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Imaging Phenotype vs. Genotype in Non-Hypertrophic Heritable Cardiomyopathies: Dilated Cardiomyopathy and Arrhythmogenic Right Ventricular Cardiomyopathy

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Abstract

Advances in cardiovascular imaging increasingly afford unique insights into heritable myocardial disease. As clinical presentation of genetic cardiomyopathies may range from nonspecific symptoms to sudden cardiac death, accurate diagnosis has implications for individual patients as well as related family members. The initial consideration of genetic cardiomyopathy may occur in the imaging laboratory, where one must recognize the patient with arrhythmogenic right ventricular cardiomyopathy (ARVC) among the many with ventricular arrhythmia referred to define myocardial substrate. Accurate diagnosis of the patient presenting with dyspnea and palpitations whose first-degree relatives have lamin A/C cardiomyopathy may warrant genetic testing1, 2 plus imaging of diastolic function and myocardial fibrosis3. As advances in cardiac imaging afford detection of subclinical structural and functional changes, the imaging specialist must be attuned to signatures of specific genetic disorders. With increased availability of both advanced imaging as well as genotyping techniques, this review seeks to provide cardiovascular imaging specialists and clinicians with the contemporary information needed for more precise diagnosis and treatment of heritable myocardial disease. A companion paper in this series covers imaging phenotype and genotype considerations in hypertrophic cardiomyopathy (HCM). This review details clinical features, imaging phenotype and current genetic understanding for two of the most common non-HCM conditions that prompt myocardial imaging - dilated cardiomyopathy (DCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC). While all modalities are considered herein, considerable focus is given to CMR with its unique capabilities for myocardial tissue characterization.

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I. Dilated Cardiomyopathy

DCM has a prevalence of at least 1 in 25004 and an incidence of 7 per 100,000/year5. The condition was classically defined as ‘idiopathic’ when a single member in a family was affected without a known cause and as ‘familial’ when the DCM phenotype was present in two or more related family members.6, 7 However, substantial work over the past two decades has confirmed that genetic factors are the underlying cause of both idiopathic and familial forms, and that a careful examination of relatives of an index case often reveals other affected family members and a familial pattern of disease. These systematic studies of idiopathic and familial cases have shown that dilated cardiomyopathies may be confined to ventricular enlargement and systolic dysfunction, or occur in the setting of extracardiac features such as skeletal myopathy and elevated serum creatine kinase levels (muscular dystrophy-associated cardiomyopathies are not included in this review). Consideration of a primary genetic disorder presumes that other secondary causes such as metabolic disorders, acute inflammatory conditions, valvular heart disease, toxins and ischemic heart disease have been excluded. Notably, presumed secondary DCM may occur in the setting of genetic predisposition[8].

The incidence of DCM is increasing in part due to advances in diagnostics and increased awareness among physicians. In the early stages of disease, minimal symptoms may be present and diagnosis delayed, a situation that often becomes apparent when other ostensibly ‘healthy’ family members of a patient are evaluated and additional cases ascertained. Many cases of DCM have an apparent genetic origin with 30% to 50% of cases suspicious for a primary genetic etiology.[9–11] These estimates are complicated by the fact that DCM is classified as a ‘mixed’ cardiomyopathy in deference to the broad list of genetic and exogenous causes in major classification guidelines.[12] Although tempting to apply these guidelines as a mere roadmap to finding the ‘singular’ cause of a patient’s DCM, it is likely that both genetic and non-genetic factors interact to cause many instances of disease. In spite of the probable heterogeneity of etiology in DCM, the high risk of disease to biological relatives provides a compelling reason to assess each case of cardiomyopathy for the possibility of a primary genetic cause.

DCM: Imaging Phenotype

The phenotype of DCM is defined principally by cardiac enlargement and impaired systolic function6, 7, 12. Echocardiography readily detects both. Similar features can be recognized by contrast x-ray ventriculography or nuclear imaging. For instance, DCM may be diagnosed in the patient whose symptoms are initially ascribed to ischemic heart disease and undergoes stress nuclear scinitigraphy that shows a dilated, hypocontractile LV with no ischemia. Variability in cutoff values for abnormal chamber size across modalities, age, gender and indices of body size should be taken into account when assessing for cardiac enlargement. Recognizing abnormal myocardial relaxation via mitral inflow and tissue Doppler velocities is particularly important, since some genetic conditions classified as DCM such as lamin A/C cardiomyopathy predominantly affect diastolic function in the initial stages of disease. While many other conditions such as hypertensive heart disease may also manifest as diastolic dysfunction, these echo-Doppler findings warrant consideration of potential genetic etiologies when recognized in the context of a family history of cardiomyopathy or clinical markers of high risk (e.g. malignant ventricular arrhythmia). While more precise etiologic determination may be limited, echo-Doppler

provides valuable information on the degree of pulmonary hypertension and LV filling pressures with prognostic implications[13].

Left ventricular noncompaction (LVNC) may present as a distinct genetic cardiomyopathy[14], but also may represent a phenotypic feature in a spectrum of other heritable cardiomyopathies15.

Clues to a specific genetic cause may come from techniques like cardiac magnetic resonance (CMR). An appropriate protocol to evaluate the patient with DCM of unknown etiology should include three important techniques for myocardial characterization: T2* quantification16, T2-weighted imaging or T2 mapping17, and late gadolinium enhancement (LGE)18. Briefly, T2* is an MR relaxation parameter whose value is influenced by tissue iron aggregates. The introduction of T2*-based screening of patients with thalassemia, a genetic disease associated with myocardial siderosis due to transfusion-related iron overload, has dramatically reduced mortality in this population. Notably, patients with sickle cell disease may develop hepatic siderosis but our laboratory and others19, 20 have not found significant myocardial overload in these patients despite lifelong exogenous iron overload, suggesting that additional yet-undefined genetic factors may influence myocardial siderosis. A normal myocardial T2* exceeds 20 ms at 1.5 Tesla; a diffusely shortened myocardial T2* in a patient presenting with cardiomyopathy without secondary causes such as chronic transfusions warrants consideration of hereditary hemochromatosis (HH). T2* screening of large HH cohorts has not been reported to provide a contemporary estimate of cardiac involvement, though histopathologic detection at autopsy examination after sudden cardiac death suggest it may be underrecognized21.

