



## Test Information Sheet

### Cardiology Genetics: Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

**Also known as:** Familial Polymorphic Ventricular Tachycardia (FPVT), Catecholamine-Induced Polymorphic Ventricular Tachycardia (CPVT)

**Mendelian Inheritance in Man Number:** CPVT1: 604772; CPVT2: 611938<sup>1</sup>

#### **Clinical Features:**

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a potentially fatal cardiac arrhythmia in individuals with a structurally normal heart. The disorder is characterized by syncope, typically beginning in the first decade of life, which may be triggered by physical activity or intense emotion. In patients with CPVT, stress-induced release of catecholamines causes a dysfunction of calcium-ion channel in myocytes. The ion channel dysfunction induces ventricular arrhythmias, which can lead to syncope or sudden cardiac death. Spontaneous recovery from the arrhythmia is possible, but the ventricular tachycardia can progress to ventricular fibrillation and sudden death<sup>2</sup>. The incidence of CPVT within the population is not precisely known, but is estimated to be 1:10,000<sup>3</sup>. Symptoms include syncope, dizziness, arrhythmia, and sudden cardiac death. Diagnosis may prove difficult, due to normal echocardiogram and electrocardiogram at a resting state. Testing must be performed under stress-inducing conditions in order to accurately evaluate a possible diagnosis.

#### **Inheritance Pattern:**

CPVT1 (associated with RYR2 mutations) is inherited in an autosomal dominant manner, where by definition an affected individual with a disease-causing mutation has a 50% chance of transmitting the mutation to their child. CPVT2 (associated with CASQ2 mutations) is inherited in an autosomal recessive manner, where by definition the parents of an affected child are obligate heterozygotes. Siblings of affected individuals have a 25% risk of inheriting the disease.

CPVT1 and CPVT2 have been seen to exhibit incomplete penetrance and variable expressivity among families.

#### **Genetics:**

CPVT1 is caused by autosomal dominant mutations in the RYR2 gene, which encodes the cardiac ryanodine receptor channel. Heterozygous mutations in RYR2 are responsible for an estimated 50% - 55% of CPVT.<sup>2,4</sup>

CPVT2 is caused by autosomal recessive mutations in the CASQ2 gene. CASQ2 encodes calsequestrin, a calcium buffering protein. Heterozygous carriers usually do not show symptoms. Mutations in CASQ2 are responsible for an estimated 1% - 2% of CPVT.<sup>2</sup>

Molecular genetic testing makes it possible to confirm a clinical diagnosis in a symptomatic individual as well as to identify asymptomatic family members at risk for CPVT. For the asymptomatic individual, testing will not provide information regarding age of onset or severity of symptoms, but may lead to increased surveillance and initiation of treatment.

#### **Reasons for Referral:**

1. Confirmation of a clinical diagnosis in symptomatic patients
2. Risk assessment of asymptomatic family members of a proband with CPVT
3. Genetic counseling and recurrence risk calculation
4. Differentiation of hereditary CPVT from other acquired or genetic heart conditions
5. Prenatal diagnosis in families with a known mutation

**Test Method:**

Using genomic DNA obtained from a blood specimen (2-5 mL in EDTA), the entire coding region of two genes (RYR2 and CASQ2) and their splice junctions are sequenced using a novel solid-state sequencing-by-synthesis process that allows sequencing a large number of amplicons in parallel.<sup>5</sup> For analysis, DNA sequence is assembled and compared to the published genomic reference sequences. The presence of any potentially disease-associated sequence variant(s) is confirmed by conventional dideoxy DNA sequence analysis. A reference library of at least 800 alleles is used to evaluate the frequency of novel sequence variants if indicated. If appropriate, testing of one affected relative or, if not available, of both biological parents, is performed to clarify variants of unknown significance at no additional charge.

**Test Sensitivity:**

It is estimated that 50%-70% of patients with CPVT will have a disease-causing mutation in RYR2 or CASQ2.<sup>3</sup> The exact percentage of individuals with CPVT who will have a disease-causing mutation that can be identified by sequencing of the two genes tested for in this panel is currently unknown but estimated to be at least 51%. The technical sensitivity of this testing approach is estimated to be 98% for mutations identifiable by sequence analysis. Gross deletions and duplications would not be identified using this method. De novo mutations have been observed and may account for half of autosomal dominant CPVT, likely due to the high rate of premature death.<sup>2</sup> Less frequent are mutations in the CASQ2 gene.

**Specimen Requirements and Shipping/Handling:**

- **Blood:** A single tube with 2-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- **Buccal Brushes:** CANNOT be accepted.
- **Other Specimens:** Contact us for specific inquiries and specimen requests.
- **Prenatal Diagnosis:** Available only if a familial mutation has been identified. Contact us for more information.

**Required Forms:**

- Cardiology Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions
- We highly recommend submitting relevant clinical information (ECG Reports, clinic notes, etc) with samples.

**CPT Codes and Turn-Around-Times:**

Test #	Description	CPT codes	Turnaround time
386	CPVT panel in a new patient	83891x1, 83900x1, 83901x51, 83904x51, 83909x3, 83912x1	Approx. 8 weeks
901	DNA testing of a relative for a single known mutation	83891x2, 83898x2, 83894x2, 83904x4, 83892x2, 83912x2	Approx. 3 weeks
902	Prenatal diagnosis for a known mutation	83891x5, 83898x10, 83894x5, 83904x10, 83892x2, 83912x5	Approx. 2 weeks

**Possible ICD9 Codes:** Tachycardia, unspecified = 785.0                      Conduction disorder unspecified = 426.9  
 Cardiac Dysrhythmia unspecified = 427.9                      Cardiac Dysrhythmias = 427

**References Cited:**

1. Online Mendelian Inheritance in Man. [www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM](http://www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM)
2. GeneReviews: Catecholaminergic Polymorphic Ventricular Tachycardia. Napolitano, C, Priori, S, and Bloise, R. <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=cvt> Accessed September 24, 2009.
3. Liu N, Ruan Y, Priori SG. Catecholaminergic Polymorphic Ventricular Tachycardia. *Progress in Cardiovascular Diseases*. 51(1); 2008. 23-30
4. Priori SG, Napolitano C, Memmi M, Colombi B, Drago F, Gasparini M, DeSimone L, Coltorti F, Bloise R, Keegan R, Cruz Filho FE, Vignati G, Benatar A, DeLogu A. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2002; 106: 69-74.
5. Bennett S. *Pharmacogenomics*. 5(4):433-8, 2004

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