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Imaging Phenotype vs Genotype in Nonhypertrophic Heritable Cardiomyopathies

Dilated Cardiomyopathy and Arrhythmogenic Right Ventricular Cardiomyopathy

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Advances in cardiovascular imaging increasingly afford unique insights into heritable myocardial disease. Because the clinical presentation of genetic cardiomyopathies may range from nonspecific symptoms to sudden cardiac death, an 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 arrhythmias referred to define the myocardial substrate. Accurate diagnosis of the patient presenting with dyspnea and palpitations whose first-degree relatives have lamin A/C (LMNA) cardiomyopathy may warrant genetic testing[1,2] plus imaging of diastolic function and myocardial fibrosis.[3] Because advances in cardiac imaging afford the detection of subclinical structural and functional changes, the imaging specialist must be attuned to the signatures of specific genetic disorders. With the increased availability of both advanced imaging and genotyping techniques, this review seeks to provide cardiovascular imaging specialists and clinicians with the contemporary information needed for more precise diagnosis of heritable myocardial disease. A companion article in this series covers imaging phenotype and genotype considerations in hypertrophic cardiomyopathy. This review details the clinical features, imaging phenotypes, and current genetic understanding for 2 of the most common nonhypertrophic cardiomyopathy conditions that prompt myocardial imaging: dilated cardiomyopathy (DCM) and ARVC. Although all imaging modalities are considered herein, considerable focus is given to cardiac magnetic resonance (CMR), with its unique capabilities for myocardial tissue characterization.

Dilated Cardiomyopathy

DCM has a prevalence of at least 1 in 2500[4] and an incidence of 7 per 100 000/y.[5] 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 2 or more related family members.[6,7] However, substantial work in the past few decades has confirmed that genetic factors are the underlying cause of both idiopathic and familial forms and that careful examination of the 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 DCMs may be confined to ventricular enlargement and systolic dysfunction, or they may 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 a 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 the 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" cardiomyop-

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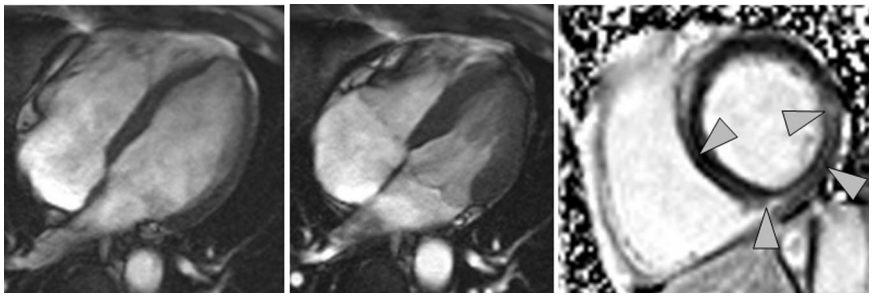

Figure 1. CMR imaging in a 52-year-old man with ventricular arrhythmia on ambulatory ECG monitoring whose family history included a grandparent with sudden cardiac death at a young age. Echocardiography showed normal LV systolic function and mitral valve prolapse. CMR was performed and confirmed normal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

athy in deference to the broad list of genetic and exogenous causes in major classification guidelines.[12] Although it is tempting to apply these guidelines as a mere road map to finding the "singular" cause of a patient's DCM, it is likely that both genetic and nongenetic factors interact to cause many instances of the disease. Despite 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 function.[6,7,12] 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 who undergoes stress nuclear scintigraphy that shows a dilated, hypocontractile left ventricle with no ischemia. Variability in cutoff values for abnormal chamber size across modalities, age, sex, and indices of body size should be taken into account when assessing for cardiac enlargement. Recognizing abnormal myocardial relaxation from mitral inflow and tissue Doppler velocities is particularly important, because some genetic conditions classified as DCM, such as LMNA cardiomyopathy, predominantly affect diastolic function in the initial stages of the disease. Although 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 (eg, malignant ventricular arrhythmia). Whereas a more precise etiologic determination may be limited, echo Doppler provides valuable information on the degree of pulmonary hypertension and left ventricular (LV) filling pressures, with prognostic implications.[13] LV noncompaction may present as a distinct genetic cardiomyopathy,[14] but it also may represent a phenotypic feature along a spectrum of other heritable cardiomyopathies.[15]

