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# Update on Genes Associated with Arrhythmogenic Cardiomyopathy

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## Abstract

Arrhythmogenic cardiomyopathy is a rare genetic entity characterized by progressive fibro-fatty replacement of myocardium leading to malignant arrhythmias, syncope, and sudden cardiac death. Mostly it affects the right ventricle, but cases have also been described with biventricular and even isolated left ventricular involvement. The disease affects mainly young males and arrhythmias are usually induced by exercise. Arrhythmogenic cardiomyopathy has a genetic origin and is basically caused by deleterious alterations in genes encoding desmosomal proteins, especially plakophilin-2. To date, more than 400 rare genetic alterations have been identified in 18 genes, mainly with autosomal dominant inheritance, but some recessive forms have also been reported (Naxos disease and Carvajal syndrome). A comprehensive genetic analysis identifies a rare variant as potential cause of the disease in around 60% of patients, suggesting the existence of unknown genes as well as other genome alterations not yet discovered. Genetic interpretation classifies some of these rare variants as ambiguous, playing an uncertain role in arrhythmogenic cardiomyopathy. This makes a proper translation of genetic data into clinical practice difficult. Moreover, incomplete penetrance and variable phenotypic expression makes it difficult to arrive at the correct diagnosis. In the present chapter, we focus on recent advances in the knowledge regarding the genetic basis of arrhythmogenic cardiomyopathy.

**Keywords:** sudden cardiac death, Arrhythmogenic cardiomyopathy, arrhythmias, genetics, desmosome

## 1. Introduction

Arrhythmogenic cardiomyopathy (ACM), (Online Mendelian Inheritance in Man -OMIM- 107970) is a rare (prevalence 1:2500–5000) inheritable structural heart disease first described by Fontaine *et al* in 1978 [1]. ACM is characterized by progressive replacement of myocardium by fibro-fatty infiltrates, predominantly of the right ventricle (RV) [2], but biventricular forms have also been reported in nearly 50% of cases [3, 4]. Moreover, isolated forms affecting only the left ventricle have been reported in 15% of cases [5, 6]. The name of this disease has been changed over the last years as the knowledge of it has been increased. First, it was called arrhythmogenic right ventricular dysplasia (ARVD), but some studies

revealed that patients had normal hearts at birth and the disease was progressive and genetically determined [4]. For this reason, from that moment on, it was called arrhythmogenic right ventricular cardiomyopathy (ARVC). However, when it was obvious that this disease not only affects the RV but that it also can affect the LV or even both ventricles, it was necessary to modify its name to ACM. The heart tissue affected in ACM patients shows localized/diffuse atrophy with progressive fibro-fatty infiltration. These structural alterations are assessed by echocardiography, cardiac magnetic resonance, angiography, and biopsy of the myocardial wall, if necessary. Structural alterations in the myocardium are responsible for electrical abnormalities, with or without impaired mechanical function, subsequent ventricular arrhythmias, syncope and even sudden cardiac death (SCD) [7, 8]. Unfortunately, SCD is often the first symptom of the disease, usually during exercise in young males (less than 35-year-old). Despite both genders being affected, males are the main affected population (the ratio of men to women is 3:1) [9].

ACM is a cardiac disease with a clearly genetic implication, and pathogenic alterations in genes encoding desmosomal proteins are the main cause of the disease. In recent years, continuous advances in the genetic and molecular basis of ACM are occurring despite some pathophysiological mechanisms involved in ACM being not yet completely understood [10]. For example, it has been shown that myocardial inflammation is a common trait in ACM patients, but it is not clear if it is a primary phenomenon or reactive to ACM pathology [4, 11, 12]. The fibrosis mechanism is another characteristic hallmark poorly understood so far. It has been described a complex network of interactions between cytokines, growth factors, and hormones that promote cardiac fibrosis [12, 13]. One thing that seems certain is that canonical and non-canonical TGF $\beta$  signaling pathway are both involved in the induction of myocardial fibrosis in ACM [12]. The origin of adipocytes in the myocardium of ACM patients is not yet resolved today. Thus, it is not clear if the signals for adipogenesis are autonomous to desmosome-expressing cells (intracellular signal) or non-autonomous from desmosome-expressing cells to adipogenic cell (paracrine signal) [12]. However, several signaling pathways have been described that are involved in the adipogenic phenotype of ACM such as WNT, Hippo–Yes-associated protein (YAP), peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) and microRNA (miRNA) signaling [12].

