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Arrhythmogenic Right Ventricular Cardiomyopathy Overview

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Summary

The purpose of this overview is to increase the awareness of clinicians regarding genetic causes of arrhythmogenic right ventricular cardiomyopathy (ARVC) and provide a basic view of genetic risk assessment of at-risk asymptomatic relatives of a proband with ARVC in order to inform cardiac surveillance and allow early detection and treatment of ARVC to improve long-term outcomes.

The following are the goals of this overview.

Goal 1

Describe the clinical characteristics of ARVC.

Goal 2

Review the genetic causes of ARVC.

Goal 3

Provide an evaluation strategy to identify the genetic cause of ARVC in a proband.

Goal 4

Inform genetic risk assessment in family members of a proband.

Goal 5

Review management of ARVC.

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1. Clinical Characteristics of Arrhythmogenic Right Ventricular Cardiomyopathy

Clinical Description

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a primary cardiomyopathy that is often diagnosed after an individual presents with arrhythmia findings. Presenting manifestations include heart palpitations, syncope, or even sudden death. ARVC typically presents in adults (mean age of first presentation in one large cohort study was 36 ± 14 years [Groeneweg et al 2015]), although it may less commonly be seen in children, most often during the late second decade.

ARVC typically affects the right ventricular apex, the base of the right ventricle, and the right ventricle outflow tract. The arrhythmias in ARVC most frequently arise from the right ventricle and have left bundle branch block morphology. The disease is progressive and is characterized by fibrofatty replacement of the myocardium. Pathology in ARVC may also extend to involve the left ventricle, resulting in regional left ventricular dysfunction.

Note: There is a movement within clinical cardiology to merge ARVC with other arrhythmogenic cardiomyopathies because the left ventricle can become involved, or even become predominantly involved, especially in individuals with *DSP* pathogenic variants; left ventricular involvement has also been reported in individuals with variants in genes encoding other desmosomal proteins (e.g., *DSC2*) that were previously associated with ARVC. The 2010 Task Force Criteria (see Diagnosis) are still used to establish a clinical diagnosis of ARVC [Marcus et al 2010], and these criteria do not incorporate other arrhythmogenic cardiomyopathies, leading to potential underdiagnosis. An international expert panel convened to reevaluate the diagnostic approach to arrhythmogenic cardiomyopathies and developed new criteria, the Padua Criteria [Corrado et al 2020]. There are ongoing studies to evaluate the proposed Padua Criteria in larger cohorts. Readers should be aware of the potential overlap/differentiation between ARVC and other arrhythmogenic cardiomyopathies.

Progression. The four described stages of ARVC are the following [Te Riele et al 2021, Wallace & Calkins 2021]:

1. The concealed phase is the earliest phase and is without electrical, structural, or histologic changes as typically seen in ARVC. If scar formation is present, it can be so minimal that it goes undetected by cardiac MRI. However, affected individuals might experience sustained ventricular arrhythmias, and there is a potential risk of sudden cardiac death.
2. An overt electrical disorder characterized by symptomatic arrhythmias including palpitations, syncope, and presyncope attributable to ventricular ectopy or sustained or nonsustained ventricular tachycardia
3. Right ventricular failure
4. A biventricular pump failure (resembling dilated cardiomyopathy) [Dalal et al 2006]

Cardiomyopathy in ARVC is not always isolatedto right ventricular involvement. There is evidence that the left ventricle can often become involved as well. The cohort of individuals with ARVC followed by Bhonsale et al [2015] had an overall incidence of left ventricular dysfunction of 14% over the follow-up interval, with 5% experiencing heart failure. In a separate cohort, 55% of individuals with *DSP* pathogenic variants experienced left ventricular predominant cardiomyopathy [Smith et al 2020].

Arrhythmia. The principal characteristic of arrhythmogenic cardiomyopathies is the tendency for ventricular arrhythmia in the absence of overt ventricular dysfunction. Arrhythmias in ARVC include ventricular tachycardia and ventricular fibrillation. Atrial fibrillation has also been described in ARVC. One recent study identified atrial fibrillation occurring in one in seven individuals with a diagnosis of definite ARVC (by 2010 Task Force Criteria), with atrial fibrillation onset at a median age of 51 years [Baturova et al 2020]. The risk of atrial fibrillation increases with severity of the ARVC phenotype compared to individuals who have an ARVC-

related pathogenic variant but do not have clinical manifestations of ARVC (and thus do not meet 2010 Task Force Criteria).

