



# Genotype–phenotype Correlates in Arrhythmogenic Cardiomyopathies

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## Abstract

**Purpose of the Review** The definition of arrhythmogenic cardiomyopathy (ACM) has expanded beyond desmosomal arrhythmogenic right ventricular cardiomyopathy (ARVC) to include other genetic cardiomyopathies with a significant arrhythmia burden. Emerging data on genotype–phenotype correlations has led recent consensus guidelines to urge genetic testing as a critical component of not only diagnosis but also management of ACM.

**Recent Findings** Plakophilin-2 (*PKP2*) ARVC/ACM is most likely to meet ARVC Task Force Criteria with right sided involvement and ventricular arrhythmias, while desmoplakin (*DSP*) ACM may have a normal electrocardiogram (ECG) and has a subepicardial LV scar pattern. Extra-desmosomal ACM including ACM associated with transmembrane protein 43 and phospholamban variants may have characteristic ECG patterns and biventricular cardiomyopathy. Lamin A/C and SCN5A cardiomyopathy often have heart block on ECG with DCM, but are distinct from DCM in that they have significantly elevated arrhythmic risk. Newer genes, especially filamin-C (*FLNC*) also may have distinct imaging scar patterns, arrhythmia risk, and risk predictors.

**Summary** Recognition of these key differences have implications for clinical management and reinforce the importance of genetic testing in the diagnosis and the emerging opportunities for genotype-specific management of ACM patients.

**Keywords** Genotype · Arrhythmogenic cardiomyopathy · Risk stratification · Arrhythmogenic right ventricular cardiomyopathy

## Introduction

Arrhythmogenic cardiomyopathy (ACM) is an evolving diagnosis that has grown in recent years to encompass both the narrowly defined arrhythmogenic right ventricular cardiomyopathy (ARVC), and also more broadly non-ischemic cardiomyopathy (NICM) with a higher than expected arrhythmic burden [1, 2•]. ARVC is a narrow diagnosis describing an often right dominant cardiomyopathy caused by abnormalities of the desmosomal proteins meeting a set of task force criteria [1]. Expert consensus has defined the genetic basis of ARVC, highlighting its predominant association with pathogenic variants in genes encoding the cardiac desmosome [3]. The definition of ACM includes ARVC, but is broader,

also including biventricular and left dominant forms of disease, and may have extra-desmosomal genetic causes. Specially, an expert consensus in the field has defined ACM as diseases that encompass structural abnormalities (both by imaging and pathology) and ventricular arrhythmia [4]. There is some debate whether this should include only genetic forms of ACM, or any form of arrhythmic cardiomyopathy, regardless of underlying cause (such as cardiac sarcoidosis) [2•]. What is clear, and documented in recent practice guidelines, is that genetic testing is a critical piece of management in these conditions. There are important genotype–phenotype correlations that inform risk stratification for malignant arrhythmias and increasingly genotype-specific therapeutic approaches indicated depending on the underlying molecular cause [5•]. Genotype informs family screening as well.

The genetic basis of ACMs began with the understanding of the genetic basis of ARVC in the early 2000s. While the first diagnostic criteria for ARVC were published in 1994 and included recognition of a familial pattern, genetic understanding lagged behind until the linkage of plakoglobin (*JUP*) to autosomal recessive severe ARVC in 1998 [6–8].

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This focused etiology of ARVC to the desmosome, the protein structure adhering cellular junctions. From there, association of the more common autosomal dominant form of ARVC with the rest of the desmosomal proteins followed quickly with discovery of desmoplakin (*DSP*), plakophilin-2 (*PKP2*), desmoglein-2 (*DSG2*), and desmocollin-2 (*DSC2*) [9–13]. At the same time, understanding of the genetic architecture of dilated cardiomyopathy (DCM) was emerging. During this era conduction defects were linked to the lamin A/C (*LMNA*) gene, but it would be some years before this was formally associated with similarly arrhythmic outcomes [14, 15]. Desmin (*DES*) was also linked to an ACM phenotype [16]. There were additional non-desmosomal forms of ARVC identified, including a founder population in Newfoundland segregating a transmembrane protein 43 (*TMEM43*) variant and the Dutch founder variant in the phospholamban (*PLN*) gene [17, 18]. Following, more rare forms of ACM were identified, and recently, filamin-C (*FLNC*) has emerged as a more common cause of a very arrhythmic biventricular cardiomyopathy that often looks like ARVC [16, 19–22]. Natural history and family reports of these all these phenotypes have overlapped and also varied widely. This is not surprising, as all these genetic ACMs are associated with incomplete penetrance and highly variable expressivity [4, 23]. Therefore, large numbers of each subtype were needed to elucidate specific patterns. Now with two decades of data on the natural history of genetic ACM cohorts, clear genotype–phenotype correlations are beginning to emerge (Table 1).

