# Arrhythmogenic Right Ventricular Dysplasia in Neuromuscular Disorders

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**ABSTRACT**

**OBJECTIVES:** Arrhythmogenic right ventricular dysplasia (ARVD) is a rare, genetic disorder predominantly affecting the right ventricle. There is increasing evidence that in some cases, ARVD is due to mutations in genes, which have also been implicated in primary myopathies. This review gives an overview about myopathy-associated ARVD and how these patients can be managed.

**METHODS:** A literature review was done using appropriate search terms.

**RESULTS:** The myopathy, which is most frequently associated with ARVD, is the myofibrillar myopathy due to desmin mutations. Only in a single patient, ARVD was described in myotonic dystrophy type 1. However, there are a number of genes causing either myopathy or ARVD. These genes include lamin A/C, ZASP/cypher, transmembrane protein-43, titin, and the ryanodine receptor-2 gene. Diagnosis and treatment are identical for myopathy-associated ARVD and nonmyopathy-associated ARVD.

**CONCLUSIONS:** Patients with primary myopathy due to mutations in the desmin, dystrophia myotonica protein kinase, lamin A/C, ZASP/cypher, transmembrane protein-43, titin, or the ryanodine receptor-2 gene should be screened for ARVD. Patients carrying a pathogenic variant in any of these genes should undergo annual cardiological investigations for cardiac function and arrhythmias.

**KEYWORDS:** cardiomyopathy, right ventricle, arrhythmias, conduction defects, myopathy, neuromuscular, sudden cardiac death

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## Introduction

Occasionally, neuromuscular disorders (NMDs) also manifest in the heart.[1] Most frequently, only the myocardium is affected, but in metabolic myopathies or myotonic dystrophy, all tissues of the heart may be affected. Arrhythmogenic right ventricular dysplasia (ARVD), also known as arrhythmogenic right ventricular cardiomyopathy (ARVC), is a rare, genetic disorder predominantly affecting the right ventricle.[2,3] ARVD is associated with severe rhythm abnormalities, occasionally leading to sudden cardiac death (SCD).[4] ARVD has been only occasionally reported in association with NMD.[5] This review deals with ARVD in NMDs and provides an overview about those NMDs in which ARVD has been reported and how these patients can be managed.

## Methods

Data for this review were identified by searches of MEDLINE, Current Contents, EMBASE, Web of Science, Web of Knowledge, LILACS, SCOPUS, and Google Scholar for references to relevant articles using the search terms "arrhythmogenic right ventricular dysplasia", "arrhythmogenic right ventricular cardiomyopathy", "ARVD", "ARVC", "ARVD/C", "right ventricle", "right ventricular dysfunction", "conduction defects", and "arrhythmias" in combination with "myopathy", "neuromuscular disorder", and "skeletal muscle". Randomized (blinded or open label) clinical trials, longitudinal studies, case series, and case reports were considered. Abstracts and reports from meetings were not included. Only articles in English, French, Spanish, or German and published between 1966 and 2016 were considered. Appropriate articles were studied and discussed for their usefulness to be incorporated in this review. Reference lists of the appropriate articles were reviewed for further articles matching the search terms. An article was included if it reported patients with ARVD/ARVC with or without primary myopathy in association with a genetic defect or a biochemical or immunohistochemical defect on muscle biopsy. Articles reporting patients with ARVD but without an underlying genetic, biochemical, or immunohistological defect were excluded.

## Results

Seventy-six articles were included. Eighty-two articles were excluded because they did not match the inclusion criteria.

