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Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

Synonyms: ARVC, ARVD, Arrhythmogenic Right Ventricular Cardiomyopathy, Arrhythmogenic Right Ventricular Dysplasia

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Summary

Clinical characteristics. Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is characterized by progressive fibrofatty replacement of the myocardium that predisposes to ventricular tachycardia and sudden death in young individuals and athletes. It primarily affects the right ventricle; with time, it may also involve the left ventricle. The presentation of disease is highly variable even within families, and some affected individuals may not meet established clinical criteria. The mean age at diagnosis is 31 years (±13; range: 4-64 years).

Diagnosis/testing. The diagnosis of ARVD/C is made using a combination of noninvasive and invasive tests to evaluate cardiac structure and rhythm. The eight genes known to be associated with ARVD/C are: *TGFB3* (locus name: ARVD1), *RYR2* (ARVD2), *TMEM43* (ARVD5), *DSP* (ARVD8), *PKP2* (ARVD9), *DSG2* (ARVD10), *DSC2* (ARVD11), and *JUP* (ARVD12). Four additional genes associated with ARVD/C have been mapped but not identified (locus names ARVD3, ARVD4, ARVD6, and ARVD7). Additional loci remain undetermined.

Management. *Treatment of manifestations:* Management is individualized and focused on prevention of syncope, cardiac arrest, and sudden death through use of antiarrhythmic medication, implantable cardioverter-defibrillators, and (rarely) heart transplantation. Individuals with clinical signs of right heart failure and/or left ventricular dysfunction and a history of ventricular tachycardia should be treated aggressively.

Evaluation of relatives at risk: Molecular genetic testing of at-risk relatives in families in which the disease-causing mutation is known: those with the family-specific mutation warrant annual clinical screening of cardiac function and rhythm between ages ten and 50 years. If genetic testing has not been performed or did not identify a disease-causing mutation in an affected family member, clinical screening is recommended for asymptomatic at-risk first-degree relatives every three to five years after age ten years.

Genetic counseling. ARVD/C is typically inherited in an autosomal dominant manner. A proband with autosomal dominant ARVD/C may have the disorder as a result of a *de novo* mutation. The proportion of cases caused by *de novo* mutations is unknown. Each child of an individual with autosomal dominant ARVD/C has a 50% chance of inheriting the mutation. ARVD/C may also be inherited in a digenic manner (i.e., one ARVD/C-causing mutation in each of two genes). Prenatal diagnosis for pregnancies at increased risk is possible if the disease-causing mutation(s) have been identified in the family.

Diagnosis

Diagnostic Criteria

Diagnostic criteria for arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), initially proposed by an International Task Force [McKenna et al 1994], were revised by Marcus et al [2010] (see full text) to incorporate new knowledge and technology to improve diagnostic sensitivity while maintaining diagnostic specificity. Individuals are classified as having a definite, borderline, or possible diagnosis of ARVD/C.

Definite diagnosis of ARVD/C:

- Two major criteria **or**
- One major **and** two minor criteria **or**
- Four minor criteria from different categories

Borderline diagnosis of ARVD/C:

- One major criteria **and** one minor **or**
- Three minor criteria from different categories

Possible diagnosis of ARVD/C:

- One major criteria **or**
- Two minor criteria from different categories

Global and/or Regional Dysfunction and Structural Alterations

Major

- **By 2D echo**
  - Regional RV akinesia, dyskinesia, or aneurysm
    AND
  - ONE of the following (end diastole):
    - PLAX (parasternal long axis) RVOT (right ventricular outflow tract) ≥32 mm (corrected for body surface area [PLAX/BSA] ≥19 mm/m^2)
    - PSAX (parasternal short axis) RVOT ≥36 mm (corrected for body surface area [PSAX/BSA] ≥21 mm/m^2)
    - Fractional area change ≤33%
- **By MRI**
  - Regional RV akinesia or dyskinesia or dyssynchronous RV contraction
    AND
  - ONE of the following:
    - Ratio of RV end-diastolic volume to BSA ≥110mL/m^2 (male) or ≥100 mL/m^2 (female)
    - RV ejection fraction ≤40%
- **By right ventricular angiography.** Regional RV akinesia, dyskinesia or aneurysm

Minor

- **By 2D echo**
  - Regional right ventricular akinesia or dyskinesia
    AND
  - ONE of the following (end diastole):
    - PLAX RVOT ≥29 to <32 mm (corrected for body surface area [PLAX/BSA] ≥16 to <19 mm/m^2)
    - PSAX RVOT ≥32 to <36 mm (corrected for body surface area [PSAX/BSA] ≥18 to <21 mm/m^2)
    - Fractional area change >33 to ≤40%
- **By MRI**
  - Regional RV akinesia or dyskinesia or dyssynchronous RV contraction
    AND
  - ONE of the following:
    - Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (female)
    - RV ejection fraction >40% to ≤45%

Tissue Characterization of Walls

Major. Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in at least one sample, with or without fatty replacement of tissue on endomyocardial biopsy

Minor. Residual myocytes 60% to 75% by morphometric analysis (or 50%-65% if estimated), with fibrous replacement of the RV free wall myocardium in at least one sample, with or without fatty replacement of tissue on endomyocardial biopsy

Repolarization Abnormalities

Major: Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals age >14 years (in the absence of complete right bundle branch block QRS ≥120ms)

Minor

- Inverted T waves in leads V1 and V2 in individuals >14 years of age (in absence of complete right bundle branch block) or in V4, V5, or V6.
- Inverted T waves in leads V1, V2, V3, and V4 in individuals age >14 years in the presence of complete right bundle branch block

Depolarization/Conduction Abnormalities

Major: Epsilon waves (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)

Minor

- Late potential by signal-averaged ECG (SAECG) in at least one of three parameters in the absence of a QRS duration of ≥110 ms on the standard ECG
- Filtered QRS duration (fQRS) ≥114 ms
- Duration of terminal QRS <40 uV (low amplitude signal duration) ≥38 ms
- Root-mean-square voltage of terminal 40 ms ≤20 uV
- Terminal activation duration of QRS >55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3 in the absence of complete right bundle branch block

Arrhythmias

Major: Nonsustained or sustained ventricular tachycardia of left bundle branch morphology with superior axis (negative or indeterminate QRS in leads II, III and aVF and positive in lead aVL)

Minor

- Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III and aVF and negative in lead aVL) or of unknown axis
- >500 ventricular extrasystoles per 24 hours (Holter)

Family History

Major

- ARVD/C confirmed in a first-degree relative who meets current Task Force criteria [Marcus et al 2010]
- ARVD/C confirmed pathologically at autopsy or surgery in a first-degree relative
- Identification of a pathogenic mutation categorized as associated or probably associated with ARVD/C in the person under evaluation. See Molecular Genetic Testing.

Minor

- History of ARVD/C in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria [Marcus et al 2010]
- Premature sudden death (age <35 years) due to suspected ARVD/C in a first-degree relative
- ARVD/C confirmed pathologically or by current Task Force criteria in second-degree relative

Additional Information beyond the Diagnostic Criteria

Note: The phenotype of ARVD/C is widely variable and some affected individuals may not meet either the strict criteria outlined in McKenna et al 1994 [Nava et al 2000, Hamid et al 2002, Gerull et al 2004] or the more current Marcus et al [2010] criteria; however, such individuals may still be at risk for cardiovascular events including arrhythmias and, therefore, warrant continuing care by a cardiologist.

Of note, additional considerations regarding the noninvasive and invasive tests of cardiac structure and rhythm described above are outlined below.

Noninvasive Testing

ECG changes may develop over time; therefore, individuals suspected of having ARVD/C who do not show these changes should undergo serial ECGs [Quarta et al 2010].

Echocardiography

- 3D echocardiography, an experimental imaging modality, may be useful in diagnosis, as right ventricular myocardial mechanics such as velocity, displacement, strain, and strain rate can be better assessed with 3D echocardiography than with conventional 2D echocardiography [Teske et al 2007]. However, interpretation is variable based on the center's expertise in reading 3D echocardiograms; guidelines have not been established.
- 3D echocardiography can be considered for persons with defibrillators for whom cardiac MRI is contraindicated [Prakasa et al 2006].

