

Arrhythmogenic Right Ventricular Cardiomyopathy Panel

Disorder also known as: Arrhythmogenic Cardiomyopathy (ACM); Arrhythmogenic Right Ventricular Dysplasia (ARVD); Uhl's Anomaly; Right Ventricular Dysplasia

Panel Gene List: *CTNNA3, DES, DSC2, DSG2, DSP, FLNC, JUP, LDB3, LMNA, PKP2, PLN, RYR2, SCN5A, TGFB3, TMEM43, TTN*

Additional genes from our cardiology test menu may be added to this panel by selecting test code 483C.

Clinical Features:

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a potentially life-threatening heart muscle disease. It is a disorder of the intracellular desmosomal junctions of cardiomyocytes, responsible for providing and maintaining cell-to-cell adhesion. Cardiomyocyte death and progressive fibrofatty replacement of the right ventricular myocardium are pathognomonic hallmarks of ARVC, which predispose to ventricular tachyarrhythmia and sudden cardiac death (SCD). The disease prevalence is estimated at 1:1000 to 1:2500, but may be higher in certain populations because of non-diagnosed or misdiagnosed cases. Patients with ARVC typically develop symptoms between the second and fifth decade of life (mean age at diagnosis 31 years), but age of onset is widely variable.^{1,2}

The most common presenting symptoms of ARVC are heart palpitations, syncope, and SCD. Sometimes, SCD is the first presenting symptom, particularly in young persons and athletes. Many patients may even be asymptomatic and diagnosed only after routine electrocardiogram (ECG). Therefore, disease presentation and severity is also variable. Diagnostic criteria were established by McKenna et al. in 1994 and revised in 2010.^{3,4} Diagnosis using these criteria is based on genetic, electrocardiographic, structural, and functional findings.

Inheritance Pattern/Genetics: Autosomal Dominant or Autosomal Recessive

Test Methods:

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV) (excluding exon 6 of the *PKP2* gene and the following genomic regions of the *TTN* gene: chr2:179527692-179527782, 179523898-179523982, 179523731-179523815). 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; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm

regions with inadequate sequence or copy number data by NGS. 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 Combined Cardiac Panel is available as a separate test if the ARVC Panel is negative.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in the ARVC Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with clearly defined ARVC 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	Protein	Inheritance	Disease Association(s)
<i>CTNNA3</i>	CATENIN ALPHA 3	AD	ARVC
<i>DES</i>	DESMIN	AD, AR	ARVC, AV block, DCM, LGMD, myopathy
<i>DSC2</i>	DESMOCOLLIN 2	AD, AR	ARVC, ARVC+ skin/hair findings, DCM
<i>DSG2</i>	DESMOGLEIN 2	AD	ARVC, DCM
<i>DSP</i>	DESMOPLAKIN	AD, AR	ARVC, DCM, Carvajal syndrome and related disorders
<i>FLNC</i>	FILAMIN C	AD	RCM, HCM, ARVC, DCM, myopathy
<i>JUP</i>	JUNCTION PLAKOGLOBIN	AD, AR	ARVC, Naxos disease and related disorders
<i>LDB3</i>	LIM DOMAIN-BINDING 3	AD	ARVC, DCM, LVNC, LDB3-related myopathies
<i>LMNA</i>	LAMIN A/C	AD, AR	ARVC/ARVC-like disease, DCM, LMNA-related neuromuscular, lipodystrophy, and premature aging disorders
<i>PKP2</i>	PLAKOPHILIN 2	AD	ARVC, BrS
<i>PLN</i>	PHOSPHOLAMBAN	AD	ARVC, DCM, HCM
<i>RYR2</i>	RYANODINE RECEPTOR 2	AD	ARVC, CPVT, DCM, LVNC
<i>SCN5A</i>	SODIUM CHANNEL, VOLTAGE-GATED, TYPE V, ALPHA SUBUNIT	AD	ARVC/ARVC-like disease, BrS, DCM, Heart block, LQTS, SIDS, SSS
<i>TGFB3</i>	TRANSFORMING GROWTH FACTOR, BETA-3	AD	ARVC, Loeys-Dietz syndrome-5, TAAD
<i>TMEM43</i>	TRANSMEMBRANE PROTEIN 43	AD	ARVC, EMD
<i>TTN</i>	TITIN	AD, AR	ARVC, DCM, TTN-related myopathies and muscular dystrophies

Abbreviations: AD – Autosomal dominant; A-fib – Atrial fibrillation; AR – Autosomal recessive; ARVC – Arrhythmogenic Right Ventricular Cardiomyopathy; AV block – atrioventricular block; BrS – Brugada Syndrome; CPVT – Catecholaminergic Polymorphic Ventricular Tachycardia; DCM – Dilated Cardiomyopathy; EMD – Emery Dreifuss Muscular Dystrophy; HCM – Hypertrophic Cardiomyopathy; LGMD – limb-girdle muscular dystrophy; LQTS – Long QT Syndrome; LVNC – left ventricular non-compaction; RCM – Restrictive cardiomyopathy; SIDS- Sudden Infant Death Syndrome; SUDEP – sudden unexpected death and epilepsy; SSS – Sick Sinus Syndrome

References:

1. McNally E, MacLeod H, Dellefave-Castillo L. Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. 2005 Apr 18 [Updated 2014 Jan 9]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1131/>
2. Nava A, Bauce B, Basso C, Muriago M, et al. Clinical profile and long-term follow-up of 37 families with arrhythmogenic right ventricular cardiomyopathy. *J Am Coll Cardiol*. 2000; 36: 2226-33. (PubMed: 11127465)
3. McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia / cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. *Br Heart J*. 1994; 71: 215-8 (PubMed: 8142187)
4. Marcus FI et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: Proposed modification of the Task Force Criteria. *Eur Heart J*. 31:806-814, 2010 (PubMed: 20172912)