Prognosis. Two long-term studies of individuals with ARVC suggested that survival was greater than 72% at six years following diagnosis. In individuals with ARVC, cardiac mortality and need for transplant are less than 5% [Bhonsale et al 2015, Groeneweg et al 2015]. An individual with a prior history of sustained ventricular tachycardia or fibrillation is at increased risk for subsequent ventricular arrhythmias and sudden cardiac death. Prognosis is worse for individuals with more than one ARVC-related pathogenic variant, with an increased propensity to arrhythmias and progression to cardiomyopathy [Bao et al 2013, Rigato et al 2013, Bhonsale et al 2015, Groeneweg et al 2015].

Prevalence. The prevalence of clinical ARVC is estimated at 1:1,000-1,250 in the general population, although most of this data derives from cohorts of European ancestry [Wallace & Calkins 2021]. The prevalence of ARVC 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].

Diagnosis

Diagnostic criteria for ARVC, initially proposed by an international task force [McKenna et al 1994], were revised by Marcus et al [2010] (full text) to incorporate new knowledge and technology to improve diagnostic sensitivity while maintaining diagnostic specificity. Diagnostic criteria rely on a combination of EKG and signal averaged EKGs, imaging studies that include 2D echocardiography, cardiac MRI or right ventricular (RV) angiography, presence of arrhythmia documented by telemetric monitoring, genetic testing, and family history. Individuals are classified as having a definite, borderline, or possible diagnosis of ARVC based on the number of major and/or minor diagnostic criteria present.

A definite diagnosis of ARVC is **established** in a proband with the following findings from different categories:

- Two major criteria; OR
- One major AND two minor criteria; OR
- Four minor criteria

A borderline diagnosis of ARVC is considered in a proband with:

- One major AND one minor criterion; OR
- Three minor criteria from different categories

A possible diagnosis of ARVC is considered in a proband with:

- One major criterion; OR
- Two minor criteria from different categories

Imaging Findings: Global and/or Regional Cardiac Dysfunction and Structural Alterations

Major

- By 2D echo
  - Regional RV akinesia, dyskinesia, or aneurysm; AND
  - ONE of the following (end-diastole):
    - Parasternal long axis (PLAX) RV outflow tract (RVOT) ≥32 mm; corrected for body surface area (BSA) ≥19 mm/m^2
    - Parasternal short axis (PSAX) RVOT ≥36 mm; corrected for 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 ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female)
    - RV ejection fraction ≤40%
- By RV angiography. Regional RV akinesia, dyskinesia, or aneurysm

Minor

- By 2D echo
  - Regional RV akinesia or dyskinesia; AND
  - ONE of the following (end-diastole):
    - PLAX RVOT ≥29 mm to <32 mm; corrected for BSA ≥16 to <19 mm/m^2
    - PSAX RVOT ≥32 mm to <36 mm; corrected for 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 mL/m^2 to <110 mL/m^2 (male) or ≥90 mL/m^2 to <100 mL/m^2 (female)
    - RV ejection fraction >40% to ≤45%

Endomyocardial Biopsy or Autopsy Findings

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

Minor. Residual myocytes 60%-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

EKG Findings

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 ≥120 ms)
- **Minor**
  - Inverted T waves in leads V1 and V2 in individuals age >14 years (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 EKG in at least one of three parameters in the absence of a QRS duration of ≥110 ms on standard EKG
  - 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 and Molecular Genetic Testing

Major

- ARVC confirmed in a first-degree relative who meets 2010 Task Force Criteria [Marcus et al 2010]
- ARVC confirmed pathologically at autopsy or surgery in a first-degree relative
- Identification of a pathogenic variant categorized as associated or probably associated with ARVC in the proband

Minor

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

2. Genetic Causes of Arrhythmogenic Right Ventricular Cardiomyopathy

A pathogenic variant in one of the genes associated with arrhythmogenic right ventricular cardiomyopathy (ARVC) is identified in up to 66% of probands with a clinical diagnosis of ARVC (see Table 1) [Wallace & Calkins 2021]. Approximately 2%-4% of individuals with ARVC have more than one pathogenic variant identified (e.g., biallelic variants in one ARVC-related gene, heterozygous variants in more than one ARVC-related gene) [Groeneweg et al 2015, Murray et al 2020]. The genes listed in Table 1 are associated with autosomal dominant ARVC, with the exception of *DSC2* and *DSG2*, which are associated with both autosomal dominant and autosomal recessive ARVC [Wong et al 2014, Qadri et al 2017, Chen et al 2019].

Table 1. Genes Associated with Arrhythmogenic Right Ventricular Cardiomyopathy (ClinGen Gene Validity Classifications: Definitive and Moderate)

Gene [1]	% of ARVC Caused by Pathogenic Variants in Gene [2]	ClinGen Gene Validity Classification	Comment	Selected Allelic Disorders	OMIM Gene Entry
PKP2	34%-74%	Definitive	May be more likely to cause VT [Bao et al 2013]	Brugada syndrome	602861
DSG2	5%-26%	Definitive	Founder variant in population from East Asia [3]	DCM	125671

Table 1. continued from previous page.

