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

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). 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. Sequence variants are reported according to the Human Genome Variation Society (HGVS) guidelines. Copy number variants are reported based on the probe coordinates, the coordinates of the exons involved, or precise breakpoints when known. 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.

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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. For *PKP2*, sequencing of exon 6 is not performed, and *TTN*, sequencing of exons 1-171 and 199-363 only. For *SCN5A*, exon level coverage for exons 2-12 and 21-28 only.

Gene	Protein	Inheritance	Disease Association(s)
CTNNA3	CATENIN ALPHA 3	AD	ARVC
DES	DESMIN	AD, AR	ARVC, AV block, DCM, LGMD, myopathy
DSC2	DESMOCOLLIN 2	AD, AR	ARVC, ARVC+ skin/hair findings, DCM
DSG2	DESMOGLEIN 2	AD	ARVC, DCM
DSP	DESMOPLAKIN	AD, AR	ARVC, DCM, Carvajal syndrome and related disorders
FLNC	FILAMIN C	AD	RCM, HCM, ARVC, DCM, myopathy
JUP	JUNCTION PLAKOGLOBIN	AD, AR	ARVC, Naxos disease and related disorders
LDB3	LIM DOMAIN-BINDING 3	AD	ARVC, DCM, LVNC, LDB3-related myopathies
LMNA	LAMIN A/C	AD, AR	ARVC/ARVC-like disease, DCM, LMNA-related neuromuscular, lipodystrophy, and premature aging disorders
PKP2	PLAKOPHILIN 2	AD	ARVC, BrS
PLN	PHOSPHOLAMBAN	AD	ARVC, DCM, HCM
RYR2	RYANODINE RECEPTOR 2	AD	ARVC, CPVT, DCM, LVNC
SCN5A	SODIUM CHANNEL, VOLTAGE-GATED, TYPE V, ALPHA SUBUNIT	AD	ARVC/ARVC-like disease, BrS, DCM, Heart block, LQTS, SIDS, SSS
TGFB3	TRANSFORMING GROWTH FACTOR, BETA-3	AD	ARVC, Loeys-Dietz syndrome-5 , TAAD
TMEM43	TRANSMEMBRANE PROTEIN 43	AD	ARVC, EMD
TTN	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)

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