



Laboratory for Molecular Medicine  
Partners Center for Personalized Genetic Medicine  
<http://www.hpcgg.org/lmm>  
CLIA#22D1005307

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

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

### **Background:**

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) is a form of heritable heart disease estimated to affect approximately 1/5,000 individuals in the general population. Characteristic features include progressive replacement of myocytes by fibrofatty tissue, predominantly in the right ventricle. Left ventricular involvement with fibrofatty replacement, chamber enlargement and myocarditis 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 ARVD/C pathogenic variants 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 pathogenic variants have been identified include plakophilin-2 (PKP2), desmoplakin (DSP), desmoglein-2 (DSG2), desmocollin-2 (DSC2) and plakoglobin gene (JUP). About 50% of ARVD/C patients are found to have a pathogenic variants 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 (ARVD2), characterized by juvenile sudden cardiac death and polymorphic ventricular tachycardia (Tiso 2001) and 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 (Beffanga 2005, Nattel 2006). Recently, a missense variant was identified in the transmembrane protein 43 (TMEM43) (Merner 2008).

Recessive syndromic ARVD/C known as "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 as well as homozygous pathogenic variants in the DSP gene. Another recessive syndrome with clinical overlap is Carvahal syndrome syndrome (dilated cardiomyopathy, wooly hair and palmoplantar keratoderma), which is caused by homozygous DSP pathogenic variants (reviewed in Van Tintelen 2007).

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 for ARVD/C are found not to carry that variant (genotype negative), they can be definitely diagnosed as unaffected with ARVD/C and reassured that neither they nor their offspring will be at higher risk compared to the general population to develop the disorder.

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

**Epidemiology:**

- Estimated prevalence of 6/10,000
- 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 are not variant carriers, 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; *DSP*, *PKP2*, *JUP*)

- 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 pathogenic 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 positive test result confirms the presence of the variant in an asymptomatic family member.
- 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 looked at by 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 Pathogenic Variant

- Cost: \$400
- CPT codes: 83891(1), 83894(1), 83898(1), 83904(1), 83909(1), 83912(1)

**References**

GeneTests Disease Review for Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy, Autosomal Dominant: [www.GeneTests.com](http://www.GeneTests.com).

Antoniades L, Tsatsopoulou A, Anastasakis A, Syrris P, Asimaki A, Panagiotakos D, Zambartas C, Stefanadis C, McKenna WJ, Protonotarios N (2006). Arrhythmogenic right ventricular cardiomyopathy caused by deletions in plakophilin-2 and plakoglobin (Naxos disease) in families from Greece and Cyprus: genotype-phenotype relations, diagnostic features and prognosis. *Eur Heart J*. Sep;27(18):2208-16.

Awad MM, Dalal D, Tichnell C, James C, Tucker A, Abraham T, Spevak PJ, Calkins H, Judge DP (2006). Recessive arrhythmogenic right ventricular dysplasia due to novel cryptic splice mutation in PKP2. *Hum Mutat*. Nov;27(11):1157.

Awad MM, Dalal D, Cho E, Amat-Alarcon N, James C, Tichnell C, Tucker A, Russell SD, Bluemke DA, Dietz HC, Calkins H, Judge DP. (2006). *DSG2* mutations contribute to arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Am J Hum Genet*. Jul;79(1):136-42

Beffagna G, Occhi G, Nava A, Vitiello L, Ditadi A, Basso C, Bauce B, Carraro G, Thiene G, Towbin JA and others (2005). Regulatory mutations in transforming growth factor-beta3 gene cause arrhythmogenic right ventricular cardiomyopathy type. *Cardiovasc Res* 65(2):366-73.

Bauce B, Basso C, Rampazzo A, Beffagna G, Daliento L, Frigo G, Malacrida S, Settimo L, Danieli G, Thiene G, Nava A. (2005). Clinical profile of four families with arrhythmogenic right ventricular cardiomyopathy caused by dominant desmoplakin mutations. *Eur Heart J.* Aug;26(16):1666-75.

