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Catecholaminergic Polymorphic Ventricular Tachycardia

Synonyms: Catecholamine-Induced Polymorphic Ventricular Tachycardia, CPVT

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Summary

Clinical characteristics

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterized by 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 may occur 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 onset of symptoms (usually a syncopal episode) is between age seven and 12 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% have one or more syncopal spells. Sudden death may be the first manifestation of the disease.

Diagnosis/testing

The diagnosis of CPVT is established in the presence of a structurally normal heart, normal resting EKG, and exercise- or emotion-induced bidirectional or polymorphic ventricular tachycardia OR in individuals who have a heterozygous pathogenic variant in *RYR2*, *CALM1*, *CALM2*, *CALM3*, *CASQ2*, or *KCNJ2* or biallelic pathogenic variants in *CASQ2*, *TECRL*, or *TRDN*.

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Management

Treatment of manifestations: Recent studies have demonstrated that (1) nadolol is the most effective beta blocker in CPVT; (2) nonselective beta blockers (nadolol and propranolol) are superior to selective beta blockers; (3) a significant burden of life-threatening arrhythmias persists after left cardiac sympathetic denervation; (4) an implantable cardioverter defibrillator is effective for those individuals in whom arrhythmias are not adequately controlled by drug therapy.

Prevention of primary manifestations: Beta blockers are indicated for all clinically affected individuals, and for individuals with a pathogenic variant(s) in one of the genes associated with CPVT with a negative exercise stress test, 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 an exercise stress test.

Surveillance: Follow-up visits with a cardiologist every six to 12 months (depending on disease severity) are very important, especially until puberty, since body weight increases rapidly and drug dosages must be continually adjusted. Limitation on physical activity can be defined on the basis of an 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; allowed exercise intensity should be individualized based on exercise stress test results.

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

Evaluation of relatives at risk: Because treatment and surveillance are available to reduce morbidity and mortality, 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 EKG, Holter monitoring, echocardiography, and – most importantly – exercise stress testing.

Genetic counseling

RYR2-, *CALM1*-, *CALM2*-, *CALM3*-, and *KCNJ2*-related CPVT are inherited in an autosomal dominant manner.

CASQ2-related CPVT is typically inherited in an autosomal recessive manner. However, because a subset of individuals (still unquantified but rare) with heterozygous *CASQ2* pathogenic variants show a mild CPVT phenotype, autosomal dominant inheritance may not be ruled out for *CASQ2*-related CPVT, and clinical screening is indicated accordingly in individuals who are heterozygous for a *CASQ2* pathogenic variant.

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

- **Autosomal dominant inheritance.** Each child of an individual with autosomal dominant CPVT has a 50% chance of inheriting the pathogenic variant.
- **Autosomal recessive inheritance.** If both parents are known to be heterozygous for a *CASQ2*, *TECRL*, or *TRDN* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of inheriting one pathogenic variant and being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants. Heterozygote testing for at-risk relatives requires prior identification of the *CASQ2*, *TECRL*, or *TRDN* pathogenic variants in the family.

Once the CPVT-related pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Catecholaminergic polymorphic ventricular tachycardia (CPVT) **should be suspected** in individuals who have one or more of the following [Priori et al 2013a]:

- Syncope occurring during physical activity or acute emotion; mean onset is age seven to 12 years. Less frequently, first manifestations may occur later in life; individuals with a first event up to age 40 years have been reported.
- History of exercise- or emotion-related palpitations and dizziness in some individuals
- Sudden unexpected cardiac death triggered by acute emotional stress or exercise
- Family history of juvenile sudden cardiac death triggered by exercise or acute emotion
- Exercise-induced bidirectional or polymorphic ventricular arrhythmias
  - EKG 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 90-120 beats per minute.
  - 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 arrhythmias [Priori et al 2021].
  - Notably, 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].
- Ventricular fibrillation occurring in the setting of acute stress

* Note: The resting EKG of individuals with CPVT is usually normal. 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, particularly in the precordial leads [Leenhardt et al 1995, Aizawa et al 2006]. Overall, these features are inconsistent 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, Giudicessi & Ackerman 2019].