Currently, clinical diagnosis is based on the presence of a series of diagnostic items (major and minor) called Task Force criteria. It was firstly proposed in 1994 [14], but it was revised in 2010 to improve diagnostic sensitivity maintaining its specificity and included genetics as a diagnostic item [15]. Nowadays it takes into account structural assessment (echocardiography, magnetic resonance, RV angiography), histological (endomyocardial biopsy), electrocardiographic (12-lead ECG and Signal-Averaged ECG, Holter monitoring, exercise testing, electrophysiological study), and familial factors (genetic study according to the Rhythm Society/ European Heart Rhythm Association Consensus Statement) [16]. Recently, it has been proposed “The Padua Criteria”, a new diagnostic criteria based on 2010 TFC multi-parametric approach to include biventricular and arrhythmogenic left ventricular cardiomyopathy (ALVC) involvement [4, 17]. However, it has to be validated by future clinical studies in large cohorts of ACM patients. The diagnosis of ACM is confirmed if 2 major, 1 major and 2 minor, or 4 minor criteria from different categories are present. A borderline diagnosis is considered with 1 major and 1 minor or 3 minor criterions from different categories and a possible diagnosis with only 1 major or 2 minor criterions. The disease can be classified into four phases:

- The early “*silent phase*” that can manifest as SCD because arrhythmias occur without structural abnormalities;

- The “*overt electrical disorder*” in which RV arrhythmias are associated with structural abnormalities;
- The “*phase of right ventricular failure*” with extension of the fibro-fatty substitution that leads to RV dysfunction; and,
- The phase of “*biventricular failure*” which is often indistinguishable from dilated cardiomyopathy (DCM).

The diagnostic tools are evolving together with the knowledge of the disease because detecting ACM at an early stage is crucial for the patient. All the treatment approaches are focused on preventing life-threatening arrhythmias, delay the course of the heart failure, and relieve symptoms [12]. The different options include pharmacological treatment, the placement of an implantable cardioverter-defibrillator (ICD), radiofrequency ablation, and even heart transplantation in severe cases at high risk of death. To date, ICD is the only proven lifesaving therapy; other treatment options may reduce the arrhythmic burden and alleviate symptoms, without evident impact on prevention of SCD [18]. There are some studies that have demonstrated the efficacy of ICD therapy in the prevention of SCD in patients affected by ACM [19–22]. However, it is associated with a significant morbidity due to device-related complications and inappropriate ICD interventions [1]. Decisions about the placement of an ICD are based on an estimated patient risk of SCD that is determined by several parameters including electrical instability, proband status, extent of structural disease, cardiac syncope, male gender, exercise practice, and deleterious genetic alterations. Unfortunately, there are no conclusive data concerning risk stratification or the best approach in patients with ACM, so treatment should be personalized [23].