Cardiac MRI

- MRI images demonstrating ARVD are included in Murphy et al [2010].
- Cardiac MRI analysis should also include assessment of global and regional right ventricular function and right ventricular myocardial fibrosis.
- Not all centers are experienced in the diagnosis of ARVD by cardiac MRI. Because identification of right ventricular free wall thinning and fatty infiltration on cardiac MRI in persons with a mild ARVD phenotype can be subject to a high degree of intra-observer variability, cardiac MRI is best performed in centers with experience.
- Data are not yet available to guide evaluation of at-risk family members using cardiac MRI [Sen-Chowdhry et al 2006].
- Cardiac MRI has not been able to detect early changes of ARVD in children; however, this could result from the absence of manifestations in children rather than a failure of the method [Fogel et al 2006]. Further studies are needed.

Invasive Testing

- **Electrophysiologic (EP) study findings.** Ventricular tachycardia easily induced with ventricular pacing and extrastimulation
- **Right ventricular angiography (RVA) findings.** Enlarged right ventricle with segmental abnormalities
- **Right ventricular endomyocardial biopsy findings.** Fibrofatty replacement of the myocardium (predominantly in the apex, right ventricular outflow tract, and right ventricular inflow tract) and/or atrophy of the right ventricular myocardium

  Note: (1) The biopsy must sample an affected region to be diagnostic. (2) Recent studies have demonstrated a possible role for immunohistochemical staining of the myocardium for intercalated disk proteins [Asimaki et al 2009]; however, further studies are needed [van Tintelen & Hauer 2009].
- **3D electroanatomic voltage mapping** maps low voltage areas of the right ventricle that correlate with fibrofatty replacement [Corrado et al 2005]. This method is still experimental.

Molecular Genetic Testing

The eight genes in which mutations are known to cause ARVD/C are *TGFB3, RYR2, TMEM43, DSP, PKP2, DSG2, DSC2,* and *JUP*. See Table 1.

Note: Five of the genes (*DSP, PKP2, DSG2, DSC2,* and *JUP)* encode proteins that are important to desmosome structure/function and may be referred to as ‘desmosomal genes’ in this *GeneReview*.

Evidence for additional locus heterogeneity includes as-yet undetermined loci/genes as well as the following loci for which no genes have yet been identified:

- ARVD3 (14q12-q22) [Severini et al 1996]
- ARVD4 (2q32.1-q32.3) [Rampazzo et al 1997]
- ARVD6 (10p14-p12) [Li et al 2000, Matolweni et al 2006]
- ARVD7 (10q22.3) [Melberg et al 1999]

Note:

1. Guidelines for genetic testing recommendations are available [Hershberger et al 2009]. The Heart Rhythm Society/European Heart Rhythm Association published an Expert Consensus Statement for genetic testing for cardiomyopathies [Ackerman et al 2011].
2. The overall yield of genetic testing for all available genes in probands who meet the revised Task Force criteria [Marcus et al 2010] approximates 50% [Quarta et al 2011]. Thus, if molecular genetic testing does not identify a disease-causing mutation in an individual who meets diagnostic criteria, the clinical diagnosis of ARVD/C is unchanged.
3. Because of the complexity of interpreting genetic testing results (see also Clinical Description), Ackerman et al [2011] note that extreme caution should be taken in interpreting results. Consideration should be given to referring patients to specialty centers to perform the genetic testing.
4. Because of a significant level of reduced penetrance (see Penetrance), it may be appropriate to offer molecular genetic testing to simplex cases (i.e., a single occurrence of the clinical diagnosis of ARVD/C in a family).
5. Molecular genetic testing should be considered in individuals who are suspected of having ARVD/C based on criteria of the International Task Force [Marcus et al 2010], but who do not meet criteria for a definite clinical diagnosis. For some of these individuals, identification of a disease-causing mutation in one of the ARVD/C-related genes fulfills the remaining criteria.
6. Although some ARVD/C-related genes are more frequently mutated in ARVD/C than others (Table 1), molecular genetic testing for all ARVD/C-related genes should be performed simultaneously (usually as part of a multi-gene panel) because up to 57% of persons with ARVD/C have been shown to have compound heterozygosity or digenic heterozygosity (see Clinical Description for more details) [Barahona-Dussault et al 2010, Bauce et al 2010, Christensen et al 2010b, Xu et al 2010, Nakajima et al 2012]. Because ARVD/C multi-gene panels vary by methods used and genes included, the ability of a panel to detect a causative mutation(s) in any given individual also varies.
7. Genetic testing is also warranted in those who otherwise meet criteria of the Task Force [McKenna et al 1994, Marcus et al 2010] in order to identify the causative mutation and enable genetic testing of at-risk family members (see Management and Genetic Counseling).

Table 1.

Summary of Molecular Genetic Testing Used in Arrhythmogenic Right Ventricular Dysplasia / Cardiomyopathy

Gene [1] (Locus Name)	Proportion of ARVD/C Attributed to Mutation of This Gene [2]	Test Method	Mutations Detected [3]
PKP2 (ARVD9)[4]	Overall populations (Netherlands, USA, Canada, UK, Denmark, Italy, France, Switzerland): 22.6% [2] 10%-52% (<10% in UK, Greece/Cyprus; 39%-52% in Netherlands, USA, China) [2]	Mutation scanning / sequence analysis [4]	Sequence variants [5]
	2.8%	Deletion/duplication analysis [6]	Exonic and whole-gene deletions/duplications [7]
DSG2 (ARVD10)	3%-19%	Mutation scanning / sequence analysis [4]	Sequence variants [5]
		Deletion/duplication analysis [6]	Exonic and whole-gene deletions/duplications; none reported to date
DSP (ARVD8)	1%-16%	Mutation scanning / sequence analysis [4]	Sequence variants [5]
		Deletion/duplication analysis [6]	Exonic and whole-gene deletions/duplications; none

Gene [1] (Locus Name)	Proportion of ARVD/C Attributed to Mutation of This Gene [2]	Test Method	Mutations Detected [3]
			reported to date
DSC2 (ARVD11)	1%-13%	Mutation scanning / sequence analysis [4]	Sequence variants [5]
		Deletion/duplication analysis [6]	Exonic and whole-gene deletions/duplications; none reported to date
RYR2 (ARVD2)	Rare	Mutation scanning / sequence analysis [4]	Sequence variants [5]
		Deletion/duplication analysis [6]	Exonic and whole-gene deletions, none reported to date
TGFB3 (ARVD1)	Rare	Mutation scanning / sequence analysis [4]	Sequence variants [5]
		Deletion/duplication analysis [6]	Exonic and whole-gene deletions/duplications; none reported to date
JUP (ARVD12)	Rare	Mutation scanning / sequence analysis [4]	Sequence variants [5]
		Deletion/duplication analysis [6]	Exonic and whole-gene deletion/duplications; none reported to date
TMEM43 (ARVD5)	Unknown	Mutation scanning / sequence analysis [4]	Sequence variants [5]
		Deletion/duplication analysis [6]	Exonic and whole-gene deletions/duplications; none reported to date

1. See Table A. Genes and Databases for chromosome locus and protein name.
2. From Jacob et al [2012], a comprehensive overview of all published studies to date to yield overall population prevalence of the gene in which mutations are identified
3. See Molecular Genetics for information on allelic variants.
4. Sequence analysis and mutation scanning of the entire gene can have similar detection frequencies; however, detection rates for mutation scanning may vary considerably between laboratories based on the specific protocol used.
5. Examples of mutations detected by sequence analysis may include small intragenic deletions/insertions and missense, nonsense, and splice site mutations; typically, exonic or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
6. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
7. La Gerche et al [2010], Li Mura et al [2013], Roberts et al [2013]

Test characteristics. See Clinical Utility Gene Card [Te Rijdt et al 2014] for information on test characteristics including sensitivity and specificity.

