ARRHYTHMIC GENOTYPES IN FAMILIAL DILATED CARDIOMYOPATHY: IMPLICATIONS FOR GENETIC TESTING AND CLINICAL MANAGEMENT

Short title: Arrhythmic dilated cardiomyopathy

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Abstract

Cardiac arrhythmias are frequently seen in patients with dilated cardiomyopathy (DCM) and can precipitate heart failure and death. In patients with non-ischaemic DCM, the utility of implantable cardioverter-defibrillator (ICD) devices to improve patient outcomes has come into question, with accumulating evidence of lack of survival advantages and significant complication rates. Algorithms devised to identify high-risk individuals who might benefit most from ICD implantation have focussed on clinical criteria with little attention paid to the underlying aetiology of DCM. Malignant ventricular arrhythmias often occur as a nonspecific consequence of DCM, but can also be a primary manifestation of disease in heritable forms of DCM and may precede DCM onset. We undertook a literature search and identified 11 genes that have been associated with DCM and ventricular arrhythmias in multiple kindreds. Many of these genes fall into a diagnostic grey zone between left-dominant arrhythmogenic right ventricular cardiomyopathy and arrhythmic DCM. Genes associated predominantly with arrhythmic DCM included *LMNA* and *SCN5A*, as well as the more recently-reported DCM disease genes, *RBM20*, *FLNC*, and *TTN*. Recognition of arrhythmic DCM genotypes is important, as this may impact on clinical management. In particular, prophylactic ICD implantation and early heart transplantation may be indicated in genotype-positive individuals. Collectively, these findings argue in favour of including genetic testing in standard-of-care management of familial DCM. Further studies in genotyped patient cohorts are required to establish the long-term health and economic benefits of this strategy.

Key words: Dilated cardiomyopathy, genetics, arrhythmia, sudden death

Introduction

Cardiac arrhythmias are a major cause of clinical deterioration and demise in patients with dilated cardiomyopathy (DCM). In keeping with this, current international guidelines recommend prophylactic intervention with implantable cardioverter-defibrillators (ICD) in patients with heart failure and left ventricular ejection fraction <35% [1,2]. The risk-benefit ratio of routine ICD implantation has recently been questioned however, with longitudinal evidence of a 44% decline in sudden cardiac death over the past two decades [3], and clinical trial data showing no survival advantages and significant complication rates of ICDs in patients with non-ischemic systolic heart failure [4]. Moreover, many cases of sudden cardiac death occur in individuals with only mild or moderate reductions in ejection fraction [5]. Collectively, these findings have prompted review of indications for ICD use, particularly in the setting of non-ischaemic heart failure, and have highlighted the need to identify subsets of high-risk patients who might derive the greatest benefit [3-6].

Risk stratification criteria devised to date have focussed on non-invasive parameters including clinical history, ventricular size and function, ECG characteristics such as QRS fragmentation and T-wave alternans, late gadolinium enhancement on cardiac magnetic resonance imaging, and autonomic nervous system activity [7-9]. These parameters have had only modest success in predicting sudden cardiac death in patients with non-ischemic DCM and have limited clinical utility. A notable omission from these criteria is consideration of the *cause* of DCM. Ventricular (and atrial) arrhythmias may arise as a non-specific *consequence* of DCM in association with secondary structural and electrical chamber remodelling. However, cardiac arrhythmias can also be primary manifestations of the disease process itself. A better understanding of the aetiology of DCM could shed new light on personal arrhythmia risk.

Genetic variation has an important role in the pathogenesis of DCM and long lists of putative disease genes have been compiled [10]. Disease-causing gene mutations can be identified in ~25%-40% of families with DCM and in ~10%-25% of sporadic DCM cases [10,11] but because of the high costs and the relatively low yield, clinical genetic testing has not been part of routine patient care [12]. An exception to this has been the subset of patients with DCM and conduction-system abnormalities, in whom screening of the *LMNA* and *SCN5A* genes is recommended in clinical practice guidelines [12].

In recent years, there has been emerging evidence that a number of genes in addition to *LMNA* and *SCN5A* have significant arrhythmic phenotypes. Recognition of these arrhythmic genotypes is paramount, as variant carriers need may require aggressive early intervention. In this article, we will provide an overview of current knowledge of cardiac arrhythmias in genotyped individuals with familial or sporadic DCM, and the implications for genetic testing and clinical management.