Clues to a specific genetic cause may come from techniques like CMR. An appropriate protocol to evaluate the patient with DCM of unknown etiology should include 3 important techniques for myocardial characterization: T2* quantification,[16] T2-weighted imaging or T2 mapping,[17] and late gadolinium enhancement (LGE).[18] In brief, T2* is an MR relaxation time whose value is shortened in tissues with 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 others[19,20] have not found significant myocardial overload in these patients, despite lifelong exogenous iron overload, suggesting that additional, as-yet-undefined genetic factors may influence myocardial siderosis. A normal myocardial T2* exceeds 20 ms at 1.5 T; a diffusely shortened myocardial T2* in a patient presenting with cardiomyopathy without secondary causes such as chronic transfusions warrants consideration of hereditary hemochromatosis. T2* screening of large hereditary hemochromatosis cohorts has not been reported to provide a contemporary estimate of cardiac involvement, although histopathologic detection at autopsy examination after sudden cardiac death suggests that it may be underrecognized.[21] T2 increases with tissue water's increased content or lower protein binding and may identify regions of myocardial inflammation or edema.[22] The MR 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. Although findings such as midmyocardial 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, LGE findings of nonischemic cardiomyopathy may coexist with infarct scar, which should prompt the interpreting team to consider nonischemic cardiomyopathy superimposed on ischemic heart disease. Genotypic evidence supporting DCM as an end-stage phenotype of hypertrophic cardiomyopathy[25] underscores the importance of considering a genetic cardiomyopathy when appropriate phenotypic findings are detected by cardiac imaging (Figure 1). LGE positivity in a patient with ventricular arrhythmia as well as a concern-

Table 1. Genetic Causes of DCM*

Authors, Reference	Phenotype	Frequency, %	Chromosomal Location	Locus	OMIM	Gene Symbol	Gene	Location
Durand et al[45]	Autosomal-dominant FDC	56	1q32	CMD1D	191045	*TNNT2*	Cardiac troponin T	Sarcomere
Mogensen et al[44]			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
	With mitral prolapse		6q12–q16	CMD1K	172405	*?*	?	
Schmitt et al[42]			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	601493600958	*ZASP/ LDB3*	ZASP/LIM domain binding 3	Sarcomere
Daehmlow et al[38]			11p11	CMD1M	600824	*MYBPC3*	Myosin-binding protein C	Sarcomere
Knoll et al[37]			11p15.1	CMD1A	601439	*CSRP3*	Cysteine-glycine–rich protein 3	Sarcomere
Bienengraeber et al[36]			12p12.1	CMD1O	160760	*ABCC9*	Cardiac K_{ATP} channel	Ion channel
Kamisago et al[35]			14q11.2–13	CMD1A	104311	*MYH7*	Cardiac β-myosin heavy chain	Sarcomere
Li et al[34]			14q24.3	CMD1U	102540	*PSEN1*	Presenilin 1	Nuclear membrane
Olson et al[33]			15q14		191010	*ACTC*	Cardiac actin	Sarcomere
Olson et al[32]			15q22.1	CMD1N	604488	*TPM1*	α-Tropomyosin	Sarcomere
Valle et al[31]			17q12			*TCAP*	Tinin cap (telethonin)	Sarcomere
Murphy et al[30]	Autosomal-recessive FDC	16	19q13.42		191044	*TNNI3*	Cardiac troponin I	Sarcomere
			Unknown		212110			
Gold et al[29]	X-linked DC	10	Xp21	XLCM	300377	*DMD*	Dystrophin	Cytoskeleton
Fatkin et al[1]	Autosomal-dominant FDC with skeletal muscle disease	7.7	1q11–q23	LGMD1B	150330	*LMNA*	LMNA	Nucleoskeleton
Tsubata et al[28]			5q33–34	LGMD2F	601411	*SGCD*	δ-Sarcoglycan	Cytoskeleton
Barresi et al[27]			4q11	LGMD2E	600900	*SGCB*	β-Sarcoglycan	Cytoskeleton
			6q23	CMD1F	602067			
Fatkin et al[1]	Autosomal-dominant FDC with conduction defects	2.6	1q1–q1	CMD1A	150330	*LMNA*	LMNA	Nucleoskeleton
			2q14–q22	CMD1H	604288			
McNair et al[26]			3p22.2	CMD1E	600163	*SCN5A*	Sodium channel, voltage-gated, type V, $\alpha-$polypeptide	Ion channel

FDC indicates familial dilated cardiomyopathy.
*Organized by phenotype and sequentially by chromosome location.