**History.** The term ARVD was coined and first reported by Fontaine et al.[6] The first classical description of the entity

in 24 cases was provided by Marcus et al.[7] In 1996, it was first demonstrated that fibrofatty changes of the right ventricle result from apoptosis of cardiomyocytes.[8] The first mutation associated with ARVD, a deletion in the plakoglobin gene, was reported in 2000.[9] The second gene mutated in ARVD, desmoplakin, was reported in 2002.[10] The third mutated gene responsible for ARVD is the gene for plakophilin-2, which was reported in 2004.[11] The first long-term follow-up of ARVD patients was carried out by Hulot et al.[12] Causative desmoglein-2 mutations were first described in 2006.[13] Desmocollin-2 mutations in ARVD were first described in 2006.[14] In 2013, Kim et al.[15] showed in a patient-specific induced pluripotent stem cell model that the induction of adult-like metabolic energetics from an embryonic/glycolytic state and abnormal activation of peroxisome proliferator-activated receptor-gamma underlie the pathogenesis of ARVD. Fontaine and Chen pointed out in 2014 that the right ventricular (RV) myocardium is frequently replaced by fatty tissue in the majority of healthy subjects and clinically unaffected mutation carriers, giving rise to false-positive results on cardiac MRI.[16]

**Clinical presentation.** ARVD is a hereditary disorder predominantly affecting the RV-free wall.[17] ARVD may be asymptomatic or might manifest as hepatomegaly, palpitations, syncope, dyspnea, exercise intolerance, or coma.[17] Symptoms and signs of left ventricular dysfunction, including leg edema, are rare. Hepatomegaly with hepatojugular reflux is the most severe form of the disease. Histologically, ARVD is characterized by the development of a fibrofatty RV wall, which predisposes for arrhythmias and RV dysfunction.[18–20] The most frequently reported arrhythmias and conduction disturbances include premature ventricular contractions, sustained or nonsustained re-entrant ventricular tachycardia with a left bundle branch block pattern, supraventricular ectopic beats, supraventricular tachycardia, atrial flutter, permanent atrial fibrillation, and sick sinus syndrome.[5,17] AV blocks are rare in ARVD but frequent in desminopathies and myotonic dystrophy. Over time, the left ventricle may be affected as well.[20,21] Myocarditis with a loss of left ventricular function is the determinant of prognosis at the end stage of the disease.[22] Clinical presentation is highly variable even within a family, and a number of affected individuals do not meet the diagnostic criteria.[20]

**Etiology.** ARVD is associated with a number of mutated desmosomal and nondesmosomal genes (Table 1), but in a large number of cases, the underlying genetic defect cannot be identified. Desmosomal genes mutated in ARVD include desmocollin-2, desmoglein-2, desmoplakin, plakoglobin, and plakophilin-2 (Table 1). Nondesmosomal proteins include transmembrane protein-43, ryanodine receptor-2, dystrophia myotonica protein kinase, desmin, lamin A/C, ZASP/cypher, titin, and transforming growth factor-β3 (Table 1).[23] In mice, mutations in the phospholamban gene were associated with ARVD and myopathy.[24] In a study on dogs, mutations in the striatin gene were associated with ARVD (Table 1).[25] The pathogenicity of mutations in the ryanodine receptor-2 gene, the phospholamban gene, and the striatin gene in human ARVD is currently under debate.

**Diagnosis.** ARVD is diagnosed according to criteria established in 1994, which were revised in 2010 (Task Force Criteria [TFC] and revised TFC for ARVD) (Table 2).[26] Diagnostic criteria, particularly for pediatric ARVD, have also been proposed.[27] According to the TFC, ARVD is diagnosed in case that encompasses the following set of major and minor six items: imaging (echocardiography and cardiac MRI) and histopathological findings, electrocardiographic abnormalities, arrhythmia history, and genetic factors (Table 2).[19] Based on these criteria, ARVD patients are classified as possible, borderline, or definite ARVD.[17] The MRI criteria implemented in the TFC include regional RV wall-motion abnormalities, reduced ejection fraction, and an increased RV end-diastolic volume index.[19] Detection of epsilon waves on routine ECG may contribute to the diagnosis of ARVD.[28] Three types of epsilon waves can be differentiated in ARVD, ie, wiggle waves, small spike waves, and smooth potential waves, that form an atypical prolonged R′ wave.[29] In addition to RV parietal block, reduced QRS amplitude, epsilon waves, and ventricular tachycardia with left bundle branch block morphology, T-wave inversion is another typical ECG characteristic in ARVD patients.[30] The rate of T-wave inversion is increased in patients with epsilon waves than in patients without epsilon waves.[10,29] MRI features that have not yet been implemented in the TFC include ventricular fatty infiltration and late gadolinium enhancement (LGE). Ventricular fatty infiltration and LGE can be found on cardiac MRI in two-thirds of ARVD patients.[19] Fatty infiltration and LGE are particularly found among those who fulfill major the TFC for ARVD (Table 2).[19] Imaging abnormalities usually occur after ECG abnormalities, which include depolarization and repolarization abnormalities. Among the latter, T-wave inversion is the most common.[17] Patients with an identified mutation are more likely to meet the TFC for ARVD than those without a mutation.[31] Patients without an implantable cardioverter defibrillator (ICD) experience ventricular arrhythmias and SCD more frequently than those with an ICD.[31] Differential diagnoses of ARVD include myocarditis, sarcoidosis, RV outflow tract tachycardia, congenital abnormalities, pulmonary hypertension, dilated cardiomyopathy, and athletic cardiac adaptation.[17]