Spectrum of Arrhythmic Phenotypes Associated with Dilated Cardiomyopathy Disease Genes

We undertook a literature search to investigate cardiac phenotypes associated with DCM-causing genetic variants and identified 11 genes in which both DCM and ventricular arrhythmias had been reported in multiple families and/or sporadic cases (Table 1). These genes encode proteins involved in diverse aspects of cardiomyocyte structure and function with no clear common pathogenetic mechanism. Classification of these genes based on phenotype alone was challenging, as most fell in a diagnostic grey zone between DCM and arrhythmogenic right ventricular cardiomyopathy (ARVC), a disorder characterized by fibrofatty infiltration of the right ventricle and early arrhythmias (Figure 1). An alternative classification based on genotype would be equally problematic, as these genes have each been

associated with multiple different phenotypes (Table 1). A caveat to both classification methods is the variable level of evidence for disease causation, with many of these associations relying on reports of single predicted-pathogenic variants in sporadic cases.

ARVC is most frequently caused by desmosomal gene variants that result in altered cell-cell coupling, inflammation and fibrosis with eventual chamber dilatation and dysfunction. Approximately 75% of patients with ARVC have biventricular involvement and left-dominant forms are not uncommon [13,14]. Genes such as *DSP, DSG2,* and *DSC2,* fall into this category (Figure 2). Another subset of arrhythmic genes, including *TMEM43, PLN,* and *DES,* encode non-desmosomal proteins and have also been associated with ARVC, DCM, or overlap syndromes, all of which are frequently complicated by malignant ventricular arrhythmias [13-24] (Figure 2). Interestingly, *TMEM43* and *PLN* variants are relatively uncommon but have been seen as founder mutations in specific populations. *DES* variants are associated with a range of cardiac and skeletal myopathies, including ARVC, DCM, and restrictive cardiomyopathy, with disease phenotypes often including cardiac conduction abnormalities, ventricular arrhythmias and sudden cardiac death [20-24]. A third subset of genes primarily cause arrhythmic forms of DCM, with some reported associations with ARVC (Figure 2). While some of these genes, such as *LMNA* and *SCN5A,* are widely known for their arrhythmic phenotypes, the arrhythmic potential of other, more recently-reported DCM disease genes, particularly *RBM20* and *FLNC,* is less well recognized. Characteristics of these arrhythmic DCM disease genes are highlighted below.

LMNA

The *LMNA* gene encodes the nuclear lamina proteins, lamins A and C. Mutations in this gene were first reported two decades ago [25], and are now recognized to be one of the most common causes of familial DCM, accounting for ~5% cases. *LMNA* mutations have a

distinctive phenotype in which conduction-system abnormalities or atrial fibrillation may precede the onset of DCM by several decades [25-28]. Longitudinal studies have demonstrated that *LMNA* mutation carriers typically have downhill clinical course as a result of progressive heart failure or malignant ventricular arrhythmias [26-28]. Factors proposed to predict adverse outcomes include male sex, loss-of function mutations (frameshift insertion/deletions, splice site loss), a left ventricular ejection fraction <45% or increased left ventricular end-diastolic diameter, and the presence of non-sustained ventricular tachycardia [26,27]. Studies in murine models have shown that lamin A/C deficiency results in altered nuclear morphology and abnormal nuclear-cytoskeletal connections that may impair the mechanical stability of cardiomyocytes [29]. The hearts of human *LMNA* mutation carriers are often notable for the presence of marked fibrosis, which may contribute to the high propensity for ventricular arrhythmias [25,30].

SCN5A

SCN5A encodes the cardiac sodium channel, Nav1.5, and like *LMNA*, mutations in this gene have been associated with DCM, conduction-system abnormalities and atrial and ventricular arrhythmias [31-34]. The vast of majority of reported mutation have been missense variants, with a predilection for location in the S3 and S4 transmembrane domain, implicating disruption of voltage-sensing mechanisms [33]. DCM-associated *SCN5A* mutations have variably been shown to have loss-of-function or gain-of-function effects on cardiac sodium channel activity [29,34,35]. There has been debate about whether contractile impairment is a consequence of atrial or ventricular ectopy/tachyarrhythmias or rather than a primary phenotypic feature. However, DCM is often seen in the absence of a substantial arrhythmic burden, suggesting that it is a *bona fide* disease manifestation. Mechanisms other than direct modulation of channel activity may be involved, including down-regulation of Nav1.5

expression, channel mislocalization due to altered cytoskeletal anchoring, or altered intracellular pH and Ca^{2+} homeostasis [32,36,37].