ing family history for heritable disease may warrant genetic testing; however, recognition that patients with genetic cardiomyopathies may be LGE-negative at presentation underscores the 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: >25 different genes have been linked to the DCM phenotype (Table 1).[1,26–46] Early work identified the genes predominantly responsible for coding cytoskeletal proteins, and a "cytoskeletal hypothesis" implicating dysfunction of structural networks was proposed (Figure 2).[47,48] More recent data have 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 the pathogenesis of each gene have been difficult to obtain, in part because most studies have been conducted in cohorts of modest size (<200 families), with each individual gene often accounting for <2% of cases in a given study. An exception to this has been the LMNA gene (*LMNA*), which currently represents

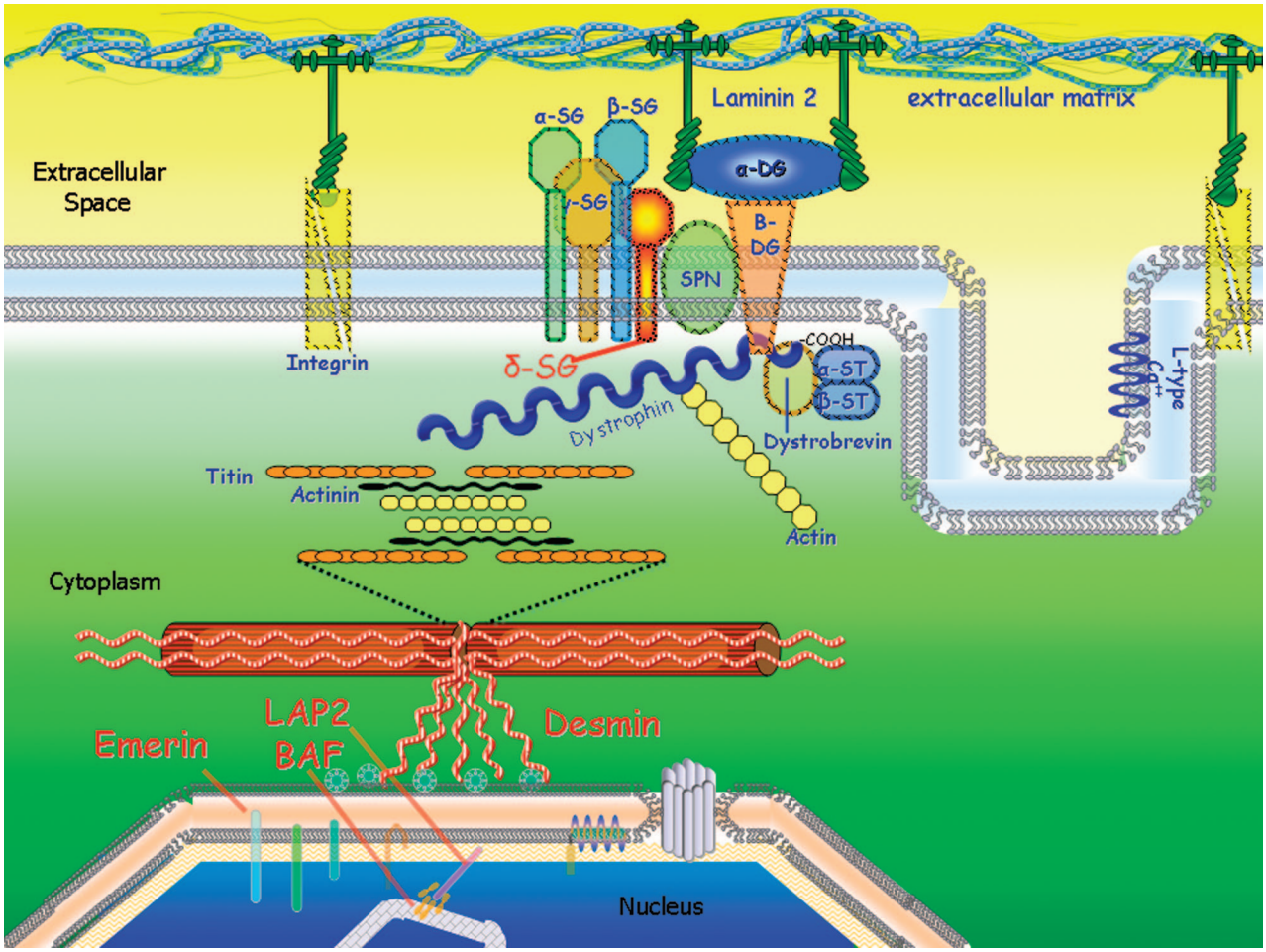

Figure 2. Proteins of the cytoskeletal network. Mutations in many cytoskeletal genes cause DCM (Table 1), supporting the "cytoskeletal hypothesis." BAF indicates barrier to autointegration factor; DG, dystroglycan; LAP2, lamina-associated polypeptide 2; L-type Ca, L-type calcium channel; SG, sarcoglycan (α, β, γ, and δ isoforms shown); SPN, sarcospan; and ST, syntrophin.

the most commonly recognizable cause of DCM, particularly when 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 large research centers was limited. More recently, several laboratories have developed cardiomyopathy panels including >20 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 and 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, although it may help determine whether the disease is primarily due to a genetic defect versus 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 are mutations in other DCM genes, as *LMNA* mutation carriers appear to be at elevated risk for sudden death and a 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. Because 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, which are restricted to 1 or only a few families, 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 multigenerational involvement, equal numbers of affected males and females, and male-to-male transmission. Other inheritance patterns, though less common, have been described; 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 ECG and echocardiography are important to identify latent cases. A review of the medical records of deceased individuals in a family can also be critical in uncovering past cases who were not recognized as manifesting the phenotype.

Arrhythmogenic Right Ventricular Cardiomyopathy