Gene [1]	% of ARVC Caused by Pathogenic Variants in Gene [2]	ClinGen Gene Validity Classification	Comment	Selected Allelic Disorders	OMIM Gene Entry
DSP	2%-39%	Definitive [4]	• LV>RV involvement compared to *PKP2* [Smith et al 2020] • Can present as myocarditis or sarcoidosis-like phenotype [5]	DCM	125647
DSC2	1%-2%	Definitive [6]	• ARVC can be nonsyndromic or assoc w/mild palmoplantar keratoderma & woolly hair. • Founder variant in Hutterite population [7]		125645
JUP	0.5%-2%	See footnote 8.	• Heterozygous variant causes nonsyndromic ARVC. • Biallelic variants cause Naxos disease (ARVC w/palmoplantar keratoderma & peculiar woolly hair).		173325
TMEM43	Rare	Definitive [9]	Founder variant in population from Newfoundland, Canada [10]	Auditory neuropathy; *TMEM43*-related myopathies	612048
DES	Rare	Moderate	Founder variant in Dutch population [11]	DCM; conduction system disease; myofibrillar myopathy; Kaiser-type neurogenic scapuloperoneal syndrome	125660
PLN	Rare	Moderate		DCM; HCM	172405

Table 1. continued from previous page.

Gene [1]	% of ARVC Caused by Pathogenic Variants in Gene [2]	ClinGen Gene Validity Classification	Comment	Selected Allelic Disorders	OMIM Gene Entry
Unknown [12]	~40%				

ARVC = arrhythmogenic right ventricular cardiomyopathy; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LV = left ventricle; RV = right ventricle; VT = ventricular tachycardia

1. Genes are organized first by strength of ClinGen classification, then frequency of causation of ARVC, and then alphabetically.

2. See Bao et al [2013], Rigato et al [2013], Groeneweg et al [2015], Lazzarini et al [2015], and James et al [2021]. The proportion of ARVC attributed to specific genes varied by cohort studied, suggesting that the relative contribution of the different genes associated with ARVC may differ based on ethnicity and also on the medical care setting at the time of diagnosis (since the criteria for diagnosis of ARVC and for genetic testing may differ).

3. Homozygosity for *DSG2* variant c.1592T>G (p.Phe531Cys) was identified in 8/18 individuals studied and allele frequency was 0.12% in the East Asian population [Chen et al 2019].

4. See ClinGen: Arrhythmogenic Cardiomyopathy with Woolly Hair and Keratoderma.

5. Truncating variants in *DSP* have also been identified in individuals with a myocarditis phenotype (delayed enhancement on cardiac MRI, increased FDG uptake on FDG-PET, and biopsy findings of myocarditis) and sarcoidosis-like phenotype [Smith et al 2020, Ammirati et al 2022, Lota et al 2022].

6. See ClinGen: Familial Isolated Arrhythmogenic Right Ventricular Dysplasia.

7. DSC2 variant c.1660C>T (p.Gln554Ter) is a founder variant in the Hutterite population; homozygosity for p.Gln554Ter is associated with early-onset ARVC [Wong et al 2014].

8. ClinGen includes *JUP* as having "Clinical Actionability" for ARVC but does not provide the gene-disease validity classification (see https://search.clinicalgenome.org/kb/genes/HGNC:6207).

9. See ClinGen: Arrhythmogenic Right Ventricular Dysplasia 5.

10. TMEM43 variant c.1073C>T (p.Ser358Leu) is a highly penetrant founder variant in the Newfoundland, Canada, population characterized by left ventricular involvement and higher risk for sudden cardiac death [Dominguez et al 2020].

11. DES variant c.38C>T (p.Ser13Phe) is a Dutch founder variant that confers variable expression with right ventricular involvement that is consistent with ARVC but also conduction system disease, which is less common with ARVC [van Tintelen et al 2009].

12. James et al [2021], Christensen et al [2022]

Note: Studies from large population databases as well as from genetic testing in non-cardiology populations have identified pathogenic variants in genes encoding desmosomal proteins (i.e., *DSC2*, *DSG2*, *DSP*, *JUP*, and *PKP2*), indicating that pathogenic variants in these genes are less likely to be associated with highly penetrant monogenic ARVC [Haggerty et al 2017, Hall et al 2018, Abicht et al 2021, Bourfiss et al 2022]. These studies suggest that additional genetic variants, cardiovascular comorbidities, and non-genetic factors contribute to the penetrance of *DSC2*, *DSG2*, *DSP*, *JUP*, and *PKP2*-related ARVC.