RBM20

RNA binding motif protein 20 is a component of the RNA splicing machinery and is involved in regulation of constitutive and alternative splicing. *RBM20* mutations have been associated with a particularly aggressive phenotype with early onset severe DCM and a high likelihood of heart transplantation, ventricular arrhythmias and premature death [38-41]. Most of the DCM-associated *RBM20* mutations have been missense variants, with many of these located in a mutational hotspot in the arginine-serine-rich (RS) domain [38,39]. Altered titin splicing with an increased abundance of the more compliant isoform has been considered to be a major factor in *RBM20*-associated DCM [41,42]. However, *RBM20* contributes to the post-translational modification of at least 30 cardiac genes, and loss-of-function *RBM20* variants are now appreciated to have a broad spectrum of effects that impact on diverse aspects of sarcomere structure and function [42-44]. Changes in expression of genes involved in Ca^{2+} handling and increased spontaneous Ca^{2+} release from the sarcoplasmic reticulum are thought to be important determinants of arrhythmogenesis in mutation carriers.

FLNC

Filamin C is an actin-binding cytoskeletal protein that is located at Z-discs and costameres in cardiac and skeletal muscle. It is thought to contribute significantly to the mechanical stability of muscle cells and to mechanical stress sensing and signal transduction. Variants in the *FLNC* gene can result in the formation of intracellular protein aggregates and myofibrillar myopathies, and have also been identified in patients with hypertrophic cardiomyopathy and restrictive cardiomyopathy [45,46]. In 2016, two groups of investigators reported that

truncating variants in the *FLNC* gene resulted in a highly arrhythmic form of DCM that was characterized by severe early-onset ventricular dysfunction and a high prevalence of atrial arrhythmias, ventricular ectopy, ventricular tachycardia and sudden death [47,48]. Cardiac tissue from variant carriers showed reduced *FLNC* RNA and protein expression suggesting a loss-of-function effect. This was confirmed by studies in zebrafish embryos, with morpholino-mediated knockdown of filamin C resulting in dysmorphic or dilated cardiac chambers, pericardial oedema, and premature death [47,48]. Myocardial histological studies in the zebrafish embryos showed abnormal cardiomyocyte ultrastructure, with altered sarcomere alignment and irregular or absent Z-discs. In filamin C-deficient human hearts, protein aggregates are generally absent but marked ventricular fibrosis has been observed, and this may contribute to the high arrhythmia propensity [48]. In a very recent study, a subset of patients with DCM due to truncating *FLNC* variants were shown to have epicardial fibrofatty infiltration of the left ventricle, as well as dilation and interstitial fibrosis of the right ventricle [49]. Immunostaining of ventricular sections showed normal plakoglobin expression but reductions of desmoplakin staining at cell-cell junctions [49].

TTN

Truncating variants in the *TTN* gene (*TTN*tv) have been identified in 15-20% of patients with DCM and have been proposed to be the most common genetic cause of DCM [50]. However, since these variants are also present in up to 3% of the general population, their clinical significance has been questioned. Studies in zebrafish models suggest that *TTN*tv can be sufficient alone to cause DCM [51]. There is increasing evidence however that the phenotypic manifestations of *TTN*tv are likely to be modified by additional genetic and acquired factors, such as alcohol and pregnancy [52,53]. Although it has been suggested in some studies that *TTN*tv carriers have a high risk of ventricular arrhythmias, data from other studies suggest

that overall outcomes, including heart failure progression and malignant ventricular arrhythmias, are milder than those observed in patients with high-impact variants in other genes such as *LMNA* and *RBM20* [44,54,55].

Clinical Diagnosis

Taking a careful clinical history, including a family history of at least three generations, is the essential first step in diagnosing arrhythmic forms of familial DCM. A high index of suspicion is needed, and a spectrum of clinical presentations amongst different family members may be potentially relevant, including DCM, other cardiomyopathy types, conduction-system abnormalities, atrial and ventricular arrhythmias, congenital heart defects, skeletal myopathy, and sudden unexplained death. Probands and family members need to be evaluated with physical examination, echocardiography, and ECG. In patients with suspected arrhythmic DCM, cardiac magnetic resonance imaging is useful to delineate left and right ventricular size and function, and for assessment of the presence and extent of ventricular fibrosis. Additional investigation with 24-hour Holter monitoring ± electrophysiological studies should be undertaken according to standard clinical indications. Measurement of serum creatine kinase levels is often helpful even in the absence of overt symptoms and signs of skeletal myopathy, and may help to prioritise potential causative genetic variants. In all affected individuals, causes of DCM other than familial disease need to be excluded. Distinctive phenotypic patterns within families may give clues to specific genetic aetiologies, such as DCM + conduction abnormalities (*LMNA*, *SCN5A*), DCM + conduction abnormalities + raised creatine kinase levels (*LMNA*, *DES*) etc.