## PKP2

Pathogenic variants in *PKP2* are the most common cause of ACM in North America [24]. *PKP2*-associated cardiomyopathy typically presents as the most classically described form of ACM as a right-sided, exercise-induced, very arrhythmic cardiomyopathy. *PKP2*-ARVC is most likely to fit the diagnostic 2010 Task Force Criteria with precordial T wave inversions on electrocardiogram (ECG), left bundle branch arrhythmias, and right ventricular dyskinesia caused by replacement with

fibro-fatty scarring in the right ventricle, as shown in Fig. 1 panel A [1, 24]. Homozygous and compound heterozygote truncating variants in *PKP2* are associated with a severe neonatal onset cardiomyopathy with congenital heart defects [25, 26]. Pathogenic *PKP2* variants are largely loss of function variants, and there is no clear association of variant type or location with phenotype [27]. *PKP2* also has the most evidence to show a clear correlation between vigorous and especially endurance exercise and disease penetrance and progression [28]. New translational research shows specifically the damage to the desmosomal reserve in *Pkp2*-deficient mice under the setting of regular vigorous exercise [29].

## DSP

Pathogenic variants in *DSP* were initially identified in association with Carvajal syndrome in the recessive form with severe pediatric onset cardiomyopathy and arrhythmias with woolly hair and palmoplantar keratoses [13]. Subsequently, *DSP* variants were commonly found in families meeting ARVC 2010 Task Force Criteria. It was not long, however, before it became clear that *DSP*-associated disease could look very different from classic right sided ARVC with a tendency to present with left-sided disease and elevated rates of heart failure [24, 30]. The term arrhythmogenic left ventricular cardiomyopathy (ALVC) was often used associated with *DSP*. Compared to ARVC, *DSP*-associated ALVC more frequently shows consistent late gadolinium enhancement patterns on cardiac magnetic resonance (CMR) imaging and is less likely to have precordial T wave inversions which are often the first sign of disease in *PKP2*-ARVC, Fig. 1 panel B [31]. Indeed, often in *DSP* cardiomyopathy, the ECG is near normal [32]. As shown in Fig. 1, the most characteristic scar pattern in *DSP* cardiomyopathy has been described as a subepicardial ring-like scar pattern. While imaging is critical in diagnosis as referenced in Fig. 1, these individuals with often left-dominant presentation will be less likely to meet ARVC 2010 Task Force Criteria [32]. Recently, it has also been documented that *DSP* cardiomyopathy will often present with chest pain,

**Table 1** Arrhythmogenic cardiomyopathy genes and key features

Gene	Characteristic ECG	Characteristic imaging	Reference
<i>PKP2/DSG2/DSC2</i>	Precordial T wave inversions	Right sided wall motion abnormality, late gadolinium enhancement (LGE) in RV and LV lateral wall	[1, 24]
<i>DSP</i>	Normal or Lateral T wave inversions	Subepicardial ring-like LV scar	[31, 32]
<i>TMEM43</i>	Poor R wave progression	Biventricular cardiomyopathy	[37, 38]
<i>PLN</i>	Low voltage	Biventricular cardiomyopathy	[40]
<i>LMNA</i>	AV block	DCM or biventricular cardiomyopathy	[14, 44]
<i>SCN5A</i>	AV block	DCM or biventricular cardiomyopathy	[48]
<i>FLNC</i>	Normal, low voltage	Subepicardial enhancement	[53–55]

DCM dilated cardiomyopathy

**Fig. 1** Example electrocardiogram (ECG) of a precordial T wave inversions in a *PKP2* variant carrier and right ventricular basal outpouching on MRI in (a) compared with lateral T wave inversions and circumferential late gadolinium enhancement (LGE) in a *DSP* variant carrier in (b)



significant troponin elevation, and myocarditis-like picture [33, 34]. Scar pattern similarities between viral myocarditis and *DSP* cardiomyopathy can complicate diagnosis.