Table 2. Genes of Interest in the Differential Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy (ClinGen Gene Validity Classification: Limited)

Gene [1]	Selected Allelic Disorders	OMIM Gene Entry
CDH2	Agenesis of corpus callosum, cardiac, ocular, & genital syndrome	114020
CTNNA3		607667
LMNA	CMT; Emery-Dreifuss muscular dystrophy; heart-hand syndrome, Slovenian type; Hutchinson-Gilford progeria syndrome; *LMNA*-related DCM	150330
MYBPC3	DCM; HCM; left ventricular noncompaction	600958
MYH7	DCM; HCM; Laing distal myopathy; left ventricular noncompaction; myosin storage myopathy; scapuloperoneal myopathy	160760
MYL3	HCM	160790
RYR2	Catecholaminergic polymorphic ventricular tachycardia	180902

Table 2. continued from previous page.

Gene [1]	Selected Allelic Disorders	OMIM Gene Entry
SCN5A	Atrial fibrillation; Brugada syndrome; DCM; familial paroxysmal ventricular fibrillation; long QT syndrome; progressive conduction system disease; sick sinus syndrome	600163
TGFB3	Loeys-Dietz syndrome	190230
TJP1		601009
TTN	DCM; HCM; hereditary myopathy w/early respiratory failure; Salih myopathy; Udd distal myopathy – tibial muscular dystrophy	188840

See ClinGen Gene Validity Classification: ARVC.

1. Genes are organized alphabetically.

3. Evaluation Strategy to Identify the Genetic Cause of Arrhythmogenic Right Ventricular Cardiomyopathy

Molecular genetic testing is recommended in individuals who both fulfill diagnostic criteria as well as those with suspected arrhythmogenic right ventricular cardiomyopathy (ARVC) to (1) confirm the diagnosis of ARVC, as identification of an ARVC-related pathogenic variant is a major diagnostic criteria in the 2010 Task Force Criteria [Marcus et al 2010]; (2) guide management in those with more than one ARVC-related pathogenic variant identified [Towbin et al 2019, James et al 2021]; and (3) enable testing of at-risk relatives (see Genetic Risk Assessment and Surveillance for Cardiac Involvement).

Note: American College of Cardiology / American Heart Association / Heart Rhythm Society (AHA/ACC/HRS) guideline for management of ventricular arrhythmias and prevention of sudden cardiac death recommend genetic counseling and molecular genetic testing for individuals with clinically diagnosed or suspected ARVC as a class IIa recommendation (i.e., a moderate level of evidence supports the recommendation is reasonable, can be useful/effective/beneficial, and the benefits outweigh the risks) [Al-Khatib et al 2018].

Establishing the specific genetic cause of ARVC usually involves an evaluation with a cardiologist including medical history, physical examination, cardiology assessment, family history, and molecular genetic testing. Note: Molecular genetic testing should begin with a proband with a clinical diagnosis of ARVC or suspected ARVC rather than an unaffected family member; molecular testing of an affected individual will provide the most informative results [James et al 2021].

Medical Evaluation

Medical history and physical examination are directed at identifying physical features associated with specific genetic causes of ARVC (Table 1).

Cardiology evaluation includes imaging to visualize the right ventricle, stress testing, and telemetric cardiac rhythm monitoring, as dictated by personal and family history.

Family history should include a three-generation family history with attention to heart palpitations, syncope, and sudden death in relatives; and documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing, cardiovascular and physical examinations, and postmortem examination. Founder variants associated with ARVC have been reported in individuals of Dutch and Hutterite ancestry as well as in individuals from East Asia and Newfoundland, Canada (see Table 1).

Molecular Genetic Testing

The molecular cause of ARVC is established in a proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in one of the known ARVC genes (see Table 1). Note: *DSC2* and *DSG2* are most often

associated with autosomal dominant ARVC; in rare instances biallelic *DSC2* or *DSG2* pathogenic variants cause autosomal recessive ARVC [Wong et al 2014, Qadri et al 2017, Chen et al 2019].

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous variant of uncertain significance does not establish or rule out the diagnosis or ARVC.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. In individuals with a clinical diagnosis of ARVC consider a multigene panel (see Option 1), whereas those with a phenotype indistinguishable from many other disorders with arrhythmia and/or cardiomyopathy may be more likely to be diagnosed using genomic testing (see Option 2).