## 2. Genetic basis

ACM can be caused by deleterious alterations located in genes encoding mainly desmosomal proteins but also proteins implicated in electric signal transmission. A comprehensive genetic analysis of all genes reported so far identify at least one rare variant as a potential cause of ACM in around 60% of the patients [24]. Genetic testing allows cascade screening of relatives identifying other genetic carriers in the family, which may be at risk of developing the disease and suffer SCD [25]. Predominantly, ACM follows an autosomal dominant pattern of inheritance, with incomplete and age-related penetrance [26] as well as polymorphic phenotypic expression [9, 27]. Autosomal recessive forms have also been reported although in a reduced number of cases (Naxos disease and Carvajal syndrome) [28–30]. In recent years, compound and/or digenic variants have been identified associated with ACM [31, 32]. In addition, alterations in number of copies (Copy Number Variation, CNV) were also associated with ACM [33]. Despite these recent advances, around 35–50% of ACM patients remain without an identified disease-associated variant [12]. For this reason, the interpretation of rare variants found in ACM patients has to be extremely careful. The “American College of Medical Genetics and Genomics (ACMG) standards and guidelines” structured a standard terminology for classifying sequence variants using available evidence weighted according to a system developed through expert opinion, work-group consensus, and community input [34]. This classification of the variants is composed of 5 terms: “pathogenic”, “likely pathogenic”, “uncertain significance”, “likely benign”, and “benign” and the classification depends on several different criteria: the variant frequency in population



database, computational (*in silico*) predictive programs, biological factors (levels of expression in the tissue, function of the gene,...), localization of the variant in conserved regions or hotspots, type of mutation, functional studies and segregation analyses. It is important to remark that a large part of the rare genetic variants identified as potentially disease-causing remains of inconclusive significance after a comprehensive genetic interpretation. It is crucial to clarify their clinical role whether definitive risk stratification can be based on genetics. Even if a conclusive pathogenic variation associated with ACM is identified, it does not indicate that the patient is going to be affected because of the variable expressivity and incomplete penetrance [4]. This represents an additional challenge to perform a genetic interpretation of rare variants. Moreover, it is known that genes associated with ACM have nearly 50% of genetic variation rate [35]. Therefore, clinical translation should be done carefully after a comprehensive personalized interpretation of all data obtained. A group of experts should discuss all data concerning each family, performing an exhaustive interpretation and translation into clinical practice helping to adopt personalized measures to reduce risk of lethal events.

In the human myocardium, three different structures are involved in cell-to-cell adhesion: desmosomes, adherens junctions (*fascia adherens*), and gap junctions. The majority of ACM patients present alterations in genes encoding desmosomal proteins. Currently, more than 1000 rare genetic variants have been identified in 18 genes, but only around 400 rare genetic alterations have been classified as definitely pathogenic [36]. All other rare variants remain with an ambiguous role and further data is needed to conclude if they play a decisive role in ACM. **Table 1** shows information related to the genetic role and ventricular involvement of the ACM causal genes (plakophilin-2 -*PKP2*-, desmocollin-2 -*DSC2*-, desmoglein-2 -*DSG2*-, desmoplakin -*DSP*-, plakoglobin -*JUP*-, desmin -*DES*-, transforming growth factor beta-3 -*TGFβ3*-, transmembrane protein 43 -*TMEM43*-, lamin A/C -*LMNA*-, titin -*TTN*-, phospholamban -*PLN*-,  $\alpha$ T-catenin -*CTNNA3*-, voltage-gated sodium channel -*SCN5A*-, Cadherin 2 -*CDH2*-, Filamin C -*FLNC*-, Ryanodine Receptor 2 -*RYR2*-, RNA-Binding Motif Protein 20 -*RBM20*-, Tight Junction Protein ZO-1 -*TJP1*-) [4, 11]. **Figure 1** presents the intracellular localization of proteins codified by ACM-associated genes and their prevalence in causing the disease.

## 2.1 Desmosomal genes

Desmosomes are classified as a calcium-dependent anchoring junction that tethers cells together through its extracellular contacts and internally links to the intermediate filament (IF) cytoskeleton [37]. This cell union provide structural resilience that allows heart tissue to resist mechanical stress. Moreover, it has been described that desmosomal proteins have a role in the regulation of transcription of genes involved in adipogenesis and apoptosis, and play a major role in myocardial electrical conduction through regulation of gap junctions and calcium homeostasis [4]. Deleterious alterations are mainly located in genes encoding desmosomal proteins that are responsible for around 60% of all ACM cases [4, 17]. Concretely, the main gene associated with ACM is *PKP2*, being responsible for approximately 35–40% of cases [35, 38, 39]. Pathogenic variants in *PKP2* are found in around 75% of genotype-positive ACM cases in American cohorts, and nearly 60% of genotype-positive index cases in European cohorts [4, 40]. In general, rare variants in genes encoding desmosomal proteins are more associated with right ventricular involvement. However, rare deleterious alterations in *DSP* are often associated with left ventricular involvement, and *DSG2* and *PKP2* with biventricular ACM, although the latter is observed in all gene groups at later stages of disease progression [4, 9].