T2 increases with tissue water content, and may identify regions of myocardial inflammation or edema[22]. The magnetic resonance parameter T2 was recently reported to be increased in patients with dystrophin-associated cardiomyopathy[23].

LGE is the essential CMR technique for myocardial characterization in DCM, providing both diagnostic and prognostic value[24]. LGE imaging leverages contrast-induced T1-shortening to distinguish between necrotic/fibrotic and normal myocardium. While findings such as mid-myocardial fibrosis may be nonspecific, they reliably distinguish DCM from infiltrative and ischemic cardiomyopathies. Notably, relying on angiography alone to exclude coronary artery disease as the cause of DCM could potentially misclassify up to 13% of cases[18]. Similarly, both LGE findings of nonischemic cardiomyopathy may coexist with infarct scar, that should prompt the interpreting team to consider nonischemic cardiomyopathy superimposed on ischemic heart disease. Genotypic evidence supporting DCM as an end-stage phenotype of HCM[25] underscores the importance of considering a genetic cardiomyopathy when appropriate phenotypic findings are detected by cardiac imaging (Fig. 1). LGE-positivity in a patient with ventricular arrhythmia as well as a concerning family history for heritable disease may warrant genetic testing; however, recognition that patients with genetic cardiomyopathies may be LGE-negative at presentation underscores variability in phenotype and opportunities for imaging advances to better define signatures of genetic myocardial disease.

DCM: Current Status of Genetic Testing

DCM is characterized by high genetic heterogeneity – over twenty-five different genes have been linked to the DCM phenotype (Table 1)[1, 26–46]. Early work identified genes predominantly responsible for coding cytoskeletal proteins, and a ‘cytoskeletal hypothesis’ implicating dysfunction of structural networks was proposed (Fig. 2).47, 48 More recent data has revealed that perturbations in proteins beyond the cytoskeleton can lead to DCM, and the idea of a ‘final common pathway’ now extends to sarcomeric, ion channel, nuclear

lamina, and desmosomal proteins. Accurate prevalence estimates for pathogenesis of each gene have been difficult to obtain, in part because most studies have been in cohorts of modest size (<200 families) with each individual gene accounting for often <2% of cases in a given study. An exception to this has been the lamin A/C (*LMNA*) gene that currently represents the most commonly recognizable cause of DCM, particularly if accompanied by conduction system disease[49], accounting for up to 10% of cases.[50, 51]

The broad genetic heterogeneity of DCM genes initially delayed the development of clinical genetic testing. Many cytoskeletal proteins are large; the large size of these genes made genetic testing costly, and utilization of such testing outside of large research centers was limited. More recently, several laboratories have developed cardiomyopathy panels including over twenty genes offered in a single panel. Testing is available in the United States and Europe and is probably less available in other regions of the world, although even in the United States testing may not always be covered by commercial insurance carriers.

DCM Benefits/Limitations of Testing

For many patients, the greatest benefit of genetic testing comes in evaluating family members at risk of developing the DCM phenotype. For the index patient with evident DCM, genetic testing is not needed to confirm the diagnosis, though it may help determine if the disease is primarily due to a genetic defect vs. another etiology. At-risk family members who have borderline changes on echocardiography may be considered for early treatment to prevent or delay progressive cardiac dysfunction, although studies supporting this approach in true genetic cases are lacking. It should be noted that mutations in *LMNA* may be more malignant than mutations in other DCM genes as *LMNA* mutation carriers appear to be at elevated risk for sudden death and more rapid or severe course of heart failure.

Testing should generally be undertaken after formal genetic counseling and a discussion of the benefits and limitations of testing in the context of the individual patient as well as the overall family structure. Since current genetic testing panels fail to identify a pathogenic mutation in up to 50% of cases, patients should be counseled on this important limitation of current testing. Private mutations are common making predictions of genotype to phenotype unreliable, with the possible exception of *LMNA* mutations which are expected to be more severe. Variants of unknown significance can be encountered and may be difficult to interpret even after additional individuals in the family undergo testing. It has been recommended that strong consideration be given for referral to centers with experience in cardiomyopathy genetics if genetic testing is to be undertaken.[52]

DCM: Family Screening

In deference to the large role of genetic factors in DCM, recommendations for collecting a detailed family history and offering genetic counseling have been proposed.[52] The most common inheritance pattern is autosomal dominant showing multi-generational involvement, equal number of affected males and females, and male-to-male transmission. Other inheritance patterns, while less common, have been described and indeed the specific pattern of inheritance within a family can be used to guide genetic counseling and testing. In addition to evaluating a complete and accurate family history, direct clinical testing of first-degree relatives by objective measures such as electrocardiography and echocardiography are important to identify latent cases. A review of records of deceased individuals can also be critical in uncovering past cases in a family that were not recognized as manifesting the phenotype.

II. Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

ARVC is an inherited cardiomyopathy characterized by fibrofatty replacement of right ventricular (RV) myocardium leading to RV failure and arrhythmias[53, 54]. Prevalence estimates in the general population range from 1:1000 to 1:5000[55, 56]. It often affects young men who have an athletic lifestyle. Presenting symptoms range from palpitations to exertional syncope and sudden cardiac death[54]. Arrhythmias in ARVC most frequently originate from the right ventricle and have a left bundle branch block (LBBB) morphology. The disease often affects the RV outflow tract, the base of the RV and the RV apex, collectively termed the 'triangle of dysplasia'. Early-stage patterns of RV involvement are poorly understood, making it difficult to diagnose early disease by imaging. Major and minor diagnostic criteria have been proposed that encompass structural, electrophysiologic and histopathologic variables[57, 58]. Identification of abnormalities in RV structure and function constitutes an important part of the diagnosis of ARVC and accounts for a major or minor criterion based on the severity of the abnormality. The task force criteria, initially proposed in 1994, were recently revised to include quantitative data for RV functional evaluation, underscoring the importance of thorough assessment of the RV in suspected ARVC[58].

ARVC is a familial disease in at least 50% of cases, usually transmitted as an autosomal dominant trait with variable penetrance[59, 60]. Reduced penetrance and variable expressivity, together with the availability of small families for clinical evaluation, might explain the underestimation of ARVC as heritable disease. Family history alone cannot replace the prospective evaluation of family members in establishing inheritance of ARVC. In the absence of definite knowledge of gene-carrier status, the major clinical challenge consists in differentiating mild or atypical manifestations in family members from the so-called 'phenocopies', i.e. non-hereditary diseases that can mimic ARVC such as idiopathic RV outflow tract tachycardia, myocarditis and sarcoidosis.