**Myopathies associated with ARVD.** Primary myopathies in which ARVD has been additionally described so far include desminopathy and myotonic dystrophy type 1. In addition, several mutated genes have been published, which cause myopathy or ARVD.[22,32–34] However, so far, no patient presenting with both myopathy and ARVD due to these genetic defects has been reported.

*Desminopathy.* In a Swedish family in which 17 patients had desminopathy due to the mutation c.1255C>T,

**Table 1.** ARVD-associated mutated genes with or without myopathy (genes are listed according to frequency in ARVD patients).

| GENE | PROTEIN | CM | OM | NRC | REFERENCE |
|---|---|---|---|---|---|
| *PKP2* | Plakophilin-2 | ARVD9 | Brugada syndrome | 338 al§ | 31, 62, 63 |
| *TMEM43* | TMEM43 | ARVD5 | Myopathy# | 295 | 58, 64 |
| *DSG2* | Desmoglein-2 | ARVD10 | Left ventricle | 100 al§ | 31, 65, 66 |
| *DSP* | Desmoplakin | ARVD8 | Carvajal syndrome | 83 al§ | 31, 67 |
| *TGFB3* | Growth factor | ARVD1 | Loeys Dietz syndrome | 38 | 68 |
| *RYR2* | Ryanodine-2 | ARVD2 | Statin myopathy | 25 | 47 |
| *DSC2* | Desmocollin-2 | ARVD11 | None | 24 al§ | 31, 69 |
| *DES* | Desmin | ARVD& | Myopathy | 16 | 35, 39, 50 |
| *TTN* | Titin | ARVD | Myopathy* | 11 | 34 |
| *JUP* | Plakoglobin | ARVD12 | None | 10 al§ | 31, 70 |
| *LMNA* | Lamin A/C | ARVD | Myopathy | 5 | 71 |
| *ZASP* | Cypher | ARVD | Myopathy | 3 | 22 |
| *CTNNA3* | alphaT-catenin | ARVD | None | 2 | 72 |
| *DMPK* | Proteinkinase | ARVD& | Myotonic dystrophy | 1 | 42 |
| *SCN5 A* | Sodium-channel | ARVD | Brugada syndrome | 1 | 73 |
| *PLN* | Phospholamban | ARVD | Myopathy | only in mice | 24 |
| *STRN* | Striatin | ARVD | None | only in dogs | 25 |

**Notes:** *Limb girdle muscular dystrophy. #Emery–Dreifuss muscular dystrophy. &ARVD and myopathy in the same patient; genes responsible for ARVD3, ARVD4, ARVD6, and ARVD7 have been mapped but were not yet identified. §Data are taken from Table 4.
**Abbrevations:** al, at least; ARVD, arrhythmogenic right ventricular dysplasia; CM, cardiac manifestation; OM, other manifestations; DES, desmin; DSC2, desmocollin-2; NRC, number of so far reported cases; PKP2, plakophilin-2; TMEM43, transmembrane protein-43 (inner nuclear membrane protein).

