

Laboratory for Molecular Medicine
Harvard Medical School and Partners Healthcare
Center for Genetics and Genomics
<http://www.hpcgg.org/lmm>

65 Landsdowne Street
Cambridge, MA 02139
Tel: 617-768-8500
Fax: 617-768-8513

CLIA# 22D1005307

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) Gene Tests

Background:

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) is a heritable heart disease estimated to affect approximately 1/5,000 individuals in the general population. Characteristic features include progressive replacement of cardiac myocytes by fibrofatty tissue, predominantly in the right ventricle. Left ventricular involvement is reported in up to 75% of patients. Individuals typically present with ventricular tachyarrhythmias and sudden death in young individuals and athletes is common. A clinical diagnosis of ARVD/C is often difficult to confirm thus in addition to personal and family histories, a combination of noninvasive and invasive tests is needed to make a diagnosis. In addition, genetic testing to identify at-risk individuals is highly advantageous.

In about 50% of cases with isolated ARVD/C the disease is familial. Autosomal dominant transmission is the predominant mode of inheritance although incomplete penetrance and variable expressivity are common. Most pathogenic ARVD/C variants (often called mutations) identified to date occur in components of the desmosome, an intracellular structure involved in cell-cell adhesion. Desmosomes help to resist shearing forces and are therefore most prevalent in tissues exposed to mechanical stress, such as the myocardium and epithelium.

Desmosomal genes in which dominant variants have been identified include plakophilin-2 (*PKP2*), desmoplakin (*DSP*), desmoglein-2 (*DSG2*) and desmocollin-2 (*DSC2*). About 50% of ARVD/C patients are found to have a variant in one of these genes, most of which occur in *PKP2* (reviewed in Awad 2008). Three additional extradesmosomal genes have been implicated in ARVD/C. Variants in the cardiac ryanodine receptor (*RYR2*) cause a distinct clinical entity with similarity to ARVD/C (ARVD2), characterized by juvenile sudden cardiac death and polymorphic ventricular tachycardia (Tiso 2001). In addition, variants in the untranslated regions of transforming growth factor beta 3 (*TGFB3*) were found in one family as well as an unrelated ARVD/C proband (Befanga 2005, Nattel 2006). Recently, a disease causing missense variant was identified in the transmembrane protein 43 (*TMEM43*) (Merner 2008).

ARVD/C can also occur as part of rare recessive syndromes (reviewed in Van Tintelen 2007). Naxos disease (ARVD/C with non-epidermolytic palmoplantar keratoderma and wooly hair) has been associated with a homozygous 2 bp deletion in the *JUP* gene and homozygous *DSP* variants have been described in patients with a similar clinical presentation (Naxon-like disease). Homozygous *DSP* variants have also been described in Carvajal syndrome (dilated cardiomyopathy, wooly hair and palmoplantar keratoderma).

In addition to confirming the diagnosis of ARVD/C in patients with suspected disease, genetic testing allows for early identification and diagnosis of individuals at greatest risk for developing ARVD/C, prior

to the expression of typical clinical manifestations. If a pathogenic variant is identified in such a preclinical individual, regular follow up is indicated. If clinically unaffected relatives of a proband with an identified pathogenic variant are found not to carry that variant (genotype negative), they can be definitely diagnosed as unaffected and reassured that neither they nor their offspring will be at higher risk compared to the general population to develop ARVD/C.

Synonyms:

- ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL

ARVD/C Genetic Tests

- Direct DNA sequencing will be performed to detect variants in the genes most commonly associated with ARVD/C:

Gene	Protein	Locus	Exons Tested	Reference Sequence
<i>DSP</i>	Desmoplakin	6p24 (ARVD8)	1-24	NM_004415.2
<i>DSG2</i>	Desmoglein 2	18q12.1-q12.2 (ARVD10)	1-15	NM_001943.2
<i>DSC2</i>	Desmocollin 2	18q12.1 (ARVD11)	1-15, 15b, 16	NM_024422.2, NM_004949.2 (15b)
<i>PKP2</i>	Plakophilin 2	12p11 (ARVD9)	1-14	NM_004572.3
<i>TMEM43</i>	Transmembrane protein 43	3p25.1 (ARVD5)	1-12	NM_024334.1

Epidemiology:

- Estimated prevalence of ~1/5,000
- No known racial predilection

Clinical Manifestations (variable, and may not occur in every patient):

- Shortness of breath, chest pain, exercise intolerance, edema, syncope, fatigue, dizziness
- Ventricular tachyarrhythmias
- Syncope or cardiac arrest
- Cardiac structure and rhythm abnormalities as seen on noninvasive and invasive testing

Inheritance Pattern:

Autosomal dominant (majority of cases; *DSP*, *DSG2*, *DSC2*, *PKP2*, *TMEM43*)

- The presence of a pathogenic variant in one copy of the above listed genes is sufficient to cause ARVD/C.
- Children of an affected individual with an identified pathogenic variant have a 50% (or 1 in 2) chance of inheriting the same variant.
- Reduced penetrance and variable expressivity is common.
- If parents do not carry a variant identified in their affected child, the risk to have a second affected child is low (<3-4%) but above the population risk because of the possibility of germline mosaicism.