ARVC: Imaging Phenotype

Echocardiography is widely available and is often the first imaging modality to assess cardiac structure and function in known or suspected ARVC (Fig. 3, Data Supplement 1). Three-dimensional echocardiography has been shown to accurately quantify RV size and systolic function compared to CMR[61]. Inherent limitations imposed by acoustic window with ultrasound-based cardiac imaging in some patients may preclude visualization of the segmental RV abnormalities that constitute phenotypic hallmarks of ARVC. X-ray right ventriculography is invasive and has fallen out of favor due to the availability of noninvasive imaging techniques. The modified ARVC/D Task Force Criteria[62] provide detailed cutoffs regarding abnormal RV size and wall motion; briefly, RVEF ≤40% by CMR or regional akinesia, dyskinesia or aneurysm by 2D echo, CMR or RV angiography constitute major criteria for ARVC.

Cardiovascular computed tomography (CT) may sometimes be used to diagnose ARVC, particularly in the setting of contraindication to magnetic resonance (Fig. 3). While CT-based recognition of intramyocardial fat holds appeal[63], cine reconstructions (Data Supplement 2) are essential to assess regional RV wall motion given the challenges (even with CT's high spatial resolution) of defining fibrofatty replacement in a thin, diseased RV.

CMR is uniquely suited to evaluate ARVC: it not only provides excellent functional information for the RV, but also can provide tissue characterization to depict fibrosis and fatty infiltration in the RV[64, 65]. CMR provides accurate quantitative assessment of RV size and global and regional RV systolic function, important parts of the revised task force criteria. Limitations inherent to CMR remain presence of MR-incompatible devices or

foreign bodies, severe claustrophobia and advanced renal disease that precludes use of the powerful late gadolinium enhancement technique for myocardial characterization.

CMR findings in ARVC include fat infiltration of the myocardium (Fig. 4), global and regional RV dysfunction, and myocardial fibrosis. Dark blood imaging may demonstrate replacement of ventricular myocardium with hyperintense fat signal, which infrequently appears as a signal void on a corresponding fat-suppressed image. The incidence of fat infiltration in ARVC ranges from 60%–100% in the literature, likely related to differences in patient selection[66]. Fat infiltration often affects the basal right ventricle, RV outflow tract, and the RV anterior wall close to the tricuspid inlet. Relying on intramyocardial fat visualization to make the diagnosis is problematic due to often abundant epicardial fat, underscoring the need to carefully distinguish between abnormal fat infiltrating the RV myocardium and fat in the atrio-ventricular groove. Fat suppression helps distinguish epicardial fat from the unaffected RV wall, though failure to distinguish normal epicardial fat from pathologic RV infiltration may result in misdiagnosis/over diagnosis of ARVC[67]. ARVC should be kept distinct from both fatty infiltration of the right ventricle and adipositas cordis. It is well known that a certain amount of intramyocardial fat is present in the right ventricular antero-lateral and apical regions even in the normal heart, and that intramyocardial and epicardial fat increase with increasing body weight and with aging[68, 69], though prevalence is unknown[70–72]. However, both the fibro-fatty and fatty variants of ARVC show, besides fatty replacement of the right ventricular myocardium, degenerative changes of the myocytes and interstitial fibrosis, with or without extensive replacement-type fibrosis. As such, the suggestion of RV intramyocardial fat by dark blood imaging should prompt closer attention to segmental RV function and late gadolinium enhancement in the corresponding location to reduce ‘false-positive’ imaging-based diagnosis.

Among CMR criteria, global and regional function are most useful in the diagnosis and are very reproducible[73]. RV regional dysfunction often precedes global dysfunction and affects the triangle of dysplasia. Regional functional changes include focal hypokinesis, dyskinesis and aneurysms (Data Supplement 2). By the time of diagnosis, the majority of probands with ARVC have global RV dysfunction. Reproducible CMR-derived measures of RV volumes and function, with published nomograms[58], are invaluable in the longitudinal evaluation of patients with borderline abnormalities and can be used to assign major or minor criteria for ARVC.

Evaluation of plakophillin-2 (PKP2) mutation-positive asymptomatic first-degree relatives revealed minor crinkling contractions in the RV base that resembled an accordion[74]. This sign was seen with a high prevalence in mutation-positive relatives and none of the first-degree relatives who did not carry the pathologic mutation. Reproducibility of this finding has not been systematically assessed, and the diagnostic and prognostic significance remains unknown.

LGE imaging can non-invasively demonstrate RV fibrosis (Fig. 5), and is an essential component of the CMR examination of patients with suspected ARVC[64]. The extent of RV myocardial fibrosis correlates with the degree of RV dysfunction, and predicts inducibility of ventricular arrhythmias[64]. LGE also assists in distinguishing phenocopies of ARVC like sarcoidosis which occasionally results in isolated cardiac involvement[75]. Multiple, patchy regions of LV hyperenhancement favors a diagnosis of sarcoidosis[76] and may also be seen in myocarditis. Notably, fat infiltration is distinctly absent in both conditions.

Recent evidence suggests that ARVC is a biventricular cardiomyopathy; the extent and severity of LV involvement may be related to the underlying genotype, and can appear early in the disease course77. Histopathologic data suggest an inflammatory component in left-

dominant arrhythmogenic cardiomyopathy; further studies are needed to define T2 imaging's potential utility in delineating this feature of the disease. In PKP2-related ARVC, the most common mutation in the Unites States, LV fat infiltration is seen in up to 25% of these patients and most commonly affects the postero-lateral LV epicardium74. Recently, tagged cine CMR has revealed regional LV dysfunction in the postero-lateral LV wall in patients with early ARVC even in the presence of normal global function[78]. Mid-myocardial hyperenhancement by LGE, which may be seen in DCM, and sub-epicardial hyperenhancement have been reported in ARVC, particularly in desmoplakin (DSP) mutation carriers[79]. This underscores limitations in defining the underlying genetic abnormality by imaging phenotype alone. Individual patient assessment continues to require aggregate data assessment – history, examination, serologies, electrocardiography, imaging – in making the correct diagnosis.

