ARRHYTHMIAS AS PRESENTATION OF GENETIC CARDIOMYOPATHY

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Abstract

There is increasing evidence regarding the prevalence of genetic cardiomyopathies, for which arrhythmias may be the first presentation. Ventricular and atrial arrhythmias presenting in the absence of known myocardial disease are often labelled as "idiopathic", or "lone". While ventricular arrhythmias are well-recognized as presentation for arrhythmogenic cardiomyopathy in the right ventricle, the scope of arrhythmogenic cardiomyopathy has broadened to include those with dominant left ventricular involvement, usually with a phenotype of dilated cardiomyopathy. In addition, careful evaluation for genetic cardiomyopathy is also warranted for patients presenting with frequent PVC's, conduction system disease, and early onset atrial fibrillation, in which most detected genes are in the cardiomyopathy panels. Sudden death can occur early in the course of these genetic cardiomyopathies, for which risk is not adequately tracked by left ventricular ejection fraction. Only a few of the cardiomyopathy genotypes implicated in early sudden death are recognized in current indications for implantable cardioverter defibrillators which otherwise rely upon a left ventricular ejection fraction 0.35 in dilated cardiomyopathy. The genetic diagnoses impact other aspects of clinical management such as exercise prescription and pharmacologic therapy of arrhythmias, and new therapies are coming into clinical investigation for specific genetic cardiomyopathies. The expansion of available genetic information and implications raises new challenges for genetic counseling, particularly with the family member

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who has no evidence of a cardiomyopathy phenotype and may face a potentially negative impact of a genetic diagnosis. Discussions of risk for both probands and relatives need to be tailored to their numeric literacy during shared decision-making. For patients presenting with arrhythmias or cardiomyopathy, extension of genetic testing and its implications will enable cascade screening, intervention to change the trajectory for specific genotype-phenotype profiles, and enable further development and evaluation of emerging targeted therapies.

Introduction

There is increasing recognition of the prevalence of genetic cardiomyopathies. Genetic cardiomyopathies often present with cardiac arrhythmias, which, in the absence of clinical heart failure, may too readily be labelled as "idiopathic," "isolated," or "lone." Many of these disorders are now considered arrhythmogenic cardiomyopathies (ACM). This term reflects evolution from the initial recognition of families with sudden death, ventricular arrhythmias, and morphologic disease of the right ventricle (RV), defined first as arrhythmogenic RV dysplasia and then arrhythmogenic RV cardiomyopathy (ARVC), linked to genetic desmosomal disease.[1] As described in the 2019 Heart Rhythm Society Expert Consensus Statement,[2] the scope of ACM has expanded to include those predominantly expressed in the left ventricle (LV), most commonly with a dilated cardiomyopathy phenotype. In this review, the broad term ACM will encompass both the desmosomal and other genetic diseases primarily affecting the right ventricle (ACM-RV) and those primarily affecting the left ventricle (ACM-LV), with recognition that both ventricles are often involved together. The distinct phenotype of hypertrophic cardiomyopathy, which is notorious for its presentation as sudden death in athletes, receives separate consideration. Consideration of genetic cardiomyopathy is increasingly relevant, however, also for patients presenting with early onset atrial fibrillation, conduction system disease, or frequent PVCs, any of which can be the presenting symptoms in the absence of HF.

When evaluating a patient with new arrhythmias and possible CM, it is useful to consider three contexts according to the relative timing and severity of arrhythmias and myocardial dysfunction:

1. Arrhythmias dominate the clinical picture with mild or no apparent impairment of left ventricular function.

2. Arrhythmias appear in parallel with other evidence of CM not previously recognized.

3. Arrhythmias have developed only after CM and HF are advanced.

This review will focus on evaluation and recognition of patients in the first two settings with atrial fibrillation, conduction system disease, or ventricular arrhythmias (VA) as the presentation of genetic cardiomyopathy. The major morphologic phenotypes of genetic CM will then be reviewed, including examples of genetic variants associated with arrhythmias, recognizing that the reported prevalence and prognosis of pathogenic variants vary among different regions, and continue to evolve with new information.

Initial Evaluation in Patients Presenting with Arrhythmias

Historical features to be elicited should focus on evidence of other cardiac disease. Abnormal ECGs may have been reported in the past. Prior cardiac evaluation may have been triggered by atypical chest pain, which can occur for multiple reasons with cardiomyopathies. Comparison of current to past activity level, such as during previous family holidays, can reveal unrecognized decline in exercise tolerance. Some pathogenic myocardial variants also affect skeletal muscle, so patterns of muscle weakness can suggest genetic heart disease. The history should note other features specific to some cardiomyopathies, such as familial partial lipodystrophy with LMNA disease.

A 3-generation family history should be obtained,[2,3] to include not only heart failure, CM, and "enlarged heart", but also skeletal muscle disease, early onset atrial fibrillation (AF), pacemaker implantation, or sudden cardiac death (SCD), sometimes hidden within a diagnosis of "massive heart attack", drowning, single motor vehicle accident, or occurring in infants. CM can also be part of recognized genetic syndromes with prominent non-cardiac features (which will not be reviewed here).

Electrocardiography

ECG documentation of the arrhythmia can suggest the nature of underlying cardiomyopathy. Baseline abnormalities of repolarization, hypertrophy, or conduction favor the presence of underlying disease.[4] The morphology of PVCs and other VA can be helpful as discussed below. High voltage of left ventricular hypertrophy suggests hypertrophic cardiomyopathy (HCM), often with prominent septal forces, while voltage can decrease progressively with some genetic CM, such as with LMNA or desmoplakin diseases. Ambulatory cardiac monitoring is useful for identifying arrhythmias and quantifying whether frequency of AF or PVCs is sufficiently high to contribute to ventricular dysfunction.

Echocardiography

Transthoracic echocardiography is widely available, inexpensive, and remains the standard first-line imaging for evaluation of patients presenting with ventricular arrhythmia. It can help to exclude underlying coronary artery or valvular disease, and may identify features such as ventricular dilation, global and/or regional ventricular systolic dysfunction, atrial enlargement or abnormal myocardial wall thickness that indicate CM phenotypes. Assessment of global longitudinal strain enhances recognition of early disease and of serial changes in systolic function during the course of genetic cardiomyopathies.[5]

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) is the recognized gold standard for quantitative measurement of ventricular size, function, morphology, and myocardial tissue characteristics. It allows visualization of myocardial edema, inflammation, and fibrosis. Gadolinium contrast accumulates in areas of expanded extracellular matrix, allowing recognition of myocardial fibrosis as regions of late gadolinium enhancement (LGE). When trying to determine whether VA are "benign", the presence of LGE is a relatively reliable indicator of myocardial disease and a potential substrate for scar-related arrhythmias (Figure

1).[6] The morphology and location of LGE allows for the discrimination of non-ischemic fibrosis from scarring related to myocardial infarction. The extent of LGE has been linked to risk of VA/SCD in dilated cardiomyopathy (DCM)[7–9] and some signature LGE patterns have been associated with specific genotypes.[10]

Diffuse interstitial fibrosis may not result in visible LGE but can be appreciated by novel imaging techniques.[11] Parametric mapping (T1, T2, and extra-cellular volume, ECV) allows for further discrimination of myocardial edema, inflammation, infiltration, and fibrosis. Global elevation of the native myocardial T1 and the ECV are indicators of diffuse fibrosis and associated with increased arrhythmia risk, even when focal LGE is not apparent.[12,13]

Imaging of the right ventricle (RV) presents challenges, as CMR may not detect thin areas of fibrosis that can nonetheless cause ventricular tachycardia (VT).[14] Discrimination of LGE in the thin RV free wall is further complicated by bordering epicardial fat, which can be distinguished using pre-contrast T1 mapping. Co-registration of the native T1 map with LGE images may increase diagnostic sensitivity for detection of fibro-fatty infiltration that is a hallmark of desmosomal disease.

Overlap Between Inflammatory and Genetic Cardiomyopathies

Inflammatory cardiomyopathies, most commonly sarcoidosis and Chagas disease in endemic areas, need to be distinguished from genetic cardiomyopathies. Cardiac sarcoid with predominant RV involvement can be hard to distinguish from ACM-RV.[15] In the absence of confirmed extracardiac sarcoid, the diagnosis of active cardiac sarcoidosis may depend upon focal cardiac areas of increased fluoro-deoxy-glucose uptake on positron emission tomography after myocardial glucose uptake is suppressed during a no-carbohydrate diet. However, this distinction is complex because some genetic cardiomyopathies, notably those due to *DSP* and other desmosomal mutations, can also cause areas of inflammation.[16]

The distinction between inflammatory and genetic CM is further blurred by evidence that they can occur together. An early pathologic series of ARVC showed lymphocytic myocarditis in 2/3 of hearts.[17] Case series document patients who presented with acute chest pain, troponin elevations, and imaging typical of myocarditis, but who were later found to have desmoplakin CM.[18,19] Some genes implicated in familial CM may increase susceptibility to viral myocarditis.[20] In vitro and murine models of desmosomal variants have shown activation of nuclear factor kappaB signaling with increased levels of inflammatory cytokines.[21] In recent small studies, auto-antibodies to components of the intercalated disks have been described in families with ACM-RV and proposed for diagnosis of desmosomal disease.[22,23]

Current Selection of Patients for Genetic Testing

Beyond recommendations for the 3-generation family history, formal indications are evolving for genetic testing in the evaluation of arrhythmias and cardiomyopathies. The family history should not be considered a reliable proxy for the presence of genetic disease, which can occur with a negative family history. A suggestive family history may increase the likelihood of finding a pathogenic variant by up to 2-fold, but its absence does not signify

absence of genetic CM. Clinical penetrance is highly variable and many family histories are incomplete. In a recent study of genetic CM with recurrent VA, family history was negative for sudden cardiac death (SCD) in 65% patients and for CM in 73%.[24] In a large Maastricht registry, the presence of an arrhythmia phenotype of AF, conduction disease, or VA at the time of CM diagnosis doubled the rate of positive genetic tests for CM.[25]

Underlying genetic CM should remain a consideration even in the presence of an acquired cause of CM. Compared to a control population without CM, patients with CM in the settings of excess alcohol consumption, cardiotoxicity from anthracycline chemotherapy, or peri-partum cardiomyopathy all had higher prevalence of genetic CM variants, often truncating *TTN* variants.[26–28]

The AHA Scientific Statement on Inherited Cardiac Disease indicated, based on a moderate level of consensus, that genetic testing can be useful in patients with familial or "idiopathic" cardiomyopathy.[29] Genetic testing was also recommended by the AHA/ACC guidelines for HCM and by the Heart Failure Society of America for HCM, DCM, and ACM, with lower strength of recommendation for RCM.[30,31] The Heart Rhythm Society emphasizes the importance of genetic testing for possible ACM,[2] which has major implications for consideration of ICDs (Table 1). All these recommendations emphasize the importance of genetic counseling and a multidisciplinary team experienced in the care of genetic CM.