Establishing the Diagnosis

According to the most recent version of the International Guidelines on Sudden Cardiac Death [Priori et al 2015, Al-Khatib et al 2018, Wilde et al 2022], the diagnosis of CPVT **is established**:

- In the presence of a structurally normal heart, normal resting EKG, and exercise- or emotion-induced bidirectional or polymorphic ventricular tachycardia;

  OR

- In individuals who have a heterozygous pathogenic (or likely pathogenic) variant in *RYR2*, *CALM1*, *CALM2*, *CALM3*, *CASQ2*, or *KCNJ2* or biallelic pathogenic (or likely pathogenic) variants in *CASQ2*, *TECRL*, or *TRDN* (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype:

- **A multigene panel** that includes the genes listed in Table 1 and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used, and yields results similar to a multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing CPVT whereas some multigene panels may not. **Genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

Gene [1, 2]	MOI	Proportion of CPVT Attributed to Pathogenic Variants in Gene [3]	Proportion of Pathogenic Variants [4] Detectable by Method	
			Sequence analysis [5, 6]	Gene-targeted deletion/duplication analysis [7]
CALM1	AD	<1%	~100%	Unknown [8]
CALM2	AD	<1%	~100%	Unknown [8]
CALM3	AD	<1%	~100%	Unknown [8]
CASQ2	AR (AD) [9]	5%	~100%	Unknown [8]
KCNJ2	AD	<1%	~100%	Unknown [8]
RYR2	AD	60%-70%	~99%	Rare [10]
TECRL	AR	<1%	~100%	Unknown [8]
TRDN	AR	<1%	~100%	Unknown [8]

Table 1. continued from previous page.

Gene [1, 2]	MOI	Proportion of CPVT Attributed to Pathogenic Variants in Gene [3]	Proportion of Pathogenic Variants [4] Detectable by Method	
			Sequence analysis [5, 6]	Gene-targeted deletion/duplication analysis [7]
Unknown [11]		~25%	NA	

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; NA = not applicable
1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. Wilde et al [2022]
4. See Molecular Genetics for information on variants detected in these genes.
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants 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.
6. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
8. No data on detection rate of gene-targeted deletion/duplication analysis are available.
9. *CASQ2*-related CPVT is typically inherited in an autosomal recessive manner. However, a subset of individuals (still unquantified but rare) with heterozygous *CASQ2* pathogenic variants may show a mild CPVT phenotype [Wilde et al 2022]; therefore, autosomal dominant inheritance may not be ruled out for *CASQ2*-related CPVT, and clinical screening of *CASQ2* heterozygotes is indicated.
10. Exon 3 *RYR2* deletion has been reported in a family with CPVT associated with left ventricular non-compaction [Campbell et al 2015].
11. Approximately 25% of individuals with CPVT have no pathogenic variant identified in any of the known genes listed in this table [Priori et al 2021].

Clinical Characteristics

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% have one or more syncopal spells.

Few clinical studies [Leenhardt et al 1995, Priori et al 2002, Roston et al 2018] 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 bidirectional or polymorphic ventricular tachycardia (VT).

- Spontaneous recovery may occur when these arrhythmias self-terminate;

  OR

- VT 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 disorder in previously asymptomatic individuals (no history of syncope or dizziness) who die suddenly during exercise or while experiencing acute emotions [Priori et al 2002, Krahn et al 2005, Watanabe et al 2013]. Atypical triggers (e.g., playing musical instruments or even rest) have been reported in a minority of individuals [Roston et al 2018]. However, the correct identification of triggers is often difficult, and is a common limitation of rare disease registry data.

The mean onset of CPVT symptoms (usually a first syncopal episode) is between age seven and 12 years [Leenhardt et al 1995, Priori et al 2002, Postma et al 2005, Roston et al 2018]; onset as late as the fourth decade of life has been reported.

Instances of sudden infant death syndrome have been associated with pathogenic variants in *RYR2* [Tester et al 2007].

Family history of sudden death in relatives younger than age 40 years is present in approximately 30% of probands with CPVT [Priori et al 2002, Watanabe et al 2013].