Option 1

A multigene panel should minimally include definitive genes (as classified by ClinGen; see Table 1), including *DSC2*, *DSG2*, *DSP*, *JUP*, *PKP2*, *TMEM43*, and moderate genes (*DES*, *PLN*). It is reasonable to include other genes of interest, including *CTNNA3*, *LMNA*, *RYR2*, *TGFB3*, and *TTN* (see also Table 2). Note: (1) A larger multigene panel will increase diagnostic yield but will also increase identification of variants of uncertain significance [Dellefave-Castillo et al 2022]. (2) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (3) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most appropriate. (4) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (5) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. (6) Large deletions/duplications have been reported in *DES*, *DSC2*, *DSG2*, *DSP*, *PKP2*, *PLN*, and *TMEM43*; thus, testing methods should include analysis to detect single- or multiexon deletions/duplications.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

More comprehensive genomic testing (when available) including **exome sequencing** and **genome sequencing** may be considered. Alternatively, broader cardiomyopathy gene panels can be considered as first-line testing, as there is phenotypic and genotypic overlap with dilated, hypertrophic, and left ventricular noncompaction cardiomyopathies [Dellefave-Castillo et al 2022]. A broader cardiomyopathy panel can also be considered as an intermediate test prior to using comprehensive genomic testing. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

4. Genetic Risk Assessment and Evaluation of Relatives At-Risk

A basic view of arrhythmogenic right ventricular cardiomyopathy (ARVC) genetic risk assessment for at-risk family members is presented in this section; issues that may be specific to a given family or genetic cause of nonsyndromic ARVC are not comprehensively addressed.

Note: If a proband has a specific syndrome associated with ARVC (e.g., Naxos syndrome or Carvajal syndrome), counseling for that condition is indicated. Genetic risk assessment in families with syndromic ARVC is not discussed further in this section.

Genetic Risk Assessment

DES, *DSC2*, *DSG2*, *DSP*, *JUP*, *PKP2*, *PLN*, and *TMEM43* are associated with autosomal dominant ARVC, with the exception of *DSC2* and *DSG2*, which are associated with both autosomal dominant and (rarely) autosomal recessive ARVC.

Both *DSC2*-related ARVC and *DSG2*-related ARVC are typically inherited in an autosomal dominant manner.

- Autosomal recessive *DSC2*-related ARVC has been reported in the Hutterite population in association with the founder variant c.1660C>T (p.Gln554Ter) [Wong et al 2014]. It is not known if heterozygosity for this founder variant is associated with an increased risk for ARVC.
- Autosomal recessive *DSG2*-related ARVC has been reported in two families to date [Qadri et al 2017].

Approximately 2%-4% of individuals with ARVC have more than one pathogenic variant. These individuals have either biallelic pathogenic variants in one gene (compound heterozygous or homozygous pathogenic variants) or double heterozygosity* for pathogenic variants in more than one ARVC-related gene [Xu et al 2010, Bao et al 2013, Rigato et al 2013, Bhonsale et al 2015, Groeneweg et al 2015, Lin et al 2018, Chen et al 2019, Murray et al 2020, Brodehl et al 2021, Te Riele et al 2021]. Individuals with more than one ARVC-related pathogenic variant have a propensity to more severe disease, including a younger age of onset, arrhythmias, and progression to cardiomyopathy [Bao et al 2013, Rigato et al 2013, Bhonsale et al 2015, Groeneweg et al 2015, Chen et al 2019, Brodehl et al 2021].

* The presence of pathogenic variants in two different ARVC-related genes may be referred to in cardiology literature as "digenic ARVC." In genetics literature, the term "digenic" more typically refers to expression of a phenotype that requires the presence of pathogenic variants in two different genes. While additional genetic variants may modify outcome and result in more specific disease, nonsyndromic ARVC can be caused by the presence of one pathogenic variant in one ARVC-related gene.

Risk to Family Members (Autosomal Dominant Inheritance)

Parents of a proband

- The majority of individuals diagnosed with autosomal dominant ARVC inherited a pathogenic variant from a heterozygous parent [van Lint et al 2019]. A parent who is heterozygous for an ARVC-related pathogenic variant may or may not have ARVC-related clinical findings.
- If a proband has two pathogenic variants in the same ARVC-related gene, both parents may be heterozygous. If a proband has pathogenic variants in two different ARVC-related genes, both parents may be heterozygous or, less commonly, one parent may have two pathogenic variants.
- Rarely, a proband with autosomal dominant ARVC may have the disorder as the result of a *de novo* pathogenic variant. In one study, 1.4% of affected individuals had the disorder as the result of a *de novo* pathogenic variant [van Lint et al 2019].

- If the status of the parents is unknown:
  - And a molecular diagnosis has been confirmed in the proband, targeted molecular genetic testing is recommended for the parents of the proband to confirm their genetic status, clarify their need for cardiac surveillance, and allow reliable recurrence risk assessment;
  - And a molecular diagnosis has not been confirmed in the proband, recommendations for the evaluation of parents include cardiac MRI or echocardiogram, EKG, and Holter monitoring.