Arrhythmia Mechanisms and Phenotypes in Genetic CM

Atrial Fibrillation

The association between atrial fibrillation and atrial flutter (here abbreviated together as AF) and CM is well-recognized, occurring in up to 30% of patients with inherited cardiomyopathies, increasing to 40–50% in severe HF.[36,37] AF can also lead to the tachycardia-induced CM phenotype, which does not preclude an underlying genetic CM, as described below. This has been attributed to rapid ventricular response, but also to the irregularity of AF, which may cause impairment in cardiomyocyte excitation-contraction coupling.[38]

AF may often be the first presentation of genetic CM with other clinical evidence of disease developing years later.[39,40] Familial AF has also been reported in families with pathogenic variants in genes associated with inherited CM.[40–42] Such cases appeared to be rare until data from population-based studies began to emerge, in which loss-of-function variants in *TTN* were associated with AF,[43] raising questions of when patients with unexplained AF should be screened for disease-associated variants in both CM and arrhythmia genes.[44,45] A recent study sequenced 1,293 patients with early-onset AF (diagnosed before age 66) for genes included on commercial cardiomyopathy and arrhythmia panels (Figure 2A). A disease-associated variant was found in 10.1% patients overall, and in 16.7% with AF onset before 30 years (Figure 2B).[40] Most implicated variants were in genes associated with DCM, followed by HCM and ACM-RV, with fewer in genes associated with channelopathies. In early onset AF without clinical CM, the CM genes most often implicated were *TTN*, *MYH7*, *MYH6*, and *LMNA*. In these patients presenting with AF before age 66, presence of a pathogenic or likely pathogenic variant conferred a 1.5-fold

higher risk of death during median 10-year follow-up, an effect that was most marked in younger patients.[46]

Multiple mechanisms for AF have been described. Both automaticity and reentry may play roles. Paroxysmal AF often appears to be initiated by rapid activity originating in the posterior left atrium in musculature that includes sleeves of myocardium along the pulmonary veins, and this rapid focal activity may perpetuate AF or initiate reentrant waves. Atrial fibrosis and oxidative stress have been proposed as key mediators of AF initiation and maintenance. Atrial fibrosis can facilitate both automaticity and reentry by creating areas of slow conduction and intra-atrial reentry paths and diminishing coupling between myocyte bundles.[47] Fibrosis is common in HF as progressively elevated filling pressures cause left atrial distention, myocyte stretch, and fibrosis, creating areas of slow conduction and intra-atrial re-entry.[48] The extent to which underlying genetic disease contributes to the initiating electrophysiologic perturbations and the fibrosis that sustains AF is not well defined.

When AF and a pathogenic CM gene are identified, a next step is to evaluate for other evidence of the CM phenotype (Table 2). Finding a decreased LVEF in the setting of a new AF diagnosis could reflect limitations to imaging during an irregular and/or fast heart rhythm, reversible LV dysfunction secondary to AF, and/or an underlying DCM phenotype, so re-assessment is indicated after AF therapy. The frequency of AF is increased in association with any CM genotype, with truncating *TTN* variants and *LMNA* variants being commonly implicated for DCM (Figure 3).[25] When evaluation of new AF instead reveals a hypercontractile LV with LVH meeting criteria for HCM, the most likely genetic variants are in sarcomeric proteins, particularly MYH7.[49]

AF also occurs in restrictive cardiomyopathy, which is less common than HCM and DCM (Table 2). Most RCM results from acquired or systemic disease, but can be due to amyloidosis, for which the common genetic cause is mutant transthyretin (*TTR*). AF may be the initial presentation of ATTR-CM (transthyretin amyloid cardiomyopathy) when other signs have been overlooked.[50] In an international ATTR-CM registry, AF occurred in half of the subjects with the VAL122Ile mutation.[51] Pathogenic variants in *DES* and *FLNC* have been associated with an increased incidence of AF in either DCM or RCM phenotype.

Anticoagulation and Pacing for AF with Genetic CM—Regardless of the CHADS2-VASC score, anticoagulation for AF is generally recommended for all patients with a clinical diagnosis of HCM, all women and most men with DCM, and more recently for ACM-RV as well.[2,52,53] Anticoagulation is indicated for all patients with AF and cardiac amyloidosis regardless of LVEF or HF severity. Therapy for AF in ATTR-CM is most effective early after diagnosis, as only 17% of patients with advanced disease can maintain sinus rhythm.[55] ATTR-CM amyloidosis has been associated with frequent development of a left atrial thrombus despite anticoagulation.[56]

While CM variants are well-described in early onset AF, it is not clear how identification of a CM variant should influence care for a patient with early-onset AF as the first presentation.[44,45] For instance, it is not known whether the stronger recommendations for

anticoagulation with CM should extend to patients with AF and positive genotype in the absence of CM phenotype. Should patients with AF as their only manifestation of an ACM phenotype restrict activity or be evaluated for risk of VA/SCD? Although these questions remain unanswered, for a patient with AF and an arrhythmogenic genotype who then develops a need for permanent pacing, implantation of a defibrillator device should be considered.

Conduction Disease

Right bundle branch block (RBBB) is the most common conduction delay encountered in the absence of known heart disease. The incidence of complete RBBB without known heart disease varies from < 1% in young airmen[57] to 1.3% in the Women's Health Initiative,[58] and increases with age. There is no consistent association with mortality after adjustment for known cardiovascular risk factors.[59] During cardiac evaluation, however, RBBB can be an early clue to RV desmosomal disease and is also common with cardiac sarcoidosis and Chagas' disease.[54]

Left bundle branch block (LBBB) is seen in 0.1 – 1% of the population without known cardiac disease. In the Framingham Heart Study, 28% of patients developing LBBB without prior cardiac history had a new diagnosis of HF within a mean 3 years,[60] a rate 7-fold higher than without LBBB. The association of new LBBB with future heart failure may reflect subclinical CM or ischemic heart disease, and/or impaired LV function from dyssynchrony that can improve with biventricular pacing.[61] LBBB occurs in approximately 25–30% of all DCM but was present in over 50% of patients with *LMNA* variants in one series.[25]

LMNA variants are associated with progressive conduction system disease as well as with AF and VA (Figure 3). This may relate in part to its predilection to cause fibrosis in the septum. Some degree of atrioventricular block is present at diagnosis in 38% to 78% of LMNA CM.[62,63] By the time VA appear, most patients have PR prolongation and up to 1/3 have complete heart block. Complete heart block requiring a pacemaker may occur several years before evidence of DCM, which develops in almost all patients who reach their seventh decade with cardiac LMNA disease.[62]

Primary cardiac conduction defects also occur due to genetic variants that may not cause CM. Loss of function mutations in *SCN5A*, encoding the cardiac sodium channel, are a well-recognized cause of progressive conduction system disease (Lenègre disease) in humans and in mice, but DCM is not a common feature of these mutations.[64,65] Other *SCN5A* mutations have been associated with atrioventricular block and DCM,[66] and with PVC's and related CM with subsequent VA as discussed below.

Conduction disease is also common in ATTR-CM. Prolonged PR interval and prolonged QRS are present in almost half of patients at the time of presentation with cardiac transthyretin deposits.[56] About one in 10 patients with ATTR-CM presents with high degree AV block and one of the remaining 9 will progress to complete heart block.

In addition to *LMNA*, *SCN5A*, and transthyretin, other genes associated with both conduction disease and CM include *FLNC* and *DES*. Conduction disease also commonly

accompanies the muscular dystrophies (see below). Atrial standstill can occur with Emery-Dreifuss dystrophy and Friedreich's ataxia. An important implication of conduction disease in a patient with a CM is for consideration of an ICD, especially if pacing is contemplated. It is now increasingly well-recognized that sudden cardiac death (SCD) may occur early in the course of the disease as well as after progression to HF with LVEF 0.35, for which ICDs are generally recommended regardless of the need for pacing or etiology of HF (Table 1).

The mechanisms underlying conduction disease in CM are not well-defined. Lenègre disease (which does not usually progress to CM) can be caused by *SCN5A* mutations that have been shown to cause ventricular fibrosis in mice.[64] Amyloid infiltration is similarly thought to cause conduction block.[67] Multiple mechanisms, including altered transcriptional regulation of multiple downstream genes, have been proposed in LMNA cardiomyopathy.[68]

Ventricular Arrhythmias

PVC's, non-sustained VT (NSVT), sustained monomorphic VT, and polymorphic VT/ ventricular fibrillation can all occur in any CM later in the course of disease, associated with myocardial fibrosis, electrical remodeling, neurohormonal activation, depletion of energy stores and relative ischemia, as well as from proarrhythmic effects of drugs and electrolyte abnormalities.[69] In arrhythmogenic cardiomyopathies, VA may emerge early, sometimes as the first presentation of CM.[70] Initial evaluation seeks to distinguish ACM from idiopathic VA that occur in the absence of structural heart disease and are usually benign.[71] Fibrosis, seen with LGE on CMR imaging, strongly favors myocardial disease rather than an idiopathic arrhythmia, and often corresponds to the site of origin of VA (Figure 1).

VA can be due to automaticity, triggered activity, or reentry. Fibrosis is commonly associated with VA and sudden death risk in CM. Fibrosis can diminish cellular coupling which can slow conduction and facilitate automaticity or propagation of wavefronts initiated by automatic foci. *LMNA, DSP*, and *FLNC* mutations are associated with prominent fibrosis (often in specific locations such as the septum in LMNA-associated CM) and it is possible that the extent and distribution of fibrosis contributes to their arrhythmic propensity. The extent to which mutations also disrupt cellular electrophysiology varies and is not well defined for most genes.

One exception is *SCN5A* mutations which cause multiple arrhythmia syndromes. Some *SCN5A* mutations are clearly associated with CM, while others (type 3 Long QT syndrome, Lenègre disease, Brugada syndrome) generally are not.[72,73] However, there is growing recognition that Brugada syndrome can be associated with abnormal contractile function[74], and DCM related to bundle-branch block has been described with other *SCN5A* mutations.[75] Mutant sodium channels may alter intracellular sodium and calcium homeostasis, leading to frequent ectopy and DCM.[76,77] Sodium channel mis-localization and dysfunction are also seen with mutations in other DCM-associated genes,[78] consistent with an emerging appreciation of a role of the sodium channel in interacting with macromolecular complexes to regulate cell structure, distinct from its role in ion conduction, as discussed below.[79] The unusual syndrome of Multifocal ectopic Purkinje-related

premature contractions (MEPPC) is discussed below. In addition, HF itself, regardless of cause, has been associated with sodium channel dysfunction in animal models.[80,81]

There is also increasing appreciation that CM due to genes that do not code for ion channels may nevertheless lead to impaired ion channel function. Patients with ACM-RV due to *PKP2* mutations can develop arrhythmias when there is little structural abnormality. These mutations reduce expression or localization of multiple genes whose protein products are involved in intracellular calcium homeostasis (type 2 ryanodine receptors, ankyrin 2, L-type calcium channels, triadin, and calsequestrin-2), disrupting intracellular calcium handling and increasing susceptibility to ventricular arrhythmias caused by triggered activity, consistent with the exercise induced arrhythmias and sudden death observed in ACM-RV.[73,82] Similarly, ACM-RV mutations have also been shown to directly affect cardiac sodium channel abundance and intracellular localization, effects that likely perturb normal conduction and increase susceptibility to VA. Re-entrant VT in ACM-RV, however, is often associated with areas of fibro-fatty replacement that develop during the disease.

***Sites of VA Origin: ECG* Correlations—**The QRS morphology of PVCs or VT can point to their sites of origin and provides clues to the presence and type of CM (Figure 4). VA with a dominant S wave in V1 are designated as having LBBB morphology and usually originate from the RV or interventricular septum. An LBBB pattern with an inferior axis (tall R waves in the inferior leads) is typical of RV outflow or periaortic LV outflow tract origin, both common locations for idiopathic arrhythmias as well as VA in ACM. VA of RV origin are usually present in ACM-RV (Figure 4A). VA with a dominant R wave in V1 are designated as having an RBBB morphology, usually originating from the LV (Figure 4B) and associated with myocardial disease.

