

STATE-OF-THE-ART PAPER

# Genetics of Arrhythmogenic Right Ventricular Cardiomyopathy

## A Practical Guide for Physicians

Frank I. Marcus, MD,\* Sue Edson,† Jeffrey A. Towbin, MD‡

*Tucson, Arizona; Grand Junction, Colorado; and Cincinnati, Ohio*

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically transmitted disease. However, the genetics are more complex than in other inherited conditions wherein a single gene abnormal mutation may be causative. In ARVC, 5 causative desmosomal genes have been identified, but because only 30% to 50% of patients with ARVC have 1 of these gene abnormalities, it is assumed that there are other genes not yet identified. Frequently, patients with ARVC have >1 genetic defect in the same gene (compound heterozygosity) or in a second complementary gene (digenic heterozygosity). In addition, a family member may have an ARVC gene defect and have development of the disease or have no or minimal manifestations of the disease. Clinical genetic testing is commercially available. It is beneficial for first-degree family members of a person with ARVC to have genetic testing but only if there is a known genetic abnormality in the affected person. If the affected family member (proband) with ARVC does not have a genetic defect identified, then it will not be identified in the family member. Genetic counseling is strongly advised for family members of the proband. (J Am Coll Cardiol 2013; 61:1945–8) © 2013 by the American College of Cardiology Foundation

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is caused by abnormalities in heart cells that connect to each other through cell-cell contacts known as the intercalated disc, with abnormalities in a portion of the intercalated disc called the desmosome. Typically, this abnormality causes a disruption of the normal structure and function of specific desmosomal proteins, leading to “pulling apart” of these cell-cell contacts. In ARVC, the muscle cells affected initially are primarily in the right ventricle, although the left ventricle may be involved later in the course of ARVC or occasionally be an early or predominant site of the disease (1). ARVC is inherited as an autosomal dominant trait, meaning that the risk of a family member inheriting an abnormal gene is 50% for all offspring of the genetically affected proband, whether male or female. Only 30% to 50% of patients with ARVC have an abnormal gene that has been identified as causative of the disease (Table 1) (2,3). This percent is variable and ranges from 26% to 58%, with the higher percent in patients with clinical familial disease (4,5). Other ARVC patients may have abnormal genes, but

they have not yet been found. Mutations may be inherited from a parent or may be the result of a new mutation. Approximately 20% to 30% of patients with ARVC have a family history of ARVC or of sudden death. Once a person has a mutation, whether inherited or a new mutation, there is a 50% chance that the mutation will be passed on to the children of the person with the mutation.

Desmosomes are present not only in the cardiac muscle but also in the skin and hair follicles. If both parents have the same genetic desmosomal abnormalities, then the children will all inherit the desmosomal defect that may involve the skin as well as the heart. One of these conditions is known as Naxos disease and involves mutations in genes encoding the cell adhesion proteins plakoglobin and desmoplakin (6). The affected persons have thickened palms and soles of their feet as well as the cardiac manifestation of right ventricle cardiomyopathy. Another variety of this type of inheritance has been reported from Ecuador and is called Carvajal syndrome in which the cardiac involvement primarily involves the left ventricle.

A person who has a gene mutation for ARVC inherits the risk of having the disease but may or may not develop signs and symptoms of the disease. Other factors such as the presence of an additional gene abnormality or 2 abnormalities within the same class of genes such as plakophilin-2, exposure to certain viruses, athletic lifestyle, and so forth, can determine whether the person is clinically affected with ARVC. This is an area of active research.

From the \*Section of Cardiology, Department of Medicine, University of Arizona College of Medicine, Tucson, Arizona; †ARVD Heart for Hope, Grand Junction, Colorado; and the ‡Department of Pediatric Cardiology, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio. The underlying research reported in the paper was funded by the U.S. National Institutes of Health. The authors have reported they have no relationships relevant to the contents of this paper to disclose.

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**Abbreviation and Acronym**

**ARVC** = arrhythmogenic right ventricular cardiomyopathy

**Genetic Testing**

Genetic testing can be useful to determine whether a person who is suspected of having ARVC has the disease. It is also useful to identify relatives who do not

have signs or symptoms of ARVC but have the gene defect. Mutation-specific testing is recommended when a genetic diagnosis of ARVC is made in the family member (proband) to determine the possible risk in close relatives (7). The test can be helpful in several ways. If a person has a gene thought to be causal for ARVC and has first-degree relatives (brothers, sisters, children), the finding of the same gene defect in a family member indicates that they are at risk and should be evaluated at intervals to determine whether the disease becomes evident. If an abnormal gene is present in the proband and not in family members, it is unlikely that the family members have the disease or will have the disease based on that genetic abnormality. However, the proband may have a second gene defect not identified that could confound this assumption. If no genetic abnormalities are found in the proband, this is not unequivocal evidence that the disease is not caused by a gene mutation because fewer than half of the genetic causes of ARVC are currently known. When the affected proband has the causative gene definitively identified and family members are found to carry the same gene defect, periodic heart screening is required whether or not they have signs or symptoms of the disease. If genetic testing is not performed in relatives, there may be a psychological impact on these persons who must reconcile themselves to lifelong screenings without the prospect of a definite diagnosis. The other alternative would be to presume that they do not have the disease and accept the possibility that a minority of them and/or their children could experience a tragic cardiac event.