ARVC is an inherited cardiomyopathy characterized by fibrofatty replacement of the 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 morphology. The disease often affects the RV outflow tract, the base of the right ventricle, 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 a thorough assessment of the right ventricle in cases of 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 a 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"; that is, nonhereditary 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 used to assess cardiac structure and function in cases of known or suspected ARVC (Figure 3; online-only Data Supplement I). Three-dimensional echocardiography has been shown to accurately quantify RV size and systolic function compared with CMR.[61] Inherent limitations imposed by the acoustic window with ultrasound-based cardiac imaging in some patients may preclude visualization of the segmental RV abnormalities that constitute the phenotypic hallmarks of ARVC. X-ray right ventriculography is invasive and has fallen out of favor owing to the availability of noninvasive imaging techniques. The modified ARVC Task Force Criteria[58] provide detailed cutoffs regarding abnormal RV size and wall motion; in brief, an RV ejection fraction $\leq$40% by CMR, or regional akinesia, dyskinesia, or aneurysm by 2D echo, CMR, or RV angiography constitute major criteria for ARVC.

Cardiovascular computed tomography may sometimes be used to diagnose ARVC, particularly in the setting of contraindications to CMR (Figure 3). Although computed tomography–based recognition of intramyocardial fat is appealing,[62] cine reconstructions (online-only Data Supplement II) are essential to assess regional RV wall motion given the challenges (even with the high spatial resolution of computed tomography) of defining fibrofatty replacement in a thin, diseased right ventricle.

CMR is uniquely suited to evaluate ARVC: it not only provides excellent functional information for the right ventricle, but it also can provide tissue characterization to depict fibrosis and fatty infiltration in the right ventricle.[63,64] CMR provides accurate quantitative assessment of RV size and of global and regional RV systolic function, important parts of the revised task force criteria. Limitations inherent to CMR include the presence of CMR-incompatible devices or foreign bodies, severe claustrophobia, and advanced renal disease that precludes use of the powerful LGE technique for myocardial characterization.

CMR findings in ARVC include fat infiltration of the myocardium (Figure 4), global and regional RV dysfunction, and myocardial fibrosis. Dark-blood imaging may demonstrate replacement of ventricular myocardium with a hyperintense fat signal, which infrequently appears as a signal void on a corresponding fat-suppressed image. In the literature, the incidence of fat infiltration in ARVC has been reported to range from 60% to 100%, likely related to differences in patient selection.[65] 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, owing to the often-abundant epicardial fat and underscoring the need to carefully distinguish between abnormal fat infiltrating the RV myocardium and fat in the atrioventricular groove. Fat suppression helps distinguish epicardial fat from the unaffected RV wall, although failure to distinguish normal epicardial fat from pathologic RV infiltration may result in a misdiagnosis and/or overdiagnosis of ARVC.[66] ARVC should be kept distinct from both fatty infiltration of the right ventricle and adipositas cordis. It is well known that a certain

