

Arrhythmogenic Right Ventricular Cardiomyopathy/ Dysplasia and Related Disorders via *DSP* Gene Sequencing -- Test #203

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).

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 (AD) with age- and gender-dependent penetrance. Autosomal recessive (AR) variants of ARVC/D with hair and skin abnormalities have been described. 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). At least 32 *DSP* mutations have been reported. Fifteen of these were detected in patients with AD-ARVC/D and included nonsense, missense and splicing mutations (see for example Rampazzo et al. Am J Hum Genet 71:1200-1206, 2002). A single adenine insertion (2034insA) was reported in a large family with arrhythmogenic left ventricular cardiomyopathy (ALVC) (Norman et al. Circulation 112:636-642, 2005). Other *DSP* mutations were found in the AR variants of ARVC/D including Skin Fragility-Woolly Hair Syndrome (SFWS), Dilated Cardiomyopathy with Woolly Hair and Keratoderma (DCWHK), Ectodermal Dysplasia, and Epidermolysis Bullosa.

Description of This Particular Test: The *DSP* gene encodes desmoplakin, which is the most abundant protein of desmosomes. This test involves bidirectional DNA sequencing of all 24 coding exons and splice sites of the *DSP* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced.

Reference Sequences: Genomic: NC_000006.11 mRNA: NM_004415.2 Protein: NP_004406.2 (CCDS 4501.1)

Indications for Test: Candidates for this test are patients presenting with symptoms suggestive of: ARVC/D (OMIM 107970), ALVC (Norman et al. 2005), SFWS (OMIM 607655), DCWHK (OMIM 605676), Ectodermal Dysplasia (OMIM 604536) and Epidermolysis Bullosa (OMIM 609638).

Sensitivity of Test: This test will detect mutations in up to 16% of patients with clinical diagnosis of ARVC/D (Bauce et al. Eur Heart J 26:1666-1675, 2005).

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

Specimen Requirements: See bottom of page 2 of Requisition Form.

Price: Sequencing of *DSP* Gene, Exons 1- 24 \$ 1820

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x 41	83898 \$ 600	Sequencing x 41	83904 \$ 900
Separation x1	83894 \$ 110	Interpretation/Report x1	83912 \$ 140

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/11) (CAP#: 7185561, AU ID: 1407125 expires 12/20/10)

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