### DSG2 and DSC2

Variants in *DSG2* and *DSC2* are the rarer causes of ARVC. Current evidence suggests that the phenotype is similar to *PKP2* ARVC; however, there is not sufficient current case volume data to draw statistically robust comparisons. Initial evidence suggests that *DSG2*-associated ARVC may have an earlier age of onset than *PKP2* ARVC, and be more likely to have left-sided involvement; however, this may be complicated by selection bias in tertiary referral centers [24, 30]. There are some reports that autosomal recessive *DSC2* variants may be more common in Asian populations, and there is a homozygous founder variant in the Hutterite population [35, 36].

### TMEM43

TMEM43 is a membrane protein involved in nuclear envelope structure outside of the desmosome. It was identified as a candidate gene for ARVC and founder with a common haplotype initially in 15 Newfoundland ARVC families [17]. There is only one variant proven to cause ARVC in *TMEM43*: p.S358L [3]. Functional studies have shown that the p.S358L variant affects the expression and distribution of proteins in the intercalated

disc, including *JUP*, resulting in an ARVC phenotype [37]. This phenotype, however, is unique in that it is particularly penetrant, and significantly arrhythmic, particularly in young males. ECG findings may be unique with notable poor R wave progression more common than precordial T wave inversion. Additionally, in *TMEM43* ARVC, there is significant LV involvement as well. The most unique feature of *TMEM43* ARVC is that it is appreciated to be nearly fully penetrant, whereas desmosomal ARVC penetrance rates range, but are averaged 30–50% in ARVC families [30, 38].

### PLN

PLN is a transmembrane sarcoplasmic reticulum phosphoprotein that is involved with regulating calcium handling and contractility in the cardiomyocyte. It was initially described as causing familial cardiomyopathy. The Dutch founder variant p.R14del, however, was identified in causing a particularly arrhythmic cardiomyopathy and phenotype similar to desmosomal ARVC [18, 39]. It was found to be a common cause of both ARVC and familial DCM in the Netherlands, in up to 15% of cases. The phenotype involves a low-voltage ECG, and a high frequency of ventricular arrhythmias, but also a much higher risk of biventricular cardiomyopathy and end-stage heart failure than in desmosomal ARVC (Fig. 2, panel A) [30, 40]. As many *PLN* carriers may not meet 2010 ARVC Task Force Criteria because of the overlap with DCM, it is important to appreciate their high arrhythmic risk [2, 39, 41].

## LMNA

LMNA is a complicated nuclear protein that has been associated with over 10 different clinical syndromes, including Emery-Dreifuss muscular dystrophy and limb-girdle muscular dystrophy [42]. It was also described to cause a unique isolated cardiac phenotype with a dilated cardiomyopathy with significant conduction defects [14]. There have been several reports of *LMNA* carriers showing an ARVC phenotype meeting diagnostic criteria; however importantly, *LMNA* cardiomyopathy has shown to have signature clinical features and necessitating important risk stratification outside of the DCM phenotype [15, 43, 44]. *LMNA* carriers have progressive cardiac conduction defects including heart block (Fig. 2, panel B), and a higher risk of malignant arrhythmias than typical DCM patients. Risk stratification studies suggest that males with a pathogenic nonsense variant compared to a pathogenic missense variant are at increased risk of malignant arrhythmias [45–47]. Families with pathogenic *LMNA* variants also have a higher incidence of atrial arrhythmias than typically described in other ACM phenotypes [48].

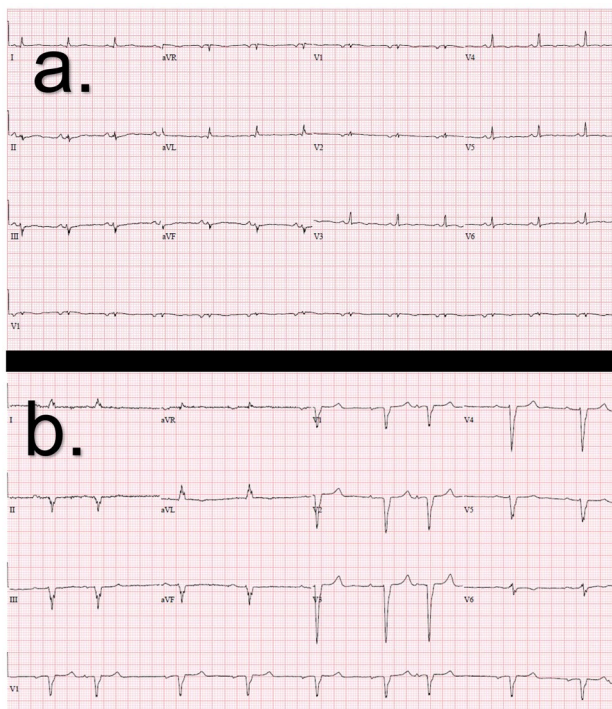
## SCN5A

The sodium channel ( $\text{Na}_v1.5$ ) is associated with wide variety of inherited arrhythmic syndromes [49]. Typically, *SCN5A* variants had been associated with a primarily arrhythmic phenotype in LongQT Type 3 and in Brugada syndrome. Case