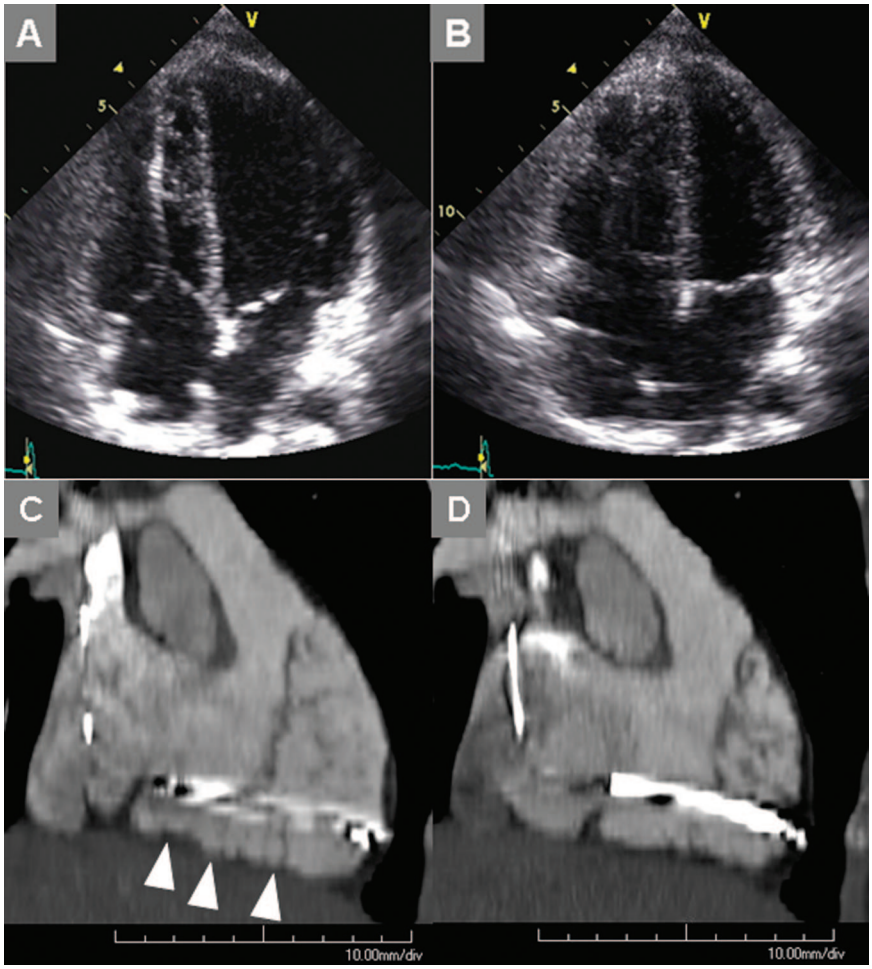

Figure 3. Transthoracic echocardiogram at end diastole (A) and end systole (B) indicates RV dysfunction in a 32-year-old woman who underwent defibrillator placement shortly after surviving sudden cardiac death. She was then referred for cardiac computed tomography to assess for possible ARVC. Maximum-intensity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

amount of intramyocardial fat is present in the RV anterolateral and apical regions, even in the normal heart, and that intramyocardial and epicardial fat increases with increasing body weight and age,[67,68] although the prevalence is unknown.[69–71] However, both the fibrofatty and fatty variants of ARVC show, besides fatty replacement of the RV myocardium, degenerative changes in 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 LGE in the corresponding location to reduce the number of false-positive imaging-based diagnoses.

Among CMR criteria, global and regional function is most useful in the diagnosis and is very reproducible.[72] RV regional dysfunction often precedes global dysfunction and affects the triangle of dysplasia. Regional functional changes include focal hypokinesis, dyskinesis, and aneurysms (online-only Data Supplement II). 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.