ARVC: Current Status of Genetics

Since the discovery of the first ARVC locus in 1994[80], multiple disease loci have been mapped but the disease-causing genes remained elusive (Table 2)46, 81–89. The genetic cause of the recessive variant Naxos syndrome was elucidated first, as it is a highly penetrant disease with a clear-cut cutaneous phenotype[89]. Notably, epidermal cells in the palms and soles as well as cardiomyocytes are exposed to high shear stress and share components of the mechanical junctional apparatus (desmosome and fascia adherens) that is responsible for cell-to-cell adhesion. Proteins from three separate families assemble (Fig. 6)[56] to form desmosomal cadherins (desmoglein and desmocollin), armadillo proteins (plakoglobin and plakophillin), and plakins (desmoplakin).

A plakoglobin deletion was first found in Naxos disease[89]. This was followed by discovery of mutations in desmoplakin[86], plakophilin-2[46], desmoglein-2[85], desmocollin-2[87], and plakoglobin[81] in the dominant forms. A recessive mutation of desmoplakin has been reported in another cardiocutaneous disease Carvajal syndrome[84]. Thus, ARVC was found to be mainly a disease of the desmosome[56], and plakophilin-2 is the most frequently identified gene[90].

Extradesmosomal genes implicated in ARVC include the genes encoding cardiac ryanodine 2 receptor (RyR2)88, transforming growth factor β3 (TGF-β3)82, and transmembrane protein 43 (TMEM43)83.

Mutations in the cardiac *RyR2* cause ARVC2, characterized by effort-induced polymorphic ventricular arrhythmias and sudden death at young age. The ARVC2 phenotype is more similar to catecholaminergic polymorphic ventricular tachycardia than to ARVC since affected individuals do not show the typical electrocardiographic features and structural abnormalities, and are limited to mild or absent right ventricular hypokinesis.

Mutations in the untranslated regions of transforming growth factor (*TGF-β3*) have been identified in one large family and an unrelated proband with ARVC1 linkage (locus 14q24.3)[82]. It has been demonstrated that this protein stimulates production of components of the extracellular matrix and modulates expression of desmosomal genes *in vitro*.

Finally, a missense mutation in the *TMEM43* has been identified in the ARVC5 phenotype in the Newfoundland founder population[83]. Affected patients show right precordial R-wave reduction and ventricular extrasystoles on ECG, and have early LV involvement and a high incidence of sudden death. At present, definitive proof that TGF-β3 and TMEM43 contribute to ARVC is missing, and these extrademosomal genes are currently screened in just a few research laboratories. Comprehensive mutation screening of the five desmosomal (*JUP*, *DSP*, *PKP2*, *DSG2*, and *DSC2*) ARVC genes is routinely carried out by sequence

analysis. This approach can detect rare variants in at least 30–60% of probands, according to different cohorts[91].

Plakophilin-2, desmoplakin, and desmoglein-2 account for the majority of isolated variants, although a high variability in their prevalence has been reported in different cohorts of probands[87, 92–96]. For instance, the high prevalence of PKP2 mutations (70%) among ARVC families in the Netherlands can be ascribed to founder effects[87]. Preliminary genotype-phenotype correlations suggest that *PKP2* ARVC patients usually present with the classic, right-dominant disease, while other series with a relatively higher prevalence of desmoplakin mutations consist of patients who show a more diverse phenotype, including the so-called left dominant ARVC[79, 95, 97].

Finally, preliminary genotype-phenotype data suggest that disease severity is greater in double mutations carriers, further emphasising the need to screen all known disease-causing genes even after isolation of a pathogenic mutation[98, 99].

ARVC: Benefit/Limitations of Genetic Testing

Candidates for genetic screening include both index cases and family members of gene-positive ARVC probands[56, 90, 91].

Genetic analysis in the diagnosis of index cases—As a general rule, there is no role at present for routine genetic screening to confirm a definite clinical diagnosis. In fact, a positive result from genotyping is supportive but not always confirmatory of ARVC diagnosis, while a negative genetic screening is non-contributory. About 50% of ARVC probands do not carry a defect in a known desmosomal gene. On the other hand, the identification of a rare genetic variant raises the index of suspicion but cannot be diagnostic *per se*. The latter uncertainty is typical for missense mutations and is mainly ascribable to the marked allelic heterogeneity of the main desmosomal genes and to the high prevalence of private mutations.

When a rare genetic variant is identified in ARVC, there are two possibilities: a) the genetic variant has been previously reported as causally linked to ARVC, and in such cases the diagnosis can be confirmed, or b) mutation screening yields a novel genetic variant. In the latter (most frequent) situation, pathogenicity must be proven by traditional criteria as with other heritable cardiomyopathies: i-the absence of the variant in a significant number of healthy individuals; ii-clinical correlation within families i.e. cosegregation with the disease; iii-a change in amino acid polarity and/or size; iv-a change involving a conserved amino acid; v-localization of the variant within a functional protein domain; and vi-*in vitro* functional studies.

PKP2 mutation variants require careful interpretation[87, 92, 94, 96]. In fact, increasing evidence suggests that some PKP2 mutations labelled as “pathogenic” may not be causal since they have been subsequently identified in healthy controls. Recently, Xu et al.[98] demonstrated that among 38 ARVC index cases carrying PKP2 variants, 9 were compound heterozygotes and 16 double heterozygotes, i.e. showing an additional mutation in another desmosomal gene. These findings suggest that many PKP2 mutations may have a contributory role rather than causal for ARVC development and this might be true also for other desmosomal gene variants.

Cascade genetic screening of family members—Predictive testing of relatives is the main current indication for genetic analysis in ARVC, as in other inherited cardiomyopathies[91]. However, its implementation suffers from most of the limitations of confirmatory testing in index cases. In fact, before using any novel genetic variant for

predictive testing in family members, it is mandatory to prove its pathogenicity. Co-segregation with the phenotype is not always easy to demonstrate because of the reduced penetrance and the variable expressivity of ARVC. Conversely, functional studies for every novel genetic variant are not practically feasible. Also for these reasons, genetic counselling is mandatory in each patient undergoing genetic screening to emphasize that it is the allele, rather than the disease, that is inherited.