Genetically Related (Allelic) Disorders

RYR2. Patogenic variants in *RYR2* have been identified in individuals with catecholaminergic polymorphic ventricular tachycardia (CPVT) [Priori et al 2000, Laitinen et al 2001]. CPVT, an autosomal dominant disorder characterized by stress-related, bi-directional ventricular tachycardia in the absence of both structural heart disease and a prolonged QT interval [Coumel et al 1978, Leenhardt et al 1995], may present with syncopal events in childhood and adolescence. Mutation of *RYR2* has been associated with early cardiac death.

It has been suggested that CPVT and ARVD/C represent a phenotypic spectrum; however, families with both CPVT and ARVD have not been described, and unique *RYR2* pathogenic

variants have been associated with each disorder. Therefore, it is debated whether individuals with pathogenic variants in *RYR2* should all be classified as having CPVT instead of some as having ARVD/C.

RYR2 pathogenic variants have been identified in persons with "atypical" or "borderline" long QT syndrome (LQTS) who did not have pathogenic variants identified in the five genes associated with LQTS [Tester et al 2005].

***DSP*.** Carvajal syndrome [OMIM 605676] is an autosomal recessive disease characterized by ventricular dilated cardiomyopathy, palmoplantar keratoderma, and woolly hair [Carvajal-Huerta 1998, Norgett et al 2000]. A homozygous nonsense *DSP* mutation was reported to cause Carvajal syndrome in an Ecuadorian family with documented consanguinity.

Some variation in findings has been reported:

- An individual with autosomal recessive ARVD, woolly hair, and a pemphigous-like skin disorder was found to have biallelic *DSP* mutations [Alcalai et al 2003].
- Compound heterozygous *DSP* mutations have been reported to cause keratoderma without cardiac involvement [Whittock et al 2002].
- Compound heterozygous *DSP* missense mutations have been observed in an individual with ARVD, but not palmoplantar keratoderma or woolly hair [Bauce et al 2010].
- Heterozygous missense *DSP* mutations are reported to cause features of Carvajal syndrome with hypo/oligodontia (missing teeth) [Chalabreysse et al 2011].

***JUP*.** Naxos disease, an autosomal recessive form of ARVD/C, has been observed on the island of Naxos, Greece. Naxos disease also includes palmoplantar keratoderma and peculiar woolly hair [OMIM 601214]. Naxos disease is caused by a homozygous 2-nucleotide deletion in *JUP*, the gene encoding junction plakoglobin (also known as γ-catenin), a key component of desmosomes and adherens junctions [McKoy et al 2000]. Penetrance is complete by adolescence [Protonotarios et al 2001].

***DSC2*.** Two sibs, the offspring of consanguineous parents, had ARVD, mild palmoplantar keratoderma, and woolly hair; they were homozygous for a base pair deletion in exon 12 (1841delG, Phe614fsTer625) [Simpson et al 2009].

***PKP2, SG2, TGFB3, and TMEM43*.** No other phenotypes have been associated with mutation of these genes.

Clinical Characteristics

Clinical Description

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a myocardial disorder that predominantly affects the right ventricle. ARVD/C is a progressive disorder characterized by fibrofatty replacement of the myocardium, predisposing to ventricular tachycardia and sudden death in young individuals and athletes [Marcus et al 1982, Thiene et al 1988, Corrado et al 1998, Fontaine et al 1998]. The disease often affects the right ventricular apex, the base of the right ventricle, and the right ventricle outflow tract. The arrhythmias in ARVD/C most frequently arise from the right ventricle and have a left bundle branch block morphology.

Pathology in ARVD/C may also extend to involve the left ventricle [Horimoto et al 2000, Hamid et al 2002]. A recent study of cardiac MRI findings revealed that despite preserved global left ventricular function, regional left ventricular dysfunction was seen in people with ARVD/C [Jain et al 2010]; larger studies are needed to validate this finding.

The most common presenting symptoms are heart palpitations, syncope, and death. The four described phases of ARVD/C are: (1) concealed phase (no clinical manifestations of ARVD/C, but potential risk of sudden cardiac death); (2) an overt electrical disorder (characterized by symptomatic arrhythmias); (3) right ventricular failure; and (4) a biventricular pump failure (resembles dilated cardiomyopathy) [Dalal et al 2005]. Left ventricle involvement can occur at any of the above stages [Sen-Chowdhry et al 2007].

In a long-term study of 132 living affected individuals from 37 families, none were diagnosed in infancy and two were diagnosed at ages four and six years [Nava et al 2000]. The mean age at diagnosis was 31 years (±13; range: 4-64 years).

The principal characteristic of arrhythmogenic cardiomyopathies is the tendency for ventricular arrhythmia and sudden death in the absence of overt ventricular dysfunction. The increased risk for sudden death in ARVD/C is thought to relate to sudden ventricular arrhythmias.

A gender bias was identified with those with pathogenic variants in *PKP2* (ARVD9). Among individuals with a heterozygous *PKP2* mutation, 67% of males (compared to 35% of females) met Task Force criteria for diagnosis [McKenna et al 1994]; however, gender differences in age of diagnosis or survival were not significant [Dalal et al 2006]. Note that these findings may not be applicable to other genetic forms of ARVD/C.

Studies that have investigated the propensity to arrhythmia in ARVD include the following:

- The risk of sudden death from ARVD/C is controversial [Firoozi et al 2003, Tabib et al 2003]. In a study of 160 probands fulfilling clinical criteria for ARVD/C, 24 died during follow-up giving an overall mortality rate of 18.5% and an annual mortality rate of 2.3% [Hulot et al 2004]. Mean age at death (±SD) was 54 years (±19). Of the 24 deaths, 21 were cardiovascular deaths, among which seven were sudden cardiac deaths and 14 were a result of progressive heart failure (7 ventricular tachycardia or fibrillation occurring during an acute episode of severe cardiac failure, 5 terminal heart failure, and 2 rapid deaths after cardiac transplantation) [Hulot et al 2004].
- Lemola et al [2005] reported that of 24 persons with ARVD/C who received an implantable cardioverter-defibrillator (ICD), ten received appropriate shocks, four had inappropriate shocks, three had a heart transplant, one died of heart failure, and one died suddenly despite delivery of several device charges. The authors note that not every ICD discharge may be associated with an arrhythmia leading to sudden death; some arrhythmias occur in normal cardiac function and, therefore, the denotation of "appropriate shocks" may be misleading.
- In a study of 100 persons with ARVD/C (diagnosed clinically or via autopsy), 31 experienced sudden cardiac death [Dalal et al 2005]. Of those diagnosed with ARVD/C while living, the death-free survival rate was 94% in persons older than age 60 years (mainly as a result of receiving ICDs to prevent sudden cardiac death).
- In a long-term study of 11 families with pathogenic variants in *TMEM43*, Hodgkinson et al [2005] found that 50% of males considered at high risk for sudden death associated with ARVD/C died by age 39 years and 50% of females considered at high risk died by age 71 years. Mortality in these families was reduced by 28% in males who received an ICD. In another study of 137 persons in 15 families, males had a median age of disease onset of 32 years and females 44 years [Merner et al 2008]. Penetrance was 100% by age 63 years in males and age 76 years in females. In this study, the relative risk of dying of sudden cardiac death was 6.8 times greater in affected males than affected females.

ARVD/C is present in 4% to 22% of athletes with sudden cardiac death [Corrado et al 2003, Maron et al 2009]. There is some debate over whether high-intensity endurance exercise can cause development of ARVD/C.

- La Gerche et al [2010] studied athletes with a history of arrhythmias of right ventricular origin to determine if they met the 1994 Task Force criteria [McKenna et al 1994], for ARVD/C. Sequence analysis of five genes that encode desmosomal proteins (*PKP2, JUP, DSP, DSC2*, and *DSG2*) revealed lower than expected mutation rates, particularly in athletes performing the most exercise. These findings support the notion that intense exercise can induce ARVD/C without an identifiable genetic predisposition.
- A multi-center study of 108 probands with ARVD/C revealed that 34% were competitive or professional athletes [Marcus et al 2009]. These studies lend further support to the hypothesis that vigorous or sustained athletic activity facilitates the phenotypic expression of the disease due to the repetitive stretch of the thin walled right ventricle with an underlying genetic desmosomal protein abnormality.