Dalal D, James C, Devanagondi R, Tichnell C, Tucker A, Prakasa K, Spevak PJ, Bluemke DA, Abraham T, Russell SD, Calkins H, Judge DP (2006). Penetrance of mutations in plakophilin-2 among families with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Am Coll Cardiol.* Oct 3;48(7):1416-24.

Dalal D, Molin LH, Piccini J, Tichnell C, James C, Bomma C, Prakasa K, Towbin JA, Marcus FI, Spevak PJ, Bluemke DA, Abraham T, Russell SD, Calkins H, Judge DP (2006). Clinical features of arrhythmogenic right ventricular dysplasia/cardiomyopathy associated with mutations in plakophilin-2. *Circulation.* Apr 4;113(13):1641-9.

Gerull B, Heuser A, Wichter T, Paul M, Basson CT, McDermott DA, Lerman BB, Markowitz SM, Ellinor PT, MacRae CA, Peters S, Grossmann KS, Drenckhahn J, Michely B, Sasse-Klaassen S, Birchmeier W, Dietz R, Breithardt G, Schulze-Bahr E, Thierfelder L (2004). Mutations in the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy. *Nat Genet.* Nov;36(11):1162-4.

Heuser A, Plovie ER, Ellinor PT, Grossmann KS, Shin JT, Wichter T, Basson CT, Lerman BB, Sasse-Klaassen S, Thierfelder L, MacRae CA, Gerull B (2006). Mutant desmocollin-2 causes arrhythmogenic right ventricular cardiomyopathy. *Am J Hum Genet.* Dec;79(6):1081-8.

Merner ND, Hodgkinson KA, Haywood AF, Connors S, French VM, Drenckhahn JD, Kupprion C, Ramadanova K, Thierfelder L, McKenna W, Gallagher B, Morris-Larkin L, Bassett AS, Parfrey PS, Young TL (2008). Arrhythmogenic right ventricular cardiomyopathy type 5 is a fully penetrant, lethal arrhythmic disorder caused by a missense mutation in the TMEM43 gene. *Am J Hum Genet.* Apr;82(4):809-21.

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 (2006). Mutations in desmoglein-2 gene are associated with arrhythmogenic right ventricular cardiomyopathy. *Circulation.* Mar 7;113(9):1171-9.

Rampazzo A, Nava A, Malacrida S, Beffagna G, Bauce B, Rossi V, Zimbello R, Simionati B, Basso C, Thiene G, Towbin JA, Danieli GA (2002). Mutation in human desmoplakin domain binding to plakoglobin causes a dominant form of arrhythmogenic right ventricular cardiomyopathy. *Am J Hum Genet.* Nov;71(5):1200-6.

Syrris P, Ward D, Evans A, Asimaki A, Gandjbakhch E, Sen-Chowdhry S, McKenna WJ (2006). Arrhythmogenic right ventricular dysplasia/cardiomyopathy associated with mutations in the desmosomal gene desmocollin-2. *Am J Hum Genet.* Nov;79(5):978-84.

Syrris P, Ward D, Asimaki A, Evans A, Sen-Chowdhry S, Hughes SE, McKenna WJ (2007). Desmoglein-2 mutations in arrhythmogenic right ventricular cardiomyopathy: a genotype-phenotype characterization of familial disease. *Eur Heart J.* Mar;28(5):581-8.

Yang Z, Bowles NE, Scherer SE, Taylor MD, Kearney DL, Ge S, Nadvoretzkiy VV, DeFreitas G, Carabello B, Brandon LI, Godel LM, Green KJ, Saffitz JE, Li H, Danieli GA, Calkins H, Marcus F, Towbin JA (2006). Desmosomal dysfunction due to mutations in desmoplakin causes arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circ Res.* Sep 15;99(6):646-55.