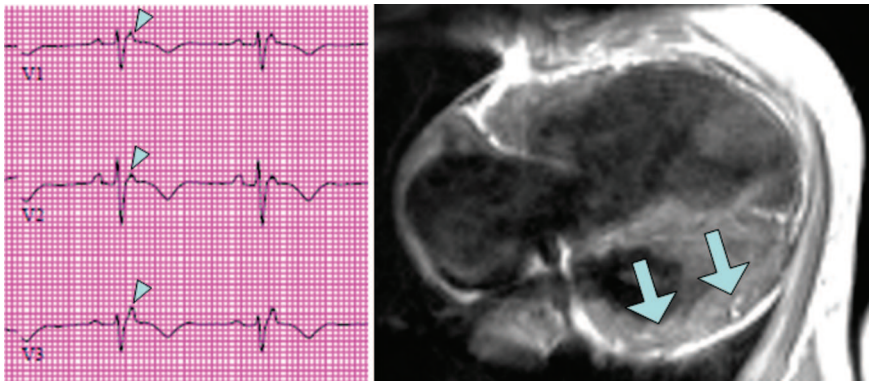

Figure 4. ECG of a patient who presented with fatigue demonstrates classic ε waves of ARVC (left, arrowheads). Dark-blood CMR image shows extensive fatty infiltration that also involves the LV myocardium (right, arrows).

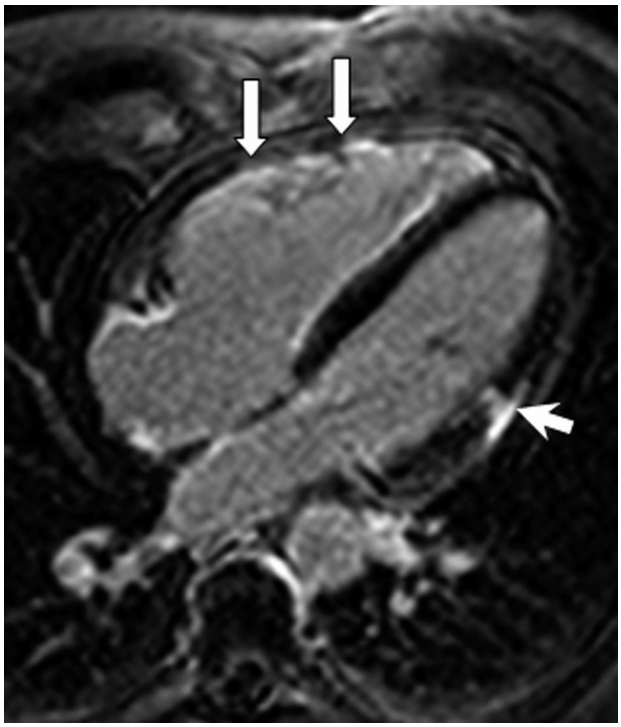

Figure 5. LGE image in the horizontal long-axis plane shows diffuse hyperenhancement of the RV myocardium, suggestive of fibrosis (arrows). Also shown is an area of focal hyperenhancement in the lateral LV myocardium (arrowhead).

Evaluation of plakophillin-2 (PKP2) mutation-positive, asymptomatic, first-degree relatives revealed minor crinkling contractions in the RV base that resembled an accordion.[73] 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 noninvasively demonstrate RV fibrosis (Figure 5) and is an essential component of the CMR examination of patients with suspected ARVC.[63] The extent of RV myocardial fibrosis is correlated with the degree of RV dysfunction, and it predicts inducibility of ventricular arrhythmias.[63] LGE also assists in distinguishing phenocopies of ARVC-like sarcoidosis, which occasionally results in isolated cardiac involvement.[74] Multiple, patchy regions of LV and septal hyperenhancement favor a diagnosis of sarcoidosis[75] 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 course.[76] Histopathologic data suggest an inflammatory component in left-dominant arrhythmogenic cardiomyopathy; further studies are needed to define the potential utility of T2 imaging 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 posterolateral LV epicardium.[73] Recently, tagged cine CMR has revealed regional LV dysfunction in the posterolateral LV wall in patients with early ARVC, even in the presence of normal global function.[77] Midmyocardial hyperenhancement by LGE, which may be seen in DCM, and subepicardial hyperenhancement have been reported in ARVC, particularly in desmoplakin mutation carriers.[78] This underscores the limitations in defining the underlying genetic abnormality by imaging phenotype alone. Individual patient assessment continues to require aggregate data assessment–history, examination, serologies, ECG, and imaging–in making the correct diagnosis.