Gene	Protein	Frequency (%) <sup>*</sup>	Inheritance Pattern	Ventricular Disease <sup>**</sup>
<b>Desmosome</b>				
<i>PKP2</i>	plakophilin-2	19–46	AD/AR	RV, BIV
<i>DSP</i>	desmoplakin	1–16	AD/AR	LV, BIV
<i>DSG2</i>	desmoglein-2	2.5–10	AD/AR	RV, LV, BIV
<i>DSC2</i>	desmocollin-2	1–8	AD	RV, BIV
<i>JUP</i>	plakoglobin	Rare	AD/AR	RV, BIV
<b>Adherens junction</b>				
<i>CTNNA3</i>	$\alpha$ T-catenin	Rare	AD	RV, BIV
<i>CDH2</i>	cadherin 2	Rare	AD	RV, BIV
<i>TJP1</i>	tight Junction Protein ZO-1	Rare	AD	?
<b>Cytoskeletal structure</b>				
<i>LMNA</i>	lamin A/C	Rare	AD	LV, BIV
<i>DES</i>	desmin	Rare	AD	LV, BIV
<i>FLNC</i>	filamin C	Rare	AD	LV, BIV
<i>TMEM43</i>	transmembrane protein 43	Rare	AD	RV, BIV
<i>TTN</i>	titin	Rare	AD	RV, LV, BIV
<b>Ion transport</b>				
<i>SCN5A</i>	voltage-gated sodium channel	Rare	AD	LV, BIV
<i>RYR2</i>	ryanodine Receptor 2	Rare	AD	?
<i>PLN</i>	phospholamban	Rare	AD	LV, BIV
<b>Cytokine</b>				
<i>TGFB3</i>	transforming growth factor, beta-3	Rare	AD	RV
<b>Slicing factor</b>				
<i>RBM20</i>	RNA-Binding Motif Protein 20	Rare	AD	LV

<sup>\*</sup>Taken from Austin et al. (2019) [51].

