

Arrhythmogenic Right Ventricular Cardiomyopathy/ Dysplasia via *PKP2* Gene Sequencing -- Test #204

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 (AD) 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). 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; Gerull et al. Nat Genet 36:1162-1164, 2004). Over 70 heterozygous *PKP2* mutations, distributed throughout the coding region, have been reported. The majority of mutations were nonsense, small insertion/deletion or splice site mutations, which are predicted to result in nonsense mediated mRNA decay or a truncated protein (<http://www.biobase-international.com>). *PKP2* mutations have been detected in patients with diverse ethnic backgrounds and represent a major cause of ARVC/D (van Tintelen et al. Circulation 113:1650-1658, 2006).

Description of This Particular Test: The *PKP2* gene encodes plakophilin-2, a component of the cardiac desmosome. As required, this test involves bidirectional DNA sequencing of all 14 coding exons and splice sites of the *PKP2* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced.

Reference Sequences: Genomic: NC_000012.11 mRNA: NM_004572.3 Protein: NP_004563.2 (CCDS 8731.1)

Indications for Test: All patients with symptoms suggestive of ARVC/D.

Sensitivity of Test: This test will detect mutations in up to 43% of patients with clinical diagnosis of ARVC/D (van Tintelen et al. Circulation 113:1650-1658, 2006; Dalal et al. Circulation, 113:1641-1649, 2006).

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 *PKP2* Gene, Exons 1- 14 \$ 820

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x 14	83898 \$ 240	Sequencing x14	83904 \$ 370
Separation x1	83894 \$ 60	Interpretation/Report x1	83912 \$ 80

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

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