Arrhythmogenic Right Ventricular Cardiomyopathy Panel

Disorder also known as: Arrhythmogenic Right Ventricular Dysplasia (ARVD); Uhl Anomaly; Right Ventricular Dysplasia

Panel Gene List: *DES, DSC2, DSG2, DSP, JUP, 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 from the submitted specimen, the coding regions and splice junctions of the 13 genes (except for exon 6 for *PKP2*) 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). 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 13 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 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)
DES	DESMIN	AD, AR	DCM, ARVC, AV block, myopathy, LGMD
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
JUP	JUNCTION PLAKOGLOBIN	AD, AR	ARVC, Naxos disease and related disorders
LMNA	LAMIN A/C	AD, AR	DCM, HCM, ARVC/ARVC-like disease, LMNA-related neuromuscular, lipodystrophy and premature aging disorders
PKP2	PLAKOPHILIN 2	AD	ARVC, BrS
PLN	PHOSPHOLAMBAN	AD	DCM, HCM, ARVC
RYR2	RYANODINE RECEPTOR 2	AD	ARVC, CPVT
SCN5A	SODIUM CHANNEL, VOLTAGE-GATED, TYPE V, ALPHA SUBUNIT	AD, AR	BrS, DCM, ARVC/ARVC-like disease, Heart block, LQTS, SSS, SIDS
TGFB3	TRANSFORMING GROWTH FACTOR, BETA-3	AD	ARVC, Loeys-Dietz syndrome
TMEM43	TRANSMEMBRANE PROTEIN 43	AD	ARVC, EMD
TTN	TITIN	AD, AR	DCM, ARVC, TTN-related myopathies and muscular dystrophies

Abbreviations: AD – Autosomal dominant; AR – Autosomal recessive; ARVC – Arrhythmogenic Right Ventricular Cardiomyopathy; BrS – Brugada Syndrome; RCM – Restrictive Cardiomyopathy; CPVT – Catecholaminergic Polymorphic Ventricular Tachycardia; DCM – Dilated Cardiomyopathy; EMD – Emery Dreifuss Muscular Dystrophy; HCM – Hypertrophic Cardiomyopathy; LQTS – Long QT Syndrome; SSS – Sick Sinus Syndrome; SIDS- Sudden Infant Death 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)