There are several observations that complicate the interpretation of genetic testing for ARVC. In general, the ARVC genes cause mutations in desmosomal proteins that disturb cell-cell contacts. The gene that has most commonly been reported to cause clinical signs or symptoms of ARVC is called plakophilin-2. However, this genetic abnormality may require a second mutation in that gene or in another desmosomal gene to cause signs or symptoms of ARVC. The interpretation of an “abnormal gene” for ARVC must also take into consideration the probability that the gene that is identified as abnormal is indeed causative. A truly abnormal desmosomal gene identified as causing the disease is not supposed to be found in >1 in 400 persons who do not have the disease. Yet it has been reported that 1 in every 200 healthy Finnish people have a desmosomal mutation that may predispose to ARVC (8). Other studies have shown that in persons of Asian descent, as many as 6% of healthy controls have an “abnormal” plakophilin-2 gene (5,9). The genetic test laboratory generally provides information relating to the specificity of the suspected genetic

abnormality but because of the complex genetics of ARVC, even these reports can be difficult to interpret. Genetic counseling is important to help clarify the results.

An additional problem in interpreting tests results is that as many as 48% of people who clearly have the disease may have at least 2 different genetic mutations (4,10-13). In general, persons who have 2 mutations usually have more severe signs and symptoms of ARVC. Because not all the genes associated with ARVC have been identified, consider the following scenario: A person has clinical evidence of ARVC, and a “pathological gene” (e.g., plakophilin-2) is identified. That person may have an additional gene defect that has not been recognized. Suppose that proband’s family members are tested genetically and do not have the plakophilin-2 gene, and they assume that they do not have the possibility of developing ARVC. However, those persons actually do have a chance of having an unknown gene that is present in the affected proband (together with the plakophilin-2 mutation) that actually causes the disease. If this unidentified gene is transmitted from the proband with ARVC who has the 2 gene defects to the family members, then the disease may develop in them even though the plakophilin-2 mutation is not transmitted (14). That is important because the family members who have the otherwise unknown gene defect are clearly at risk but may have been told otherwise. Therefore, the family members who are “gene negative” should probably have intermittent examinations for the disease even if they, too, test gene negative.

Periodic examinations of persons who test positive for an ARVC genetic abnormality but do not have evidence of the disease should be performed as follows: Cardiac evaluation should begin at 10 to 12 years of age because the disease rarely expresses itself before then. Suggested tests include an electrocardiogram, signal-averaged electrocardiogram, echocardiogram, possibly a magnetic resonance imaging examination, and a Holter monitor. It is suggested that evaluation be done every 2 years between the ages of 10 and 20 years, and every 5 years after 20 years of age. Screening can be stopped

**Table 1** **Desmosomal Genetic Mutations and Distribution of Desmosomal Genetic Abnormalities in 2 Large Series of Patients With Arrhythmogenic Right Ventricular Cardiomyopathy**

Desmosomal Genetic Mutations	Series A (4)	Series B (5)
Total number of patients	198	175
Patients with positive desmosomal genetic abnormalities	52 (26.7%)	102 (58%)
<b>Distribution of Desmosomal Genetic Abnormalities (n = 52)* (n = 102)†</b>		
Plakophilin-2	73.0%	78.4%
Desmoglein-2	9.6%	13.5%
Desmoscollin-2	5.8%	3.6%
Desmoplakin	7.7%	2.7%
Junctional plakoglobin	3.8%	0.9%

\*Of patients with plakophilin-2 genetic variants, 25 of 38 (65.7%) were found to have a second plakophilin-2 abnormality or a second abnormal desmosomal gene. †12 of 102 patients (11.8%) with genetic variants had 2 or more abnormal desmosomal genes.

at age 50 to 60 years because the disease uncommonly presents after that.

A person with ARVC who clearly has the disease may not personally benefit from genetic testing because the presence or absence of a gene defect would not alter the treatment or prognosis in that person because a definitive clinical prediction cannot be based on the genetics at this time. It is not known whether the minority of patients with >1 genetic abnormality for ARVC should have an implantable cardioverter-defibrillator inserted for less than the usual indications because they may be more likely to develop severe disease (15). Uncommonly, other diseases such as sarcoidosis can mimic signs and symptoms of ARVC. Therefore, positive gene identification for ARVC could be helpful to exclude the likelihood of the person having a different heart disease.

### Clinical Genetic Testing

Clinical genetic testing for ARVC genetic abnormalities is available in the United States and should be performed in certified diagnostic laboratories (see Addendum). It usually requires submitting a small blood sample. Currently, there are 5 abnormal desmosomal genes that have been identified and are being analyzed as part of a panel for routine genetic testing.