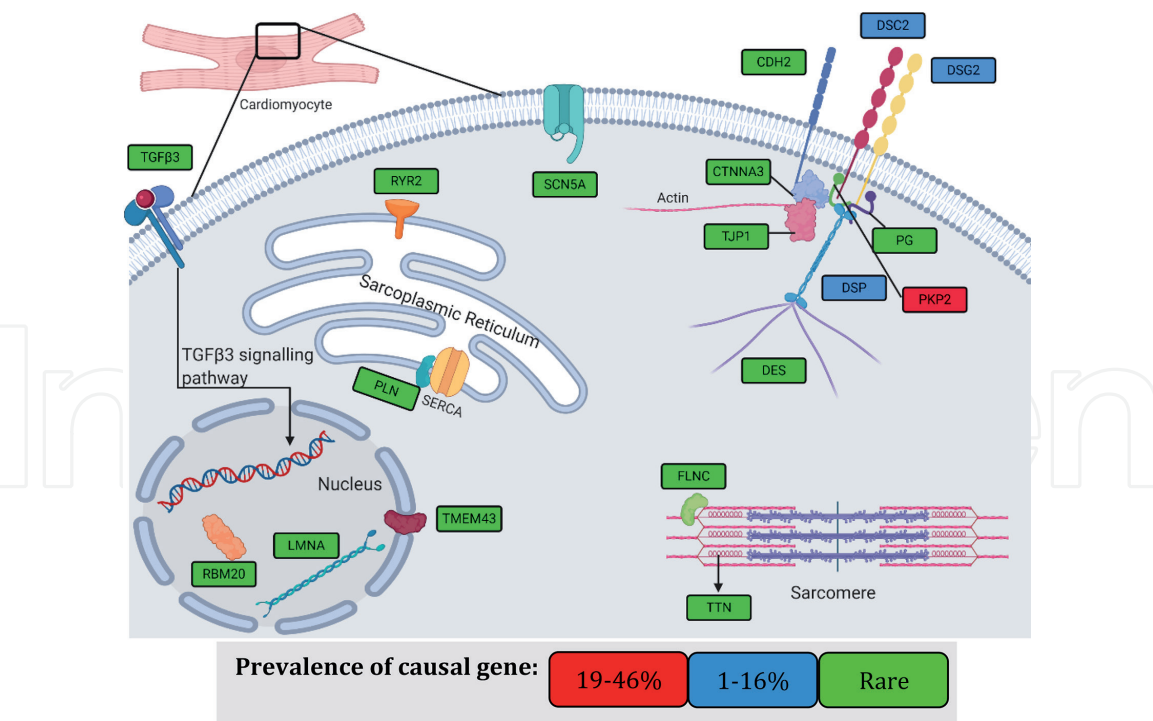
<sup>\*\*</sup>Taken from Patel et al. (2020) [4].

? = Not conclusive association with ACM. AD = autosomal dominant; AR = autosomal recessive; BIV = biventricular disease; LV = left ventricle; RV = right ventricle.

**Table 1.**  
Genes associated with ACM.

### 2.1.1 Plakophilin-2

The most prevalent form of ACM is caused by rare pathogenic alterations in the *PKP2* gene (ENSG00000057294), which encode plakophilin-2 protein (*PKP2*, ENSP00000070846). It is an essential armadillo repeat protein located in the outer dense plaque of cardiac desmosomes that interacts with multiple other cell adhesion proteins [41]. To date, more than 300 rare genetic variants potentially pathogenic have been identified in *PKP2* [42]. Most of the ACM-linked pathogenic variants in the *PKP2* gene have an autosomal dominant pattern of inheritance, even though recessive form was also described in 2006 [30]. Lately, calcium handling dysregulation caused by disruption of *PKP2* has been described [43]. It seems that *PKP2* is necessary to maintain transcription of genes that control intracellular calcium cycling. This could be the cause of life-threatening arrhythmias even in the absence of structural disease in those patients that present alterations in *PKP2*, which are the majority of ACM patients.



**Figure 1.**  
Schematic representation of the intracellular localization of proteins codified by genes associated with ACM.  
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### 2.1.2 Desmoplakin

Desmoplakin is the most abundant protein of the desmosomes, encoded by the *DSP* gene (ENSG00000096696). Desmoplakin has two isoforms produced by alternative splicing: the longest desmoplakin I isoform (ENSP00000369129) and the shorter desmoplakin II (ENSP00000396591). Desmoplakin isoform I has been reported to be a force constituent of desmosomes and the major isoform present in cardiac tissue, even though expression of isoform II (DSPII) occurs in different heart compartments [44]. Nowadays, almost 250 rare variations in the *DSP* gene have been linked to ACM [42], mainly with autosomal dominant pattern of inheritance. The *DSP* gene was also implicated in Carvajal syndrome, an autosomal recessive cardiocutaneous form of ACM that was described as a variant of Naxos disease (see below, plakoglobin section) [45].

