;T</td>
<td>p.Val4653Phe</td>
<td></td>
</tr>
</tbody>
</table>

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

**Normal gene product.** The ryanodine receptor (RyR2) is the main Ca\(^{2+}\)-releasing channel of the SR in the heart [George et al 2003]. It plays a central role in the so-called “calcium-induced calcium release” process that couples the electrical activation with the contraction phase of the cardiac myocytes. Following the Ca\(^{2+}\) entry through the voltage-gated channels of the plasmalemma, the ryanodine receptor releases the Ca\(^{2+}\) ions stored in the SR that are required for contraction of the muscle fibers.

**Abnormal gene product.** The calcium concentration gradient between the SR (in the mM range) and cytosol (in the nanomolar range) is remarkable. Thus, when RyR2 channels open, the Ca\(^{2+}\) ions may flow easily along their concentration gradient. Every condition that destabilizes the RyR2 structure may cause uncontrolled flux since the electrochemical calcium gradient is high. In vitro studies have shown that defective RyR2 proteins lose the capability to finely control the calcium release process upon adrenergic (catecholamine) stimulation. The presence of an abnormal RyR2 basal activity (i.e., Ca\(^{2+}\) leakage in unstimulated conditions) and an altered RyR2 binding with its regulatory subunit, FKBP12.6, has been postulated, but experimental data are contradictory. More recently the “store overload-induced calcium release” hypothesis has been put forth by Jiang et al [2004] and Jiang et al [2005]. According to their model, the effect of RYR2 pathogenic variants would be to reduce the amount of Ca\(^{2+}\) in the SR required to determine spontaneous spillover. This may be due to intramolecular domain-domain interaction as shown by George et al [2006] (and other authors) who demonstrated that mutant ryanodine receptor proteins promote weakened domain interaction (“unzipping”) and channel hyperactivation or hypersensitization. Finally, increased sensitivity (increased open probability at a given calcium concentration) to luminal or cytosolic calcium has been reported [Priori & Chen 2011].

**CASQ2**

**Gene structure.** The CASQ2 coding regions encompass 1197 nucleotides and 11 exons. For a detailed summary of gene and protein information, see Table A, *Gene*.

**Pathogenic allelic variants.** Fifteen CASQ2 pathogenic variants, all of which cause the clinical phenotype in homozygous or compound heterozygous forms, have been associated with CPVT. The latter occur in non-consanguineous parents [di Barletta et al 2006]. Heterozygotes for one CASQ2 pathogenic variant are usually healthy. See Table 3.
Table 3.

Selected CASQ2 Pathogenic Variants

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Protein Amino Acid Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.62delA</td>
<td>p.Glu21GlyfsTer15</td>
<td>NM_001232.3</td>
</tr>
<tr>
<td>c.97C&gt;T</td>
<td>p.Arg33Ter</td>
<td>NM_001232.3, NP_001223.2</td>
</tr>
<tr>
<td>c.919G&gt;C</td>
<td>p.Asp307His</td>
<td></td>
</tr>
</tbody>
</table>

Note on variant classification: Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants.

Note on nomenclature: GeneReviews follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. CASQ2 encodes for the cardiac isoform of calsequestrin, calsequestrin-2, an SR protein functionally and physically related to the ryanodine receptor. CASQ2 protein forms polymers at the level of the terminal cisternae of the SR in close proximity to the ryanodine receptor; its function is that of buffering the Ca^{2+} ions.

Abnormal gene product. Only one CASQ2 pathogenic variant has been functionally characterized in vitro. The available data suggest that the pathophysiology of CASQ2-related CPVT may be related to the following mechanisms: loss of polymerization of CASQ monomers, loss of calcium buffering capability, and indirect destabilization of the RyR channel opening process.

TRDN

Gene structure. The TRDN isoform 1 coding regions encompass 2190 nucleotides and 41 exons. For a detailed summary of gene and protein information, see Table A, Gene.

Pathogenic allelic variants. Three TRDN pathogenic variants, all of which cause the clinical phenotype in homozygous or compound heterozygous forms, have been associated with CPVT. See Table 4.

