Cardiovascular Diseases Genetic Testing Program

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Panel

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), also known as Arrhythmogenic Right Ventricular Dysplasia (ARVD), is a disorder of the cardiac desmosome. It is characterized by myocyte loss and fibrofatty infiltration of the myocardium. ARVC is associated with an increased susceptibility to ventricular tachyarrhythmia and sudden cardiac death. ARVC primarily affects the right ventricle, however the left ventricle can also be affected.

The estimated prevalence of ARVC has been reported as high as 1 in 1,000. The majority of affected individuals present with heart palpitations, syncope, or sudden cardiac death between the second and fifth decade of life. Diagnostic criteria for ARVC were established by McKenna et al in 1994, and were revised in 2010. The diagnostic approach includes electrocardiographic findings, presence of arrhythmias, structural defects, histopathological features, and genetic/family history information.

ARVC is primarily associated with mutations in the desmosomal genes *JUP*, *DSP*, *DSC2*, *DSG2*, and *PKP2*; however mutations in several nondesmosomal genes have also been described. Current genetic testing will identify a disease-causing mutation in approximately 50% of affected individuals. Autosomal dominant, autosomal recessive and digenic inheritance have all been described. Compound heterozygosity has been reported in a significant number of individuals with ARVC. ARVC is known to exhibit reduced penetrance and variable expressivity.

Indication

The ARVC Panel is indicated for individuals with clinical suspicion for ARVC.

Genes sequenced in the ARVC Panel:
DSC2, *DSG2*, *DSP*, *JUP*, *PKP2*, *RYR2*, *TGFB3*, *TMEM43*, *LMNA*, *PLN*, *DES*, *TTN*, and *LDB3*.

Molecular Genetics Laboratory

Shipping Instructions

Please enclose a test requisition form with sample. All information must be complete before sample can be processed. Samples may be shipped at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship to:

Molecular Genetics Lab
Cincinnati Children's Hospital
3333 Burnet Ave. NRB 1042
Cincinnati, OH 45229

Phone: 513-636-4474
Fax: 513-636-4373

Methodology:

Next Generation Sequencing: All coding exons, as well as their flanking regions, of the genes listed in the panel are enriched from the patient's genomic DNA and sequenced using a solid-state sequencing-by-synthesis process. DNA sequences are assembled and compared to the published genomic reference sequences in Genome Reference Consortium Build 37. Dideoxy DNA sequencing is used to provide data for bases with insufficient coverage and to confirm the reported variants from next-generation sequencing. This assay does not detect variants in the promoter regions, deep intronic regions, or other regulatory elements, and does not detect large deletions or mosaicisms. Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen).

Sensitivity & Accuracy:

Analytical Sensitivity and Specificity
Validation testing indicates an analytic sensitivity of greater than 99.7% and an analytic specificity of 100%.
Clinical Sensitivity
Based on the literatures, the clinical sensitivity is determined to be over 42.5%.

References:

1. McNally E, MacLeod H, Dellefave L. Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy, Autosomal Dominant. 2005 Apr 18 [Updated 2009 Oct 13]. In: Pagon RA, Bird TD, Dolan CR, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-.

2. Basso C, Wichter T, Danieli GA, Corrado D, Czarnowska E, Fontaine G, McKenna WJ, Nava A, Protonotarios N, Antoniades L, Wlodarska K, D'Alessi F, Thiene G. 2004. Arrhythmogenic right ventricular cardiomyopathy: clinical registry and database, evaluation of therapies, pathology registry, DNA banking. *European Heart Journal*. 25: 531-534.

3. Pilichou K, Nava A, Basso C, Beffagna G, Bauce B, Lorenzon A, Frigo G, Vettori A, Valente M, Towbin J, Thiene G, Danieli GA, Rampazzo A. Mutations in desmoglein-2 gene are associated with Arrhythmogenic right ventricular cardiomyopathy. *Circulation*. 2006;113:1171–9.

4. The McKenna paper and the revision mentioned above for the diagnostic criteria of ARVC.

5. 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. *British Heart Journal*. 1994: 71: 215-8 (PubMed: 8142187).

6. Marcus FI et al. Diagnosis of Arrhythmogenic right ventricular cardiomyopathy/dysplasia: Proposed modification of the Task Force Criteria. *European Heart Journal*. 31:806-814, 2010 (PubMed: 20172912).

Specimen:

Peripheral blood in EDTA tube
Adult: 3-5mL
Child: 3-5mL
Infant: 1-3mL
For other specimen types, please contact us at 513-636-4474

Turnaround Time:

Panel Analysis 8-10 weeks
Known Mutation Analysis 1-2 weeks

CPT Codes:

Panel Sequencing: 81403, 81405, 81406 x7, 81408, 81479 x3
Additional Family Members: 81403

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