

Arrhythmogenic Right Ventricular Cardiomyopathy/ Dysplasia via *DSC2* Gene Sequencing -- Test #206

Brief Description of Clinical Features: Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D, OMIM 107970) is a heart disease primary affecting the right ventricle. It is characterized by myocardial atrophy, fibrofatty replacement of the ventricular myocardium and inflammatory infiltrates. With disease progression and occasional left ventricle involvement, heart failure may result. The most common symptoms include ventricular arrhythmias, recurrent syncope, seizures and sudden death after physical or emotional stress. ARVC/D is present in ~20% of young sudden cardiac death victims (Corrado et al. N Engl J Med 339:364-369, 1998). ARVC/D affects between 1/1000 and 1/5000 people worldwide with a higher prevalence in men compared to women (Corrado and Thiene, Circulation, 113:1634-1637, 2006). See also the Cardiomyopathy Association at (www.cardiomyopathy.org) and McNally et al. (GeneReviews, 2009, www.genetests.org).

Genetics: ARVC/D is a heterogeneous disease that is inherited in about 50% of the cases (Basso et al. Eur Heart J 25:531-534, 2004). The mode of inheritance is most often autosomal dominant with age- and gender-dependent penetrance. Autosomal recessive variants of ARVC/D with hair and skin abnormalities have been described (Protonotarios et al. Br Heart J 56:321-326, 1986). To date, eight genes have been implicated in ARVC/D. Mutations in three genes: *PKP2*, *DSP* and *DSG2*, encoding desmosomal proteins, account for the great majority of known genetic causes of ARVC/D (McNally et al. GeneReviews, 2009, www.genetests.org; Bhuiyan et al. Circ Cardiovasc Genet 2:418-427, 2009). More recently, mutations in the *DSC2* gene were reported in patients with ARVC/D (Heuser et al. Am J Hum Genet 79:1081-1088, 2006). To date, six heterozygous *DSC2* mutations have been reported. Mutations were a mix of missense, splicing and small insertion or deletions. Recently, a homozygous single base deletion, c.1841delG, predicted to result in a truncated protein, has been detected in a consanguineous family of Pakistani origin (Simpson et al. Cardiology 113:28-34, 2009). Affected siblings presented with ARVC with left ventricular involvement, mild palmoplantar keratoderma and woolly hair.

Description of This Particular Test: The *DSC2* gene encodes the desmocollin-2 protein. This test involves bidirectional DNA sequencing of all 16 coding exons and splice sites of the *DSC2* gene. The full coding sequence of each exon plus ~50 bp of flanking DNA on either side are sequenced.

Reference Sequences: Genomic: NC_000018.9 mRNA: NM_024422.3 Protein: NP_077740.1 (CCDS 11892.1)

Indications for Test: Patients with ARVC/D and no mutations in the *PKP2*, *DSP* or *DSG2* genes, and patients with ARVC associated with palmoplantar keratoderma and woolly hair (Simpson, 2009).

Sensitivity of Test: This test will detect mutations in ~2% of patients with clinical diagnosis of ARVC/D (Bhuiyan et al. Circ Cardiovasc Genet 2:418-427, 2009).

Turn Around Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: **Sequencing of *DSC2* Gene, Exons 1- 15, 17** **\$ 900**

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x 16	83898 \$ 260	Sequencing x16	83904 \$ 400
Separation x1	83894 \$ 70	Interpretation/Report x1	83912 \$ 100

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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