Genetic Testing

Unlike many other disorders, genetic testing in DCM cases is not performed to establish a diagnosis but rather, to find the underlying genetic aetiology. To date, the main benefit of genetic testing has been to enable cascade predictive testing of asymptomatic family members and this has been used to guide clinical follow-up strategies. Historically, the overall cost-efficacy and treatment impact of genetic testing in DCM was considered relatively modest, and this resulted in a class II recommendation ("may be useful") in international guidelines [12]. With advances in next-generation sequencing technologies, human genome sequencing has become more available and affordable, and its value needs to be revisited. Efforts to revise genetic testing guidelines by authoritative bodies such as the Heart Failure Society of North America are both timely and warranted [11]. Recognition of families with arrhythmic DCM genotypes is particularly important in the light of accumulating evidence that this information can directly impact on clinical management. To this end, genetic testing should be considered in any newly-diagnosed patients with familial DCM, especially if there is a suspicion of arrhythmic events in the index case or in family members.

Implications of Genetic Diagnosis for Family Management

Heart failure and arrhythmias in affected family members are generally treated using pharmacological, device therapy, and heart transplantation in accordance with standard clinical guidelines [1,2]. In decisions regarding invasive ablation procedures for patients with atrial or ventricular arrhythmias, the impact of a genetically-determined cardiomyopathic substrate on procedural success and recurrence rates needs to be considered.

There are emerging data to suggest that genetic information may allow gene-targeted and more personalized therapeutic strategies. For example, it has been recommended that carriers of pathogenic *LMNA* variants should receive ICDs rather than pacemakers, and undergo early heart transplantation [2,26-28]. Similar aggressive approaches may be

warranted in carriers of other highly arrhythmic gene variants. Although treatments to date have mainly provided symptomatic relief, gene-specific therapies that are directed against primary pathogenetic mechanisms are increasingly being explored. An example of this is the p.R222Q *SCN5A* variant that has been associated with arrhythmic DCM [33,34]. This is now recognised to be a particularly important *SCN5A* variant that is recurrently seen in DCM families but absent from population databases [233,34,56-59]. Electrophysiological studies have shown that this variant has a gain-of-function effect on cardiac sodium channel activity [34,57,58]. Although treatment with drugs that have sodium channel blocking properties is generally contraindicated for treatment of ventricular arrhythmias in patients with heart failure [2], we and others have found that drugs such as flecainide, amiodarone, and quinidine, have been remarkably effective in p.R222Q *SCN5A* carriers, resulting in a spectacular reduction of arrhythmia burden and improved left ventricular function [34,57-59]. Similarly, calcium channel blocking drugs are broadly contraindicated in patients with low ejection fraction [1], but may have a specific role in patients with gain-of-function *RBM20* variants [44]. Several biologically-targeted drug therapies have shown promising results in animal models of *LMNA* deficiency and pilot human studies have been performed or are currently underway [60-62, and NCT03439514].

Unaffected genotype-positive family members require baseline clinical evaluation and periodic surveillance to detect symptoms and signs of declining cardiac function and/or arrhythmia onset. In the absence of clinical trial data, the efficacy of pre-emptive intervention is unknown. Future studies in large cohorts of genotyped individuals are clearly needed in order to address important questions such as who, when, and how to treat asymptomatic variant carriers in order to attenuate or prevent disease onset.

In all family members, attention should be given to treatment of co-morbidities and lifestyle factors that may exacerbate the disease phenotype. In recent years, exercise has been shown to

accelerate disease progression in patients with ARVC [63], but the impact of exercise on arrhythmic forms of DCM is unknown. Interestingly, regular moderate exercise was shown to be beneficial in a murine model of lamin A/C-deficient DCM [61]. In contrast, acute strenuous exercise exacerbated skeletal muscle dysfunction in filamin C mutant mice [64]. Family members should also receive genetic counselling and psychosocial issues need to be addressed. Genetic testing and ongoing family management is ideally performed in the setting of a multidisciplinary clinic.

Further comparative studies in genotyped patient cohorts are required to better define the range of genotypes that give rise to arrhythmic forms of familial DCM, and to document natural history and outcomes. Such studies will only be possible in the first instance, if genetic testing of DCM families is more widely adopted. Genetic testing holds the key to a better understanding of molecular underpinnings of arrhythmic DCM and the development of gene-targeted therapies. Mechanistic and intervention studies in experimental models and genotyped human cohorts are needed.

Conflicts of interest

None.

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Figure Legends

Figure 1. Phenotype overlap between arrhythmogenic right ventricular cardiomyopathy (ARVC) and dilated cardiomyopathy (DCM). There is a diagnostic grey zone between left-dominant forms of ARVC and arrhythmic forms of DCM.

Figure 2. Genes associated with a high propensity for DCM and ventricular arrhythmias**.** These arrhythmic genes included desmosomal genes that predominantly cause ARVC (group 1), non-desmosomal genes associated with ARVC, DCM or both (group 2), and genes that predominantly cause DCM (group 3).