  Because ARVC may be asymptomatic, both the maternal and paternal lineages should be considered as possibly contributing to familial ARVC.
- If the proband has a known pathogenic variant that cannot be identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If one parent of the proband is heterozygous for an ARVC-related pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If one parent of the proband has biallelic ARVC-related pathogenic variants, all sibs will inherit an ARVC-related pathogenic variant.
- If both parents of a proband are heterozygous for an ARVC-related pathogenic variant, sibs have a 75% chance of inheriting one or two ARVC-related pathogenic variants and a 25% chance of inheriting neither pathogenic variant.
- Sibs who inherit an ARVC-related pathogenic variant are at increased risk for ARVC and should undergo surveillance for cardiac involvement. Risk is further increased in sibs who inherit more than one ARVC-related pathogenic variant. Individuals with more than one ARVC-related pathogenic variant have an increased propensity to arrhythmias and progression to cardiomyopathy [Bao et al 2013, Rigato et al 2013, Bhonsale et al 2015, Groeneweg et al 2015].
- If the parents are clinically unaffected but their genetic status is unknown, sibs are still presumed to be at increased risk for ARVC (and surveillance for cardiac involvement is recommended) because of the possibility of reduced penetrance in a heterozygous parent or parental germline mosaicism.

Offspring of a proband

- Each child of an individual with one ARVC-related pathogenic variant has a 50% chance of inheriting the pathogenic variant.
- Each child of an individual with biallelic pathogenic variants in one ARVC-related gene will inherit one pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if one or both parents are affected or have a pathogenic variant, family members are at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Evaluation of Relatives at Risk

It is appropriate to clarify the status of apparently asymptomatic relatives of an individual with ARVC in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures to reduce the risk of syncope, cardiac arrest, and sudden death. Clinical evaluation, genetic counseling, and targeted genetic testing of at-risk relatives (if the proband has a known ARVC-related pathogenic variant) constitute a class I recommendation in the American College of Cardiology / American Heart Association / Heart Rhythm Society (AHA/ACC/HRS) guideline for management of individuals with ventricular arrhythmias and the prevention of sudden cardiac death [Al-Khatib et al 2018].

Note: Predictive testing should be offered in the context of formal genetic counseling.

In order to appropriately assess the risk status of asymptomatic relatives of an individual with ARVC, it is important to ensure that:

- The proband has a clinical diagnosis of ARVC meeting the 2010 Task Force Criteria [Marcus et al 2010]; and
- The pathogenic variant (or pathogenic variants) identified in the proband (if applicable) is in a known ARVC-related gene and represents the full genetic etiology of ARVC in the proband.

If the proband meets 2010 ARVC Task Force Criteria and is identified as having a pathogenic variant in a gene not known to be associated with ARVC, then cascade genetic testing in family members is not reliable for ARVC risk assessment because the identified pathogenic variant may not represent the underlying cause of ARVC in the proband or may only partially account for the genetic risk of ARVC in the family. Cascade genetic testing can still be offered for the pathogenic variant identified in the proband, but a complete ARVC evaluation and risk assessment should still occur for all at-risk family members regardless of the results of genetic testing for the pathogenic variant identified in the proband.

Family members of an individual with a clinical diagnosis of ARVC meeting 2010 Task Force Criteria who has a known pathogenic variant(s) in an ARVC-related gene(s). Molecular genetic testing is recommended for parents, sibs, offspring, and other at-risk family members (even those age <18 years) in order to clarify their genetic status, allowing for the following:

- Identification of those individuals with a familial ARVC-related pathogenic variant(s) who have an increased lifetime risk for ARVC and should undergo surveillance for cardiac involvement. Guidelines exist for screening for cardiac involvement in asymptomatic first-degree relatives at risk for ARVC [Hershberger et al 2018].
- Identification of individuals without the familial ARVC-related pathogenic variant(s) to be discharged from high-risk cardiac surveillance. Individuals without the familial ARVC-related pathogenic variant(s) can be discharged from high-risk cardiac surveillance ONLY when their ARVC-affected relative has had a detailed discussion with a cardiologist with expertise in ARVC genetics and when this cardiogenetic expert has deemed that the pathogenic gene variant identified in the affected relative is fully causative of their ARVC disease. If the pathogenic gene variant does not fully explain the proband's phenotype, then family members should continue cardiac screening (see Surveillance for Cardiac Involvement).

Family members of an individual with a clinical diagnosis of ARVC meeting 2010 Task Force Criteria in whom the specific genetic cause of ARVC has not been identified. Screening for cardiac involvement is recommended for asymptomatic at-risk first-degree relatives (see Surveillance for Cardiac Involvement).

5. Management of Arrhythmogenic Right Ventricular Cardiomyopathy

This section provides information regarding risk assessment for arrhythmogenic right ventricular cardiomyopathy (ARVC), surveillance for cardiac involvement, and recommendations for medical and surgical management based (when possible) on the genetic cause.