ARVC: Current Status of Genetics

Since the discovery of the first ARVC locus in 1994,[79] multiple disease loci have been mapped, but the disease-causing genes remained elusive (Table 2).[46,80–88] The genetic cause of the recessive variant Naxos syndrome was elucidated first, as it is a highly penetrant disease with a clearcut cutaneous phenotype.[88] 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 3 separate families

Table 2. Genetic Causes of ARVC

Authors, Reference	Gene Symbol	Gene	Chromosomal Location	OMIM*	Mode of Inheritance	Comment
McKoy et al[88]	*JUP*	Plakoglobin	17q21	#173325	Autosomal-dominant	Naxos disease
Asimaki et al[80]				#601214	Autosomal-recessive	
Rampazzo et al[85]	*DSP*	Desmoplakin	6p24	#125647	Autosomal-dominant	Carvajal syndrome
Norgett et al[83]				#605676	Autosomal-recessive	
Gerull et al[46]	*PKP2*	Plakophilin-2	12p11	#602861	Autosomal-dominant	
Pilichou et al[84]	*DSG2*	Desmoglein-2	18q12	#125671	Autosomal-dominant	
Syrris et al[86]	*DSC2*	Desmocollin-2	18q12	#125645	Autosomal-dominant	
Extradesmosomal genes						
Tiso et al[87]	*RYR2*	Ryr2	1q42–q43	#180902	Autosomal-dominant	CPVT
Beffagna et al[81]	*TGF-β3*	TGF-β3	14q23–q24	#190230	Autosomal-dominant	
Merner et al[82]	*TMEM43*	TMEM 43	3p25	#612048	Autosomal-dominant	

CPVT indicates catecholaminergic polymorphic ventricular tachycardia.

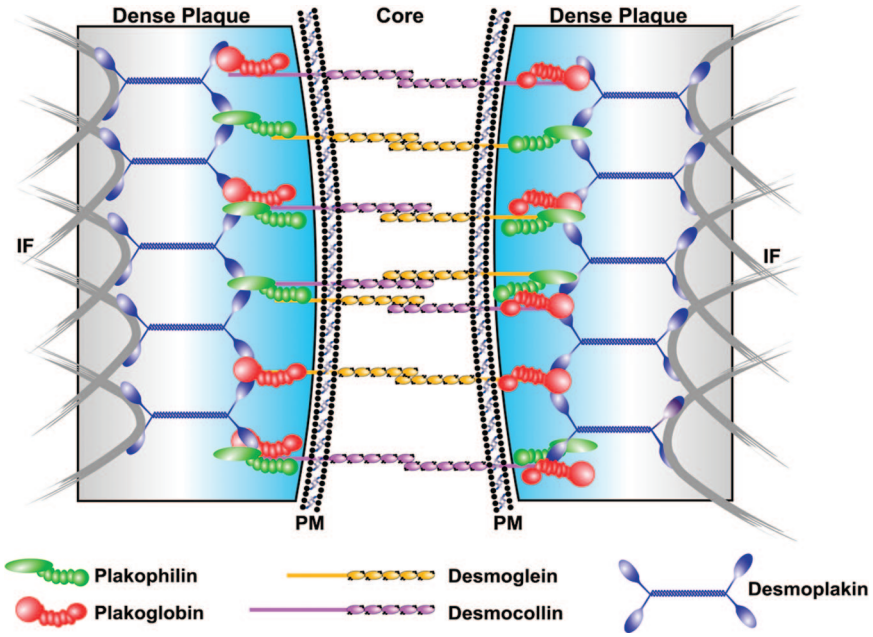

Figure 6. Components of the intercellular mechanical junction, or desmosome, between cardiomyocytes are shown. IF indicates intermediate filaments; PM, plasma membrane. Reproduced with permission from Basso et al.[56]

assemble (Figure 6)[56] to form desmosomal cadherins (desmoglein and desmocollin), armadillo proteins (plakoglobin and PKP), and plakins (desmoplakin).

A plakoglobin deletion was first found in Naxos disease.[88] This was followed by the discovery of mutations in desmoplakin,[85] PKP2,[46] desmoglein-2,[84] desmocollin-2,[86] and plakoglobin[80] in the dominant forms. A recessive mutation of desmoplakin has been reported in another cardiocutaneous disease, Carvajal syndrome.[83] Thus, ARVC was found to be mainly a disease of the desmosome,[56] and PKP-2 is the most frequently identified gene.[89]