Other. A single case report highlighted the possible pro-arrhythmic effect of an insulin tolerance test, driven by severe hypokalemia and adrenergic activation secondary to the metabolic imbalance induced by the test [Binder et al 2004]. Of note, *RYR2* is expressed in pancreatic beta cells responsible for insulin secretion, suggesting that altered glucose metabolism can represent a manifestation of *RYR2*-related CPVT [Santulli et al 2015].

Typical vs atypical CPVT phenotype. Typical CPVT can be diagnosed with the demonstration of reproducible exercise-induced bidirectional or polymorphic VT in the presence of a structurally normal heart and normal baseline/resting EKG. Atypical CPVT is associated with arrhythmias and/or syncope / cardiac arrest triggered by adrenergic activation in the absence of a reproducible pattern of arrhythmias. Other findings may occur in atypical CPVT. For details regarding genetic differences in these phenotypes, see Phenotype Correlations by Gene.

Phenotype Correlations by Gene

The typical CPVT phenotype is caused by the presence of pathogenic variants in *RYR2* or *CASQ2* [Priori et al 2021].

Atypical CPVT is caused by pathogenic variants in the "rare" genes:

- *CALM1*, *CALM2*, and *CALM3* (also called calmodulinopathies), which can also be associated with QT prolongation *
- *TRDN*, which can be associated with mild skeletal myopathy / proximal muscle weakness, T-wave inversions, and transient QT prolongation >480 ms [Clemens et al 2019] *
- *KCNJ2*, which can be associated with bidirectional VT without adrenergic trigger in the absence of the typical Andersen-Tawil extracardiac manifestations [Wilde et al 2022]
- Preliminary observations suggest that *TECRL* may be associated with CPVT and QT interval prolongation as clinical phenotypes (but not isolated long QT syndrome) [Moscu-Gregor et al 2020]. This observation awaits further confirmation.

* Although all *CALM1*, *CALM2*, and *CALM3* pathogenic variants alter calcium handling, further data are needed to determine if these phenotypes should be defined as CPVT with variable expressivity (as a result of unidentified pathophysiologic mechanisms) or as mechanistically distinct disorders.

Genotype-Phenotype Correlations

Gain-of-function pathogenic variants in *RYR2* are associated with the typical CPVT phenotype (reproducible exercise-/emotion-induced bidirectional VT with structurally normal heart) [Priori et al 2021] while the much less frequently observed loss-of-function variants can cause ventricular fibrillation and sudden death in the absence of inducible arrhythmias [Zhong et al 2021].

No genotype-phenotype correlations for *CASQ2*, *CALM1*, *CALM2*, *CALM3*, *KCNJ2*, *TECRL*, or *TRDN* have been identified.

Penetrance

The mean penetrance of *RYR2* pathogenic variants is 83% [Author, unpublished data]. Therefore, asymptomatic individuals with *RYR2*-related CPVT are a minority. To date, biallelic *CASQ2* pathogenic variants have been 100% penetrant in reported individuals. Too few individuals with heterozygous *CASQ2*, *KCNJ2*, *CALM1*, *CALM2*, or *CALM3*-related CPVT have been reported to date to allow a robust estimate of penetrance.

Nomenclature

CPVT has also been referred to as familial polymorphic ventricular tachycardia (FPVT).

Prevalence

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

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 (1:5,000-1:7,000).

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in catecholaminergic polymorphic ventricular tachycardia-related genes are summarized in Table 2.