### 2.1.3 Desmocollin-2 and Desmoglein-2

The desmosomal cadherins proteins, such as desmocollin and desmoglein are the major constituents of the desmosomal plaque. The *DSG2* gene (ENSG0000046604) encodes Desmoglein-2 protein (DSG2, ENSP00000261590) that has four extracellular cadherin domains and a transmembrane domain. Currently, more than 150 rare variants have been associated to ACM [42]. Despite the fact that most of the identified *DSG2* mutations have a dominant pattern of inheritance, a recessive pattern has been also suggested in ACM patients [46]. The *DSC2* gene (ENSG00000134755) encodes the desmocollin protein type 2 (DSC2, ENSP00000280904), the most widely distributed form of desmocollin proteins [47]. It is a type I integral membrane glycoprotein with four conserved extracellular subdomains, variable extracellular anchor domain, a single transmembrane domain, an intracellular anchor domain, and additional cytoplasmatic subdomains. It participates in calcium-dependent cell adhesion, regulation of tissue morphogenesis and intracellular signaling processes [48]. To date, nearly 120 genetic alterations have been identified in *DSC2* associated with ACM following an autosomal pattern of inheritance [42].

### 2.1.4 Plakoglobin

The plakoglobin protein (PG, ENSP00000311113) is codified by the *JUP* gene (ENSG00000173801). PG is a major protein component of cell adhesion junctions, and the only constituent common to submembranous plaques of both desmosomes and adherens junctions. It plays a crucial role in linking the desmosomal cadherins to the cytoskeleton via desmoplakin. The first genetic alteration associated with ACM was an homozygous deletion in the *JUP* gene, with an autosomal recessive pattern of inheritance [28]. In later years, it was referred to as “Naxos disease” [49]. To date, more than 30 rare genetic variants have been identified in *JUP* [42], including homozygous variants [50].

## 2.2 Non-desmosomal genes

This group includes genes encoding proteins of cytoskeletal architecture, calcium handling, sodium transport, and cytokine signaling among others. All of them have a diverse range of biological functions, but a pathogenic alterations in them can converge into similar phenotypes [51]. Genetic defects in non-desmosomal genes are thought to be more frequently associated with involvement of the left ventricle compared with rare variants in desmosomal genes that, in general, are more often associated with RV involvement [4]. There are several rare deleterious alterations in non-desmosomal genes that cause ACM that are also involved in other cardiac diseases such as DCM, Brugada syndrome (BrS), Long QT syndrome (LQTS) or Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). Thereby, in some cases, there is an overlap of symptoms that makes it challenging to determine the correct diagnosis. For this reason, it is necessary to perform more studies of genotype–phenotype correlation to increase the reliability of the diagnosis.

### 2.2.1 Desmin

The *DES* gene (ENSG00000175084) encodes the protein desmin (DES, ENSP00000363071) that is the main intermediate filament in mature skeletal and heart muscle cells. It forms a scaffold around the Z-disc and links whole contractile structure with subsarcolemmal cytoskeleton, intercalated disc, nucleus, and other components of the cytoplasm. Currently, less than 10 rare variants in this gene have been associated with ACM [42, 52, 53].

### 2.2.2 Transforming growth factor, beta-3

The *TGFβ3* gene (ENSG00000119699) encodes the transforming growth factor, beta-3 protein (TGFβ3, ENSP00000238682), a cytokine that stimulates fibrosis and modulates cell adhesion and expression of desmosomal genes [54]. To date, there are only 4 rare alterations located in *TGFβ3* as potential causes of ACM.

### 2.2.3 Transmembrane protein 43

The *TMEM43* gene (ENSG00000170876) encodes the transmembrane protein 43 (TMEM43, ENSP00000303992). It has an important role in maintaining nuclear envelope structure by organizing protein complexes at the inner nuclear membrane. Moreover, it has been suggested to have a role in an adipogenic pathway [55]. To date, around 15 ACM associated rare variants in *TMEM43* has been identified [42],



one of them (p.S358L) exhibits an aggressive phenotype presenting with a fully penetrant, biventricular ACM with LV predominance and a high predilection for SCD in males [4, 55–57].