Premature Ventricular Contractions and Non-sustained VT—PVCs are common in CM, sometimes as the initial presentation (Figure 4C), but can also be idiopathic or from structural heart disease. PVCs are noted on routine 12-lead ECG in 1.5 to 6% of adults and are associated with a greater than 2 fold increased risk of sudden death, heart failure, and cardiac death.[83–85] NSVT in DCM is associated with a greater likelihood of identifying a pathogenic variant and consistently linked to risk of adverse outcomes that include HF events as well as VA/SCD.[25]

The likelihood of underlying CM increases with multifocal PVCs and PVCs with RBBB pattern (LV origin). Fibrosis detected as LGE on CMR imaging generally indicates the presence of CM and increased risk of sustained VA.[10] In a multicenter registry of 686 patients who had ≥1000 PVCs/24 hours considered to be idiopathic with LVEF > 0.50, MRI showed LGE in 15% of patients, of whom 27% experienced VT/VF, cardiac arrest or death during median follow up of 5 years.[86] A ring-like pattern of 3 contiguous segments of LGE in the same short axis slice was associated with the greatest risk (Figure 1C), with 50% of these patients experiencing a VA event, compared to 19% of those with other LGE patterns, and 0.3% of patients with no LGE.[13]

A high density of PVCs over prolonged time can itself depress LVEF, which may normalize when they are suppressed. This PVC-induced CM is reported in 7 to 26% of patients

referred for ablation of PVCs and LVEF improves in about two-thirds of them following successful PVC suppression.[87,88] Most patients with PVC-CM have a PVC burden of more than 15%, but daily frequency can vary substantially, and depressed LVEF has also been seen with fewer PVCs. Of note, interstitial fibrosis occurs in some animal models of PVC induced myopathy[89] and LV function can recover after successful suppression of PVCs despite the presence of LGE.[90]

Notably, the majority of patients with very frequent PVCs do not have LV dysfunction, suggesting heterogeneity in susceptibility, for which genetic factors could play a role. Thus, a patient who has PVCs with reduced LVEF may have idiopathic PVCs depressing LV function, an underlying cardiomyopathic process, or a combination of primary CM with ectopy contributing to depressed ventricular function. Assessment may be further complicated by difficulty measuring ventricular function in the presence of frequent PVCs.

Multifocal ectopic Purkinje-related premature contractions (MEPPC): *Multifocal ectopic Purkinje-related premature contractions (MEPPC) is an example of a genetic syndrome with specific therapeutic implications. It was described near-simultaneously by four groups in 2012.[76,91,92] MEPPC is characterized by multifocal PVCs that have a relatively narrow QRS, consistent with an origin from the Purkinje system, and can produce ventricular dysfunction. It is due to specific variants in SCN5A that confer an unusual "gain of function" in the cardiac sodium channel. It has high penetrance in affected families. Recognition is important because pharmacologic therapy with sodium-channel blockers can suppress the PVCs with recovery of ventricular function if initiated sufficiently early in the disease.[93]*

Sustained Ventricular Arrhythmias

Sustained monomorphic ventricular tachycardia (SMVT): *Sustained monomorphic ventricular tachycardia (SMVT) is relatively uncommon among the general population of DCM, occurring in fewer than 1–3% of patients annually.[94,95] Much of our understanding of SMVT derives from the small number of patients with recurrent episodes referred for VT ablation. More than 90% of these VTs are due to scar-related reentry and fewer than 10% are due to bundle branch reentry involving the Purkinje system or a focal mechanism.[96] Ebert et al performed genetic testing on 98 consecutive patients with DCM, referred for catheter ablation of sustained monomorphic VT in the LV, finding pathogenic mutations in 38%, dominated by variants in LMNA and TTN, but also including PLN, SCN5A, RBM20, and DSP.[24] Genotype-positive patients had worse outcomes, with 81% having recurrent VT and 51% dying or requiring heart transplant during median follow-up of 28 months.*

VA have been a major component of the traditional ARVC criteria, with SMVT occurring in more than 40% of patients.[97] SMVT typically originates from areas of RV subepicardial fibro-fatty myocardial replacement giving rise to VA with a LBBB-like QRS (Figure 4A). LBBB-like VT with a superior frontal plane axis favors ACM over idiopathic VT, as it indicates an origin outside the outflow tract.[98]

Polymorphic VT/Ventricular Fibrillation: *Polymorphic VT/Ventricular Fibrillation occurs in ACM regardless of which ventricle is most affected, and in HCM. A variety of*

mechanisms associated with electrophysiologic remodeling in hypertrophy and heart failure may be involved. Genetic cardiomyopathies are associated with arrhythmogenic mechanisms linked to calcium handling and other electrophysiologic perturbations.[99] Some appear to be due to scar-related reentry[100] or associated with rapid activity in the Purkinje system driving the ventricle into fibrillation.[101] The polymorphic VT torsade de pointes associated with QT prolongation also occurs, typically in association with other factors prolonging the QT interval such as hypokalemia from diuresis, bradycardia, and QT-prolonging drugs. Polymorphic VT or VF with HCM cardiomyopathy may result not only from the myofibrillar disarray but also from ischemia, particularly with exercise, related to the excess myocardial oxygen demand and the abnormal coronary vasculature that commonly accompanies HCM.

Phenotypes of Genetic CM

The diagnosis and treatment of cardiomyopathies have traditionally focused on their classification as hypertrophic (HCM), dilated (DCM), and restrictive (RCM), based on left ventricular morphology and function (Table 2). In contrast, arrhythmogenic cardiomyopathies (ACM) are instead defined by the prominence of VA in the clinical presentation and further classified by the ventricle most affected.[102] (Figure 3). Arrhythmogenic cardiomyopathy with dominant LV involvement (ACM-LV) is usually associated with the phenotype of DCM (Table 2) and occasionally with RCM, while structural RV abnormalities of ACM with dominant RV involvement are more variable. Some degree of involvement of both ventricles is common, particularly with desmosomal disease.[102]

The rapid acceleration of genetic testing has outpaced our techniques to identify and track the associated phenotypes to inform prognosis and management. The layering of phenotype and genotype is further complicated by overlaps between the major types of CM (Table 2).

Hypertrophic CM Phenotype

Hypertrophic cardiomyopathy (HCM) can present with AF, syncope, or resuscitated SCD. The morphologic phenotype, as described in Table 2, hinges on LV wall thicknesses and patterns of hypertrophy.[103] The prevalence of genetic HCM, typically an autosomal dominant disease, is currently estimated at 1/200–250 adults, about twice as high as phenotypic prevalence.[104] Multi-center data in almost 6000 patients confirms the impression of higher clinical penetrance in men.[105] However, once diagnosed, women appear to have similar age-adjusted rates of VA and higher rates of progressive HF and mortality than men.[106]

HCM Genotypes—HCM was the one of the first cardiomyopathies to be linked to a specific mutation, the missense variant R403G in MYH7 in a large French-Canadian family.[107] Pathogenic variants are identified in about 60% of HCM, with about 1500 mutations in at least 11 genes.[108] *MYH7* and *MYBPC3* account for about 80% of those identified, with another 10% in other proteins of the sarcomeric complex. A second causal gene is present in about 5% of patients, who typically have more severe disease. However, more data is needed in non-white populations, where variant frequencies and

interpretation differ. For example, benign variants were misclassified among Americans of African ancestry,[109] and variants of unknown significance predicted to be deleterious were enriched among Singaporeans of Chinese ancestry with HCM.[110]

Implications of HCM Genotype: Genetic testing can help to distinguish HCM from the athletic heart, long-standing hypertensive heart disease, and the look-alike phenocopies (Table 2). In a meta-analysis and in a large prospective registry, the presence of sarcomeric variants in HCM was associated with earlier onset of disease and up to 2-fold higher rates of AF and VA/SCD than sarcomere-negative HCM.[108,111] Risks were intermediate for patients with variants of unknown significance (VUS).[111] Higher event rates were seen with *MYH7* variants than *MYBPC3* variants. A study of 80 patients with thin filament mutations showed less LV hypertrophy and a lower prevalence of outflow tract obstruction, but similar rates of VA and SCD, and higher progression to late- stage heart failure compared to 150 patients with thick-filament mutations.[112] It is increasingly apparent, however, that the implications will often depend more on the specific variants than on the genes affected. Recent work with mouse models of two different c*TNNT* mutations causing HCM revealed opposite responses to reducing CAMKII activation, with potential variant-specific implications for prevention of both disease progression and SCD in human HCM.[113]

Particularly in young athletes. syncope or cardiac arrest can be the presentation of HCM in asymptomatic patients, which can result from primary polymorphic VT/VF, ischemic arrhythmias, or from hemodynamic consequences of dynamic outflow obstruction. Recommendations for ICDs are guided by risk factors for sudden death as noted in Table 1, and also by a multi-component risk score that yields an estimated annual risk for discussion with patients.[114]

A new therapy targeted to decrease hypercontractility in HCM, mavacamten inhibits myosin ATPase activity and will soon be available to treat symptoms of outflow tract obstruction and improve exercise capacity in obstructive HCM.[115] It is not yet known how the specific genetic variants will influence clinical responses to mavacamten, but studies with human induced pluripotent stem cells demonstrated more response to mavacamten with an *ACTC1* variant than with a variant of the more commonly implicated *MYH7*.[116]

Sarcomeric variants causing the HCM phenotype generally share effects leading to hypercontractility, impaired relaxation, and high energy expenditure, typically with hypersensitivity to calcium. Some of the same variants can cause a restrictive CM (see below) with features overlapping with HCM. Sarcomeric variants associated with DCM generally affect different sections of the sarcomeric genes, causing decreased calcium sensitivity, decreased contractility, and eventually the dilated LV with low LVEF.[117]

Dilated Cardiomyopathy Phenotype

Dilated cardiomyopathy (DCM) can present with AF or VA, less commonly conduction disease. The phenotype is generally defined by decrease in LVEF and/or increase in LV volume or dimension (Table 2),[104,118] and usually excludes structural causes such as myocardial infarction and primary valve disease. Historical estimates of 1/2500–10,000 prevalence have been revised, currently up to 1/250–1/400 adults.[104] The U.S. DCM

Consortium of 25 U.S. HF programs studied 1220 patients meeting criteria of both LVEF < 0.50 and LV end-diastolic dimension of   95th percentile, and their first-degree relatives available for study,[119] revealing absolute rates of 11% incidence of familial DCM (defined as LV with *both* criteria in a first-degree relative), and a higher rate of 24.1% using an expanded definition including *either* criterion.) Models extrapolating to complete families yielded estimates of 29.7% with familial DCM meeting both criteria and 56.9% by either criterion. Prevalence of genetic cause of DCM by the narrow definition was higher in Black probands, 39.4% versus 28%, without difference between Hispanic and non-Hispanic ethnicity.

DCM Genotypes—Pathogenic variants have been found in 20–50% of genotyped populations with DCM, usually with rates 1.5 to 2-fold higher in subgroups with a positive family history.[120,121] Positive genotypes are also more common in patients who have arrhythmias at presentation (Figure 5). Unrecognized viral myocarditis has likely been over-implicated as a cause of DCM, as the path of post-viral DCM has been difficult to follow in human studies, although extensively investigated in animal models. LGE on CMR that was at one time considered evidence of myocarditis is now increasingly recognized as typical of genetic CM, as discussed above.

DCM is associated with the largest sets of implicated genes, often 40–50, among which the prevalence of specific variants varies across regions.[122] Many variants are now being re-scrutinized as too common in the unaffected population or insufficiently linked to CM by accumulating data. Two recent large series suggest that fewer than 20 genes are clearly implicated.[25,123] Variants in *TTN* and the sarcomeric proteins together account for up to half of positive testing in patients with DCM. Examples of other variants commonly cited as causing DCM are shown in Table 3.