Pathogenic variants in desmosomal genes have also been identified in 5% of individuals meeting criteria for dilated cardiomyopathy. Although these individuals did not meet criteria for ARVD/C, some did have a history of ventricular arrhythmias and one individual had fibrofatty infiltration on autopsy, leading to the speculation that variants in these desmosomal genes can predispose to heart failure or ventricular arrhythmias [Elliott et al 2010, Bhuiyan & Wilde 2011].

Aquaro et al [2010] studied persons with a prior history of frequent premature ventricular contractions (PVCs) of left bundle branch block morphology and inferior axis. Using cardiac MRI, they assessed functional parameters of the left and right ventricles and then separated the group into those with and those without right ventricular abnormalities. They found that those who had multiple right ventricular abnormalities had a worse outcome (ventricular tachycardia, appropriate ICD shock, sudden cardiac death) than those who did not have right ventricular abnormalities. Further studies are needed to demonstrate the extent to which cardiac MRI can be used to stratify risk.

Compound and digenic heterozygosity of desmosomal genes in ARVD/C. Compound heterozygosity (mutation of both alleles of the same gene) and digenic heterozygosity (heterozygous mutation of two different genes) have been seen in autosomal dominant ARVD/C. Many studies have reported on two pathogenic variants in ARVD/C-related genes encoding demosomal proteins.

- It is questioned whether certain heterozygous *PKP2* mutations are sufficient to cause disease or if biallelic mutation is necessary [Xu et al 2010]. In an early study of six first-degree relatives of a proband with a *PKP2* pathogenic variant, two met clinical criteria for ARVD/C and four had either a normal phenotype or mild disease manifestations [Gerull et al 2004]. In a second family, two individuals with a *PKP2* pathogenic variant died of sudden death at young ages, whereas of five living relatives with the pathogenic variant, only one met clinical criteria [Gerull et al 2004]. Subsequent reports have documented families in which relatives with the same pathogenic variant as the proband do not meet ARVD/C clinical criteria.

  In 42% of individuals with ARVD, Xu et al [2010] identified either compound heterozygosity for two *PKP2* mutations or digenic heterozygosity (one heterozygous *PKP2* mutation and a second heterozygous mutation in an ARVD/C-related gene encoding a demosomal protein). Xu et al [2010] found a more severe phenotype in those who had compound and digenic heterozygosity when at least one mutation occurred in *PKP2*. In addition, they speculated that one pathogenic variant in *PKP2* may not be sufficient to cause disease because some individuals with one *PKP2* pathogenic variant did not meet revised Task Force criteria [McKenna et al 1994], whereas those in the family with two pathogenic variants had ARVD.

- Bauce et al [2010] found 7.1% of 42 index cases were compound heterozygotes or digenic heterozygotes. When those who were heterozygous for multiple mutations were compared to family members who were heterozygous for a single mutation, the phenotype ranged from no heart disease to severe disease with left ventricular and right ventricular dilatation being more severe in those who were heterozygous for multiple mutations than in those who were heterozygous for a single mutation.

- Bauce et al [2010] also found that some individuals meeting ARVD diagnostic criteria had two pathogenic variants, but that other family members who had a single pathogenic variant did not have a clinical diagnosis of ARVD.

- Barahona-Dussault et al [2010] reported that 43% of their ARVD population with mutations (38% of the study population met the McKenna et al [1994] Task Force criteria) had a pathogenic variant in an ARVD-related desmosomal gene, and of these, two (20%) were compound heterozygotes and one (10%) was a digenic heterozygote.

- Nakajima et al [2012] found that four of seven probands who met Revised Task Force criteria for ARVD/C had two pathogenic variants: three were compound heterozygotes and one was a digenic heterozygote [Marcus et al 2010]. The majority of family members of these four probands (who likely would have inherited one of the pathogenic variants) remained asymptomatic, suggesting a single variant may not be sufficient to cause clinical manifestations of ARVD.

- In a study of 65 probands who met ARVD Task force criteria [McKenna et al 1994], Christensen et al [2010b] found pathogenic variants in ARVD-associated desmosomal genes in 18, including six with digenic heterozygous mutations, one with compound heterozygous *PKP2* mutations, and one with biallelic *DSP* mutations. The phenotype ranged from severe to mild in compound heterozygotes and digenic heterozygotes.

- Tan et al [2010] also studied whether compound or digenic heterozygosity confers a more severe disease. Of those individuals with a diagnosis of ARVD based on the 1994 Task Force criteria [McKenna et al 1994], the study found no increase in frequency of compound or digenic heterozygous pathogenic variants in a cohort of young (age ≤21 years) individuals with ARVD/C compared to middle age and older affected individuals. Overall, more research is needed on the effects of pathogenic variants in ARVD/C-related desmosomal genes, and on whether some genes/mutations could have a more severe impact in the compound or digenic heterozygous state versus others that could manifest disease as a single heterozygous mutation.

Genotype-Phenotype Correlations

Currently, insufficient data limit genotype-phenotype correlations. Furthermore, marked variation in phenotype can be observed in individuals from the same family who have the same pathogenic

variant [Gerull et al 2004, Dalal et al 2006].

Mutation of *DSP* and *DSG2* has been associated with more left ventricular involvement than the traditional right ventricular dilatation associated with ARVD/C [Bauce et al 2010].

Penetrance

In the single family with a pathogenic variant in *DSP* reported by Rampazzo et al [2002], penetrance was estimated at 50%. Other estimates of penetrance in kindreds with autosomal dominant ARVD/C are as low as 20%-30% [Sen-Chowdhry et al 2005].

Further studies are needed to establish the penetrance of ARVD/C caused by mutation of other genes.

Genetic variation in ARVD/C-related genes encoding proteins of desmosome structure/function (i.e., *DSP, PKP2, DSG2, DSC2,* and *JUP)* that would be considered rare and pathogenic have been identified in 16.2% of healthy Dutch controls compared to 58.3% of Dutch persons meeting 2010 revised Task Force criteria for ARVD/C – an approximately 3.5-fold higher rate in the latter [Kapplinger et al 2011].

However, approximately one in six healthy controls genotyped had a variant in a gene encoding desmosomal proteins that would have been called pathogenic. Kapplinger et al observed that radical mutations (insertions/deletions, splice junction and nonsense mutations) were significantly more prevalent in persons with ARVD/C than in controls (49.9% vs. 0.47% respectively), leading them to propose that this type of genetic variant has a higher likelihood of being associated with ARVD/C pathogenicity. Regarding missense mutations, Kapplinger et al identified three associations with ARVD/C pathogenicity: rare missense mutations identified in a person of northern European origin is more likely pathogenic than one identified in a person of different origin; specific amino-terminal regions of *DSP* and *DSG2* may contain mutation hot spots that have more missense mutations in persons with ARVD/C than controls; and missense mutations that involve a highly conserved residue in *PKP2* and *DSG2* are more likely pathogenic.

Kapplinger et al do address the concern that variants identified in a control population (with the majority being missense mutations) could be less penetrant in the heterozygous state compared to compound heterozygosity or digenic heterozygosity in those with ARVD/C.

Similarly, Lahtinen et al [2011] screened a Finnish ARVD/C population and general population samples and found pathogenic variants in ARVD/C-related genes encoding proteins of desmosome structure/function in one in 200 Finns, including identified founder mutations. Some of those with variants in the general population were actually symptomatic; however, the high mutation prevalence does demonstrate reduced penetrance for many in the general population, as the estimated prevalence of ARVD in the Finnish population is 1:1000 to 1:5000.

Andreasen et al [2013] found that for ARVD/C, 18% of the desmosomal variants previously classified in the literature as pathogenic were found in the Exome Sequencing Project population. This corresponds to a genotype prevalence of 1:5 when the prevalence in the general population is 1:5000, yielding an overrepresentation of genetic variants previously associated with cardiomyopathy in new population-based exome data and leading Andreasen et al to suspect that a high number of these variants may be disease modifiers, or possibly non-pathogenic.