p.Pro419Ser in the desmin gene, manifesting as myofibrillar myopathy, three patients had ARVD.[5,35] Desmin encodes for an intermediate filament protein located in the cytoskeleton and expressed in cardiac, skeletal muscle, and smooth muscle cells.[36] The Swedish family had been reported earlier, and the causative gene was initially located on chromosome 10q22.3.[5] A muscle biopsy from one of these patients showed myopathic changes and rimmed vacuoles, as well as the accumulation of desmin, dystrophin, and other proteins.[5] On electron microscopy, granulofilamentous changes and myofibril disorganization were found.[5] All three patients with ARVD died early at the age of 39, 59, and 63 years, but it was not mentioned if death was due to SCD or not. In a study of 22 patients with ARVD, mutations in the desmin gene were found only in a single patient.[37] In this cohort, 43% of the patients carried a mutation in one of the genes involved in ARVD (Table 1).[37] In a study of 50 patients with congenital myopathy, desminopathy with ARVD was diagnosed in a single patient.[38] In a study of 50 patients from two families with two different desmin mutations, one patient presented with an ARVD-like phenotype.[39] In a study of 22 patients with desmin mutations, two presented with an ARVD phenotype (Table 3).[40] All patients showed cardiac involvement characterized by high-grade AV block at young ages and important RV involvement. A right bundle branch block was recorded in 10 patients and RV heart failure in six patients.[40] Interestingly, both the right and left ventricles are affected in patients with desminopathies and ARVD.[39] In a study of 10 unrelated Chinese ARVD patients, no mutation was detected in the desmin gene.[41] Desmin mutations causing ARVD, thus, seem to be a rare cause of ARVD.

*Myotonic dystrophy type 1.* The second hereditary myopathy in which ARVD has been described is myotonic dystrophy type 1. It is a multisystem trinucleotide disorder due to a CTG repeat expansion >50 in the dystrophia myotonica protein kinase gene. Cardiac involvement is common and most frequently includes conduction defects, arrhythmias, and cardiomyopathy, including noncompaction. Involvement of the right heart has been only occasionally reported. In an 11-year-old girl with sudden cardiac arrest and unsuccessful cardiopulmonary resuscitation, ARVD was suspected as the cause of SCD since microscopic examination of the right heart upon autopsy revealed a marked fibrofatty RV wall.[42] No abnormalities were found in the left ventricular myocardium. After reevaluation of the family history, it was found that some family members (father, brother and nephew of the index case, and sister of the father) suffered from myotonic dystrophy type 1. The index case was reevaluated for myotonic dystrophy type 1, and a CTG repeat expansion of 400 was detected. This was why the authors changed the diagnosis from ARVD to myotonic dystrophy. Since the patient fulfilled a number of the TFC, we regard a CTG repeat expansion in the dystrophia myotonica protein kinase gene as another possible cause of ARVD (Table 1). In another patient with myotonic dystrophy type 1, focal right atrial dysplasia with atrial flutter has been reported.[43]