Implications of Genotype for DCM—In contrast to variants causing HCM, some of the specific genes identified for DCM are consistently linked to higher likelihood of VA, disease progression, and death. In the large series from Maastricht assessing arrhythmias at the time of first CM evaluation, the adverse impact of genetic etiology on DCM outcomes was mediated primarily through increased risk associated with arrhythmia phenotypes, defined as AF, conduction disease, or VA at initial evaluation.[25] In another recent series of 487 patients with DCM, pathogenic variants in *LMNA* and desmosomal proteins were associated with increased risk of ventricular arrhythmias and sudden death, while other variants were associated with outcomes similar to DCM without an identified pathogenic variant.[121]

Many Titin Variants—Although they are not among the most frequent causes of ACM, attention is focused on *TTN* variants due to their frequency in DCM. *TTN*, the largest gene in the body, encodes titin, the largest protein in the body and an integral part of the sarcomeric complex. Extending from the Z disc to the M band, titin is involved in force transmission, cell organization, and signaling. While variants in titin are much more common than for other CM genes, the variant frequency is similar when normalized for size.[122] Because the gene is so large, and therefore missense variants so common, genetic studies to date have focused on truncating variants. Truncating *TTN* variants account for

12–25% of pathogenic variants implicated in DCM, up to 25% in familial CM and 18% of patients without family history.

Truncating *TTN* variants considered pathogenic have also been described in 2–3% of normal subjects without known cardiac disease, raising the likelihood that CM attributed to some variants may in fact be coincidental to another cause or a different pathogenic variant.[104] In a multi-national study of 639 patients with DCM, 44% of patients with *TTN* variants implicated as causal also had pathogenic variants in another DCM gene.[122]

TTN is commonly implicated in a "two-hit" cardiomyopathy, developing in the setting of an acquired insult (or another CM pathogenic variant); common clinical settings in which *TTN* variants appear to increase CM risk include postpartum, heavy alcohol use, and cancer chemotherapy. Favorable reverse remodeling with major LVEF improvement after initiation of recommended HF medications occurred in 69% of patients in the large study above, a higher rate than the 30–40% expected in general DCM.

The *TTN* variants exemplify a DCM phenotype in which systolic dysfunction usually dominates the clinical picture, with mean LVEF already reduced to 0.30 at diagnosis.[125] The most common presenting symptom in 537 patients was dyspnea, 21% presenting with palpitations and about 10% of patients with AF.[126] By the end of almost 10 years, 30% with *TTN* variants had developed AF, 45% had NSVT, and 9% had experienced sustained VT.[127] VA occurs rarely in the absence of marked left ventricular dysfunction, but LVEF, LGE, and NSVT all predict both HF and arrhythmic events, as does family history. Although not common, there are *TTN* variants with a high VA/SCD rate consistent with ACM.

Arrhythmogenic Cardiomyopathy With Dominant LV Involvement

VA occur commonly during progression of any dilated LV cardiomyopathy. However, pathogenic variants causing VA early in the course of CM are increasingly recognized. Current estimates are that about 30% of genetic DCM is associated with high risk for VA that can occur before prominent LV dilation or dysfunction,[121] but estimating the prevalence of ACM with dominant LV involvement has been hindered by lack of a consistent definition.[102] Most commonly implicated are *LMNA* and desmosomal proteins (Table 2), which together account for about 10% of all DCM patients; *RBM20* and *SCN5A* occur in about 2% each, and *FLNC* and *DES* occur in about 1% each.[128]

Lamin A/C—Pathogenic *LMNA* variants are identified in 4–8% of DCM, with "laminopathies" considered among the most malignant and highly penetrant ACM.[24,129] Differential splicing of the single lamin gene produces lamin A and lamin C, which are nuclear envelope proteins involved in regulation of DNA replication, gene expression, replication, mechanosignaling, and cytoplasmic transport. *LMNA* mutations causing cardiomyopathies can also involve skeletal muscle, such as with Emory-Dreifuss or limb-girdle dystrophy, amd are also associated with familial partial lipodystrophy.

Arrhythmias are frequently the first presentation of *LMNA* cardiomyopathy (Figure 3), often preceding the diagnosis of DCM. The most common initial rhythms are AV block or AF, but life-threatening VA can be the presentation. At first VA, mean LVEF was 0.42±0.15, while

25% of patients still had LVEF greater than 0.50. By 7 years after diagnosis, over half of patients had AV block, over half had AF, and a third had sustained VA.[63]

The risk of developing sustained VA was 3-fold higher for male sex or LVEF < 0.50 at presentation, 2.5-fold higher with non-missense mutations. Due to the high incidence of VA, the recommended indication for primary prevention ICD in the presence of *LMNA* mutation is the presence of at least 2 risk factors: male sex, non-missense variant, NSVT or LVEF < 0.45 (Table 1).[32] LVEF < 0.50 at presentation was associated with almost 5-fold risk of end-stage HF and many patients undergo heart transplantation.[63] Mitogen-activated protein kinase signaling has been implicated in the pathogenesis of LMNA disease (and perhaps other DCM), and a clinical trial of p38 MAPK inhibition is currently ongoing in patients with LVEF < 0.50.[130]

Desmoplakin And LV Desmosomal CM—*DSP* accounts for about 4% of variants causing ACM-LV and is traditionally grouped with other proteins of the desmosomal complex, which connects the myocytes with each other and also contributes to structure and function within the cell, discussed below. However, unlike the other desmosomal proteins, the VA, fibrosis, and depressed ventricular function with *DSP* variants are often dominated by LV involvement.[102]

A recent multi-center series reported 107 subjects with pathogenic desmoplakin variants.[131] Of those with decreased ventricular function, 79% had predominant LV involvement, among whom 31% also had decreased RVEF. The Arrhythmogenic Task Force criteria from 2010 for ARVC[33] were met in only 42% of desmoplakin patients with LV dominance and 57% of those with RV dominance of *DSP* disease. LGE was seen in 74% of patients with LV involvement (Figure 1B), usually sub-epicardial in the inferior wall and occasionally associated with intramural fat. Cutaneous findings of palmoplantar hyperkeratosis and curly hair seen in the autosomal recessive Naxos disease, as described below, are also prominent with the autosomal dominant desmoplakin disease of the LV and may be overlooked in patients who use hair-straighteners.[131]

As discussed above, presentations consistent with acute myocarditis, which can include VA, chest pain and troponin elevations, are described with other desmosomal disease[18,19] but may be particularly common with desmoplakin.[19,131] These patients often have sub-epicardial LGE initially, but may not return with VA or the DCM phenotype until years later.

Patients with LV dominant disease often present in their thirties. Half of VA/SCD events occur in patients with LVEF > 0.35 and 15% with LVEF > 0.55.[131] Current indications for primary prevention ICD with desmosomal disease have focused on traditional ARVC criteria, and exclude many patients with ACM-LV with *DSP* variants, who nonetheless merit special consideration to prevent sudden death before the LVEF is less than 0.35 (Table 1). Although exercise restriction is recommended for desmosomal disease with predominantly RV involvement, as described below, the association of strenuous exercise with earlier and more severe disease has not been established for desmoplakin disease in the LV, perhaps because the LV is less distended than the RV during exercise.[132]

Filamin C—*FLNC* is a recent addition to genetic CM panels, so the 1% prevalence described is likely to increase. Considered a cytoskeletal protein, filamin-C stabilizes polymerized actin and anchors membrane proteins to the cytoskeleton in both skeletal and cardiac muscle. Strong evidence associates variants in *FLNC* with DCM and the skeletal myofibrillar myopathies, but CM often occurs without recognized skeletal myopathy.[133] This ACM usually has an LV dominant phenotype but occasional biventricular and RV dominant phenotypes can occur.[134] Missense variants in *FLNC* have also been associated with both HCM and RCM phenotypes, suggesting a wide spectrum of cardiac disease.[135]

FLNC may present with AF, conduction disease, or VA prior to a diagnosis of CM.[134] Both the arrhythmogenic phenotype and the potential for bi-ventricular involvement are shared by FLNC and desmosomal cardiomyopathies (Figure 3), although the pathogenesis appears distinct. Both are also characterized by a sub-epicardial location of LGE, sometimes in a ring-like pattern.

Patients with truncating variants in *FLNC* have a cumulative 15–27% incidence of major VA or SCD events over 5-year follow-up,[121,136] which is similar to rates for LMNA and DSP for both probands and carriers. The risk of VA correlated with frequent PVCs and NSVT on ambulatory monitoring, and with the degree of LGE but not with LVEF.[137,138] ICD recommendations in the HRS Expert Consensus Statement[2] include *FLNC* with LVEF 0.45 (Table 1). Although LVEF remained stable during 5-year follow-up in most patients, 22% progressed to end-stage HF, most of whom had lower LVEF at presentation.

RNA binding-motif 20—Variants in this RNA-splicing factor gene *RBM20* are implicated in 2–3% of familial DCM.[139] This protein modulates RNA splicing for over 30 genes,[140] including those coding for titin, sarcomeric proteins, and proteins involved in calcium handling. The resulting variants of these gene products have been implicated in systolic dysfunction but other pathways are likely involved also, particularly with regard to calcium handling and VA.

RMB20 variants have shown high penetrance rates of 66%–96% and earlier age at presentation than for general DCM populations or for titin CM. Among index cases in a multicenter series of 74 patients, family histories of CM were present in 72% and of SCD in 51%.[141] VA/SCD events have been reported in 20%–44% of patients with *RBM20* variants[99,141,142] compared to 2.2% in an unselected CM registry.[138,141] VA event rates with RBM20 are similar to those with *LMNA* disease[63] and also often occur with EF > 0.45, as in 1/3 of an international series of 74 *RBM20* patients reported by Parikh et al. Special consideration for ICD implantation may thus be warranted for *RBM20*, as it is for *LMNA* (Table 1).

Data emerging from studies in pluripotent stem cells and from *RBM20* knock-out mice suggests that abnormal calcium handling may contribute to intracellular calcium overload and the VA phenotype. This might eventually provide a target for therapy of ACM with *RBM20* variants, and potentially for other CM, through modulation of calcium homeostasis.[143]

Phospholamban—Phospholamban (PLN) is a transmembrane protein of the sarcoplasmic reticulum (SR) membrane. Until phosphorylated, PLN inhibits the SR ATPase (SERCA2) from transporting calcium back into the SR, with greater inhibition by the DCM-associated variants.[144] The R14del *PLN* founder mutation accounted for 13% of 240 Dutch patients with DCM and also 12% of Dutch patients with arrhythmogenic RV cardiomyopathy[145], but occurs in less than 1% of DCM in other regions. PLN cardiomyopathy is associated with marked fibrosis in the LV posterolateral wall and occasionally with fibro-fatty infiltration of the RV that qualifies as ACM-RV.[146] Malignant VA can occur before LVEF is severely reduced and progression to heart transplantation is frequent. A pathogenic *PLN* variant is a current indication to consider early ICD placement.

The complex role of SCN5A variants in multiple arrhythmias and CM is discussed above with the specific arrhythmias.