Table 4.

TRDN Pathogenic Allelic Variants
<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Protein Amino Acid Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.53_56delACAG</td>
<td>p.Asp18AlafsTer14</td>
<td>JN900469</td>
</tr>
<tr>
<td>c.176C&gt;G</td>
<td>p.Thr59Arg</td>
<td>CCDS55053.1</td>
</tr>
<tr>
<td>c.613C&gt;T</td>
<td>p.Gln205Ter</td>
<td></td>
</tr>
</tbody>
</table>

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. These variants have been found in the same patient, who was compound heterozygous.

**Normal gene product.** *TRDN*, on chromosome 6, encodes triadin (OMIM 603283), an SR protein functionally and physically related to the ryanodine receptor. Lack of triadin is associated with a reduction of CASQ2 protein levels and ultrastructural abnormalities of the T tubules similar to those observed in the *CASQ2* knock out. This affects the calcium release process and, more specifically, results in a calcium leak during diastole similar to that observed for *RYR2* mutants.

**Abnormal gene product.** Pathogenic variants in *TRDN* found in persons with CPVT (in 2 families) have been associated with a reduction of protein expression. Although functional studies are lacking it is possible that the loss of TRDN leads to an indirect destabilization of the RyR2 channel opening process similar to that observed for pathogenic variants in *CASQ2*.

**CALM1**

**Gene structure.** *CALM1* (NM_006888.4, cDNA 4268 bp) contains six exons spread over about 10 kb of genomic DNA on chromosome 14q32.11. Two additional homolog genes (*CALM2* and *CALM3*) are present in the human genome and appear to have similar function. For a detailed summary of gene and protein information, see Table A, *Gene*.

**Pathogenic allelic variants.** Only two *CALM1* pathogenic variants have been reported in a single study (see Table 5).

**Table 5.**

*CALM1* Pathogenic Variants Discussed in This *GeneReview*
<table>
<thead>
<tr>
<th>(Alias)</th>
<th>NM_006888.4</th>
<th>NP_008819.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.161A&gt;T p.Asn53Ile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.293A&gt;G p.Asn98Ser (Asn97Ser)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

**Normal gene product.** The gene encodes a 149-amino acid protein containing typical calcium binding sites (EF hands). Besides RyR2, CALM1 also interacts with the voltage dependent calcium channels (CaV1.3)

**Abnormal gene product.** Available data suggest that mutant CALM1 has reduced calcium binding affinity and impaired calmodulin-ryanodine receptor interaction at low calcium concentration. These effects may lead to RyR2 channel instability and “leakage” similar to that observed for mutant RyR2. Calmodulin is widely expressed (especially in the CNS) and extra-cardiac phenotypes can be expected (although poorly investigated so far).

**References**

**Published Guidelines / Consensus Statements**


**Literature Cited**

cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Europace. 2011;13:1077–109. [PubMed: 21810866]


47. Tester DJ, Arya P, Will M, Haglund CM, Farley AL, Makielski JC, Ackerman MJ. Genotypic heterogeneity and phenotypic mimicry among


**Suggested Reading**


Chapter Notes

Author Notes

Fondazione Salvatore Maugeri

Revision History

- 6 March 2014 (me) Comprehensive update posted live
- 7 February 2013 (cd) Revision: multi-gene panels now listed in the GeneTests™ Laboratory Directory; mutations in TRDN identified as causative for CPVT
- 16 February 2012 (me) Comprehensive update posted live
• 7 July 2009 (me) Comprehensive update posted live

• 22 March 2007 (me) Comprehensive update posted to live Web site

• 22 May 2006 (cn) Revision: Prenatal diagnosis available for RYR2 and CASQ2

• 14 October 2004 (me) Review posted to live Web site

• 1 June 2004 (cn) Original submission

Copyright © 1993-2016, University of Washington, Seattle. All rights reserved.

For more information, see the GeneReviews Copyright Notice and Usage Disclaimer.

For questions regarding permissions: admasst@uw.edu.

Bookshelf ID: NBK1289   PMID: 20301466