Nomenclature

Arrhythmogenic right ventricular cardiomyopathy (ARVC) has had numerous names including Uhl anomaly and right ventricular dysplasia. Until 1996, ARVC was called arrhythmogenic right ventricular dysplasia (ARVD) [Richardson et al 1996]. Currently the terms ARVC and ARVD are used interchangeably.

Prevalence

The exact prevalence of ARVD/C is unknown but may be estimated at 1:1000 to 1:1250 in the general population [Peters 2006].

The prevalence of ARVD/C is greater in certain regions; in Italy and Greece (Island of Naxos), it can be as high as 0.4%-0.8% [Thiene & Basso 2001].

Differential Diagnosis

ARVD/C and anterior polar cataract (APC). A single family with ARVD/C and subscapular cataract, a rare hereditary form of lens opacity, has been described [Frances et al 1997]. The proband and his sister both had ARVD/C and APC. The gene responsible for APC previously was linked to 14q24qter. Parents of the sibs were second cousins.

DES. Pathogenic variants in *DES* have been identified in individuals with skeletal myopathy (see

Myofibrillar Myopathy) or dilated cardiomyopathy with or without cardiac conduction defects, or both myopathy and cardiomyopathy with or without cardiac conduction defects [Goldfarb et al 1998, Dalakas et al 2000]. Families with the phenotype of skeletal myopathy, dilated cardiomyopathy, and ARVD/C per the 1994 ARVD/C diagnostic criteria have been described [van Tintelen et al 2009, Otten et al 2010]. It is unknown at this point whether unique *DES* mutations cause the ARVD/C phenotype; however, mutation in both the head and tail of *DES* has been identified as causative of ARVD/C [van Tintelen et al 2009, Otten et al 2010].

Cardiomyopathy. Many forms of cardiomyopathy may mimic aspects of ARVD/C. Cardiomyopathies may arise from genetic, toxic, or immunologic insults. Clinical testing may be useful to distinguish cardiomyopathy from ARVD/C. See Dilated Cardiomyopathy Overview.

Active myocarditis. Inflammation of the myocardium defines acute myocarditis. Myocarditis may arise from viral or other pathogen exposure as well as toxic or immunologic insult. Clinical testing may be useful to distinguish myocarditis from ARVD/C.

Coronary artery disease and myocardial infarction. Coronary artery disease, or atherosclerotic narrowing of the coronary arteries, may lead to acute or chronic ischemic conditions that may mimic aspects of ARVD/C. Clinical testing may be useful to distinguish these from ARVD/C.

Right ventricular outflow tract tachycardia (RVOT) is a clinical arrhythmia condition that is not typically associated with structural heart disease as is seen in ARVD/C. ECG and cardiac imaging may be useful to distinguish these disorders.

Brugada syndrome is characterized by ST segment abnormalities in leads V_1-V_3 on the ECG and a high risk of ventricular arrhythmias and sudden death. Considerable clinical overlap may be present. One discriminating factor: the right ventricular dilation and fibrofatty infiltration characteristic of ARVD/C is rarely seen in Brugada syndrome.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), the following evaluations are recommended if not performed at the time of diagnosis:

- ECG
- Echocardiogram and/or MRI, depending on the expertise of the imaging center
- Electrophysiology study to assess the risk of ventricular arrhythmias and assess the appropriateness of device insertion (such as an implantable cardioverter defibrillator). A cardiac catheter ablation of tissue causing abnormal rhythms can be performed during the electrophysiology study; however, ablation is typically not effective in individuals with ARVD/C because of the multiple sites of primary ventricular tachycardias.

Treatment of Manifestations

Most affected individuals live a normal lifestyle.

Management of individuals with ARVD/C is complicated by incomplete information on the natural history of the disease as well as variable expressivity of the disease. Management of patients should be individualized and based on the specific results of detailed investigation.

Management is focused on prevention of syncope, cardiac arrest, and sudden death (see Prevention of Primary Manifestations). Recent studies suggest that individuals who present with clinical signs of right heart failure and/or left ventricular dysfunction and have a history of ventricular tachycardia are at high risk and should be treated aggressively [Hulot et al 2004].

Education regarding sudden death risk to affected adults and parents of affected children is an important aspect of management.

Heart transplantation is considered when ARVD/C has progressed to right or left ventricular heart failure. Severe diffuse biventricular involvement simulating dilated cardiomyopathy and requiring heart transplantation seems to be rare.

Prevention of Primary Manifestations

Antiarrhythmia medications

- Beta-blockers
- Amiodarone

- Sotalol

Note: In a study of 95 patients with ARVD/C by Marcus et al [2009], neither beta blocker therapy nor sotalol were protective against ventricular arrhythmias. However, amiodarone was associated with lower risk for any clinically relevant arrhythmias. Larger studies are needed to confirm this finding.

Implantable cardioverter-defibrillators (ICDs). ICD placement should be considered in anyone with a clinical diagnosis of ARVD/C.

The ACC/AHA/ESC (American College of Cardiology/American Heart Association Task Force/European Society of Cardiology) guidelines, which are based on experience and previously published reports [Zipes et al 2006], recommend as a Class I indication (i.e., procedure/treatment SHOULD be performed) ICD implantation for prevention of sudden cardiac death in individuals with documented sustained ventricular tachycardia or ventricular fibrillation who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than one year. Class II indications (i.e., it is REASONABLE to perform procedure/treatment) for ICD implantation include extensive disease (e.g., left ventricular involvement) or family members with sudden death, or undiagnosed syncope when ventricular fibrillation or ventricular tachycardia cannot be excluded as cause of syncope while the patient was on optimal medical therapy.

Persons who appear to be at the highest risk for a fatal arrhythmia are those who have been resuscitated, are unresponsive to or intolerant of antiarrhythmic therapy, or have first-degree relatives with a history of sudden cardiac arrest.

The appropriate time to place an ICD in an individual at moderate risk for a fatal arrhythmia is not known because ICD efficacy in ARVD/C may be affected by progressive fibrofatty involvement of the right ventricle, which may obscure appropriate sensing of the ICD.

In one study, 44 of 67 persons with ARVD/C with ICDs [Piccini et al 2005] received appropriate* shocks from their ICD for treatment of a sustained ventricular arrhythmia and 16 of 67 received inappropriate shocks for sinus tachycardia, supraventricular tachycardia/atrial fibrillation, or oversensing (i.e., adding an atrial rhythm to the ventricular beat or detecting more waves than are occurring, giving the appearance that the heart is beating faster than it actually is). However, it is difficult to determine whether the ventricular tachycardia was sustained or whether it would have self-corrected without the shock. This study found that appropriate ICD therapies occurred more frequently for persons with definite ARVD/C compared to those with probable ARVD/C. Nonetheless, nearly one third of those with probable ARVD/C received appropriate intervention from the ICD. Therefore, ICD placement should be considered even in those who do not meet 1994 international Task Force ARVD/C diagnostic criteria but have probable ARVD/C (i.e., meeting fewer criteria) and positive findings on electrophysiologic study [Piccini et al 2005].

*Note: 'Appropriate' refers to proper sensing and delivery of defibrillation based on device function.

Corrado et al [2010] studied 106 consecutive individuals with ARVD/C who received an ICD based on arrhythmic risk factors such as syncope, nonsustained ventricular tachycardia, familial sudden death, and inducibility at programmed ventricular stimulation. In follow up at 58 months, 24% had appropriate shock interventions; 16% had shocks for life-threatening ventricular flutter; and 43% with prior syncope experienced appropriate ICD intervention. They also found that syncope, nonsustained ventricular tachycardia, and left ventricular dysfunction were predictors of life-saving ICD intervention. The first appropriate intervention ranged from age 15 to 56 years. None of the 27 who had ICDs implanted because of a history of isolated familial sudden death (i.e., sudden death in an asymptomatic family member who had no prior cardiovascular events) experienced appropriate ICD discharges. Further studies with a larger number of asymptomatic individuals at risk for ARVD/C are needed to determine risks and to refine the recommendations for implantation of an ICD.