reports identified a specific variant that presented as a dilated cardiomyopathy conduction disorder with arrhythmias [19]. Extensive genotype–phenotype analysis in *SCN5A* has continued, and now, up to 18 different variants have been associated with an ACM phenotype, especially those variants located in the transmembrane voltage sensing domains of *SCN5A*. This phenotype is characterized by frequent ventricular ectopy, sinus node dysfunction, conduction defects including atrioventricular block, and especially atrial and ventricular arrhythmias with a subsequent identification of DCM. The arrhythmia appears to consistently precede the cardiomyopathy [49].

## Recent Genes: DES, RBM20, CDH2, CTNNA3, and FLNC

Identification of rarer causes of familial ACM have implicated pathogenic changes in the desmin (*DES*), RNA-binding motif protein 20 (*RBM20*), cadherin-2 (*CHD2*),  $\alpha$ T-catenin (*CTNNA3*), and filamin-C (*FLNC*) genes [16, 21, 22, 50–52]. Data describing these ACM phenotypes are evolving, but commonly these seem to be associated with a biventricular cardiomyopathy with a high arrhythmic risk [53]. Newer data suggests that *FLNC* variants may be associated with a range of specific findings including a normal ECG to more classic T wave inversions as seen in ARVC, and that subepicardial LV enhancement on MRI is common [54, 55].



**Fig. 2** Low voltage on electrocardiogram (ECG) in a *PLN* variant carrier (a) and conduction disease in a *LMNA* variant carrier (b)

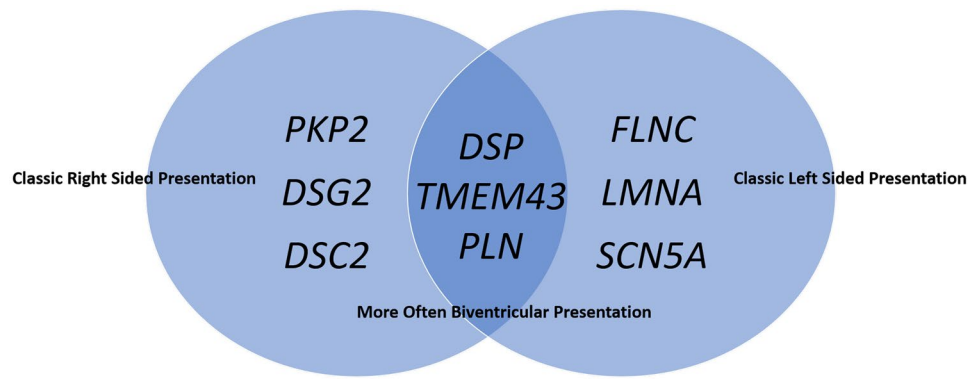
## Multiple Variants

Digenic, compound heterozygous and autosomal recessive inheritance, each of which are characterized by multiple pathogenic variants, have been reported to occur in an estimated 2–4% of families with ACM [30, 56]. This has important implications both for phenotyping in the family, but also for family screening. Individuals with multiple pathogenic variants consistently present at younger ages, and with more severe phenotypes. Digenic disease may also explain an inconsistency in phenotype such as desmosomal variant carrier who also has an additional pathogenic cardiomyopathy variant. This information is critical for family screening, as family testing should include all pathogenic variants, and relatives carrying different combinations of variants may look quite phenotypically dissimilar depending on their unique genotype [56].

## Emerging Considerations: Genome First Diagnosis

With the plummeting cost of more expansive genetic testing and the inclusion of almost all of the ACM genes as secondary findings recommended to be reported by the American College

**Fig. 3** Central illustration of gene presentation and overlap



of Medical Genetics (ACMG), there is a rising number of individuals found to carry ACM risk variants in a genome first approach, and often absent of any clinical or family history [57, 58]. Studies have shown that these individuals have considerably reduced penetrance rates compared to members of ACM families in which pathogenic variants have been identified [59, 60]. While pre-clinical cases in ACM families should follow published screening guidelines, in these phenotype-absent families, caution is warranted in interpreting these variants for management and risk stratification in these individuals [61]. It has been suggested that screening and management recommendations apply differently, in a less intensive manner in this situation [62]. This finding also highlights the likely relevance of environmental and potentially genetic modifiers on outcomes of patients with a pathogenic variant [28].