#### 2.2.4 Lamin A/C

The *LMNA* gene (ENSG00000160789) encodes lamin A (ENSP00000357283) and lamin C (ENSP00000357284), by alternative splicing. Both of them belong to the family of type V intermediate filaments that take part in the constitution of the nuclear lamina, a complex of proteins below the inner part of the nuclear membrane [58]. Genetic alterations in *LMNA* are associated with an heterogeneous group of disorders commonly named “laminopathies” [59], including cardiac disorders with DCM as the main disease. In 2012, the first association between this gene and ACM was reported [60]. To date, nearly 25 rare variants have been described in *LMNA* associated with ACM [42].

#### 2.2.5 Titin

The *TTN* gene (ENSG00000155657) encodes the titin protein (TTN, ENSP00000343764) that is a gigantic and the third most abundant protein in the muscle after actin and myosin. It is an essential component of the sarcomere linking myosin and the Z-disc, providing structural support, flexibility, and stability [4]. This gene has been associated with cardiac diseases, mainly DCM. In 2011 the first variant associated with ACM was reported [61]. To date, more than 20 rare variants have been associated with ACM [42]. Most of these variants remain as potentially pathogenic, with doubtful role due to lack of conclusive genotype–phenotype studies.

#### 2.2.6 Phospholamban

The *PLN* gene (ENSG00000198523) encodes the protein phospholamban (PLN, ENSP00000350132), a small phosphoprotein closely associated with the cardiac sarcoplasmic reticulum. It is a regulator of the sarcoplasmic reticulum  $\text{Ca}^{2+}$  (SERCA2a) pump in cardiac muscle and therefore important for maintaining  $\text{Ca}^{2+}$  homeostasis [62]. Consequently, the PLN protein is one of the major determinants of cardiac contractility and relaxation [63]. To date, only one rare pathogenic variant associated with ACM has been identified in this gene [42, 64].

#### 2.2.7 Alpha T-catenin

The *CTNNA3* gene (ENSG00000183230) encodes the protein  $\alpha$ T-catenin (CTNNA3, ENSP00000389714). Alpha T-catenin protein is located within the area composite of intercalated discs of cardiomyocytes. It is a key element for dynamic maintenance of tissue morphogenesis by integrating in the cadherin–catenin complex. In 2013, genetic variants of potentially pathogenic significance were identified in two unrelated patients suffering from ACM [42, 65]. Moreover, it has been shown that *CTNNA3* knockout mice exhibit a progressive cardiomyopathy with increased incidence of ventricular arrhythmias after acute ischemia [4, 66]. To date, no other rare variants associated with ACM have been identified in this gene.

#### 2.2.8 Voltage-gated sodium channel

The *SCN5A* gene (ENSG00000183873) encodes for the cardiac sodium channel, voltage-gated, type V, alpha subunit (SCN5A, ENSP00000410257). This gene is

mainly associated with BrS and LQTS but it was also reported in patients diagnosed with ACM [67]. Recently, a study suggested that almost 2% of ACM patients harbor rare *SCN5A* variants [68]. In total, for the moment, no more than 10 *SCN5A* rare variants associated with ACM have been described.

### 2.2.9 *Cadherin 2*

The *CDH2* gene (ENSG00000170558) encodes the protein cadherin type 2 (CDH2, ENSP00000269141) that is a large transmembrane adherens junction protein that connects actin filaments in neighboring cardiomyocyte sarcomeres [4, 69]. It is a member of the cadherin superfamily and provides strength and stability to cardiac tissue and calcium-ion-dependent adhesion among other functions. In 2017 data were published regarding the firsts cadherin variants associated with ACM in this gene [70, 71]. To date, only 3 rare variants have been associated with ACM [42, 72].

### 2.2.10 *Filamin C*

The *FLNC* gene (ENSG00000128591) encodes for the protein filamin C (FLNC, ENSP00000327145) that is an actin cross-linking protein associated with Z-discs found only in striated muscle, important for structural cell stability and membrane-triggered signal transduction [4, 51]. Pathogenic alterations in *FLNC* have been linked to skeletal myopathies as well as DCM and restrictive cardiomyopathies and possibly hypertrophic cardiomyopathy. Recently, this gene, particularly truncating variants, have been associated with ventricular arrhythmias and a high SCD risk [73, 74]. To date, it has been described that nearly 30 *FLNC* rare variants are associated with ACM [42].