Table 2. Allelic Disorders

Gene [1]	Allelic Disorder
CALM1	Long QT syndrome (LQTS)
	LQTS in combination w/epilepsy & neurodevelopmental disorders [2]
CALM2	LQTS
CALM3	LQTS [3]
KCNJ2	Andersen-Tawil syndrome (characterized by QT prolongation, prominent U waves, & extracardiac features: low-set ears, thin lips, periodic paralysis). Affected persons often present w/ventricular arrhythmias & bidirectional ventricular tachycardias.
RYR2	Pathogenic variants have been assoc w/non-typical hypertrophic cardiomyopathy or LVNC [4]
	Large deletions have been identified in persons w/LVNC w/ or w/o CPVT [5]
TRDN	*TRDN* variants have been identified in affected persons from 33 families w/LQTS. [6]

CPVT = catecholaminergic polymorphic ventricular tachycardia; LVNC = left ventricular non-compaction
1. Genes are listed in alphabetic order.
2. Crotti et al [2013]
3. Crotti et al [2019]
4. Kohli et al [2019], Kohli et al [2020], Cambon-Viala et al [2021], Duvekot et al [2021]
5. Ohno et al [2014], Campbell et al [2015]
6. Altmann et al [2015]

CASQ2. No phenotypes other than those discussed in this *GeneReview* are known to be associated with *CASQ2* germline pathogenic variants.

TECRL. See Phenotype Correlations by Gene.

Differential Diagnosis

Short-coupled ventricular tachycardia (SC-torsade de pointes [TdP]) is a clinical entity presenting with life-threatening polymorphic ventricular arrhythmias resembling in part the pattern of arrhythmias observed in individuals with catecholaminergic polymorphic ventricular tachycardia (CPVT). SC-TdP presents with polymorphic ventricular tachycardia (VT) occurring in the setting of a structurally normal heart and in the absence of any overt baseline EKG 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 and flecainide.

Table 3. Genes of Interest in the Differential Diagnosis of Catecholaminergic Polymorphic Ventricular Tachycardia

Gene(s)	Disorder	MOI	Features of This Disorder Overlapping w/CPVT	Comment / Distinguishing Features
DSC2 *DSG2* *DSP* *JUP* *PKP2* *RYR2* *TGFB3* *TMEM43*	Arrhythmogenic right ventricular dysplasia/ cardiomyopathy (ARVC)	AD (AR) [1]	Progressive fibrofatty replacement of myocardium that predisposes to VT & sudden death in young persons & athletes. It primarily affects right ventricle; w/time, may also involve left ventricle.	Persons w/CPVT do not have structural cardiac abnormalities. The evidence of overlapping phenotypes (see Genetically Related Disorders) calls for careful imaging assessment (echocardiogram, MRI) for manifestations of ARVC in all persons w/CPVT.
KCNQ1	Long QT syndrome type 1 (LQT1)	AD	Exercise-related syncope is also typically found in LQT1 variant of LQTS. As incomplete penetrance is possible in LQT1, some persons may have normal QT interval & may present w/clinical history similar to CPVT (exercise-related syncope; normal EKG).	Unlike CPVT, LQT1 does not present w/ inducible arrhythmia during graded exercise (exercise stress test). The initial description of CPVT by Philippe Coumel included persons w/borderline or mildly prolonged QT interval.

AD = autosomal dominant; AR = autosomal recessive; CPVT = catecholaminergic polymorphic ventricular tachycardia; LQTS = long QT syndrome; MOI = mode of inheritance; VT = ventricular tachycardia
1. ARVC is usually inherited in an autosomal dominant manner. It can also be inherited in a digenic or autosomal recessive manner.
2. Postma et al [2006], Tester et al [2006]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with catecholaminergic polymorphic ventricular tachycardia (CPVT), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Catecholaminergic Polymorphic Ventricular Tachycardia

System/Concern	Evaluation	Comment
Cardiac	Resting EKG	Baseline
	Holter monitoring	To assess arrhythmias that develop when heart rate ↑
	Exercise stress test [1]	Baseline for diagnosis & monitoring of therapy
	Echocardiogram &/or MRI	To evaluate for structural defects

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of CPVT to facilitate medical & personal decision making

CPVT = catecholaminergic polymorphic ventricular tachycardia; MOI = mode of inheritance
1. Exercise stress test should be performed until maximal tolerated effort, as some individuals have high heart rate threshold for induction of arrhythmias.
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Management of CPVT is summarized in a specific consensus document from the Heart Rhythm Association (HRS) and the European Heart Rhythm Association (EHRA) [Priori et al 2013b] (full text), and in the recent version of the European Society of Cardiology (ESC) guidelines on ventricular arrhythmias [Priori et al 2015] (full text). Recent studies have demonstrated that (1) nadolol is the most effective beta blocker in individuals with CPVT; (2) non-selective beta blockers (nadolol and propranolol) are superior to selective beta blockers; (3) a significant burden of life-threatening arrhythmias persists after left cardiac sympathetic denervation; (4) an implantable cardioverter defibrillator is effective for those individuals in whom arrhythmias are not adequately controlled by drug therapy [Mazzanti et al 2022, Peltenburg et al 2022].

