Catecholaminergic Polymorphic Ventricular Tachycardia Panel

Panel Gene List: *ANK2, CALM1, CALM2, CALM3, CASQ2, KCNJ2, RYR2, TECRL, 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, Autosomal Recessive

Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reported clinically significant variants are confirmed by an appropriate orthogonal method. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request. Sequencing and deletion/duplication analysis of the remaining genes on the Arrhythmia Panel is available as a separate test if the CPVT Panel is negative.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the 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 sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: CALM1 only whole gene deletions or duplications may be detected.

Gene	Protein	Inheritance	Disease Association(s)
ANK2	ANKYRIN 2	AD	LQTS, CPVT, Arrhythmia
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,LQTS, DCM
TECRL	TRANS-2,3-ENOYL-CoA REDUCTASE-LIKE PROTEIN	AR	CPVT3
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; DCM – Dilated cardiomyopathy; LQTS – Long QT syndrome; SQTS – Short 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)