### Costs for Genetic Testing

Although laboratory fees for genetic testing vary, most genetic testing laboratories accept commercial insurance. A genetic test for ARVC can cost as much as \$5,400. Some laboratories may not accept Medicare or Medicaid. Also, a credit card guarantee may be required for some insurance plans such as Blue Cross and Blue Shield, and so forth. Some laboratories have special arrangements, and a genetic counselor should be engaged in the discussion.

After the signed physician request form has been received, some genetic testing laboratories will offer to contact the patient's insurance company to determine the out-of-pocket expense after the copay and deductible. If genetic testing is being considered, it may be advisable to seek authorization from one's insurance company to determine whether subsequent diagnostic tests and treatment may be covered after genetic testing.

### Genetic Testing in Unusual Circumstances

**Genetic testing at autopsy.** Genetic testing can confirm the cause of sudden death, particularly in a young person in whom ARVC is suspected at autopsy but the diagnosis is not definitive (15). Blood samples from that person should be tested for ARVC. If the genetic test is positive, family screening is strongly advised. It should be mentioned that genetic testing for other possible causes of sudden death due to inherited diseases such as the long QT syndrome should

also be performed if there is no obvious cause for sudden death.

**Prenatal diagnosis.** The decision of persons with ARVC to conceive a child is difficult and should be made on a case-by-case basis (16). Other options to be considered are adoption, artificial insemination using donated mature eggs or sperm, and pre-implantation genetic diagnosis. Another option is the use of in vitro fertilization to conceive embryos that can be tested for the family mutation before being implanted in the mother. This procedure is restricted to severe and untreatable diseases.

Some couples may request prenatal diagnosis through amniocentesis at the beginning of the pregnancy to determine the genetic status of the fetus and to consider terminating the pregnancy if the gene mutation is present. Ethical and legal issues apply in these situations.

### Benefits of Using a Genetic Counselor

Genetic counseling is recommended for all patients with a genetically transmitted heart disease. A genetic counselor is a health-care professional who is specially trained in medical genetics and patient counseling. They assist both patients and physicians in the genetic testing process. Some genetic counseling services are offered to patients by telephone. Genetic counseling sessions usually consist of a review of the patient's diagnosis, obtaining a detailed family history, discussion of test results, review of cost and insurance issues, coordination of the testing process, and discussion of test results in family members.

Genetic counselors are trained in both the technical and psychological aspects of genetic testing. Most patients diagnosed with ARVC want to understand why their condition developed and their prognosis. They are also concerned about their family members having the disease. Genetic counselors can also help with questions about insurance and assist in completion of paperwork associated with genetic testing. Some companies provide free genetic counseling services to their patients or their physicians.

For more information regarding genetic counseling and/or referrals for a genetic counselor in your area, consult your physician, or contact the National Society of Genetic Counselors.

### Summary

At present, the interpretation of genetic tests for ARVC is not an exact science and is more complex than for other heart disorders caused by only a single gene and for which most patients will have an abnormal gene identified. The clinical application of genetic testing for ARVC is that it can be helpful to understand the cause of this disease, to identify family members who are at risk of this condition, for family planning, and for limited prognostic information. The deoxyribonucleic acid variants of undetermined significance can result in uncertainty, and incorrect explanations can cause serious errors in medical practice. Genetic testing

for ARVC has great potential benefit but should be used with caution and with the support of services that assist in the interpretation of results.

### Addendum

These commercial genetic laboratories perform genetic testing for ARVC/D:

GeneDX, 207 Perry Parkway, Gaithersburg, Maryland 20877  
Phone: (301) 519-2100  
[www.genedx.com](http://www.genedx.com)

Transgenomic (formerly PGx Health), 5 Science Park,  
New Haven, Connecticut 06511  
Phone: (877) 274-9432; Fax: (203) 786-3418  
[www.transgenomic.com](http://www.transgenomic.com)

Correlagen Diagnostics, Inc., 307 Waverly Oaks Road,  
Suite 101, Waltham, Massachusetts 02453  
Phone: (781) 647-0604; Fax: (781) 647-0626  
[www.correlagen.com](http://www.correlagen.com)

AMBRY Genetics, 15 Argonaut, Aliso Viejo, California 92856  
Phone: (949) 900-5500; Fax: (949) 900-5501  
[www.ambrygen.com](http://www.ambrygen.com)

PGx Health, Familion Genetic Tests, Five Science Park,  
New Haven, Connecticut 06511  
Phone: (877) 274-9432  
[www.pgxhealth.com](http://www.pgxhealth.com)

LabCorp, 358 South Main Street,  
Burlington, North Carolina 27215  
Phone: (336) 584-5171  
[www.labcorp.com](http://www.labcorp.com)

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**Reprint requests and correspondence:** Dr. Frank I. Marcus,  
University of Arizona Medical Center, Sarver Heart Center, 1501  
North Campbell Avenue, Tucson, Arizona 85724-5037. E-mail:  
[fmarcus@u.arizona.edu](mailto:fmarcus@u.arizona.edu).

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**Key Words:** arrhythmogenic right ventricular cardiomyopathy ■ arrhythmogenic right ventricular dysplasia ■ desmosomes ■ genetics ■ plakophilin-2.