Table 5. Treatment of Manifestations in Individuals with Catecholaminergic Polymorphic Ventricular Tachycardia

Manifestation/ Concern	Treatment	Considerations/Other
Adrenergic-dependent triggered activity	Beta-blocker therapy: nadolol (1-2.5 mg/kg/day in a single dose or divided into 2 doses per day) or propranolol (2-4 mg/kg/day divided into 3-4 doses per day)	• Nadolol is reported to be more effective than selective beta blockers [Leren et al 2016]. However, selective beta blockers can be used in persons w/ asthma or other respiratory conditions. • Chronic treatment w/full-dose beta-blocking agents prevents recurrence of syncope in majority of affected persons. • Dose needs to be individualized w/exercise stress testing & efficacy periodically retested (see Surveillance).
Arrhythmia control	Flecainide (100-300 mg/ day)	• Can be given along w/beta blockers to persons who have syncope recurrence or complex arrhythmias during exercise • Beta blockers & flecainide together are also indicated for affected persons who have experienced a previous aborted sudden death, to ↓ probability of ICD shocks. • The antiarrhythmic effects of flecainide appear to be independent of specific CPVT genetic subtype. [1]
Cardiac arrest, recurrent syncope, or polymorphic/ bidirectional VT despite optimal therapy	Implantable cardioverter defibrillator	Whenever possible, pharmacologic therapy should be maintained/optimized even in persons w/an ICD to ↓ probability of ICD firing.
	Left cardiac sympathetic denervation	• May be considered in those w/several appropriate ICD shocks while on beta blocker & flecainide & in those who are intolerant of or w/ contraindication to beta-blocker therapy. • Side effects incl palpebral ptosis, ↑ of left hemidiaphragm, & lack of sweating from left arm & face. • Recurrence of cardiac events may occur even w/LCSD, so it cannot be considered an alternative to ICD.

ICD = implantable cardioverter defibrillator; LCSD = left cardiac sympathetic denervation
1. Watanabe et al [2013]

Prevention of Primary Manifestations

Beta blockers are indicated for primary prevention in all clinically affected individuals (see Management, Treatment of Manifestations) and in individuals with pathogenic variants in the genes associated with CPVT who have a negative exercise stress test. 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 cardiac arrest when beta blockers alone cannot control the onset of arrhythmias during an exercise stress test.

Surveillance

Table 6. Recommended Surveillance for Individuals with Catecholaminergic Polymorphic Ventricular Tachycardia

System/Concern	Evaluation	Frequency
Monitoring therapy efficacy	Cardiologist eval to incl: • Resting EKG • Exercise stress test, performed at maximal age-predicted heart rate. For those on beta-blocker therapy (in whom maximal heart rate cannot be reached), test should be performed at highest tolerated workload. • Holter monitoring • Echocardiogram & MRI at least every 2 yrs	• Every 6-12 mos (per severity of clinical manifestations) • Follow-up visits are very important esp until puberty, as body weight ↑ rapidly & drug dosages must be continually adjusted.
Limitation on physical activity	• Can be defined on basis of exercise stress test done in hospital setting • Use of commercially available heart rate monitoring devices for sports participation can be helpful in keeping heart rate in safe range during physical activity but should not be considered as alternative to medical follow-up visits. • Since heart rate threshold for onset of arrhythmias is often reproducible in the same person, the advice for allowed exercise intensity should be individualized based on results of exercise stress test.	Review at each visit.