Arrhythmogenic Cardiomyopathy With Dominant RV Involvement

The major hallmark of arrhythmogenic CM with dominant RV involvement is the predominance of VA events rather than the variable abnormalities in RV morphology or function. ARVC was initially described as a cause of sudden death in athletes in Italy.[147] The first gene was identified in families on the Greek island of Naxos, in whom SCD was frequent and associated with "woolly hair" and hyperkeratosis of the hands and feet. The RV was dilated with areas of thinning and replacement by fat. The Naxos syndrome, which is autosomal recessive, is caused by mutations in *JUP*, encoding for plakoglobin, a protein of the desmosomal complex. Variants in genes encoding other components (*PKP2*, *DSP*, *DSG2*, *DSC2*) are also well-recognized causes of desmosomal disease affecting predominantly the RV. Variants in other genes such as *RYR2* have occasionally been associated with similar phenotypes.[148]

The prevalence of CM by ARVC criteria is currently estimated at 1/2000–5000 adults.[149] In a transatlantic study of 439 probands meeting this criteria, pathogenic variants were identified in 63%, up to 89% with positive family history. Plakophilin (encoded by *PKP2*) was the most common desmosomal protein implicated, accounting for 74% of identified variants; others were desmoplakin (*DSP*) 4%, desmoglein (*DSG2*) 6%, and desmocollin (*DSC2*) 2%, and only 2 patients had variants in plakoglobin (*JUP*), which are rare outside Mediterranean countries. Coexistence of multiple variants, identified in 4–16% of desmosomal cardiomyopathies, have been associated with earlier and more severe disease.[150]

Desmosomal Disease of the Right Ventricle—The desmosome is a structure that bridges the cell membrane and connects the myocytes with each other. It also contributes to the structure and integration of functions within the cell. Disruption of the desmosomal structure can lead to cell separation and death. Because desmosomes are also central to integrity of connective tissue, some pathogenic variants are associated also with the distinctive findings of the hair and skin, as discussed above. The progressive fibro-fatty deposits within the myocardium may be replacement for lost myocardial cells but have also been proposed to result from effects of displaced plakoglobin to alter nuclear signaling for

stem cells,[151] resulting in differentiation into adipocytes and fibroblasts in areas that may represent substrate for frequent PVCs and reentrant VT.

RV dilation and dysfunction are often present but visualization can be difficult. Abnormalities of the RV on the ECG and echo imaging are a prominent part of the original criteria for ARVC, later revised to also include genotype.[33] Although myocyte disconnection and damage are seen on pathologic examination, myocyte loss may be limited, and few patients progress to end-stage HF of either ventricle. The reason for predominant RV involvement with desmosomal disease is uncertain, but greater vulnerability of the thin RV myocardium to mechanical and hemodynamic stress, particularly during the ventricular dilation that occurs with exercise, has been postulated.[132] Models of desmosomal disease show early and more severe RV dysfunction and fibro-fatty replacement when the animals perform frequent exercise.[152] Clinical presentation in affected families with the RV phenotype occurs earlier with greater severity for relatives who engage in high-level exercise.[153]

Patients with desmosomal ACM affecting the RV often present in their 30s. In a series of 1001 patients and family members, 61% of probands presented with sustained VA.[149] Some patients present first with very frequent PVCs. Sustained VA occurred in 72% of patients during mean 7-year follow-up; sudden death occurred in 16% of patients without ICDs compared to < 1% in those with ICDs. Indications for ICD are based on the ARVC disease criteria[105] and specific risk factors for VA[4] (Table 1).[154] The course is usually dominated by VA, as symptomatic HF developed in only 13% of index cases in this large series, with only 4% going to heart transplantation.

Although most patients with arrhythmogenic CM have a phenotype dominated by one ventricle, disease is often present in both ventricles, particularly with the desmosomal variants. Early pathologic studies demonstrated some fibro-fatty involvement of the LV in 76% of patients with dominant RV disease whose hearts were examined after death or transplant.[155] Using CMR, a more recent study in 89 patients meeting criteria for ARVC showed LV LGE in 67% of patients, of whom most have detectable decrease in LVEF.[4] Conversely, evidence of RV involvement was found in 31% of patients with predominant LV involvement with *DSP* mutations.[156] Bi-ventricular involvement has also been found with variants in other ACM genes such as *PLN* and *FLNC*.

Restrictive Cardiomyopathy Phenotype

Unlike HCM and DCM, the phenotype of restrictive cardiomyopathy (RCM) has variable morphology and is defined instead primarily by diastolic dysfunction on echocardiography and elevated filling pressures during hemodynamic evaluation. RCM typically presents with mildly reduced LVEF, which is encompassed within the newly categorized "Mid-range LVEF" from 0.40–0.50, but this EF range should not be considered a specific phenotype. The LVEF of 0.40–0.50 is instead the intersection of many conditions including DCM which is deteriorating or improving into remission, and HCM with "burn out", as well as RCM and mildly decreased LVEF from structural heart disease (Table 2).

Aside from systemic metabolic diseases and hemochromatosis, the major genetic cause of RCM arises from variants in transthyretin *(TTR)* causing amyloid cardiomyopathy (ATTR-CM). Three ATTR-CM variants, Val122Ile associated with African descent, Thr60Ala often with concomitant neuropathy, and Val30Met with early neuropathy have been best characterized.[51] Both AF and conduction disease may present prior to recognition of amyloidosis as previously discussed. VA are relatively uncommon and small series have not demonstrated benefit of ICDs. Tafamadis, a stabilizer of the *TTR* tetramer, has slowed progression of both cardiac disease and neuropathy, and decreased mortality by 30%.[157] Patisiran, an siRNA agent and inotersen, an antisense oligonucleotide, target hepatic production and reduce circulating *TTR* by over 85%.[158] Early diagnosis directly impacts treatment benefit, as benefits of these therapies have been limited to those with few cardiac symptoms at presentation.

Although most RCM is due to acquired causes or to amyloidosis, genetic disease is increasingly recognized in the remaining cases. Sarcomeric genes are most commonly implicated, particularly those of the thin filaments and associated proteins.[159] HCM and RCM can exist with the same sarcomeric variant in different members of the same family.[160] The RCM phenotype is seen with *DES* mutations and associated skeletal muscle involvement, and has occasionally been reported with *FLN-C* variants.

Skeletal Myopathies

Heritable myopathies are a heterogeneous group of disorders that can be accompanied by CM, arrhythmias, and conduction disease. Cardiac involvement varies in onset and severity, but is occasionally the early or dominant presentation when neuromuscular manifestations are mild. Multiple genes causing CM are associated with variable degrees of skeletal myopathy (Table 3).

The most common myopathy is myotonic dystrophy type I *(MD1)*, due to expansion of an unstable trinucleotide repeat in the *DMPK* gene, in which the number of repeats and clinical severity increases from generation to generation.[161,162] Severe conduction defects, VA, and SCD may appear early in disease, but late sudden deaths are usually attributed to respiratory events[163,164] and only 10% of patients with adult-onset disease progress to reduced LVEF.

Emery-Dreifuss muscular dystrophy is due to mutations in one of several genes encoding nuclear envelope proteins. X-linked disease due to mutations in *EDMD1*, is associated with atrioventricular conduction defects, AF, and atrial standstill that can precede overt CM and neuromuscular symptoms.[165–167] Autosomal dominant Emery-Dreifuss disease and limb-girdle muscular dystrophy can both occur with *LMNA* variants, conferring high risk of arrhythmias as for other laminopathies (Figure 3).[168] Desmin *(DES)*-associated myopathy is an autosomal dominant myofibrillar myopathy that may present with prominent CM or arrhythmias, with AF and conduction disease common and SCD also described.[169]

In the Duchenne's and Becker's dystrophinopathies, the prevalence of arrhythmias generally parallels later progression of HF, which is commonly the mode of death.[120] Arrhythmias and conduction abnormalities are common with congenital syndromic myopathies and those associated with mitochondrial genetic syndromes, but rarely present early in disease.[170]

The Trait of Left Ventricular Non-Compaction

LV non-compaction (LVNC) is a morphologic description of prominent trabeculation of the LV above a thin compacted layer of myocardium, creating crypts that communicate with the LV cavity but not with the epicardial coronary arteries.[171,172] (Table 3) Areas of non-compaction can occur with abnormal embryologic development, but can appear later in life with CM and neuromuscular disorders, as well as in athletes, normal pregnant women, and up to 8% of normal subjects.[171] The trabeculation could represent a dynamic response to the intensity and regionality of wall stress, such as in HCM, where it is may function to prevent apical aneurysms.[173] Recent work has implicated variants in a member of the PR domain-containing family of transcriptional regulators (PRDM16) in development of both LVNC and DCM.[174] It has been suggested that this protein may direct myocardial adaptation to improve oxygenation in settings of chronic wall stress in athletes and pregnant women.[175] While LVNC is often listed as a separate CM phenotype, it may instead be considered a dynamic morphologic trait. The presence of LVNC in a patient with arrhythmias or CM may increase suspicion for underlying genetic CM, particularly with a positive family history. Current management of patients meeting LVNC criteria, however, is largely guided by the presence or absence of accompanying CM or arrhythmia phenotypes.

Implications of Identifying a Genetic Cardiomyopathy

The implications of identifying a pathogenic variant for CM after presentation with an arrhythmia depend upon the nature of the arrhythmia, the variant, and the current phenotypic expression of CM. With the goal of improving prognosis, the most common current consideration is the level of risk for SCD and whether to recommend implantation of a defibrillator. However, earlier identification of CM may also help to decrease CM disease progression. While the most effective therapies to stabilize CM are currently guided only by phenotype, gene-specific treatments targeting molecular etiologies are becoming available or in development.

Decisions Regarding Primary Prevention ICD

Patients presenting with life-threatening VA/SCD should be evaluated for an ICD as secondary prevention of SCD, regardless of genotype. For patients presenting with unexplained syncope, genetic variants associated with VA will lower the threshold for EP study or ICD implantation. For patients requiring pacemakers, adding defibrillation capability should be strongly influenced by genotype and phenotype.

For primary prevention of SCD with a DCM phenotype, an LVEF 0.35 is often the indication regardless of CM etiology (Table 1). However, genetic diagnosis and/or family history may trigger consideration *before* CM has progressed to an LVEF 0.35, and/or *before* waiting 3–6 months to determine the effect of HF medications on LVEF. Special consideration for early placement of a primary prevention ICD is currently an important consideration for pathogenic variants in *LMNA*, *FLNC* or *PLN*, and should be extended to other types of ACM, as discussed above. There are no randomized trials establishing ICD benefit in these subgroups; recommendations derive from scientific statements and expert consensus.[2,32] The presence and extent of LGE on CMR are increasingly linked with the

risk of VA/SCD in DCM and HCM. However, CMR may be less sensitive for assessing risk in those genetic diseases in which VA may arise from other mechanisms independent of the extent of myocardial fibrosis. ICD indications will continue to evolve both for implicated genetic variants and for other indicators of increased risk.

Although the family history cannot be relied upon to identify the presence of a known pathogenic variant, the risk of SCD with either DCM or HCM is higher in patients with a strong family history, even when the genetic variant has not been identified.[114,128] This is reflected in the guideline risk factors for HCM and as a Class IIb indication for a primary prevention ICD in patients with other CM phenotypes and family history of SCD associated with CM.[34] This reflects the likelihood that sudden death risk is influenced by as yet unspecified genetic background beyond the implicated causative variant.

All consideration of ICD implantation requires discussion of risk/benefit discussion as part of shared decision-making. Decisions regarding risk of sudden death are strongly influenced by age and trajectory of both cardiac disease and general health. Women with CM have lower rates of sudden death, and patients reaching older age without arrhythmic events are generally at lower risk of life-threatening VA, particularly with genetic CM. Patients with advanced left ventricular dysfunction, a heavy HF symptom burden, and frequent HF hospitalizations are increasingly likely to die from end-stage HF rather than from untimely VA. Indications for ICD are predicated on the anticipation that patients otherwise will live at least one year with good quality of life.[32,34]

Current Treatments to Modify Genetic CM Progression

Fibrosis and ventricular remodeling herald disease progression and worsening outcome, including arrhythmia burden, with all HF. For genetic variants associated with DCM, there is thus good rationale, without specific confirmatory data, to support early initiation of HF therapies before the LVEF falls to <0.40. A current trial in Netherlands is testing whether the mineralocorticoid receptor antagonist eplerenone will decrease progression of phospholamban CM.[176] Specific implications for therapy determined by genetic causes of DCM are currently limited, but include sodium channel blockers for the SCN5A variants associated with MEPPC.