When the pathogenicity of the allele variant is unequivocal, cascade screening of family members is of utmost value. In fact, it allows the early identification of asymptomatic carriers (healthy carriers) who would require life-long clinical evaluation due to variable and age-related penetrance of ARVC. These subjects must be considered at-risk because the disease is progressive and can appear late during life, and frequent clinical evaluation is mandatory. Sports activity increases the risk of sudden death in subjects with ARVC/D by five-fold, since acute volume overload and stretching of the RV during effort as well as sympathetic stimulation are major triggers of ventricular arrhythmias. Detection of asymptomatic individuals affected by ARVC/D at pre-participation screening has been proven to be a lifesaving strategy. The clinically unaffected family member carrying a disease gene mutation ("healthy carrier") must be considered potentially at risk because the disease is progressive and can appear late during life, and frequent clinical checkups are mandatory. According to recent guidelines, all competitive sports should be always forbidden considering the legal implications. Noncompetitive sports may be allowed, providing regular follow-up assessment.

Genetic testing that identifies non-carriers, who represent about 50% of those tested, allows them to be considered healthy–they do not need further cardiac screening for ARVC and can be reassured that they carry no risk of disease transmission to their children[56, 91]. Predictive diagnosis is usually proposed in all family members of a genotyped proband after the age of 10 years, which is the age at which cardiac screening is considered mandatory in ARVC[59].

Summary and Future Directions

With increased understanding of the genetics of cardiomyopathy, active synthesis of clinical data and family history informs the interpretation of phenotypic information yielded by contemporary cardiovascular imaging. Such synthesis has implications for not only individual patients but also at-risk family members. Those involved in imaging have a responsibility to recognize phenotypic features that suggest a genetic cause (Table 3), just as clinicians and genetics specialists should recognize where imaging may be useful to refine diagnosis and prognosis. Much work remains to be done to identify specific imaging signatures that guide diagnosis toward particular genetic mechanisms of disease. Further insight is needed from histopathology in conjunction with genetic studies to define what, if any, phenotypic signatures correspond to specific genotypes; such insights will, in turn, inform refined imaging-based diagnosis in cardiomyopathy. For some mutations, it is unknown what long-term clinical significance is for currently asymptomatic mutation carriers. Even in the case of lamin A/C gene mutations there is considerable variability in symptom onset, severity, and rate of progression. Consensus on clinical screening, imaging, and frequency of assessments in asymptomatic mutation carriers is limited and currently not based on solid prospective longitudinal data. The fact that many mutations are unique, so called 'private mutations' restricted to one or a few families, will continue to limit efforts to provide broad recommendations. As recommended by a recent expert panel[100], referral of patients and families with heritable cardiomyopathies to centers with genetic expertise should be strongly considered.

The major obstacle for a widespread clinical use of genotyping has been the high costs of mutation screening by conventional direct sequencing. With increased availability of cost-effective tools, genotyping may become available at any center that performs family evaluation for inherited cardiomyopathies. In this setting, phenotype recognition by imaging that identifies disease in its earliest or concealed stages should prompt consideration of genotyping when clinical abnormalities are still subtle but individuals are already at risk of sudden death. Obstacles to widespread myocardial characterization and precise diagnosis with CMR may include variations across scanner platforms and interpreters; we advise that patients be referred to established CMR centers when considering this modality in evaluating genetic cardiomyopathies. More broadly, the shortcomings of current imaging to detect signatures of specific genotypes should encourage researchers to develop new imaging approaches based on our advancing understanding of the genetic and molecular bases of cardiomyopathies. As our understanding of the phenotypic spectrum and genetics of DCM and ARVC unfolds, longitudinal genotype-phenotype studies that take advantage of refined myocardial imaging and preclinical models will provide mechanistic insights to further improve our ability to diagnose and treat heritable cardiomyopathies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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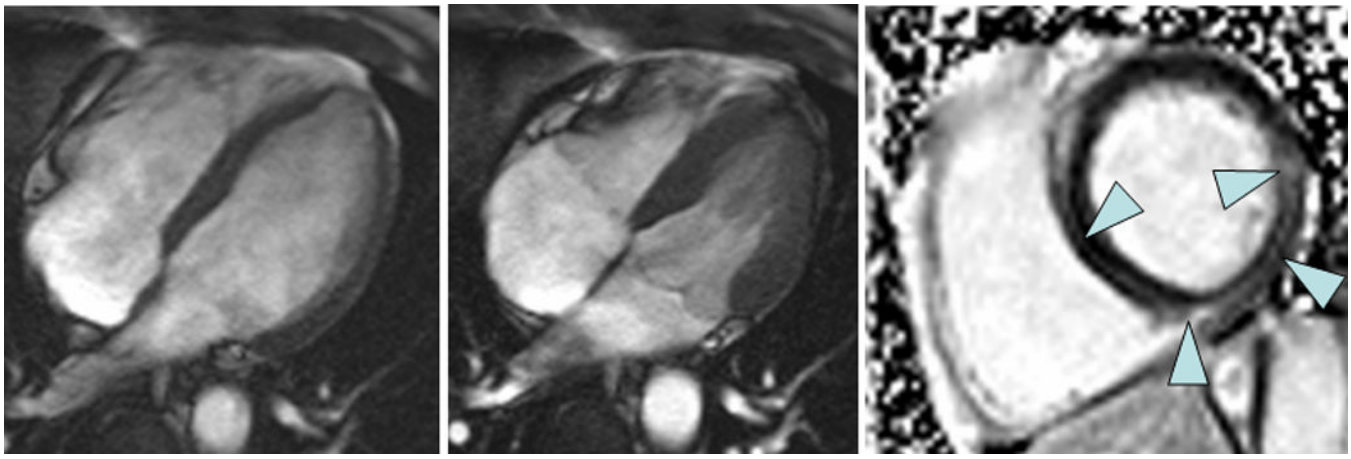

Figure 1.
A 52 year-old male with ventricular arrhythmia by ambulatory ECG monitoring whose family history included a grandparent with sudden cardiac death at a young age underwent echocardiography that showed normal LV systolic function and mitral valve prolapse. CMR was performed and confirmed normal systolic function (left panel: end-diastole, middle panel: end-systole) but revealed midmyocardial fibrosis by LGE imaging (right panel). The patient underwent genetic testing via a 23-gene panel for dilated cardiomyopathy (GeneDx, Gaithersberg, MD) that revealed a mutation in myosin binding protein C.