### 2.2.11 *Ryanodine receptor 2*

The *RYR2* gene (ENSG00000198626) encodes for the protein Ryanodine Receptor 2 (RYR2, ENSP00000355533) that is a sarcoplasmic reticulum calcium release channel that mediates the release of  $\text{Ca}^{2+}$  from the sarcoplasmic reticulum into the cytoplasm which generates calcium transients to trigger sarcomere contraction. The majority of *RYR2* deleterious alterations are associated with CPVT, but there are some studies that have been shown that rare variants in *RYR2* can also cause ACM [75, 76]. For the moment, there are nearly 20 rare variants associated with ACM [42]. However, it is necessary to continue investigating the relationship between *RYR2* and ACM to clarify the overlapping in diagnosis. There has even been described a case where the causal genetic alteration could not be identified, but the patient presented with phenotypes of both disorders [77].

### 2.2.12 *RNA-binding motif protein 20*

The *RBM20* gene (ENSG00000203867) encodes for the protein RNA-Binding Motif Protein 20 (RBM20, ENSP00000358532) that acts as a regulator of mRNA splicing of a subset of genes involved in cardiac development (sarcomeric, calcium regulation and ion regulation genes). There have been identified several rare alterations in *RBM20* implicated in DCM and ACM and that causes severe arrhythmia and SCD [78–81]. Therefore, pathogenic alterations in *RMB20* are associated with a high propensity for malignant arrhythmias usually with minor structural abnormalities [4, 80].

### 2.2.13 Tight junction protein ZO-1

The *TJP1* gene (ENSG00000104067) encodes for the protein tight junction protein Zona Occludens-1 (TJP ZO-1, ENSP00000281537), a multi-functional scaffolding protein that localizes to the intercalated discs of cardiomyocytes and interacts with proteins of gap junctions and area composita including connexin43, N-cadherin,  $\alpha$ T-catenin, and actin [4]. Recently, it has been identified that 4 rare variants in ACM patients could be deleterious according to *in silico* tools predictions [42, 82]. Case-control studies provided evidence for enrichment with *TJP1* variants in ACM patients compared with controls, supporting the causality role of *TJP1* in ACM. Further evidence from larger cohorts for the role of *TJP1* as a disease causing in ACM is still needed [4, 82].

## 3. Conclusion

Arrhythmogenic cardiomyopathy is an inherited rare cardiac disease characterized by progressive replacement of myocardium by fibrofatty tissue, leading to ventricular arrhythmias and sudden cardiac death. Structural abnormalities mainly occur in the right ventricle, but it is well recognized that also sole left ventricular involvement and even biventricular substitution is common, particularly in advanced stages of the disease. Several molecular mechanisms are involved in the phenotype of ACM such as myocardial inflammation and signaling pathways that cause fibrosis and adipogenesis. Today, most of these mechanisms are not completely understood. Task Force Criteria for the diagnosis of arrhythmogenic cardiomyopathy include several clinical tests and also genetic data. Despite progressive improvement in diagnosis, it is difficult to obtain conclusive risk stratification in families suffering from arrhythmogenic cardiomyopathy. Hundreds of rare alterations are reported in mainly genes encoding desmosomal proteins, but there are also other causal genes with several functions within the cardiac tissue. A comprehensive genetic analysis may identify the potential genetic cause of the disease in nearly 60% of cases. Genetic testing is especially useful in families with at least one affected member that carries a potential deleterious alteration because it allows early identification and adoption of therapeutic measures among relatives at risk of malignant arrhythmias. Currently, one of main challenges is the genetic interpretation and clinical translation of amount of genetic data generated by new genetic technologies.

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