**Table 2.** Diagnostic criteria for ARVD (2010 modified Task Force Criteria).[74]

| |
|---|
| **I. Global or regional dysfunction and structural alterations** |
| Major |
| Echocardiography |
| Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): |
| PLAX RVOT ≥32 mm (corrected for body size_PLAX/BSA ≥19 mm/m$^2$) |
| PSAX RVOT ≥36 mm (corrected for body size_PSAX/BSA_ ≥21 mm/m$^2$) or fractional area change ≤33% |
| MRI |
| Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: |
| Ratio of RV end-diastolic volume to BSA ≥110 mL/m$^2$ (male) or ≥100 mL/m$^2$ (female) or RV ejection fraction <40% |
| RV angiography |
| Regional RV akinesia, dyskinesia, or aneurysm |
| Minor |
| Echocardiography |
| Regional RV akinesia or dyskinesia and 1 of the following (end diastole): |
| PLAX RVOT ≥29 to <32 mm (corrected for body size _PLAX/BSA ≥16 to <19 mm/m$^2$) |
| PSAX RVOT ≥32 to <36 mm (corrected for body size _PSAX/BSA ≥18 to <21 mm/m$^2$) or fractional area change >33% to <40% |
| MRI |
| Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 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) or |
| RV ejection fraction >40% to <45% |
| **2. Tissue characterisation of wall** |
| Major |
| Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy |
| Minor |
| Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy |
| **3. Repolarisation abnormalities** |
| Major |
| Inverted T waves in V1, V2, and V3 or beyond in individuals >14 years of age (in the absence of complete RBBB QRS ≥120 ms) |
| Minor |
| Inverted T waves in V1 and V2 in individuals >14y of age (in the absence of complete RBBB) or in V4, V5, or V6 |
| Inverted T waves in V1, V2, V3, and V4 in individuals >14y of age in the presence of complete RBBB |
| **4. Depolarisation abnormalities** |
| Major |
| Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in V1 to V3 |
| Minor |
| Late potentials by SAECG in ≥1 of 3 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 V (low-amplitude signal duration) ≥38 ms |
| Root-mean-square voltage of terminal 40 ms <20 V |
| 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 RBBB |
| **5. Arrhythmias** |
| Major |
| Nonsustained or sustained ventricular tachycardia of LBBB morphology with superior axis (negative or indeterminate QRS in II, III, and aVF and positive in aVL) |
| Minor |
| Nonsustained or sustained ventricular tachycardia of RV outflow configuration, LBBB morphology with inferior axis (positive QRS in II, III, and aVF and negative in aVL) or of unknown axis |
| >500 ventricular extrasystoles per 24 h (Holter) |
| **6. Family history** |
| Major |
| ARVC/D confirmed in a first-degree relative who meets current TFC |
| ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative |
| Identification of a pathogenic mutation categorized as associated or probably associated with ARVC/D in the patient under evaluation |
| Minor |
| History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current TFC |
| Premature sudden death (<35 y of age) due to suspected ARVC/D in a first-degree relative |
| ARVC/D confirmed pathologically or by current TFC in second-degree relative |

**Notes:** Reused with permission from Marcus FI et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation*. 2010;121(13):1533–41. *Circulation* is published by the American Heart Association. Promotional and commercial use of the material is prohibited without permission from the publisher, Wolters Kluwer. Contact healthpermissions@wolterskluwer.com for information.

**Abbreviations:** ARVD, arrhythmogenic right ventricular dysplasia; aVF, augmented voltage unipolar left foot lead; aVL, augmented voltage unipolar left arm lead; BSA, body surface area; LBBB, left bundle-branch block; PLAX, parasternal long-axis view; PSAX, parasternal short-axis view; RV, right ventricular; RVOT, RV outflow tract; RBBB, right bundle-branch block; Definite ARVD, two major or one major and two minor or four minor criteria from different categories; borderline ARVD, one major and one minor or three minor criteria from different categories; possible ARVD, one major or two minor criteria from different categories.

*Mutated genes causing either myopathy or ARVD.* Lamin A/C. In addition to desminopathy and myotonic dystrophy type 1, ARVD has been reported in association with a number of other genetic defects, which also manifest as myopathy but not as both myopathy and ARVD (Table 1). Mutated genes causing either myopathy or ARVD, but which have not been reported together in the same patient, include the genes for lamin A/C, ZASP/cypher, transmembrane protein-43,

**Table 3.** Patients with desmin mutations and ARVD.

| NOP | AGE | SEX | MUTATION | NOPM | REFERENCE |
|---|---|---|---|---|---|
| 13 | np | np | p.K241E, p.A213V | 0 | 36 |
| 2 | np | npt | p.S13F | 0 | 40 |
| 7 | np | np | c.1255C>T | 7 | 35 |
| 4 | np | np | p.N342D, p.R454W | 4 | 39 |
| 1 | 15 | f | p.N116S | 1 | 37 |

**Abbreviations:** ARVD, arrhythmogenic right ventricular dysplasia; NOP, number of patients; NOPM, number of patients with myopathy; np, not provided.

and titin. In a study of 108 patients with ARVD, variants in the lamin A/C gene were found in four of them.[32] Three of these patients had conduction abnormalities on ECG and died during follow-up, two patients suddenly died, and one patient died from heart failure.[32] Postmortem analysis of the myocardium in two of these patients showed cardiomyocyte loss and a fibrofatty RV wall.[32] In another patient, lamin A/C mutations were associated with an ARVD-like phenotype.[44] In a study of a four-generation family with ARVD, dilated cardiomyopathy, conduction defects, ventricular arrhythmias, and SCD, a novel lamin A/C mutation was detected and was found to be responsible for the variable phenotypic manifestations.[45] None of the family members presented with myopathic features.