Surveillance

Screening for degree of cardiac involvement in persons diagnosed with ARVD/C is essential to ascertain severity and disease progression over time. Screening recommendations:

- ECG, annually or more frequently depending on symptoms
- Echocardiogram, annually or more frequently depending on symptoms
- Holter monitoring
- Cardiac MRI, frequency depending on symptoms and findings

Agents/Circumstances to Avoid

Individuals with right ventricular dysplasia may be discouraged from vigorous athletic activity including competitive athletics because of the strain caused on the right heart; however, conflicting views exist on restriction of vigorous athletic activity in persons with ARVD/C or those at risk for ARVD/C (see Clinical Characteristics, Clinical Description for more details).

Evaluation of Relatives at Risk

It is appropriate to offer molecular genetic testing to relatives at risk for ARVD/C (even those under age 18 years) if the pathogenic variant(s) have been identified in an affected family member so that morbidity and mortality can be reduced by early diagnosis and treatment. Predictive testing should be offered in the context of formal genetic counseling.

Note: Consideration should be given to molecular testing of all ARVD/C-related genes versus site-specific testing because of the high rate of digenic heterozygosity (a heterozygous mutation in two different genes) [Barahona-Dussault et al 2010, Wilde 2010, Xu et al 2010]. Studies have not been performed assessing the validity of this consideration.

Guidelines for screening for cardiac involvement in asymptomatic first-degree relatives at risk for ARVD/C [Hershberger et al 2009, Charron et al 2010]:

- If the family-specific pathogenic variant has been identified in the asymptomatic at-risk relative, screening for cardiac involvement is recommended yearly between ages ten and 50 years.
- If genetic testing has not been performed or did not identify a pathogenic variant in an affected family member, screening for cardiac involvement is recommended for asymptomatic at-risk first-degree relatives every three to five years after age ten years.

Screening for cardiac involvement comprises the following [Hershberger et al 2009, Charron et al 2010]:

- Medical history with attention to heart failure symptoms, arrhythmia, presyncope and syncope
- ECG, with consideration of signal averaged electrocardiogram (SAECG)
- Echocardiogram
- Holter monitoring
- Cardiac MRI

At-risk first-degree relatives with any abnormal clinical screening tests for cardiac involvement should be considered for repeat clinical screening in one year [Hershberger et al 2009].

Note: Screening for and diagnosing ARVD/C in children is difficult as early signs of ARVD/C have not been identified by current screening modalities. For example, Bauce et al [2011] studied children who were heterozygous for a pathogenic variant in a desmosomal gene (identified by family history and confirmed by genetic testing). In this study, 21 (40%) of 53 heterozygotes met revised ARVD/C diagnostic criteria (age range 11-18 years), four (8%) were borderline and 28 (53%) were unaffected (compared to 20 [38%] of 53 heterozygotes who met the 1994 ARVD/C diagnostic criteria).

- Of the 16 children under age ten years, none fulfilled 1994 ARVD/C diagnostic criteria.
- Of the 18 children age 11-14 years, six (33%) were diagnosed with ARVD/C by the 1994 ARVD/C diagnostic criteria and all had ventricular arrhythmias (2 had mild disease, 2 moderate disease, and 2 severe disease).
- Of the 19 children 14-18 years, eight (42%) were diagnosed with ARVD/C by the 1994 ARVD/C diagnostic criteria. Six (32%) had arrhythmic symptoms; all eight with the diagnosis of ARVD/C had ventricular arrhythmias (4 with sustained VT, 2 with nonsustained VT, 2 with PVCs); and on echocardiogram, one had mild disease, five had moderate disease, and two had severe disease.
- Overall, 14 individuals were diagnosed with ARVD/C and the majority (39/53, or 74%) did not have any signs or symptoms despite the presence of a pathogenic variant(s) in genes encoding desmosomal proteins.
- Therefore, continued screening for cardiac involvement despite negative findings is warranted. See Hamilton & Fidler [2009] for a review of screening for ARVD/C in the young.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is usually inherited in an autosomal dominant manner. It can also be inherited in a digenic or autosomal recessive manner.

If the proband has a specific syndrome associated with ARVD/C, such as Naxos disease or Carvajal syndrome, counseling for that autosomal recessive condition is indicated.

Risk to Family Members — Autosomal Dominant Inheritance

Parents of a proband

- Some individuals diagnosed with autosomal dominant ARVD/C have an affected parent.
- Most people with ARVD/C have a pathogenic variant in one ARVD/C-related gene. However, some individuals are identified to have two pathogenic variants in the same ARVD/C-related gene. The allelic variants are usually different and on different alleles (compound heterozygote), but they may be the same pathogenic variant on different alleles (homozygous). Rarely, a person has two mutations on the same allele.
    - Typically, one parent has one ARVD/C-causing allelic variant in the gene and the other parent has a different ARVD/C-causing allelic variant in the same gene. However, both parents should undergo confirmatory genetic testing because it is possible that one parent harbors both pathogenic variants on the same allele, which would subsequently alter inheritance and risk counseling.
    - The parents may or may not have clinical findings.
- In addition, a proband with autosomal dominant ARVD/C may have the disorder as the result of a new mutation. The proportion of cases caused by *de novo* mutation is unknown.
- Recommendations for the evaluation of parents of a proband with apparent *de novo* mutation include cardiac MRI or echocardiogram, ECG, and molecular genetic testing if the mutation(s) have been identified in the proband.

Note: Although some individuals diagnosed with autosomal dominant ARVD/C have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset or reduced penetrance of the disease in the affected parent.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected and/or has a pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. If both parents have a pathogenic variant, the risk to sibs of inheriting two pathogenic variants is 25%, one variant is 50%, and neither variant is 25%.
- When the parents are clinically unaffected, the risk to the sibs of a proband may be lower. Variable expressivity and reduced penetrance are common.
- Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Each child of an individual with autosomal dominant ARVD/C and one ARVD/C-related allelic variant has a 50% chance of inheriting the pathogenic variant. Each child of an individual with autosomal dominant ARVD/C and two ARVD/C-related allelic variants (one

inherited from each of his/her parents) will inherit one pathogenic variant.

Other family members of a proband

- The risk to other family members depends on the status of the proband's parents.
- If a parent is affected or has a pathogenic variant, his or her family members are at risk.

Risk to Family Members — Digenic Inheritance

Digenic ARVD/C results from the presence of two pathogenic variants: one variant in one ARVD/C-related gene plus another variant in a different ARVD/C-related gene.

Parents of a proband

- Typically, one parent has an ARVD/C-causing allelic variant in one gene and the other parent has an ARVD/C-causing allelic variant in a different gene. However, both parents should undergo confirmatory genetic testing because it is possible that one parent harbors both pathogenic variants and is asymptomatic.
- The parents may or may not have clinical findings.

Sibs of a proband. Assuming that each parent has one pathogenic variant, at conception each sib has a 75% chance of inheriting one or two ARVD/C-related variants (and being at increased risk of developing ARVD/C) and a 25% chance of not inheriting a pathogenic variant (and being unaffected).

Offspring of a proband. The risk to offspring of inheriting one or two pathogenic variants is 75%.

Other family members of a proband. Each sib of the proband's parents will have zero, one, or two ARVD/C-related allelic variants depending on the genetic status of the proband's parent.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant or clinical evidence of the disorder, it is likely that mutation occurred *de novo* in the proband. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing

If the pathogenic variant(s) have been identified in an affected family member, prenatal testing for pregnancies at increased risk may be available either through a clinical laboratory or a laboratory offering custom prenatal testing.