For patients with HCM, a goal is to prevent progression of hypertrophy. A recent trial in asymptomatic carriers of sarcomeric mutations in HCM families showed that early initiation of valsartan diminished a composite score of disease progression.[177] As discussed above, mavacamtem is an allosteric modulator developed to inhibit cardiac myosin and diminish hypercontractility, shown to improve symptoms and cause reverse remodeling with decreases in LVH and left atrial size.[115,178,179] Intravenous enzyme replacement is routine for the HCM look-alike phenocopy, Anderson-Fabry's disease, with genetic defect in alpha-galactosidase A, which is now also treated with an oral chaperone protein, migalastat.[180] Genetic information can also help distinguish the HCM look-alike ATTR-CM, that has multiple targeted treatments as described above.

Counseling About Genetic Testing for Genetic Cardiomyopathy

The expansion of genetic testing further increases the need for qualified genetic counseling for probands and family members. Large gaps remain in the diagnostic yield for most genetic CM. Particularly with positive family history, a negative genetic test cannot rule out a genetic cause and serial screening remains important for first-degree relatives.[2,31,181] While a variant of uncertain significance (VUS) should usually not be used for clinical decision-making,[182] its identification challenges patient understanding of the risk, as it might later be re-classified. The American College of Medical Genetics and Genomics (ACMG) has promulgated criteria under which a VUS can be reclassified as pathogenic.[182]. Importantly, the identification of a rare variant in a CM-associated gene in a patient with a CM does not establish pathogenicity of that variant.

The impact of a positive test will vary according to the genetic results and implications for therapy, lifestyle, and future expectations. Discussion of potential risks will often be influenced by sex, as the penetrance and severity of genetic CM are generally lower for women than for men, as shown in a recent meta-analysis of genotype-phenotype association in DCM for most implicated genes.[183]

Genetic testing is recommended for first-degree relatives of a proband with a pathogenic variant for CM. A positive test can potentially have negative implications for asymptomatic individuals who do not yet carry a cardiac diagnosis. The Genetic Information Nondiscrimination Act of 2008 and the Patient Protection and Affordable Care Act of 2010 provide some protection from genetic discrimination for employment and health insurance in the United States, but in most states there are gaps in protection and the laws do not offer protection from discrimination regarding life, disability, or long-term care insurance.[184] A phenotype-negative patient may elect not to be tested, but should recognize that he/she may still carry a mutation and may still transmit a pathogenic variant to children.

Patient understanding of disease risk and the need for intervention reflects their risk perceptions, which are influenced by health literacy and numeracy. Words describing possible events as "common" and "rare" are interpreted differently by providers than by patients.[185] Numeracy may be low even in highly educated populations.[186] People have greater difficulty comprehending relative risk, so absolute risk should be used.[187] Fractions are confusing, so rates using rounded denominators such as X in 100 or X in 1000 may be understood better than proportions centered on a numerator of one, such as 1 in 384.[185] Strategies such as teach-back can encourage patients to share their perceptions of risks and benefits, identifying misconceptions that can be addressed.[188]

Expanding Implications of Genetic Testing to Guide Therapy

As new therapies emerge for genetic CM, potential benefits of genetic testing for patients and families will increase. The definition of mutation-associated disease mechanisms at the molecular level is increasingly enabling the development of mechanism-based therapies. One approach is to "repurpose" existing drugs for the new indication of DCM: examples include an *in vitro* study suggesting efficacy of lovastatin in LMNA cardiomyopathy.[189] Another is to develop novel "first in class" agents that target specific

molecular mechanisms in CM subtypes. Examples of new agents that were developed using this strategy and are now becoming available include the myosin inhibitor mavacamtem for patients with hypertrophic cardiomyopathy,[178] the myosin activator omecamtiv for advanced systolic dysfunction,[190] and tafamidis to stabilize mutant transthyretin in amyloid cardiomyopathy.[157] Inhibition of multiple kinases (JNK, ERK1/2, p38α MAP kinase) has been used to correct the DCM phenotype in mice with *LMNA* DCM[191] and a clinical trial is underway in humans using a p38 MAP kinase inhibitor for *LMNA* DCM.[192] *In vivo* gene editing using adenoviral delivery of CRISPR/cas9 constructs corrected the molecular defect in mice with dystrophin-related DCM.[193] In DCM caused by titin truncating mutations, correction of the truncation by CRISPR/cas9, or proteasome inhibition that reduced the amount of mutant protein, corrected the contractile defect in cardiomyocytes derived from induced pluripotent stem cells (iPSC-CMs).[194] An intron-mediated TTN enhancer that promoted cardiac-specific TTN expression in similarly-derived cardiomyocytes promoted normal TTN expression in mice.[195] Similarly, adenoviral mediated modulation of RNA splicing in iPSC-CMs with an HCM-associated *MYBPC3* mutation corrected the hypertrophic phenotype.[196] The first-in-human gene transfection with the *LAMP2* gene has been reported for 3 patients with Danon disease, a HCM phenocopy.[197]

Tools are now becoming available to better understand and address arrhythmias in genetic CM, such as better animal and cellular models coupled to gene editing, that raise the prospect that therapies specific to mechanism, gene, and mutation are on the horizon. Development of these therapies will be enabled by increased identification of mutation carriers and their phenotypic journeys, and further advances beyond the one gene - one disease paradigm.[73] The rationale to expand genetic testing thus extends from current management of patients and families to acceleration of an exciting future that holds promise for correction of their underlying molecular defects.

Sources of Funding

Abbreviations

ACM	Arrhythmogenic cardiomyopathy
ACM-LV	Arrhythmogenic cardiomyopathy dominant in LV
ACM-RV	Arrhythmogenic cardiomyopathy dominant in RV
ARVC	traditional term for arrhythmogenic cardiomyopathy as originally linked to desmosomal disease
AF	atrial fibrillation/flutter

ATTR-CM	transthyretin amyloid cardiomyopathy
CM	cardiomyopathy
CMR	cardiac magnetic resonance imaging
DCM	dilated cardiomyopathy
HCM	hypertrophic cardiomyopathy
HF	heart failure
LGE	late gadolinium enhancement
LVEF	left ventricular ejection fraction
NSVT	non-sustained ventricular tachycardia
PVC	Premature ventricular contraction
RCM	restrictive cardiomyopathy
SCD	sudden cardiac death
SMVT	sustained monomorphic ventricular tachycardia
VA	ventricular arrhythmias
VT	ventricular tachycardia
VUS	variant of unknown significance

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KEY POINTS

1. Genetic cardiomyopathy should be considered in patients who present with "idiopathic" arrhythmias, including atrial fibrillation, conduction disease, frequent PVCs and ventricular tachycardia.

2. The presence of an apparently acquired cause of cardiomyopathy or the absence of family history does not rule out genetic cardiomyopathy.

3. The 12-lead electrocardiogram, echocardiogram, enhanced cardiac magnetic resonance imaging, and sequencing can help to layer the clinical phenotype with the genotype for arrhythmogenic cardiomyopathies.

4. Sudden death can occur early in arrhythmogenic cardiomyopathy, before the ejection fraction is low.

5. The increase in genetic information and implications raises new challenges for genetic counseling and shared decision-making.

6. Genetic testing enables cascade screening, specific treatments for some subtypes, and evaluation of emerging targeted therapies.
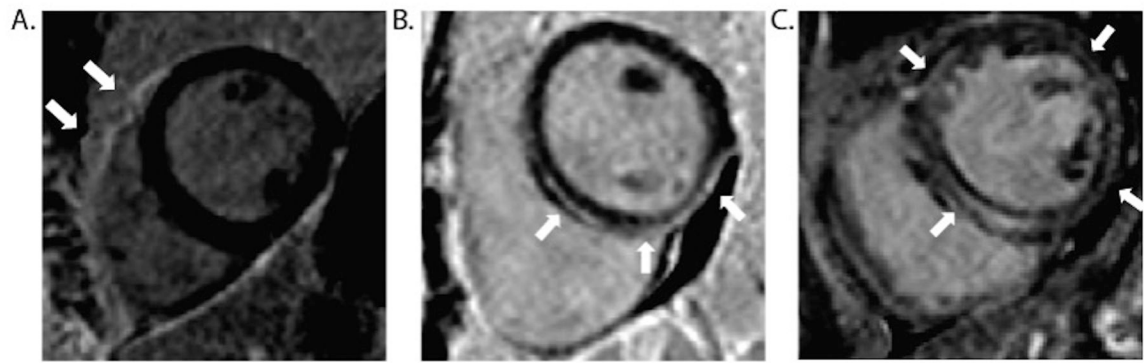
Figure 1.
Cardiac magnetic resonance (CMR) images of genetic CM showing typical patterns of late gadolinium enhancement (LGE). A. 39M with family history of arrhythmogenic right ventricular cardiomyopathy with pathogenic PKP2 variant. CMR showed normal function of the left ventricle (LV) and right ventricle (RV), with LGE of the anterior RV free wall (arrows) but no LGE in the LV. B. 21F pathogenic DSP mutation and family history of dilated cardiomyopathy, ventricular arrhythmias, and sudden death. CMR showed normal LVEF 0.58 with sub-epicardial LGE of the inferior LV wall, extending into the septum without separate RV involvement. C. 45M with atrial fibrillation and family history of dilated cardiomyopathy, CMR showed a ring-like pattern of intramural LGE in the LV. Genetic testing revealed a pathogenic LMNA variant.
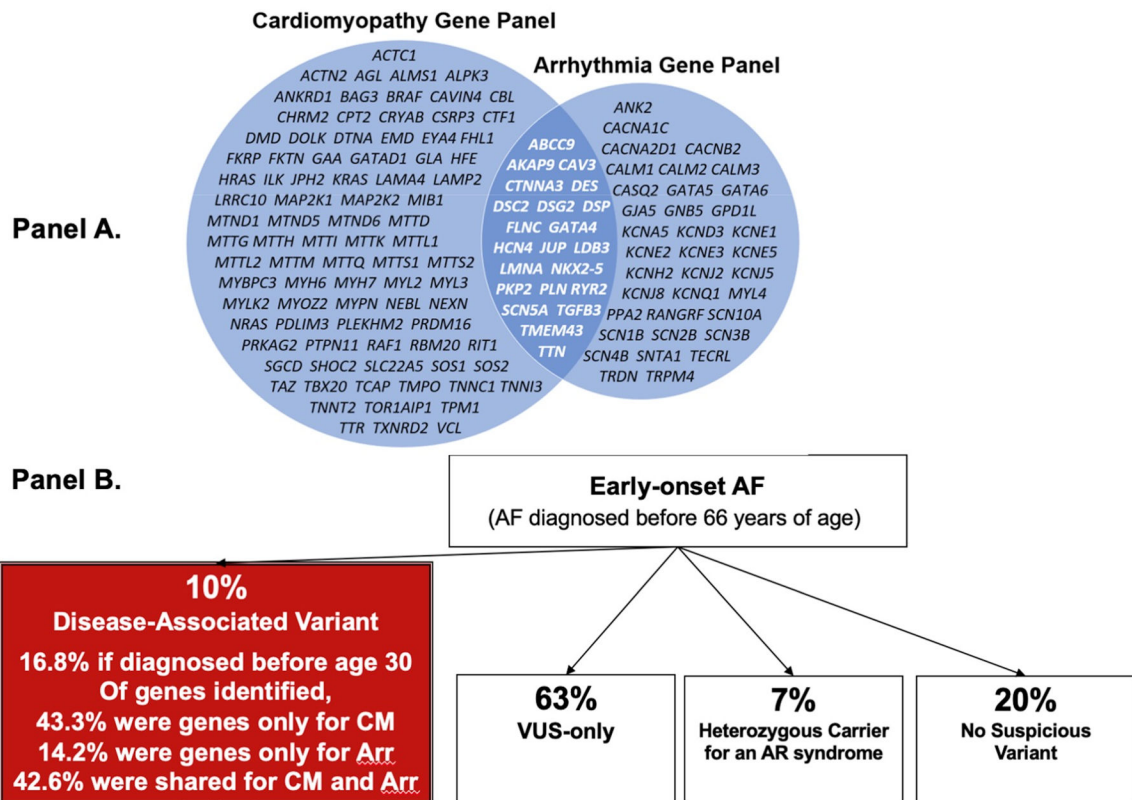
Figure 2.
Panel A presents the genes often included on comprehensive commercial panels for cardiomyopathy and arrhythmia genes, showing the overlap of genes most commonly implicated in both. **Panel B** presents the results from sequencing 1,293 participants with early-onset AF defined as AF diagnosed before age 65.[40] According to the genes listed in Panel A, 43% of disease-associated variants occurred in genes commonly included on cardiomyopathy panels, 14% in genes on arrhythmia panels, and 43% in genes included on both panels.