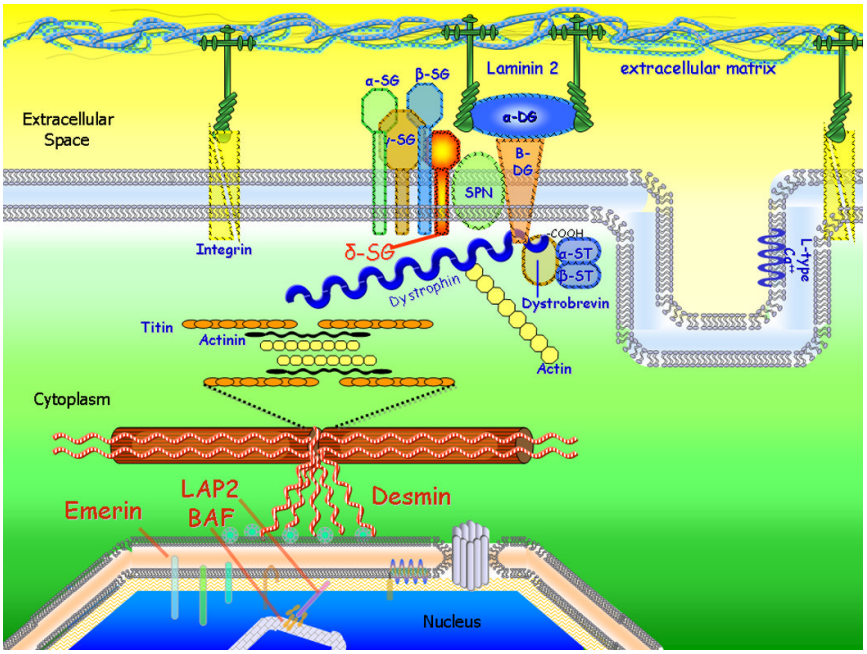

Figure 2.

Proteins of the cytoskeletal network. Mutations in many cytoskeletal genes cause dilated cardiomyopathy (Table 1) supporting the 'cytoskeletal hypothesis'. BAF=barrier to autointegration factor; DG=dystroglycan; LAP2=lamina-associated polypeptide 2; L-type Ca=L-type calcium channel; SG=sarcoglycan (alpha, beta, gamma, and delta isoforms shown); SPN=sarcospan; ST=syntrophin.

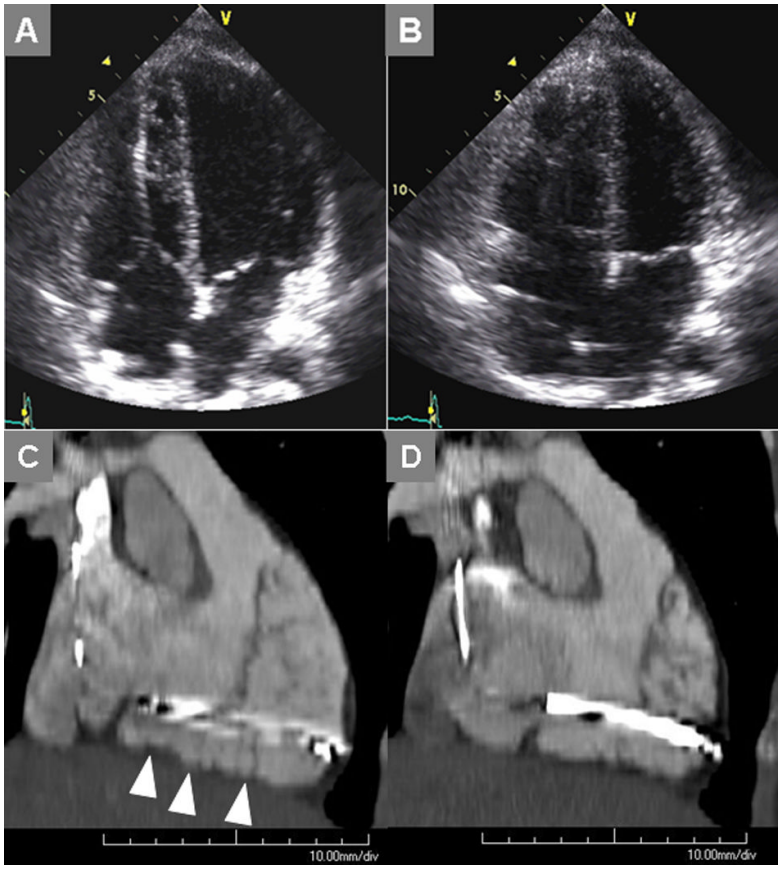

Figure 3.
Transthoracic echocardiogram at end-diastole (A) and end-systole (B) indicates RV dysfunction in a 32 year-old female who underwent defibrillator placement shortly after surviving sudden cardiac death. She was then referred for cardiac computed tomography to assess for possible ARVC. Maximum intensity projection image in an oblique sagittal plane demonstrates the scalloped RV myocardium (arrowheads) and dyskinetic segments when comparing images reconstructed at end-diastole (C) vs. end-systole.

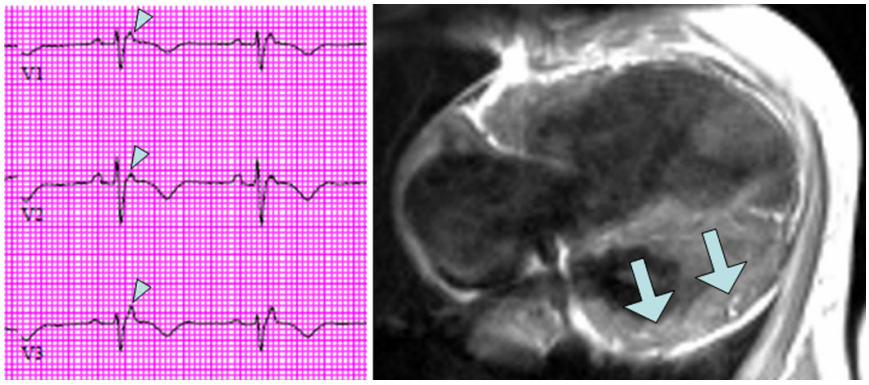

Figure 4.
Electrocardiogram from a patient who presented with fatigue demonstrates classic epsilon waves of ARVC (left, arrowheads). Dark blood cardiac magnetic resonance image shows extensive fatty infiltration that also involves the LV myocardium (right, arrows).