Autosomal Recessive (rare; *JUP*, *DSP*, *PKP2*)

- The presence of a pathogenic variant in two copies of the *DSP*, *PKP2*, or *JUP* gene is sufficient to cause ARVD/C (*PKP2*), Naxos syndrome (*JUP*), Carvajal syndrome (*DSP*) and Naxos-like disease (*DSP*).
- Each child of a carrier couple is at a 25% (or 1 in 4) chance of inheriting this condition.

Test Indications:

- Individuals with clinical features of ARVD/C
- Parents, siblings, and possibly children of a patient diagnosed with a pathogenic variant in one of the ARVD/C genes.
- Prenatal testing when a parent or child is diagnosed with ARVD/C and has an identified ARVD/C variant.

Test Outcomes:

- The detection of one pathogenic variant in *DSP*, *DSG2*, *DSC2*, *PKP2* or *TMEM43*, confirms a diagnosis of ARVD/C. If a familial pathogenic variant is known, a targeted known variant test can detect the variant in asymptomatic family members.
- A negative test result should be interpreted with caution. Sequencing does not detect large deletions spanning several exons, or variants in non-coding regions that could affect expression of these genes. In addition, variants in other genes not included in this test could be responsible for the individual's clinical features.
- Referral to a cardiology center with expertise in the management of ARVD/C is highly recommended.

Turn-Around-Times:

- ARVD/C Panel (all five genes): 6 weeks
- Any single gene test: 3 weeks (per gene)

Methodology: Bi-directional sequence analysis is performed on 82 exons and splice sites in the five genes of the ARVD/C panel. Genes may also be ordered individually. These tests do not detect variants in non-coding regions that could affect gene expression or deletions encompassing a large portion of the gene.

Analytical Sensitivity: This assay has greater than 99.9% accuracy to detect variants in the sequence analyzed.

Clinical Sensitivity: The overall detection rate of variants by screening patients with clinical symptoms and/or features of ARVD/C are:

Gene	Detection Rate
ARVD/C Panel	~50% (Awad 2008)
<i>DSP</i>	~6-16% (Pilichou, 2006; Bauce, 2005; Yang, 2006)
<i>DSG2</i>	~10-12% (Awad, 2006; Syrris, 2007; Pilichou, 2006)
<i>DSC2</i>	~1-5% (Heuser, 2006; Syrris 2006)
<i>PKP2</i>	~11-43% (Dalal, 2006; Dalal, 2006; Gerull, 2004; Pilichou, 2006)
<i>TMEM43</i>	Detection rate unknown

Cost and CPT Codes:

ARVD/C Panel (*DSP, DSG2, DSC2, PKP2, TMEM43*):

- Cost: \$3,000
- CPT codes: 83891(1), 83894(1), 83898(94), 83904(94), 83909(1), 83912(1)

DSP Gene Sequencing

- Cost: \$1,700
- CPT codes: 83891(1), 83894(1), 83898(36), 83904(36), 83909(1), 83912(1)

DSG2 Gene Sequencing

- Cost: \$1,075
- CPT codes: 83891(1), 83894(1), 83898(17), 83904(17), 83909(1), 83912(1)

DSC2 Gene Sequencing

- Cost: \$1,150
- CPT codes: 83891(1), 83894(1), 83898(18), 83904(18), 83909(1), 83912(1)

PKP2 Gene Sequencing

- Cost: \$1,500
- CPT codes: 83891(1), 83894(1), 83898(16), 83904(16), 83909(1), 83912(1)

TMEM43 Gene Sequencing

- Cost: \$700
- CPT codes: 83891(1), 83894(1), 83898(10), 83904(10), 83909(1), 83912(1)

Testing for Known Familial Variant

- Cost: \$250
- CPT codes: 83891(1), 83894(1), 83898(1), 83904(1), 83909(1), 83912(1)

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If you have any questions, please call the Laboratory for Molecular Medicine at 617-768-8500 or email us at LMM@partners.org

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