ZASP/cypher. In a study on a family with several members affected by ARVD but without myopathy, next-generation sequencing revealed a mutation in the cypher/ZASP gene.[22] Three individuals fulfilled the criteria for definitive ARVD and one individual obtained a borderline diagnosis.[22] None of the family members had developed any myopathic features.

Transmembrane protein-43. Mutations in the gene encoding transmembrane protein-43 have been shown to cause ARVD5.[46] In a study of 41 patients with Emery–Dreifuss muscular dystrophy, which is characterized by muscular dystrophy, joint contractures, and cardiomyopathy with conduction blocks, heterozygous missense mutations in the transmembrane protein-43 gene, which encodes the nuclear membrane protein LUMA, were detected in two of them.[33] Neither of these two patients had developed ARVD. In one of the patients, staining for LUMA in the muscle was reduced, and *in vitro* transfection analysis demonstrated that the LUMA mutation resulted in a failure in oligomerization, which might be important for protein complex formation in the nuclear membrane.[33] The study also showed that LUMA interacts with other nuclear membrane proteins, including SUN2 and emerin.[33]

Titin. In a study of 38 ARVD families, screening for titin gene mutations revealed 8 titin variants in 7 families, which segregated with ARVD.[34] A history of SCD was positive in 5 of the 7 families, and progressive right heart dysfunction causing death or heart transplantation occurred in 8 of the 14 cases.[34] Native gel electrophoresis, nuclear magnetic resonance, intrinsic fluorescence, and proteolysis assays of wild-type and mutant Ig10 domains of the titin gene revealed that the mutation reduced the structural stability and increased the propensity for degradation of the Ig10 domain.[34]

Ryanodine receptor-2. Whether mutations in the ryanodine receptor-2 gene cause ARVD2 in humans is under debate (Table 1).[47] Although the ryanodine receptor-2 is mainly expressed in the heart,[48] certain ryanodine receptor-2 polymorphisms have been reported in association with the development of statin-induced myopathy.[49] However, primary myopathy due to ryanodine receptor-2 mutations has not been reported. In a canine model of ARVD, the cardiac abnormality was due to a mutation in the striatin gene on chromosome 17.[25]

Frequency of mutations in desmosomal and nondesmosomal genes in ARVD. In a study of 100 unrelated ARVD patients, a search for mutations in the plakophilin-2, desmoplakin, desmoglein-2, desmocollin-2, plakoglobin, transforming growth factor-β3, transmembrane protein-43, desmin, and lamin A/C genes showed that a genetic defect could be identified in 64% of the patients.[41] In 93% of the cases, these mutations were located in desmosomal genes.[41] Plakophilin-2 mutations accounted for 54% of the mutations (Table 4).[41] In another study, clinical characteristics and outcomes were similar in patients with and without an identified genetic defect and among patients with and without familial ARVD.[31] In a study of 36 patients with ARVD, 25% had mutations in plakophilin-2, 14% had mutations in desmoplakin, 11% had mutations in desmoglein-2, 6% had mutations in plakoglobin, and 3% had mutations in desmocollin-2 (Table 4).[50] In a study of 23 ARVD patients, disease-causing mutations were identified in the plakophilin-2 gene ($n = 6$), desmocollin-2 gene ($n = 3$), desmoglein-2 gene ($n = 3$), desmoplakin gene ($n = 2$), desmin gene ($n = 1$), and ryanodine receptor-2 gene ($n = 1$) (Table 4).[37] In a study of 134 ARVD patients from 44 families, 84% carried a single desmosomal gene mutation.[51] Forty-four patients (39%) carried a desmoplakin mutation, 30 patients carried a desmoglein-2 mutation, and one patient had a desmocollin-2 mutation (Table 4).[51] In 7 patients, compound heterozygote mutations were detected and 14 patients demonstrated digenic heterozygosity.[51] In a study of 36 Japanese patients with ARVD, 10 patients had mutations in the plakophillin-2 gene, 7 patients had mutations in the desmoplakin gene, 5 patients had mutations in the demsoglein-2 gene, and two patients had mutations in the desmicollin-2 gene (Table 4).[52] In a study of 149 patients with ARVD, 22 patients had mutations in the plakophillin-2 gene, 4 patients had mutations in the desmocollin-2 gene, 4 patients had mutations in the desmoglein-2 gene, and 2 patients had mutations in the desmoplakin gene (Table 4).[53] In a study of 65 Danish patients with ARVD, 7 patients had mutations in the plakophilin-2 gene, 4 patients had mutations in the desmocollin-2 gene, four patients had mutations in the plakoglobin gene, two patients had mutations in the desmoglein-2 gene, and two patients had mutations in the desmoplakin gene (Table 4).[54]