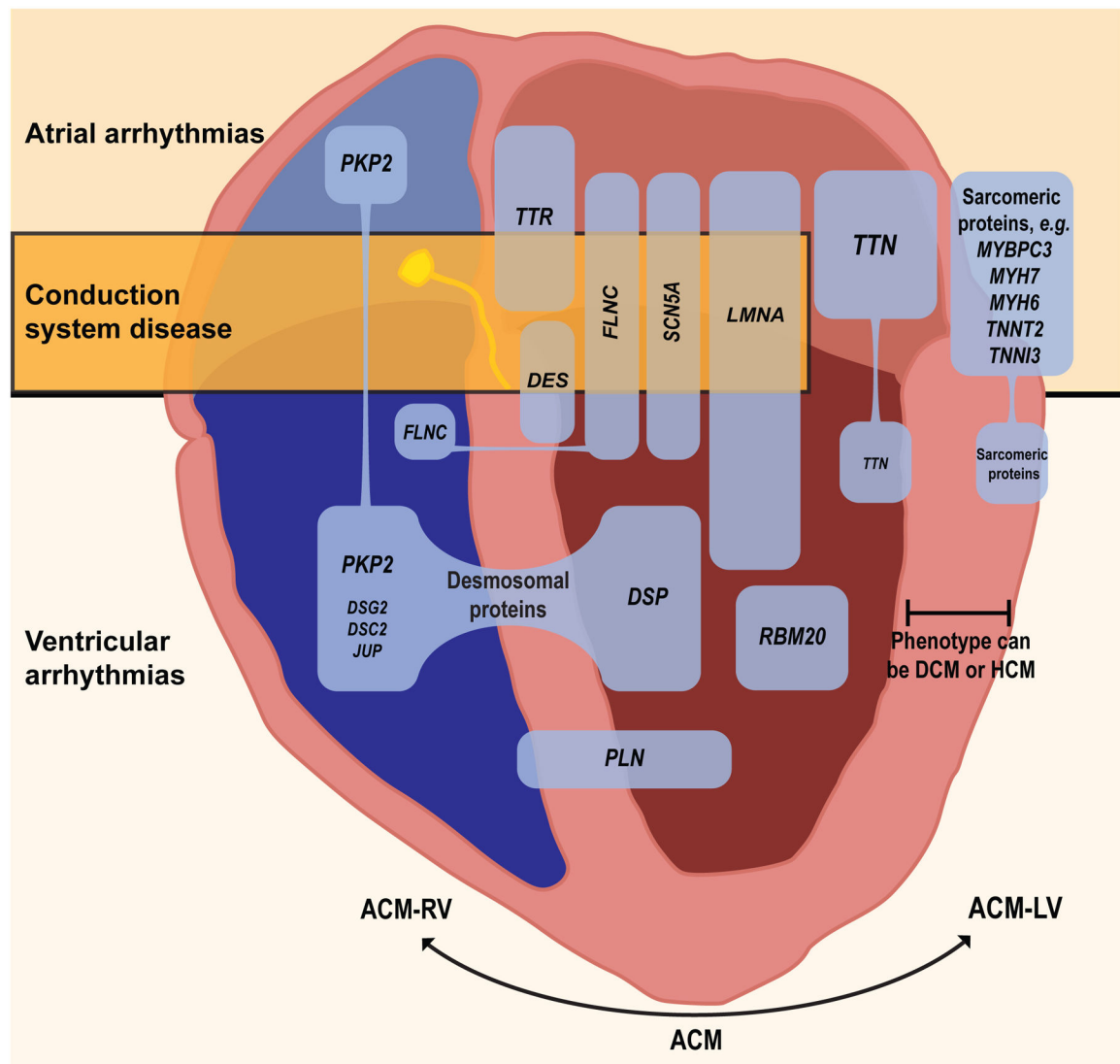CM = cardiomyopathy, Arr = arrythmia, AR = autosomal recessive

Figure 3.
Examples of selected cardiomyopathy genes commonly associated with atrial or ventricular arrhythmias or conduction disease. The common genes coding for titin and the sarcomeric proteins are associated with a large number of variants, many of which are implicated in atrial fibrillation, but a minority of which are associated with ventricular arrhythmias, and conduction disease is rare. Variants recognized in less common genes such as *LMNA* and *FLNC* are more consistently associated with ventricular arrhythmias and sudden cardiac death. Variants in genes for desmosomal proteins, phospholamban, and filamin-C can be associated with both RV and LV involvement. ACM= general term for arrhythmogenic cardiomyopathy, ACM-RV = arrhythmogenic cardiomyopathy with dominant RV involvement; ACM-LV= arrhythmogenic cardiomyopathy with dominant LV involvement, DCM = dilated cardiomyopathy, HCM = hypertrophic cardiomyopathy. (Illustration credit: Ben Smith).
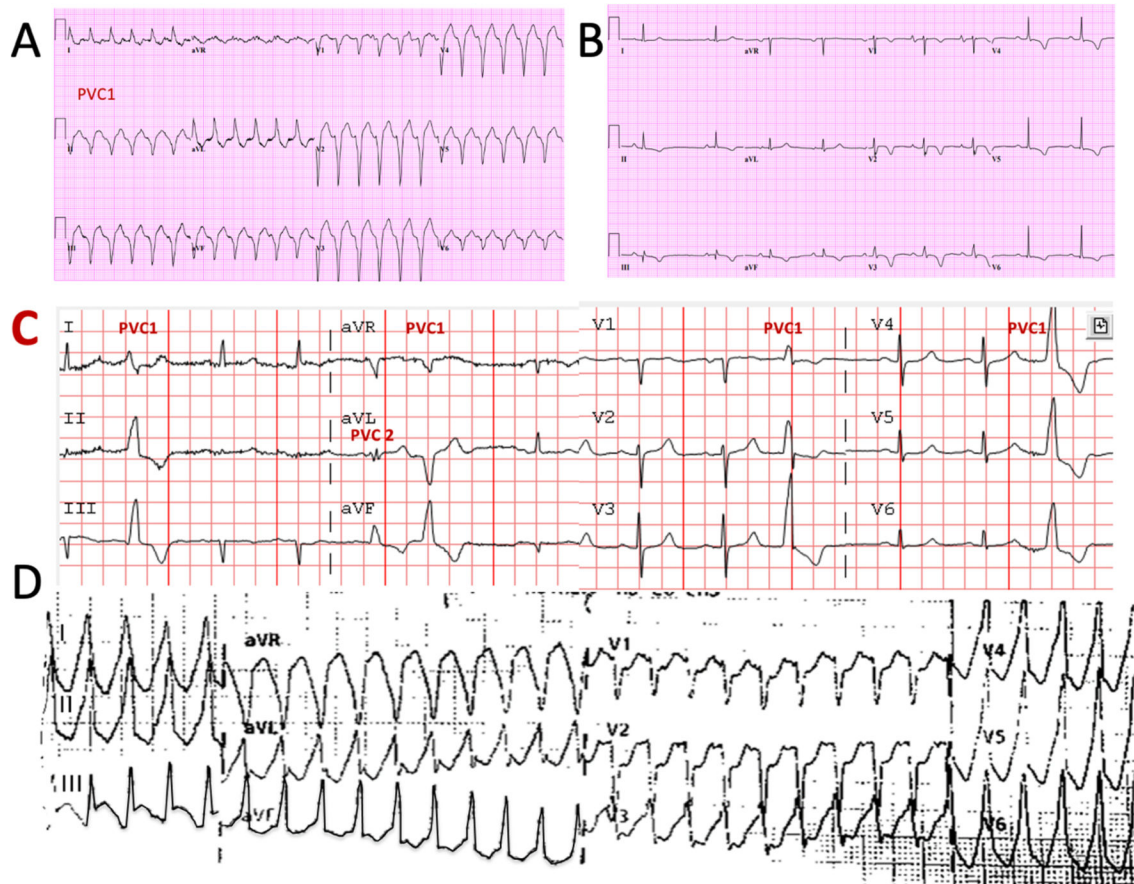
Figure 4.
Examples of 12-lead electrocardiograms (ECG) from 2 patients with arrhythmogenic cardiomyopathies **Panels A** and B are from a 53-year-old man with ACM-RV. Panel A shows SMVT with atrio-ventricular dissociation. V1 has a left bundle branch block-type configuration and the frontal plane is directed superiorly, consistent with a VT origin in the inferior RV. **Panel B** shows sinus rhythm ECG findings typical for RV disease with T-wave inversion in leads V1–V6 and inferiorly, and a slurred and prolonged terminal s-wave in V2. **Panel C** is from a 77-year old man with a long history of PVCs that had been considered benign in the absence of either known disease or concerning family history. The most frequent PVC (PVC1) has a right bundle branch configuration in V1 with dominant R waves across the precordium and inferiorly directed frontal plan axis, consistent with an origin in the periaortic LV. **Panel D** in the same patient shows the tracing during ventricular tachycardia, taken by paramedics after he presented with syncope. Genetic testing revealed a pathogenic *TTN* mutation.