### Towards Genotype-specific Management

The data is now clear that identification of these specific ACM genotypes in the cardiomyopathy population is clinically useful, as arrhythmic risk is significantly higher in ACM than in typical NICM [5•]. Central themes in presentation are displayed in Fig. 3. There may be subtle clinical clues on ECG or in scar patterns to the underlying genotype, but genetic testing provides certainty. Furthermore, genotype-specific risk prediction algorithms are emerging as a way to estimate individualized malignant arrhythmia risk. Recent data suggest that there may be genotype-specific risk predictors such as scar burden and myocardial injury in *DSP* carriers, or ECG voltage in *PLN* carriers [41, 63]. Genotype-specific arrhythmia risk prediction models have been developed for *PLN* p.R14del ACM and *LMNA* cardiomyopathy and a risk calculator has been developed largely from a desmosomal ARVC cohort for prediction of incident ventricular arrhythmias (arvcrisk.com) [41, 47, 64]. Predicting progression and incidence of heart failure has remained challenging in ACM. It may be that genotype is an important predictor of trajectory [32]. Overall, many ACM families are hoping for a “cure,” and while that may not be possible, gene-specific therapies are increasing

in number quickly. *LMNA*-related DCM was one of the first ACM clinical trials with an investigational small-molecule drug targeted towards specific genotype, but many others are now in development [65].

In families without an identifiable genetic risk factor, gene finding efforts continue. Without a clear defined genetic phenotype, however, it is becoming increasingly likely that they do not have monogenetic disease, and it may be a confluence of multiple common genetic risk alleles and environmental factors. Development of polygenic risk scores in multiple types of cardiomyopathy may aid in management in these cases [66].

### Discussion and Conclusions

The promise of precision medicine is finally emerging in ACM with enough data to establish genotype–phenotype correlations. Expert consensus statements agree, and genetic counseling and genetic testing is strongly recommended as part of the diagnosis and management of ACM patients [2•, 5•, 61]. These recommendations are based upon these data that show clear differences in disease course and outcomes based on underlying genetic cause. At base, one of the most important considerations and utility of genetic testing is separating more common disease such as NICM, myocarditis, and cardiac sarcoidosis from genetic ACM. This has profound impact on patient management, especially risk stratification for malignant ventricular arrhythmias. There are clear recommendations that genetic testing is a guideline-directed part of management when diagnosing a genetic cardiomyopathy such as ARVC. These data stress the importance in identifying those with a genetic risk factor that may not have been otherwise suspected. Indeed, in many of these families due to incomplete penetrance and variable expressivity, 50% or more of individuals with a genetic ACM may not have any clear family history of disease [30]. As a result, increasingly experts are recommending genetic testing in any suspected arrhythmic cardiomyopathy presenting under the age of 50, and in many myocarditis cases, especially those with recurrent episodes and young age of presentation [34].

Identification of a genetic cause of an individual's ACM also has critical downstream importance in family screening. Sudden cardiac death can be and is often the first symptom of disease in ACM. Therefore, identification of those at risk and regular screening is a life-saving result of genetic testing in these families. Furthermore, understanding genotype–phenotype correlations is also important in family screening, such as exercise modification in desmosomal ARVC, and screening for not only ventricular but also atrial arrhythmias in *SCN5A* and *LMNA* variant carriers [2•].

Going forward, data will continue to accumulate to refine our understanding of both ACM genotype:phenotype associations and also the interplay of genotype and environmental modifiers on ACM onset and trajectory. Individuals with genetic ACM are recommended by practice guideline to be followed in multidisciplinary expert centers who maintain an updated understanding of the latest genotype–phenotype data to incorporate into patient and family management [67]. On the horizon, however, is more complicated genotype interpretation in the non-Mendelian forms of cardiovascular disease, and the rise of polygenic risk scores for cardiac disease. The field will need to adapt once again to integration of this data into patient and family management.

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## Compliance with Ethical Standards

**Conflict of Interest** B Murray is a consultant for MyGeneCounsel. CA James receives research support from Boston Scientific Corp and is a consultant for Pfizer, Inc (compensated), Tenaya Inc. (uncompensated), and StrideBio, Inc (uncompensated).

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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