**Table 4.** Frequency of desmosomal gene mutations in ARVD.

| GENE/STUDY | NOP | PKP2 | DSG2 | DSC2 | DSP | JUP |
|---|---|---|---|---|---|---|
| Groeneweg 2015[31] | 439 | 202 | 17 | 5 | 11 | 2 |
| Zhou 2015[50] | 36 | 9 | 4 | 1 | 5 | 2 |
| Bao 2013[41] | 100 | 42 | 11 | 3 | 6 | 3 |
| Rigato 2013[51] | 134 | 0 | 30 | 1 | 44 | 0 |
| Ohno 2013[52] | 36 | 10 | 5 | 2 | 7 | 0 |
| Fressart 2010[75] | 135 | 19 | 6 | 1 | 3 | 0 |
| Klauke 2010[37] | 23 | 6 | 3 | 3 | 2 | 0 |
| Cox 2010[53] | 149 | 22 | 4 | 4 | 2 | 0 |
| Christensen 2010[54] | 65 | 7 | 2 | 4 | 2 | 2 |
| Den Haan 2010[76] | 100 | 21 | 8 | 0 | 1 | 1 |
| Total | 1217 | 338 | 100 | 24 | 83 | 10 |

**Abbreviations:** ARVD, arrhythmogenic right ventricular dysplasia; DSC2, desmocollin-2; NOP, number of patients; JUP, plakoglobin; PKP2, plakophilin-2.

Further studies are listed in Table 4. The most frequently mutated gene in ARVD among the desmosomal genes is plakophilin-2 (Table 1). The most frequently mutated gene among the nondesmosomal genes is TMEM43 (Table 1).

Comparison of function of proteins involved in ARVD. In the striated muscle, desmin is located in the periphery of the Z-disk and in the smooth muscle at the dense bodies. Desmin has been postulated to play a critical role in the maintenance of structural and mechanical integrity of the contractile apparatus in muscle tissues.[55] The specific function of the dystrophia myotonica protein kinase is unknown, but it appears to play an important role in muscle, heart, and brain cells. Dystrophia myotonica protein kinase may be involved in communication within cells and appears to regulate the production and function of important structures inside muscle cells by interacting with other proteins (eg, myosin phosphatase). Substrates of the dystrophia myotonica protein kinase are myogenin and phospholemman.[56] Desmosomal proteins are the components of the desmosome representing the major intercellular junction with basement membranes.[57] Desmosomes provide anchorage sites for intermediate filaments, which are important for the maintenance of tissue architecture, and also play a role in tissue morphogenesis and tissue differentiation, particularly with glycoproteins of the cadherin family.[57]