ACM-RV=arrhythmogenic right ventricular dysplasia, LV= left ventricle, RV=right ventricle, SMVT = sustained monomorphic ventricular tachycardia
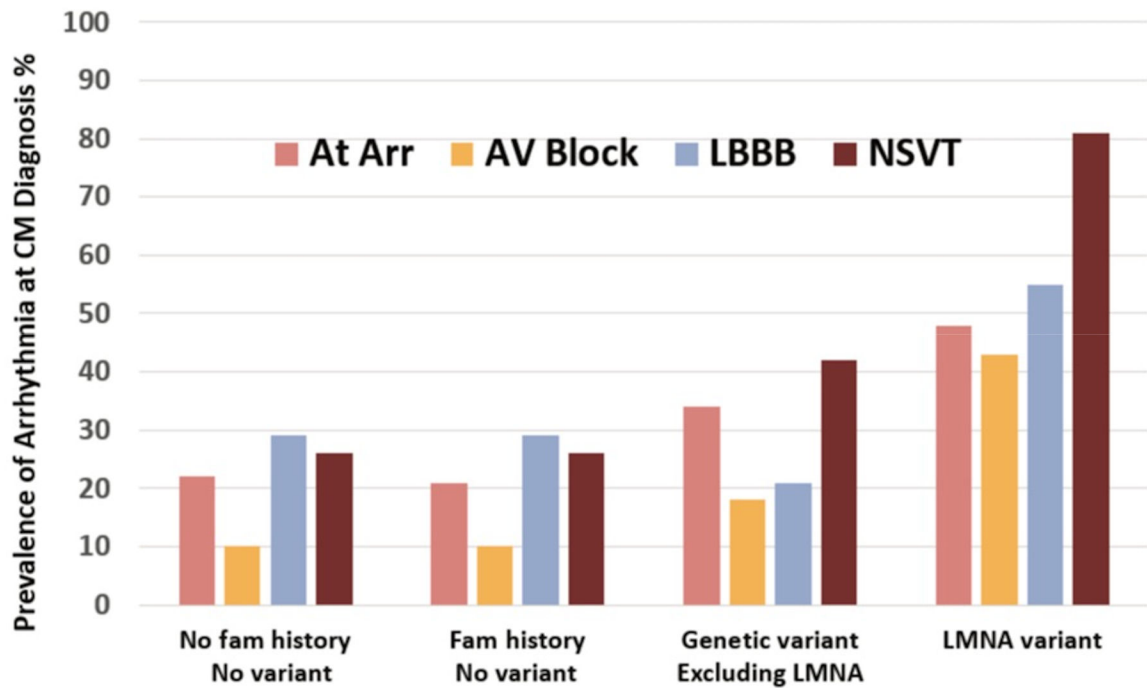
Figure 5.
Arrhythmias at the time of presentation for 689 patients with dilated cardiomyopathy in relation to the presence or absence of family history and identified pathogenic variants on genetic testing. At Arr = atrial arrhythmias, AV = atrioventricular, LBBB = left bundle branch block, NSVT = non-sustained ventricular tachycardia. Figure drawn from published data from the Maastricht Cardiomyopathy Registry, with permission from Verdonschot and Hunner.[25]

Table 1.

Recommendations for ICDs as Primary Prevention in Familial Cardiomyopathy

Phenotype	Recommended consideration for ICD	Level	Comments
Hypertrophic Cardiomyopathy	Single risk factor: Family history of sudden death Massive LVH (30 mm) Unexplained syncope LVEF < 0.50 LV apical aneurysm	IIa	From 2020 AHA/ACC Guideline for HCM[31]
	NSVT or LGE 15%	IIb	
Dilated Cardiomyopathy	Non-ischemic CM with EF 0.35, despite GDMT[**], and NYHA II-III symptoms of HF	I	From 2017 AHA/ACC/HRS Guideline for Management of Patients with Ventricular Arrhythmias and Prevention of Sudden Cardiac Death[32]
	LVEF 0.30 despite GDMT[**], NYHA Class I	IIb	
Specific genetic DCM when LVEF 0.35	Lamin A/C mutation with 2 risk factors: Male, LVEF<0.45, NSVT, Non missense variant	IIa	
	Lamin A/C 2 risk factors Male sex, LVEF < 0.45, NSVT	IIa	From 2019 HRS Expert Consensus Statement on Evaluation, Risk stratification, and Management of Arrhythmogenic Cardiomyopathy[2]
	Lamin A/C and pacing indication	IIa	
	Phospholamban LVEF < 0.45 or NSVT	IIa	
	Filamin C LVEF < 0.45	IIa	
Arrhythmogenic RV CM (ARVC)	(Resuscitated SCA, sustained VT[*]) or significant ventricular dysfunction with RVEF or LVEF 0.35	I	From 2017 AHA/ACC/HRS Guideline[32]
	3 major criteria, 2 major+ 2 minor, 1 major+ 4 minor criteria	IIa	From 2019 HRS Expert Consensus Statement[2] Major criteria: NSVT, inducible VT, LVEF 0.49 Minor criteria: Male sex, > 1000 PVCs/24 hours, RV dysfunction by 2010 criteria[33], proband status, 2 variants (cannot count both NSVT and PVCs.)
	2 major, 1 major+2 minor criteria, or 4 minor criteria	IIb	
LV Non- Compaction	NSVT associated with reduced LVEF	IIa	From 2019 HRS Expert Consensus Statement[2]
Neuromuscular disorders	Emery-Dreifuss and limb-girdle type IB dystrophies with progressive cardiac involvement	IIa	From 2017 AHA/ACC/HRS Guideline[32]
Examples of variants that can cause ACM for which there is no recommendation when LVEF 0.35 *RNA-binding motif 20 (RBM20)* *Type V voltage-gated cardiac sodium channel (SCN5A)* *Desmoplakin (DSP) ACM not meeting criteria for ACM-RV*			
Familial CM unspecified	Familial cardiomyopathy associated with sudden death	IIb	From ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities[34], and 2013 Appropriate Use Criteria for ICDs and CRTs[35]

[*]
Syncope and sustained ventricular tachycardia are considered to be secondary prevention

[**]
GDMT = guideline-directed medical therapy for at least 3 months

Table 2.

Phenotypes and Morphologies of Cardiomyopathies

Cardiomyopathy (CM) Phenotype	Diagnostic Criteria[54]	Other Morphology	Common Challenges in Diagnosis
Hypertrophic Cardiomyopathy (HCM) *Mid-range LVEF includes rare transition from HCM, "burn out" to LVEF < 0.50 (BOHCM)*	Septal thickness in men ≥ 15 mm ≥ 13 mm in women. 13-14 mm may be diagnostic in relatives of proband with known HCM or with positive genetic test. LVEF ≥ normal, usually > 0.60 LV chamber volume ≤ normal	Patterns of LV hypertrophy in HCM -Asymmetric septal hypertrophy -Inverse (sigmoid pattern) septal hypertrophy -Concentric LVH -Apical hypertrophy	Distinction from athlete's heart and severe chronic HTN, The storage diseases of *GLA* (Anderson-Fabry's), *PRKAG2*, and *LAMP2* (Danon's) which can mimic HCM morphology, Exclude aortic stenosis In older patients, exclude amyloidosis, which can also cause asymmetric septal thickening
Restrictive Cardiomyopathy (RCM) Least common CM phenotype	Functional diagnosis based on moderate-severe diastolic dysfunction and/or elevated cardiac filling pressures. Wall thickness often increased but can appear normal. LVEF usually mildly reduced, occasionally normal.	Usually marked atrial enlargement Although both ventricles affected, clinical RHF often dominates. Marked wall thickness suggests: -AMYLOIDOSIS -Inherited storage diseases -Inborn metabolic diseases	Common etiologies of radiation, connective tissue diseases, doxorubicin and other medications Some sarcomeric variants and storage diseases can appear with RCM as well as HCM phenotypes Although traditionally listed as restrictive, sarcoidosis more often has morphology of regional wall motion abnormalities, DCM phenotype or RV involvement with systolic dysfunction.
Mid-range LVEF is often a transition in DCM, either deterioration from early DCM or improvement into DCM remission **LV Dilated Cardiomyopathy (DCM)**	-Early: LVEF ≤ 0.50 and /or LVEDV > 112% normal for age/sex or LVEDD > 95% predicted sex/height - LVEF ≤ 0.40: threshold for traditionally recommended therapies for HF with low LVEF -Persistent LVEF ≤ 0.30-0.35: threshold for primary prevention ICD	Can involve LV alone or with RV involvement either from primary cause or from secondary RV failure due to chronically elevated pulmonary artery pressures	Structural heart disease such as coronary artery disease or infarction from other cause, primary valve disease
Arrhythmogenic CM Dominant in LV (ACM-LV) Usually DCM, Occasionally RCM	Morphologic criteria generally those for DCM. *Ventricular tachyarrhythmias dominate without or before severely reduced LVEF and heart failure.* Primary prevention ICD considered even when LVEF > 0.35.	Suggestive but not necessarily conclusive differences in patterns of late gadolinium enhancement between different variants Occasional ACM-LV with RCM phenotype	For frequent PVCs or NSVT, may be difficult to distinguish PVC-related CM from genetic CM causing both the arrhythmias and the CM.
Arrhythmogenic CM Dominant in RV (ACM-RV also termed ARVC) Bi-Ventricular Arrhythmogenic CM	Modified task force criteria from 2010 include combinations of major and minor criteria[33] *Ventricular arrhythmias and evidence of both ACM-RV and ACM-LV*	Abnormal RV function or structure *Bi-ventricular ACM often diagnosed from LGE in ventricle with less involvement*	Cardiac sarcoidosis can cause predominantly RV involvement with ventricular arrhythmias, RV wall motion abnormalities, aneurysms, and dilation
Trait of LV Non-Compaction (LVNC) Implications determined by CM phenotype and genotype.	Often assessed by maximum ratio of non-compacted/compacted LV myocardium > 2.3, and other criteria	Can occur with HCM, DCM, some dystrophies and other syndromic presentations	Can occur in normal hearts, pregnancy, Increased prevalence in athletic hearts

Midrange LVEF (0.40-0.50) — bracket spanning HCM, RCM, and DCM rows

ACM-LV Arrhythmogenic cardiomyopathy with dominant LV involvement, ACM-RV with dominant RV involvement

Shown within the bracket are the overlapping phenotypes contributing to "Mid-Range LVEF 0.40-0.50", a term which describes a heterogeneous group of patients rather than a phenotype with specific implications (see text).

Abbreviations: BOHCM = "burned out" HCM, LV = left ventricle, RV = right ventricle, LVEDV = LV end diastolic volume, LVEDD = LV end diastolic dimension, LVEF = LV ejection fraction

Table 3:

Genes Commonly Implicated in Genetic Dilated Cardiomyopathy

Pathogenic Variant with Moderate-Strong Association with DCM	Gene	Approximate prevalence in DCM	Other phenotypes	Association with ACM
Titin	*TTN*	12–25%	HCM (𝕞)	In small proportion of truncating variants
Lamin A/C	*LMNA*	4–8%	𝕞	High
Myosin heavy chain 7	*MYH7*	3–4%	HCM (𝕞)	Present
Troponin T2	*TNNT2*	2–4%	HCM	Present
Filamin C	*FLNC*	2–4% [**]	HCM, RCM, ACM-RV, 𝕞	High
RNA binding motif 20	*RBM20*	2%		High
Type V voltage-gated cardiac sodium channel	*SCN5A*	2–3%	Brugada syndrome	High for some variants
Desmoplakin	*DSP*	2%	ACM-RV, 𝕞	High
Phospholamban	*PLN*	< 1% [*]	ACM-RV	High
Bcl-associated athanogene 3	*BAG-3*	0.1–3% [**]	𝕞	Present [**]
Desmin	*DES*	< 1%	More often RCM 𝕞	High
Other Sarcomeric Proteins, e.g.: Myosin heavy chain 6 Tropomyosin Troponin C1 Myosin binding protein C3	*MYH6* *TPM1* *TNNC1* *MYBPC3*	Variable representation in DCM populations	HCM, 𝕞	Occasional variants implicated

ACM = arrhythmogenic cardiomyopathy, characterized by early and severe ventricular arrhythmias

ACM-RV = arrhythmogenic cardiomyopathy with dominant RV involvement

DCM = dilated cardiomyopathy phenotype, HCM = hypertrophic cardiomyopathy, RCM = restrictive cardiomyopathy

𝕞

= associated with skeletal myopathy

Associations between genotype and arrhythmia phenotypes vary due to relatively small series, referral center bias, and geographic heterogeneity.

[*] Higher prevalence of a founder mutation in Netherlands/Germany

[**] These genes were not routinely included in test panels until recently, so the prevalence and penetrance in DCM is not well-established.[25,120,124]