Requests for prenatal testing for conditions which (like ARVD/C) do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be an option for families in which the pathogenic variant(s) have been identified.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Heart Association (AHA)**
  7272 Greenville Avenue
  Dallas TX 75231
  Phone: 800-242-8721 (toll-free)
  Email: review.personal.info@heart.org
  www.americanheart.org
- **Sudden Arrhythmia Death Syndromes (SADS) Foundation**
  508 East South Temple
  Suite #202
  Salt Lake City UT 84102
  Phone: 800-786-7723 (toll-free); 801-531-0937
  Email: sads@sads.org
  www.sads.org
- **ARVD Patient Registry**
  The Johns Hopkins Hospital
  600 North Wolfe Street
  Carnegie 592
  Baltimore MD 21287
  Phone: 410-502-7161
  Fax: 410-502-9148
  Email: ctichnell@jhmi.edu
  ARVD Patient Registry
- **North American ARVD Registry**
  1501 North Campbell
  Room 5153
  PO Box 245037
  Tucson AZ 85724-5037
  Phone: 520-626-1416
  Fax: 520-626-4333
  Email: kgear@email.arizona.edu; fmarcus@shc.arizona.edu
  www.arvd.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A.

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy: Genes and Databases

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name	Locus Specific	HGMD
ARVD1	*TGFB3*	14q24.3	Transforming growth factor beta-3	TGFB3 @ LOVD ARVD/C Genetic Variants Database (TGFB3)	TGFB3
ARVD2	*RYR2*	1q43	Ryanodine receptor 2	Gene Connection for the Heart - Ryanodyne receptor mutation database RYR2 database	RYR2
ARVD3	Unknown	14q12-q22	Unknown		
ARVD4	Unknown	2q32.1-q32.3	Unknown		
ARVD5	*TMEM43*	3p25.1	Transmembrane protein 43	TMEM43 @ LOVD ARVD/C Genetic Variants Database (TMEM43)	TMEM43

ARVD6	Unknown	10p14-p12	Unknown		
ARVD7	Unknown	10q23.2	Unknown		
ARVD8	*DSP*	6p24.3	Desmoplakin	DSP @ LOVD ARVD/C Genetic Variants Database (DSP) Gene Connection for the Heart - Desmoplakin (DSP)	DSP
ARVD9	*PKP2*	12p11.21	Plakophilin-2	PKP2 @ LOVD ARVD/C Genetic Variants Database (PKP2) Gene Connection for the Heart - Plakophillin mutations database (PKP2)	PKP2
ARVD10	*DSG2*	18q12.1	Desmoglein-2	DSG2 @ LOVD ARVD/C Genetic Variants Database (DSG2)	DSG2
ARVD11	*DSC2*	18q12.1	Desmocollin-2	DSC2 @ LOVD ARVD/C Genetic Variants Database (DSC2)	DSC2
ARVD12	*JUP*	17q21.2	Junction plakoglobin	JUP @ LOVD ARVD/C Genetic Variants Database (JUP) Gene Connection for the Heart; Naxos disease database (JUP)	JUP

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) to which links are provided, click here.

Table B.

OMIM Entries for Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (View All in OMIM)

107970	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 1; ARVD1
125645	DESMOCOLLIN 2; DSC2
125647	DESMOPLAKIN; DSP
125671	DESMOGLEIN 2; DSG2
173325	JUNCTION PLAKOGLOBIN; JUP
180902	RYANODINE RECEPTOR 2; RYR2
190230	TRANSFORMING GROWTH FACTOR, BETA-3; TGFB3
600996	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 2; ARVD2
602086	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 3; ARVD3
602087	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 4; ARVD4
602861	PLAKOPHILIN 2; PKP2
604400	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 5; ARVD5

604401	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 6; ARVD6
607450	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 8; ARVD8
609040	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 9; ARVD9
609160	none found
610193	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 10; ARVD10
610476	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 11; ARVD11
611528	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 12; ARVD12
612048	TRANSMEMBRANE PROTEIN 43; TMEM43

Molecular Genetic Pathogenesis

Defects in intercellular connections are one pathogenic mode that leads to arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C). This is suggested by mutation of the genes encoding two desmosomal proteins, desmoplakin (*DSP*) and plakoglobin (*JUP*), associated with ARVD8/Carvajal syndrome and ARVD12/Naxos disease, respectively.

Altered calcium homeostasis may provide another pathogenic pathway in ARVD/C as suggested by mutation of *RYR2* (ARVD2). *RYR2* has an important role in calcium release from the sarcoplasmic reticulum and the regulation of excitation-contraction coupling. An impaired intracellular calcium concentration and altered excitation-contraction coupling may predispose to arrhythmias. In addition, impaired intracellular calcium may lead to cellular necrosis, promoting fibrosis and adipose replacement [Tiso et al 2001].

A database of all variants in the genes listed below can be found in the Leiden Open Variation Database or at www.arvcdatabase.info [van der Zwaag et al 2009]. (Links to this database are found in Table A under LSDB.)

RYR2

Gene structure. The gene comprises 105 exons, coding a 565-kd monomer, making it one of the largest human genes. For a detailed summary of gene and protein information, see Table A, **Gene Symbol**.

Pathogenic allelic variants. In a study by Tiso et al [2001], four missense mutations were identified in four Italian families in highly conserved regions of *RYR2*. These mutations differ from those found in *RYR2* in CPVT. Pathogenic variants in *RYR2* have also been identified in 'atypical' long QT syndrome [Tester et al 2005].

Normal gene product. The ryanodine receptor 2 regulates calcium flux in the intracellular space and mediates cardiac muscle excitation-contraction coupling [Tiso et al 2001].

Abnormal gene product. Mutation of *RYR2* is thought to result in an uncontrolled calcium leak in the cardiac myocyte, leading to arrhythmia.

DSP

Gene structure. The gene comprises 24 exons, coding 2871 amino acids. For a detailed summary of gene and protein information, see Table A, **Gene Symbol**.

Benign allelic variants. At least seven different benign variants have been identified in *DSP*, primarily missense alterations with one splice site [Barahona-Dussault et al 2010].

Pathogenic allelic variants. In a study by Rampazzo et al [2002], one missense mutation was identified in exon 7 of the proband in an Italian family. At least eight other mutations (nonsense and missense) have been identified in eight different families [Bauce et al 2005, Yang et al 2006].

Normal gene product. Desmoplakin, together with plakoglobin, anchors to desmosomal cadherins, forming an ordered array of non-transmembrane proteins, which then bind to keratin intermediate filaments (IFs) [Kowalczyk et al 1997, Smith & Fuchs 1998, Leung et al 2002]. Desmosomes are major cell-cell junctions, particularly abundant in epidermal cells and in cardiomyocytes [Gallicano et al 1998, Smith & Fuchs 1998]. In addition, desmosomes have been shown to maintain cell integrity as well as participate in cell death and lipid metabolism [Yang et al 2006].

Abnormal gene product. It is speculated that abnormalities in desmoplakin lead to desmosomal instability. Defective desmosomes cannot sustain the constant mechanical stress in contracting cardiomyocytes, resulting in cardiac dysfunction and cell death [Yang et al 2006].

Data from a desmoplakin-deficient mouse model suggest that abnormal desmosomes lead to abnormal β-catenin signaling through Tcf-Lef1 transcription factors resulting in dedifferentiation of myocytes into adipocytes [Garcia-Gras et al 2006].

PKP2

Gene structure. The gene comprises 14 exons. For a detailed summary of gene and protein information, see Table A, **Gene Symbol**.

Benign allelic variants. At least three different benign variants have been identified in *PKP2*, all missense alterations [Barahona-Dussault et al 2010].

Pathogenic allelic variants. In a study by Gerull et al [2004], 25 heterozygous pathogenic variants were identified in 32 of 120 unrelated probands. Of the 25 *PKP2* variants, 12 were insertion-deletion mutations, six were nonsense mutations, four were missense mutations, and three were splice-site mutations. Dalal et al [2006] identified another nine families with pathogenic variants in *PKP2*. Christensen et al [2010a] showed that 15% of Danish persons with ARVD/C had pathogenic variants in *PKP2*. Some previously reported missense mutations in *PKP2* (p.Asp26Asn, p.Ser140Phe, p.Val587Ile) were identified at a low frequency in a Danish population of healthy controls, leading them to conclude that missense variants in *PKP2* could be disease modifying but not pathogenic [Christensen et al 2010a]. Further characterization of these variants is needed.