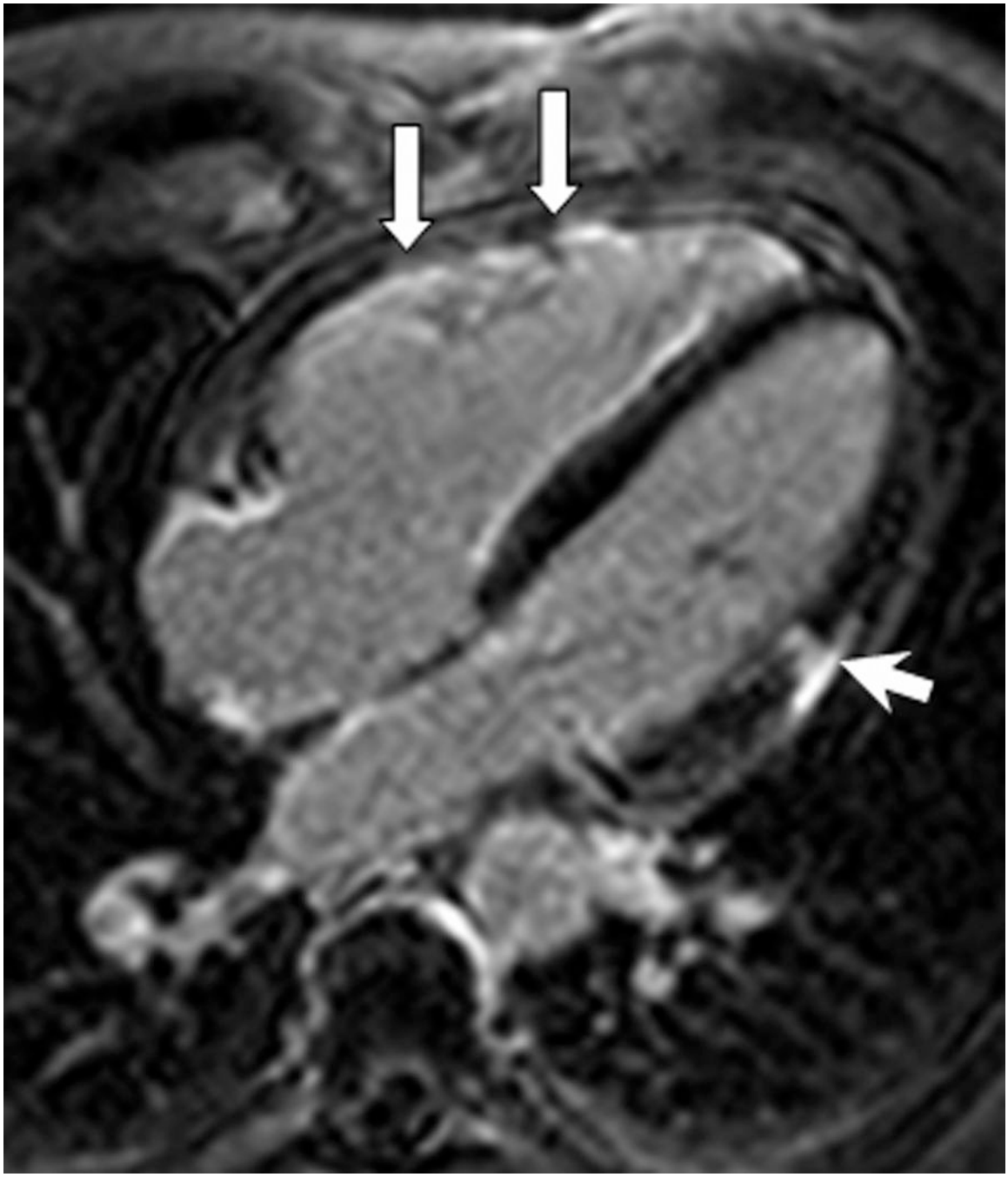

Figure 5.
LGE image in the horizontal long-axis plane shows diffuse hyperenhancement of the right ventricular myocardium suggestive of fibrosis (arrows). Also seen is an area of focal hyperenhancement in the lateral LV myocardium (arrowhead).

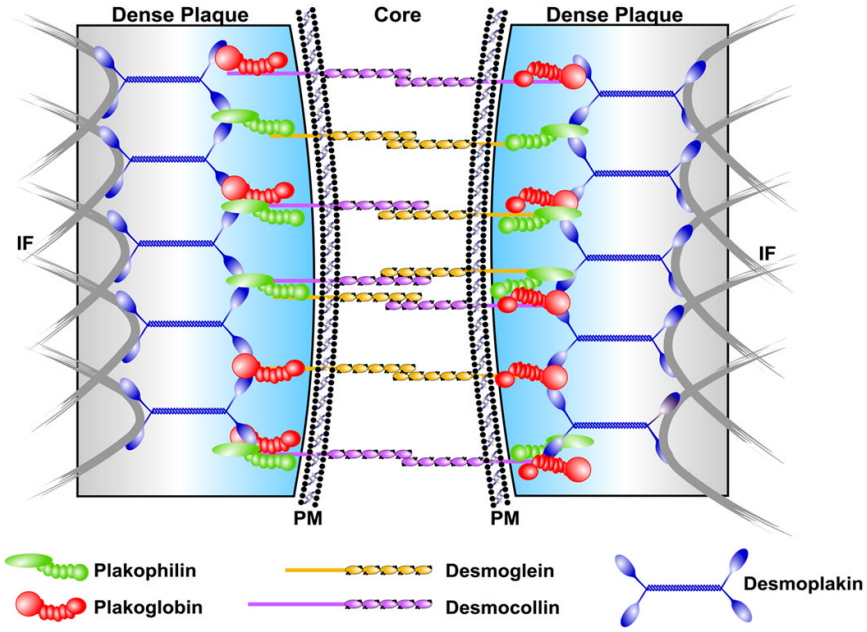

Figure 6.
Components of the intercellular mechanical junction or desmosome between cardiomyocytes are shown. IF = intermediate filaments, PM = plasma membrane. Reproduced with permission from [56].