**Treatment.** Treatment of ARVD is individualized and focused on the prevention of syncope, cardiac arrest, and SCD.[20] This is achieved by the application of antiarrhythmic drugs, ICDs,[58] and occasionally heart transplantation.[20] Heart failure therapy is indicated in cases of right heart failure.[20] In single patients, sympathectomy[59] and epicardial ablation[60] have been carried out. In advanced ARVD and intractable right heart failure, heart transplantation should be considered.[61] Concerning the treatment of myopathies associated with ARVD, no curative therapy is available. Only noninvasive or invasive symptomatic measures can be recommended. Noninvasive measures include physiotherapy, drugs against muscle cramps, muscle aching, myalgias, or dystonia, splints and braces for stabilizing weak joints, and walking aids. Invasive measures include scoliosis surgery, tracheostomy in case of muscular respiratory failure, or orthopedic surgery in case of foot, knee, or hip deformities.

## Discussion

This review shows that ARVD has been described in two types of myopathy so far, ie, myofibrillar myopathy due to desmin mutations[35] and myotonic dystrophy type 1.[42] However, the association between myotonic dystrophy type 1 and ARVD has been reported in only a single patient so far. In addition, ARVD has been reported due to mutations in genes causing either ARVD or myopathy, such as the lamin A/C, ZASP/cypher, transmembrane protein-43, titin, and ryanodine receptor–2.[22,32–34] The pathogenesis of ARVD in these myopathies remains elusive, but there are indications that the development of the right ventricle during embryogenesis is impaired due to regulatory or signaling dysfunction of the mutated proteins.[15] Simultaneous occurrence of ARVD and myopathy in patients with desminopathy may be due to the impairment of contractile and Z-disk functions in myocytes and cardiomyocytes. It has also been shown that desmin mutations may affect the expression and location of other proteins, such as desmoplakin and plakophilin-2.[39] Why ARVD only develops in some patients carrying desmin mutations remains speculative, but it can be assumed that incomplete penetrance or enhancing genetic effects could play a causative role. Simultaneous occurrence of ARVD and myopathy in myotonic dystrophy could be explained by the ubiquitous distribution of the dystrophia myotonica protein kinase, resulting in impaired development of the right ventricle and myopathy.

Generally, diagnosis and management of ARVD in patients with myopathy are identical to those for ARVD patients without myopathy, but it has to be considered that the risk of developing an AV block and the frequency of ventricular arrhythmias are higher in desminopathy and laminopathy than in desmosomal ARVD. There is no need to screen all patients with desminopathy or myotonic dystrophy particularly for ARVD, since all patients with primary myopathy require cardiac investigations for cardiac involvement at diagnosis. Generally, asymptomatic relatives of ARVD patients should be tested for mutations found in an index case. Relatives carrying the pathogenic variant should undergo annual cardiological investigations for cardiac function and arrhythmias.[20] Annual cardiological investigations should include a clinical exam, ECG, echocardiography, and 24 hours ECG. As an alternative to ECG and 24 hours ECG, implantation of a loop recorder may be useful. If the genetic defect is unknown, clinical screening for asymptomatic at-risk first-degree relatives is warranted every three to four years after the age of 10 years.[20] Whether the outcome of myopathy-related ARVD differs from that of nonmyopathy-related ARVD is unknown due to

the lack of appropriate studies. In ARVD patients carrying a transmembrane protein-43 mutation, survival is better if patients are fitted with an ICD.[58] Currently, there is no indication that early-onset ARVD is more frequently associated with NMDs than late-onset ARVD, but to solve this question, further studies are required.

## Conclusions

Myopathies, which also manifest as ARVD, include most commonly myofibrillar myopathy due to desmin mutations and rarely myotonic dystrophy type 1. Mutated genes associated with either ARVD or myopathy include lamin A/C, ZASP/cypher, transmembrane protein-43, titin, and ryanodine receptor-2. Patients with primary myopathy due to a mutation in one of these genes should be screened for cardiac involvement. The management of myopathy-related ARVD is identical to the management of nonmyopathy-related ARVD.

## Author Contributions

Designed the review, organized the literature, and wrote the first draft of the article: JF. Completed the literature search, supported in the writing, and provided critical comments: JF, CS. Both authors reviewed and approved of the final manuscript.

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