Normal gene product. Similar to desmoplakin, plakophilin-2 is a protein of the desmosome and provides structural and functional integrity to adjacent cells.

Abnormal gene product. Abnormalities in plakophilin are thought to perturb intercellular connections and lead to arrhythmia.

DSG2

Gene structure. The gene comprises 15 exons spanning 48.6 kb. For a detailed summary of gene and protein information, see Table A, **Gene Symbol**.

Benign allelic variants. At least eight different benign variants have been identified in *DSG2*, all missense alterations [Barahona-Dussault et al 2010].

A previously reported pathogenic variant, c.473T>G (p.Val158Gly), was recently reclassified as a nonsynonymous single nucleotide polymorphism (SNP), as it was identified in a control population as well as in unrelated probands with a second confirmed mutation in *DSG2* [Bhuiyan et al 2009].

Pathogenic allelic variants. At least 12 pathogenic variants have been described. Individuals have been identified as having compound heterozygous mutations [Awad et al 2006, Pilichou et al 2006, Bhuiyan et al 2009]. Some gene variants previously believed to be pathogenic have been identified in a control population [Milting & Klauke 2008, Posch et al 2008a], as well as being present in some cases of dilated cardiomyopathy [Posch et al 2008b] and, therefore, being possible susceptibility variants rather than pathogenic variants.

Normal gene product. Desmoglein-2 (DSG2) is a member of the desmoglein family and is an essential component of the desmosome. DSG2 is expressed in myocardium [Awad et al 2006, Pilichou et al 2006].

Abnormal gene product. The effect of an abnormal gene product is unknown at this point; loss of DSG2 results in early embryonic lethality in knockout mice.

DSC2

Gene structure. The gene comprises 17 exons spanning 32 kb. For a detailed summary of gene and protein information, see Table A, **Gene Symbol**.

Pathogenic allelic variants. Four pathogenic variants have been described [Heuser et al 2006, Syrris et al 2006]. One individual with a digenic *DSG2* mutation has been identified [Bhuiyan et al 2009]. There is a variant that produces a frameshift (p.Ala897LysfsTer4; previously reported as p.Glu896fsTer900) that was originally reported as pathogenic; however, it has been identified in six (1.5%) of 400 control chromosomes and is therefore reclassified as a possibly rare variant that could affect phenotypic expression of other mutations that give rise to ARVD/C [De Bortoli et al 2010].

Normal gene product. Desmocollin-2 (DSC2) is ubiquitously expressed in desmosomal tissues and is the only one of three desmocollin isoforms present in cardiac tissue. DSC2 is found in two forms, a and b, produced by alternate splicing of exon 16. Desmocollins bind to desmogleins through their extracellular domains in a Ca2+-dependent manner and their cytoplasmic domains have binding sites for plakoglobin.

Abnormal gene product. Desmocollin mutations resulting in an isoform lacking the last 37 amino acid residues of the carboxyl-terminal domain of DSC2a are unable to bind plakoglobin. It is unknown how the mutations affect desmosome formation, but it is speculated that the result would be impaired desmosomes.

TGFB3

Gene structure. The gene comprises seven exons. For a detailed summary of gene and protein information, see Table A, **Gene Symbol**.

Pathogenic allelic variants. Two pathogenic variants have been described, one in the 5' untranslated region of the gene and the second in the 3' untranslated region of the gene [Beffagna et al 2005].

Normal gene product. *TGFB3* encodes for transforming growth factor beta-3, which encodes for a cytokine-stimulating fibrosis and modulates cell adhesion.

Abnormal gene product. It is currently unknown how mutation of *TGFB3* causes ARVD/C.

TMEM43

Gene structure. *TMEM43* comprises 12 exons coding for 400 amino acids. For a detailed summary of gene and protein information, see Table A, **Gene Symbol**.

Pathogenic allelic variants. In a study by Merner et al [2008], one putative pathogenic variant, the missense change p.Ser358Leu, was identified in 15 families, all of Newfoundland ancestry. Whether this variant is the causative mutation requires further testing, as it may rather be a benign variant that is in linkage disequilibrium with the causal mutation. A second *TMTM43* variant, p.Arg312Trp, seems to be a second founder mutation as it has been found in two Newfoundland probands and their families as well as a family from the United Kingdom; haplotype analysis showed that all share the disease-associated alleles and thus share an ancestral chromosome [Haywood et al 2013].

Normal gene product. *TMEM43* codes for a novel transmembrane protein. By bioinformatics analysis, the primary sequence suggests that this protein may be a target of PPARγ. Bioinformatics predicts the protein to be a membrane protein with several post-translational modification sites [Merner et al 2008]. Functional studies are needed.

Abnormal gene product. The pathogenic mechanism of the abnormal gene product is unknown.

JUP

Gene structure. The gene comprises 13 exons, coding for 745 amino acids and an 81.75-kd protein. For a detailed summary of gene and protein information, see Table A, **Gene Symbol**.

Benign alllelic variants. One benign variant (c.2089A>T; Table 2) has been identified as cosegregating with a mutation in desmoplakin. The frequency of the genotypes at position 2089 in the Turkish population is as follows [Uzumcu et al 2006]:

- Homozygous c.2089T: 0.57
- Compound heterozygous c.2089A+c.2089T: 0.36
- Homozygous c.2089A: 0.07

Pathogenic allelic variants. In a study by Asimaki et al [2007], one pathogenic variant was identified in the proband of a German family (c.118_119dupGCA) with an autosomal dominant mode of inheritance, although segregation of the pathogenic variant was not performed in other affected relatives. A two base-pair deletion in *JUP* (c.2038_2039del) causes Naxos disease, an autosomal recessive cardiocutaneous syndrome. A benign variant, c.2089T>A, is located at position +4 after the acceptor site in exon 3 and thus Uzumcu et al [2006] could not exclude a negative modifier effect on the cardiac phenotype by hypothetic effects on splicing from homozygosity for c.2089A.

Table 2.

Selected *JUP* Variants

Class of Variant Allele	DNA Nucleotide Change (Alias [1])	Protein Amino Acid Change	Reference Sequences
Benign	c.2089A>T	p.Met967Leu	NM_002230.2 NP_002221.1
Pathogenic	c.116_118dupGCA (118_119insGCA)	p.Ser39dup	
	c.2038_2039del (PK2157del2)	p.Trp680GlyfsTer11	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

Normal gene product. *JUP* encodes a cytoplasmic protein also known as gamma catenin, which is found in both submembranous plaques of desmosomes and intermediate junctions. The protein, a member of the catenin family, forms distinct complexes with cadherins and desmosomal cadherins. It contains a distinct repeating amino acid motif called the armadillo repeat.

Abnormal gene product. Myocardial biopsy from an affected individual showed that N-cadherin and plakophilin-2 were expressed at control levels; however, plakoglobin, desmoplakin, and connexin 43 were significantly reduced at the intercalated discs.

In vivo models suggest that mutation of *JUP* affects the structure and distribution of mechanical and electrical cell junctions and could interfere with regulatory mechanisms mediated by Wnt-signaling pathways [Asimaki et al 2007].

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Chapter Notes

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Revision History

- 9 January 2014 (me) Comprehensive update posted live
- 13 October 2009 (cd) Revision: sequence analysis available clinically for *TGFB3* mutations
- 15 December 2008 (cd) Revision: clinical testing for *JUP* mutations (ARVD12); prenatal testing for ARVD/C 5 (*TMEM43)*
- 10 July 2008 (cd) Revision: sequence analysis available clinically for *TMEM43* mutations (ARVD5)
- 12 December 2007 (me) Comprehensive update posted to live Web site
- 5 April 2006 (cd) Revision: Clinical testing for *DSP* and *PKP2* available; prenatal diagnosis for *PKP2* available
- 18 April 2005 (me) Review posted to live Web site
- 6 July 2004 (em) Original submission

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