Risk Assessment for ARVC

To establish the extent of disease and needs of an individual diagnosed with ARVC the following evaluations are recommended if not performed at the time of diagnosis:

- EKG
- Cardiac imaging. Cardiac MRI has improved yield compared to echocardiography, because cardiac MRI is superior in its ability to image the right ventricle and its ability to discern fibrofatty infiltration.
- Noninvasive monitoring. Cardiac rhythm can be monitored noninvasively through patch recorders that can record heart rate/rhythm data for up to 14 days. Event monitors can gather information for 30 days. Implantable loop recorders are useful for longer-term (three to five years) monitoring. These monitors can detect irregular atrial or ventricular rhythms including nonsustained ventricular tachycardia.
- Signal-averaged EKGs may also be useful [Philips & Cheng 2016].
- Electrophysiology study to assess the risk for ventricular arrhythmias and determine if an implantable cardioverter-defibrillator may be indicated. Cardiac catheter ablation of tissue causing abnormal rhythms can be performed during the electrophysiology study (see Recommendations for Medical and Surgical Management of ARVC).

Surveillance for Cardiac Involvement

Proband. Screening for degree of cardiac involvement in persons diagnosed with ARVC is essential to ascertain severity and disease progression over time. Screening recommendations include the following:

- EKG, annually or more frequently depending on symptoms
- Holter monitoring, event monitoring, implantable loop recorder
- Exercise stress testing
- Cardiac MRI, with frequency depending on symptoms and findings
- Echocardiogram, with frequency depending on symptoms and findings and degree of left ventricular involvement (and with knowledge that echocardiogram is insufficient for evaluating the right ventricle)

Family members who have tested positive for the ARVC-related pathogenic variant(s) identified in an affected relative. Surveillance is similar as for ARVC in a proband.

First-degree relatives (i.e., parents, sibs, offspring) of an affected individual in whom the specific genetic cause of ARVC has not been identified. 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 one to three years after age ten years [Towbin et al 2019].

Screening for cardiac involvement comprises the following [Towbin et al 2019, Wilde et al 2022]:

- Medical history, with attention to symptoms of arrhythmia, presyncope, syncope, and heart failure
- EKG, with consideration of signal-averaged EKG
- Holter monitoring
- Cardiac MRI
- Echocardiogram

At-risk first-degree relatives with any abnormal clinical screening tests for cardiac involvement should be considered for repeat clinical screening in one year [Towbin et al 2019].

Children younger than age ten years are not usually screened, as manifestations of ARVC are not usually seen in children prior to age ten years. See Hamilton & Fidler [2009] for a review of screening for ARVC in younger individuals. A study in younger individuals suggested that cardiac MRI was more sensitive than echocardiogram but that it was still unusual, even with cardiac MRI, to identify ARVC in children before age ten years [Etoom et al 2015].

In children younger than age 18 years. The 2010 Task Force Criteria [Marcus et al 2010] should be used with caution, as many of the EKG diagnostic criteria are a normal finding in children, such as inverted T waves in right precordial leads (V1, V2, and V3) [Te Riele et al 2021]. Cardiac MRI has been shown to have a better positive predictive value (and especially data from echocardiogram and cardiac MRI combined) [Steinmetz et al 2018, Te Riele et al 2021].

Recommendations for Medical and Surgical Management of ARVC

Affected individuals should be monitored by a cardiologist who is knowledgeable about ARVC. Management of individuals with ARVC is complicated by its variable course and the limited specificity of clinical findings to predict arrhythmia risk. Management should be individualized and based on the specific results of detailed clinical and genetic investigation.

Gene-Specific Management Recommendations

***DSP*.** Because of the risk of left ventricular dysfunction associated with *DSP* pathogenic variants [Smith et al 2020], management for individuals with *DSP*-related ARVC should address monitoring and management for left ventricular dysfunction, including guideline-directed therapy [Towbin et al 2019, Heidenreich et al 2022].

General Management Recommendations for ARVC

Treatment recommendations for ARVC can be found in an international task force consensus statement [Corrado et al 2015]. Additional guidance is found in the American College of Cardiology / American Heart Association / Heart Rhythm Society (AHA/ACC/HRS) guideline for management of individuals with ventricular arrhythmias and the prevention of sudden cardiac death [Al-Khatib et al 2018] and in an updated Heart Rhythm Society guideline for arrhythmogenic cardiomyopathy [Towbin et al 2019].