Extradesmosomal genes implicated in ARVC include genes encoding the cardiac ryanodine-2 receptor,[87] transforming growth factor-β3,[81] and transmembrane protein 43.[82] Mutations in the gene for the cardiac ryanodine-2 receptor cause ARVC2, characterized by effort-induced polymorphic ventricular arrhythmias and sudden death at a young age. The ARVC2 phenotype is more similar to catecholaminergic polymorphic ventricular tachycardia than it is to ARVC, because affected individuals do not show the typical ECG features and structural abnormalities and are limited to mild or absent RV hypokinesis. Mutations in the untranslated regions of transforming growth factor-β3 have been identified in 1 large family and an unrelated proband with ARVC1 linkage (locus 14q24.3).[81] 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 transmembrane protein 43 gene has been identified in the ARVC5 phenotype in the Newfoundland founder population.[82] 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 transforming growth factor-β3 and transmembrane protein 43 contribute to ARVC is missing, and these extrademosomal genes are currently screened in just a few research laboratories. Comprehensive mutation screening of the 5 desmosomal genes (*JUP*, *DSP*, *PKP2*, *DSG2*, and *DSC2*) for ARVC is routinely carried out by sequence analysis. This approach can detect rare variants in at least 30% to 60% of probands, according to different cohorts.[90]

PKP-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.[86,91–95] For instance, the high prevalence of *PKP2* mutations (70%) among ARVC families in the Netherlands can be ascribed to founder effects.[86] Preliminary genotype-phenotype correlations suggest that *PKP2* ARVC patients usually present with the classic, right-dominant disease, whereas 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.[78,94,96] Finally, preliminary genotype-phenotype data suggest that disease severity is greater in double-mutations carriers, further emphasizing the need to screen all known disease-causing genes even after isolation of a pathogenic mutation.[97,98]

ARVC: Benefits and Limitations of Genetic Testing

Candidates for genetic screening include both index cases and family members of gene-positive ARVC probands.[56,89,90]

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 an ARVC diagnosis, whereas a negative genetic screening is noncontributory. Approximately 50% of ARVC probands do not carry a defect in a known desmosomal gene. On the other hand, identification of a rare genetic variant raises the index of suspicion but it cannot be diagnostic per se. The latter uncertainty is typical for mis-

Table 3. Phenotypic Clues Linking Imaging to Nonhypertrophic Genetic Cardiomyopathies*

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

*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.

‡Note that left-dominant arrhythmogenic cardiomyopathy may present with preserved LV size and systolic function.

sense mutations and reflects the marked allelic heterogeneity of the main desmosomal genes as well as the high prevalence of private mutations.

When a rare genetic variant is identified in ARVC, there are 2 possibilities: (1) the genetic variant has been previously reported as causally linked to ARVC, and in such cases, the diagnosis can be confirmed, or (2) mutation screening yields a novel genetic variant. In the latter (most frequent) situation, pathogenicity must be proved by traditional criteria, as with other heritable cardiomyopathies: (1) absence of the variant in a significant number of healthy individuals; (2) clinical correlation within families, that is, cosegregation with the disease; (3) a change in amino acid polarity and/or size; (4) a change involving a conserved amino acid; (5) localization of the variant within a functional protein domain; and (6) in vitro functional studies.

PKP2 mutation variants require careful interpretation.[86,91,93,95] In fact, increasing evidence suggests that some *PKP2* mutations labeled as "pathogenic" may not be causal because they have been subsequently identified in healthy controls. Recently, Xu et al[97] demonstrated that among 38 ARVC index cases carrying *PKP2* variants, 9 were compound heterozygotes and 16 were double heterozygotes; that is, they showed an additional mutation in another desmosomal gene. These findings suggest that many *PKP2* mutations may have a contributory rather than a causal role 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.[90] 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. Cosegregation 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 counseling 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 lifelong clinical evaluation owing to the 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 by 5-fold, because acute volume overload and stretching of the right ventricle during effort as well as sympathetic stimulation are major triggers of ventricular arrhythmias. Detection of asymptomatic individuals affected by ARVC at preparticipation 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 always be forbidden. Noncompetitive sports may be allowed, provided that regular follow-up assessments are performed.

Genetic testing that identifies noncarriers, who represent ≈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.[56,90] 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 the long-term clinical significance is for currently asymptomatic mutation carriers. Even in the case of *LMNA* 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 is not based on solid, prospective, longitudinal data. The fact that many mutations are unique, the so called "private mutations," will continue to limit efforts to provide broad recommendations. As recommended by a recent expert panel,[99] referral of patients and families with heritable cardiomyopathies to centers with genetic expertise should be strongly considered.

The major obstacle for 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 evaluations 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 in individuals who are already at risk of sudden death. Obstacles to widespread myocardial characterization and precise diagnosis by 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.

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