Catecholaminergic Polymorphic Ventricular Tachycardia Panel

Panel Gene List: *CALM1, CALM2, CALM3, CASQ2, KCNJ2, RYR2, TRDN*
Additional genes from our cardiology test menu may be added to this panel by selecting test code 482C.

Clinical Features:

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a potentially fatal cardiac arrhythmia in individuals with a structurally normal heart. In patients with CPVT, stress-induced release of catecholamines causes a dysfunction of calcium-ion channels in myocytes that induces ventricular arrhythmias. Spontaneous recovery from the arrhythmia is possible, but the ventricular tachycardia can progress to ventricular fibrillation and sudden death.[1] Symptoms, including syncope, dizziness, arrhythmia and sudden cardiac arrest/death, typically begin in the first decade of life and may be triggered by physical activity or intense emotion. Diagnosis can prove difficult due to normal echocardiogram and electrocardiogram in a resting state. Cardiac testing must be performed under stress-inducing conditions in order to accurately evaluate a possible diagnosis. Although the incidence of CPVT within the population is not precisely known, it is estimated to be 1:10,000.[2]

Inheritance Pattern/Genetics: Autosomal Dominant or Autosomal Recessive

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the 7 genes are enriched using a proprietary targeted capture system developed by GeneDx. These targeted regions are sequenced simultaneously by massively parallel (NextGen) sequencing on an Illumina platform with paired-end reads. Bi-directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing is used to confirm all potentially pathogenic variants and to obtain sequence for regions where fewer than 15 reads are achieved by NextGen sequencing. Concurrent deletion/duplication testing is performed for the genes in the panel using exon-level oligo array CGH (ExonArrayDx), except for *CALM1*. Data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. The array is designed to detect most intragenic deletions and duplications. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat array CGH analysis. Sequence and array CGH alterations are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Benign and likely benign variants, if present, are not included in this report but are available upon request.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the 7 genes included in the CPVT Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with clearly defined CPVT and a family history of disease. The technical sensitivity of the sequencing test is estimated to be 98%. The sequencing panel will not reliably detect deletions, insertions, or rearrangements greater than or equal to five base pairs (bp). Deletions or duplications of less than 500 bp are not reliably detected by array CGH.

Gene	Protein	Inheritance	Disease Association(s)
CALM1	CALMODULIN 1	AD	LQTS, CPVT
CALM2	CALMODULIN 2	AD	LQTS, CPVT
CALM3	CALMODULIN 3	AD	LQTS, CPVT
CASQ2	CALSEQUESTRIN 2	AR	CPVT
KCNJ2	POTASSIUM CHANNEL, INWARDLY RECTIFYING, SUBFAMILY J, MEMBER 2	AD	Andersen-Tawil syndrome, SQTS, AF
RYR2	RYANODINE RECEPTOR 2	AD	ARVC, CPVT
TRDN	TRIADIN	AR	CPVT, LQTS

Abbreviations: AD – Autosomal dominant; AF – Atrial fibrillation; AR – Autosomal recessive; ARVC- Arrhythmogenic right ventricular cardiomyopathy; CPVT – Catecholaminergic polymorphic ventricular tachycardia; LQTS – Long QT syndrome

References:

1. Napolitano C, Priori SG, Bloise R. Catecholaminergic Polymorphic Ventricular Tachycardia. 2004 Oct 14 [Updated 2014 Mar 6]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1289/
2. Liu et al. Progress In Cardiovascular Diseases 51 (1):23-30 (PMID: 18634915)