- Management is focused on prevention of syncope, cardiac arrest, and sudden death (see Prevention of Primary Manifestations).
- Beta blockers are considered first-line therapy [Corrado et al 2015, Towbin et al 2019, Heidenreich et al 2022].
- Anti-arrhythmia agents including sotalol and amiodarone may also be effective [Corrado et al 2015, Towbin et al 2019].
- A decrease of ventricular tachycardia burden has been observed after successful catheter ablation [Mahida et al 2019, Christiansen et al 2020, Daimee et al 2021].
- The primary treatment for ventricular tachycardia is implantable cardioverter-defibrillator placement, either transvenous or subcutaneous. Risk-benefit analysis for device insertion and management should be balanced against clinical risk stratification for arrhythmias [Orgeron et al 2018].
- Heart transplantation is considered when ARVC has progressed to right or left ventricular heart failure. Severe diffuse biventricular involvement simulating dilated cardiomyopathy and requiring heart transplantation is rare.
- Education should be provided regarding risk of sudden death to affected adults and parents/caregivers of affected children.

Prevention of Primary Manifestations

Prospective randomized trials have not been conducted in individuals with ARVC for the prevention of arrhythmias. Management relies on personalized recommendations based on clinical assessment.

Implantable cardioverter-defibrillators (ICDs). Observational studies support that ICD placement is effective in reducing the risk for sudden cardiac death in individuals with ARVC. ICD placement should be considered in anyone with a clinical diagnosis of ARVC; scoring systems have been developed to ascertain risk and guide device management [Jordà et al 2022]. Wallace & Calkins [2021] describe risk factors for ventricular arrhythmias or sudden cardiac death. Risk for ventricular tachycardia or sudden cardiac death include the following [Towbin et al 2019]:

- Prior history of sustained ventricular tachycardia or ventricular fibrillation
- Elevated burden of premature ventricular contractions (more than 1,000 in 24 hours)
- Nonsustained ventricular tachycardia
- A prior history of syncope
- Male sex. Males are more likely to be diagnosed and are 1.6 times more likely to have ventricular arrhythmias and to receive an appropriate shock from their ICD for ventricular arrhythmias than females [Akdis et al 2017].
- Intense exercise [James et al 2013, Gasperetti et al 2020]
- Degree of myocardial involvement, defined as right ventricular ejection fraction ≤45% or >2 areas of regional dysfunction [Wichter et al 2004]
- *PKP2* or *DSP* pathogenic variants. ARVC due to *PKP2* or *DSP* pathogenic variants was correlated with increased risk for a life-threatening arrhythmic event; this was greatest between ages 21 and 40 years [Al-Khatib et al 2018].

The AHA/ACC/HRS and Heart Rhythm Society (HRS) guidelines, which are based on experience and previously published reports, recommend ICD placement as a class I indication (i.e., procedure/treatment **should** be performed) for prevention of sudden cardiac death in individuals with resuscitated sudden cardiac arrest, documented sustained ventricular tachycardia or ventricular fibrillation, or significant ventricular dysfunction with right ventricular ejection fraction or left ventricular ejection fraction ≤35% who have a reasonable expectation of survival with good functional status for more than one year. Class II indications for ICD placement (i.e., it is **reasonable** to perform procedure/treatment) include syncope presumed due to ventricular arrhythmias; an ICD can be useful if meaningful survival greater than one year is expected [Al-Khatib et al 2018, Towbin et al 2019].

Agents/Circumstances to Avoid

Individuals with ARVC are discouraged from participating in frequent, intense physical exercise and intense competitive athletic activity because of the strain caused on the right heart [Corrado et al 2015, Al-Khatib et al 2018].

Pregnancy Management

The majority of individuals with ARVC tolerate pregnancy well with no additional complications [Hodes et al 2016, Platonov et al 2020]. One study found 13% of individuals with ARVC had ventricular arrhythmias and 5% had heart failure [Hodes et al 2016], and a separate study found an elevated risk of ventricular arrhythmias during the two years postpartum in women diagnosed with ARVC prior to conception, with only two events occurring during pregnancy [Platonov et al 2020]. Specific guidelines for managing ARVC in pregnancy have not been developed, but individuals with ARVC should be managed by a multidisciplinary team.

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**
  Phone: 800-242-8721
  www.americanheart.org
- **Sudden Arrhythmia Death Syndromes (SADS) Foundation**
  Phone: 801-948-0654
  www.sads.org
- **ARVD/C Patient Registry**
  The Johns Hopkins Hospital
  Phone: 410-502-7161
  ARVD/C Patient Registry

Chapter Notes

Revision History

- 11 May 2023 (sw) Comprehensive update posted live; scope changed to overview
- 25 May 2017 (ha) Comprehensive update posted live
- 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 live
- 5 April 2006 (cd) Revision: Clinical testing for *DSP* and *PKP2* available; prenatal diagnosis for *PKP2* available
- 18 April 2005 (me) Review posted live
- 6 July 2004 (em) Original submission

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