Agents/Circumstances to Avoid

Competitive sports and other strenuous exercise are always contraindicated for individuals with CPVT. All individuals showing exercise-induced arrhythmias should avoid physical activity, except for 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 [Heidbüchel et al 2006]. The risk for arrhythmias during sports in individuals who have pathogenic variants in genes associated with CPVT but no clinical phenotype (no exercise-induced arrhythmias) is not known; thus, it may be safest for these individuals to refrain from intense physical activity.

Digitalis favors the onset of cardiac arrhythmias as a result of delayed afterdepolarization 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 evaluation and molecular genetic testing if the family-specific pathogenic variant(s) are known. 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 EKG, Holter monitoring, echocardiography, 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.

See MotherToBaby for information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe 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, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

RYR2, *CALM1*, *CALM2*, *CALM3*, and *KCNJ2*-related catecholaminergic polymorphic ventricular tachycardia (CPVT) are inherited in an autosomal dominant manner.

CASQ2-related CPVT is typically inherited in an autosomal recessive manner. However, because a subset of individuals (still unquantified but rare) with heterozygous *CASQ2* pathogenic variants show a mild CPVT phenotype [Wilde et al 2022], autosomal dominant inheritance may not be ruled out for *CASQ2*-related CPVT, and clinical screening is indicated in individuals who are heterozygous for a *CASQ2* pathogenic variant.

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

Autosomal Dominant Inheritance – Risk to Family Members

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 a *de novo* pathogenic variant. The frequency of *de novo RYR2* pathogenic variants is estimated to be 30%-40%; however, accurate frequency data are not available.
- If the proband is the only family member known to have CPVT, recommendations for the evaluation of the parents of a proband include a maximal exercise stress test and molecular genetic testing if a molecular diagnosis has been established in the proband.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism

and will not detect a pathogenic variant that is present only in the germ cells. (Note: Parental mosaicism for a CPVT-related pathogenic variant has not been reported to date.)
- The family history of some individuals diagnosed with autosomal dominant CPVT 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. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

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 and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known CPVT-related pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016]. (Note: Parental mosaicism for a CPVT-related pathogenic variant has not been reported to date.)
- If the parents are clinically unaffected but their genetic status is unknown, sibs are still at increased risk for CPVT because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

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. The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected and/or is known to have the pathogenic variant, members of the parent's family are at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *CASQ2*, *TECRL*, or *TRDN* pathogenic variant. However, it is possible (although likely rare) that one or both parents of a proband are themselves affected.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a CPVT-related pathogenic variant and to allow reliable recurrence risk assessment. A maximal exercise stress test can also be considered for the parents of a proband with autosomal recessive CPVT.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or, theoretically, as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Individuals who are heterozygous for a pathogenic variant in *CASQ2* may show a mild CPVT phenotype and clinical screening is indicated accordingly (see Surveillance). Individuals who are heterozygous for a pathogenic variant in *TECRL* or *TRDN* are usually asymptomatic but current data are limited and a clinical evaluation could be considered.

Sibs of a proband

- If both parents are known to be heterozygous for a *CASQ2*, *TECRL*, or *TRDN* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of inheriting one pathogenic variant and being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Individuals who are heterozygous for a pathogenic variant in *CASQ2* may show a mild CPVT phenotype and clinical screening is indicated (see Surveillance). Individuals who are heterozygous for a pathogenic variant in *TECRL* or *TRDN* are usually asymptomatic but current data are limited and a clinical evaluation could be considered.

Offspring of a proband. The offspring of an individual with autosomal recessive CPVT are obligate heterozygotes for a pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for a *CASQ2*, *TECRL*, or *TRDN* pathogenic variant.

Heterozygote Detection

Heterozygote testing for at-risk relatives requires prior identification of the *CASQ2*, *TECRL*, or *TRDN* pathogenic variants in the family.

