PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

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Catecholaminergic Polymorphic Ventricular Tachycardia via *RYR2* Gene Sequencing

Sequential Test – Test #810 Tier 1 Only – Test #811 Tier 2 Only – Test #812

Brief Description of Clinical Features: Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) (OMIM 604772) is a heart disorder characterized by electrical instability induced by physical exercise or intense emotion (Napolitano et al. 2009 www.genereviews.org). The electrical instability may degenerate into cardiac arrest and sudden death. CPVT typically onsets in childhood or adolescence and often presents as syncope. Cardiac structural abnormalities are usually not observed. Preventive drugs (beta-blockers) and, in some cases, defibrillators are available for susceptible individuals.

Genetics: CPVT due to *RYR2* mutations is inherited in an autosomal dominant manner. The large *RYR2* (ryanodine receptor type 2) gene with 105 exons encodes the cardiac muscle calcium release channel. *RYR2* pathogenic mutations are almost entirely missense and are clustered in specific portions of the gene (eg Priori et al. Circulation 106:69-74, 2002; Medeiros-Domingo et al. J Am Coll Cardiol 54:2065-2074, 2009). In-frame deletions or insertions of one or two amino acids have also been reported. A few patients had deletion of the entire exon 3 (in-frame loss of 35 amino acids) (Marjamaa et al. BMC Med Genet 10:12, 2009). The penetrance of *RYR2* causative mutations is high, but not 100% (Napolitano et al. 2009). Some patients have been reported to carry *de novo* mutations (Roux-Buisson et al. Europace 13:130-132, 2010). CPVT can also be caused by recessive mutations in the *CASQ2* gene (diBarletta et al. Circulation 114:1012-1019, 2006). In addition to CPVT, dominant mutations in *RYR2* have been reported to be a rare cause of Arrhythmogenic Right Ventricular Dysplasia (ARVD) (McNally et al. 2009 www.genereviews.org).

Description of This Particular Test: Full gene sequencing of *RYR2* (Test #810) is performed in two tiers. Tier 1 involves bidirectional sequencing of exons 3, 8, 14-15, 37, 41-42, 44-47, 49-50, 75, 83, 88-90, 93-97, and 99-105. These 30 exons (out of a total of 105) contain about 90% of the causative mutations that have been reported to date. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on either side are sequenced. If a likely causative mutation is found in Tier 1, testing stops. Otherwise testing continues with the remaining 75 exons in Tier 2. Tiers 1 and 2 may be ordered separately (Tests #811 and 812, respectively). As requested, we will also sequence any single exon (Test #100, $190) in family members of patients with known mutations, and to confirm research results.

Reference Sequences: Genomic: **NC_000001.10** mRNA: **NM_001035.2** Protein: **NP_ 001026.2**

Indications for Test: All individuals diagnosed with CPVT are candidates for this test. Individuals with exercise or stress induced cardiac arrest or sudden unexplained death are also candidates. When dealing with affected families, PreventionGenetics recommends that gene testing be performed first on a clearly affected family member. If a likely causative mutation is found in the affected individual, then other family members can be tested at much reduced cost.

Sensitivity of Test: Priori et al. (Circulation 106:69-74, 2002) reported that about 50% of CPVT patients have mutations in the *RYR2* gene. Tester et al. (Mayo Clin Proc 79:1380-1384, 2004) reported that 14% of sudden unexplained death cases had *RYR2* mutations. *CASQ2* mutations are reported in only 1-2% of CPVT patients (Napolitano et al. 2009).

Turnaround Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Prices: **Sequencing of the *RYR2* Gene $ 1640-3990**

	CPT Codes						
Test	**83890**	**83891**	**83898**	**83904**	**83894**	**83912**	**Totals**
Tier 1 alone (Test #811)	$ 30 x1	$ 40 x1	$540 x36	$810 x36	$ 90 x1	$130 x1	**$ 1640**
Tier 2 alone (Test #812)	$ 30 x1	$ 40 x1	$1060 x77	$1600 x77	$190 x1	$150 x1	**$ 3070**
Full Gene (Test #810)	$ 30 x1	$ 40 x1	$1380 x113	$2080 x113	$270 x1	$190 x1	**$ 3990**

Accreditation: CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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