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Table 1

Genetic Causes of Dilated Cardiomyopathy*

Author (ref)	Phenotype	Frequency (%)	Chromosomal location	LOCUS	OMIM	Gene Symbol	Gene	Location
Durand et al.[45]	Autosomal dominant	56	1q32	CMD1D	191045	*TNNT2*	Cardiac troponin T	Sarcomere
Mogensen et al.[44]	FDC		3p21.1		191040	*TNNC1*	Cardiac troponin C	Sarcomere
Gerull et al.[46]			2q31	CMD1G	188840	*TTN*	Titin	Sarcomere
Li et al.[43]			2q35	CMD1I	125660	*DES*	Desmin	Cytoskeleton
			6q12-q16	CMD1K	172405	*?*	?	
Schmitt et al.[42]	(with mitral prolapse)		6q22.1	CMD1P	609909	*PLN*	Phospholamban	Calcium
			9q13	CMD1B	600884	*?*	?	
			9131	CMD1X	611615	*?*	?	
Olson et al.[41]			10q21-q23	CMD1W	193065	*VCL*	Metavinculin	Cytoskeleton
Duboscq-Bidot et al.[40]			10q22.1	CMD	608517	*MYPN*	Myopalladin	Sarcomere
Vatta et al.[39]			10q23.3	CMD1C	601493	*ZASP/LDB3*	ZASP/ LIM domain binding 3	Sarcomere
Daehmlow et al.[38]			11p11	CMD1M	600958	*MYBPC3*	Myosin-binding protein C	Sarcomere
Knoll et al.[37]			11p15.1	CMD1A	600824	*CSRP3*	Cysteine-glycine-rich protein	Sarcomere
Bienengraeber et al.[36]			12p12.1	CMD1O	601439	*ABCC9*	3	Ion channel
Kamisago et al.[35]			14q11.2-13	CMD1A	160760	*MYH7*	cardiac K_{ATP} channel	Sarcomere
Li et al.[34]			14q24.3	CMD1U	104311	*PSEN1*	Cardiac β-myosin heavy chain	Nuclear mem
Olson et al.[33]			15q14		102540	*ACTC*	Presenilin 1	Sarcomere
Olson et al.[32]			15q22.1	CMD1N	191010	*TPM1*	Cardiac actin	Sarcomere
Valle et al.[31]			17q12		604488	*TCAP*	α-tropomyosin	Sarcomere
							Tinin-cap (telethonin)	
Murphy et al.[30]	Autosomal recessive	16	19q13.42		191044	*TNNI3*	Cardiac troponin I	Sarcomere
	FDC		unknown		212110			
Gold et al.[29]	X-linked DC	10	Xp21	XLCM	300377	*DMD*	Dystrophin	Cytoskeleton
Fatkin et al.[1]	Autosomal dominant	7.7	1q11-q23	LGMD1	150330	*LMNA*	Lamin A/C	Nucleoskeleton

Author (ref)	Phenotype	Frequency (%)	Chromosomal location	LOCUS	OMIM	Gene Symbol	Gene	Location
Tsubata et al.[28]	FDC with skeletal muscle disease		5q33-34	B	601411	*SGCD*	δ-sarcoglycan	Cytoskeleton
Barresi et al.[27]			4q11	LGMD2	600900	*SGCB*	β-sarcoglycan	Cytoskeleton
			6q23	F	602067			
				LGMD2				
				E				
				CMD1F				
Fatkin et al.[1]	Autosomal dominant	2.6	1q1-q1	CMD1A	150330	*LMNA*	Lamin A/C	Nucleoskeleton
	FDC with conduction defects		2q14-q22	CMD1H	604288			
McNair et al.[26]			3p22.2	CMD1E	600163	*SCN5A*	Na channel, voltage-gated, type V, αpolypeptide	Ion channel

* organized by phenotype and sequentially by chromosome location

Table 2

Genetic Causes of Arrhythmogenic Right Ventricular Cardiomyopathy

Author (ref)	Gene	Encoded Protein	Chromosome locus	OMIM*	Mode of inheritance	Comment
McKoy et al.[89] Asimaki et al.[81]	JUP	Plakoglobin	17q21	#173325 #601214	Autosomal dominant Autosomal recessive	Naxos disease
Rampazzo et al.[86] Norgett et al.[84]	DSP	Desmoplakin	6p24	#125647 #605676	Autosomal dominant Autosomal recessive	Carvajal syndrome
Gerull et al.[46]	PKP2	Plakophilin-2	12p11	#602861	Autosomal dominant	
Pilichou et al.[85]	DSG2	Desmoglein-2	18q12	#125671	Autosomal dominant	
Syrris et al.[87]	DSC2	Desmocollin-2	18q12	#125645	Autosomal dominant	
Extradesmosomal genes						
Tiso et al.[88]	RYR2	Ryr2	1q42-q43	#180902	Autosomal dominant	CPVT*
Beffagna et al.[82]	TGF-β3	TGF β3	14q23-q24	#190230	Autosomal dominant	
Merner et al.[83]	TMEM43	TMEM 43	3p25	#612048	Autosomal dominant	

*CPVT = catecholaminergic polymorphic ventricular tachycardia

Table 3

Phenotypic Clues Linking Imaging to Non-HCM Genetic Cardiomyopathies*

Imaging Phenotype	Additional Clinical Clues†	Genetic Considerations
Dilated cardiomyopathy with diastolic dysfunction, atrial myopathy	Conduction system disease	Lamin A/C
Dilated cardiomyopathy with circumferential or confluent midwall enhancement by LGE‡	Acute myocarditis-like presentation	Left-dominant arrhythmogenic cardiomyopathy
Right ventricular dilatation, segmental contraction abnormalities, aneurysms; fibrofatty changes in myocardium	Left bundle branch-morphology ventricular arrhythmia	Arrhythmogenic right ventricular cardiomyopathy

* This summary relates to DCM and ARVC, and does not include findings related to hypertrophic cardiomyopathy or genetic cardiomyopathies associated with muscular dystrophies or inborn errors of metabolism.

† A valuable clinical clue pointing to genetic cardiomyopathy may be obtained from a meticulous family history.

‡ LGE = late gadolinium enhancement imaging. Note that left-dominant arrhythmogenic cardiomoypathy may present with preserved LV size and systolic function as well.