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.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic 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. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the CPVT-related pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for CPVT are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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**
  Phone: 800-242-8721
  Tachycardia: Fast Heart Rate
- **MedlinePlus**
  Catecholaminergic polymorphic ventricular tachycardia
- **Canadian SADS Foundation**
  Canada
  Email: info@sads.ca
  www.sads.ca
- **ERN GUARD-Heart**
  European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart
  www.guardheart.ern-net.eu
- **Sudden Arrhythmia Death Syndromes (SADS) Foundation**
  Phone: 801-948-0654
  www.sads.org
- **Sudden Arrhythmia Death Syndromes (SADS) Foundation UK**
  SADS UK
  United Kingdom
  www.sadsuk.org.uk
- **Una Famiglia per il Cuore**
  Italian Association of Families with Inherited Arrhythmias
  Via Salvatore Maugeri
  27100 Pavia
  Italy
  Phone: 0382 592055

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

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CALM1	14q32.11	Calmodulin		CALM1	CALM1
CALM2	2p21	Calmodulin		CALM2	CALM2
CALM3	19q13.32	Calmodulin-3		CALM3	CALM3
CASQ2	1p13.1	Calsequestrin-2	CASQ2 database	CASQ2	CASQ2
KCNJ2	17q24.3	Inward rectifier potassium channel 2	KCNJ2 database KCNJ2 @ ZAC-GGM	KCNJ2	KCNJ2
RYR2	1q43	Ryanodine receptor 2	RYR2 database	RYR2	RYR2
TECRL	4q13.1	Trans-2,3-enoyl-CoA reductase-like		TECRL	TECRL

Table A. continued from previous page.

TRDN	6q22.31	Triadin	TRDN homepage - Leiden Muscular Dystrophy pages	TRDN	TRDN

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Catecholaminergic Polymorphic Ventricular Tachycardia (View All in OMIM)

114180	CALMODULIN 1; CALM1
114182	CALMODULIN 2; CALM2
114183	CALMODULIN 3; CALM3
114251	CALSEQUESTRIN 2; CASQ2
180902	RYANODINE RECEPTOR 2; RYR2
600681	POTASSIUM CHANNEL, INWARDLY RECTIFYING, SUBFAMILY J, MEMBER 2; KCNJ2
603283	TRIADIN; TRDN
604772	VENTRICULAR TACHYCARDIA, CATECHOLAMINERGIC POLYMORPHIC, 1, WITH OR WITHOUT ATRIAL DYSFUNCTION AND/OR DILATED CARDIOMYOPATHY; CPVT1
611938	VENTRICULAR TACHYCARDIA, CATECHOLAMINERGIC POLYMORPHIC, 2; CPVT2
614021	VENTRICULAR TACHYCARDIA, CATECHOLAMINERGIC POLYMORPHIC, 3; CPVT3
614916	VENTRICULAR TACHYCARDIA, CATECHOLAMINERGIC POLYMORPHIC, 4; CPVT4
615441	CARDIAC ARRHYTHMIA SYNDROME, WITH OR WITHOUT SKELETAL MUSCLE WEAKNESS; CARDAR
617242	TRANS-2,3-ENOYL-CoA REDUCTASE-LIKE PROTEIN; TECRL

Molecular Pathogenesis

CALM1, *CALM2*, *CALM3*, *CASQ2*, *RYR2*, *TECRL*, and *TRDN* are involved in the control of intracellular calcium fluxes, sarcoplasmic reticulum (SR) calcium release, and the cytosolic free Ca^{2+} concentration.

RYR2 encodes the ryanodine receptor (RyR2), which 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, RyR2 releases the Ca^{2+} ions stored in the SR that are required for contraction of the muscle fibers. The *RYR2* pathogenic variants found in individuals with catecholaminergic polymorphic ventricular tachycardia (CPVT) have been shown to cause Ca^{2+} "leakage" from the SR in conditions of sympathetic (catecholamine) activation [Priori & Chen 2011]. The consequent abnormal increase of the cytosolic free Ca^{2+} concentration creates an electrically unstable substrate.

CALM1, ***CALM2***, and ***CALM3*** are three genes that encode for an identical protein, calmodulin (CaM) [Fischer et al 1988], which contains typical calcium-binding sites (EF hands) that, like RyR2, also interact with the voltage-dependent calcium channels (CaV1.3). For this reason, the mechanisms leading from pathogenic variant to the clinical phenotype can be considered similar for all three genes. The altered CaM has reduced calcium-binding affinity and impaired CaM-RyR2 interactions at low calcium concentration. Calcium release in the presence of altered CaM shows significantly increased duration of Ca2+ release events; and lower frequency of Ca2+ oscillations [Prakash et al 2022]. These effects may lead to RyR2 channel instability and "leakage" similar to that observed for *RYR2* pathogenic variants [Gomez-Hurtado et al 2016, Badone et al 2018].

CASQ2 encodes the cardiac isoform of calsequestrin, calsequestrin-2 (CASQ2), an SR protein functionally and physically related to RyR2. CASQ2 forms polymers at the level of the terminal cisternae of the SR in close

proximity to the RyR2; its function is that of buffering the Ca^{2+} ions. 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 RyR2 channel-opening process.

KCNJ2 encodes inward rectifier potassium channel 2, a potassium ion channel that conducts inwardly rectifying potassium current responsible for maintenance of the normal resting membrane potential of myocardial cells.

TRDN encodes triadin, an SR protein functionally and physically related to RyR2. Lack of triadin is associated with a reduction of CASQ2 levels and ultrastructural abnormalities of the T tubules, which affects the calcium release process and, more specifically, results in a calcium leak during diastole similar to that observed with *RYR2* pathogenic variants.

Few studies have functionally assessed the effect of pathogenic variants in ***TECRL*** leading to CPVT. The most interesting insights come from an expression study in induced pluripotent stem cell-derived cardiomyocytes [Devalla et al 2016]. This study revealed that *TECRL* pathogenic variants are associated with elevated diastolic Ca2+, smaller amplitude, and slower decay of cytosolic Ca2+ transients. Adrenergic stimulation resulted in increased delayed afterdepolarization (DAD) amplitude and triggered arrhythmia in the same way as shown with *RYR2* pathogenic variants. *TECRL* pathogenic variants were also shown in experimental models to cause impaired mitochondrial function with consequent reduced cardiac contractility [Hou et al 2022].

Mechanism of disease causation. In order to generate a CPVT phenotype there must be a diastolic calcium overload that activates the sodium calcium exchanger leading to DAD and triggered activity (TA) [Priori et al 2021]. This pathway involves several genes, many of which have been associated with CPVT.

In order to activate the DAD-TA arrhythmogenesis, the RyR2 channel is destabilized during the diastolic phase with a consequent leakage of calcium ions that follow the concentration gradient from the SR (high concentration) to the cytosol (low concentration). This condition is therefore the result of a gain-of-function effect.

A leaky RyR2 channel can be caused by *RYR2* pathogenic variants (encoding the channel pore) that directly affects channel stability.

CASQ2 pathogenic variants invariably reduce the amount of expressed CASQ2. Since CASQ2 serves as an SR calcium buffer but also as an RyR2 stabilizer, reduced CASQ2 levels as a result of *CASQ2* loss-of-function variants lead to increased RyR2 function.

While the functional consequence of *RYR2* and *CASQ2* pathogenic variants are reasonably well understood, knowledge gaps still exist for the rare CPVT-related genes. Available evidence shows that *CALM1*, *CALM2*, *CALM3*, and *TECRL* pathogenic variants lead to RyR2 leakage and propensity to DAD-TA, but the exact mechanisms are still under investigation.

A subset of *RYR2* pathogenic variants have the opposite effect of reducing the release of calcium through the channel. These are defined as loss-of-function pathogenic variants that severely reduce cytosolic Ca2+ activation and abolish luminal Ca2+ activation of RyR2 channels [Zhong et al 2021]. The mechanism by which this triggers sudden cardiac rhythm disruption is still unclear.

Chapter Notes

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- 23 June 2022 (ha/sw) Comprehensive update posted live
- 13 October 2016 (sw) Comprehensive update posted live
- 6 March 2014 (me) Comprehensive update posted live
- 7 February 2013 (cd) Revision: multigene 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 live
- 22 May 2006 (cn) Revision: Prenatal diagnosis available for *RYR2* and *CASQ2*
- 14 October 2004 (me) Review posted live
- 1 June 2004 (cn) Original submission

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