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MINI-FOCUS ISSUE ON CARDIOMYOPATHIES AND GENETIC COUNSELING

EDITORIAL COMMENT

The Ever-Expanding Landscape of Cardiomyopathies

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The second half of the 20th century saw the emergence of a disease entity, referred to as cardiomyopathies: a group of myocardial diseases associated with a risk of heart failure and sudden death. The curiosity and dedication of many minds to uncover this collection of conditions led to significant progress in the recognition of the clinical and pathological features of cardiomyopathies. Initially, this was manifest as a predominantly postmortem diagnosis. Subsequently, the clinical recognition of the cardiomyopathies has evolved over time. In 1990, the first myopathic disease due to a point mutation in the β-myosin heavy chain gene was identified in a French-Canadian family with hypertrophic cardiomyopathy (HCM) (1,2). This finding initiated a new era of cardiomyopathy research, extending the care from individual patients to entire families.

With the advent of next-generation genetic sequencing and multimodality cardiac imaging, the phenotype spectrum and genetic architecture of the 3 main cardiomyopathies, dilated cardiomyopathy (DCM), HCM, and arrhythmogenic right ventricular cardiomyopathy (ARVC) (**Figure 1**), are increasingly recognized and clinically relevant genotype-phenotype-risk associations have become evident. Patients with DCM, characterized by idiopathic left ventricular or biventricular dysfunction and dilatation often present in the third to fifth decade of life with mild symptoms (3,4). Patients with DCM frequently have ventricular arrhythmias and 30% die suddenly (5). Although ventricular arrhythmias were traditionally thought to occur at a later stage of the disease in DCM with symptomatic heart failure, recent evidence has indicated that certain genetic forms are significantly arrhythmogenic even during the early course of the disease (6–8). Beyond the widely recognized lamin A/C (*LMNA*), mutations in genes encoding filamin C *(FLNC),* desmoplakin *(DSP),* phospholamban *(PLN),* and RNA binding motif protein 20 *(RBM20)* have been associated with a substantial risk of life-threatening ventricular arrhythmias despite only mild ventricular dysfunction (8–11). Mutations in the titin gene (*TTN*), the most prevalent genetic substrate of DCM, are associated with a high incidence of ventricular arrhythmias and particular susceptibility to environmental stressors, such as viral infection, immune response, and toxic exposure (12). Genetic risk stratification helps in decision-making for the need of implantable cardioverter-defibrillator therapy. However, present knowledge of the genetic background explains only approximately 30% to 35% of DCM cases, hindering the precision care of many patients and families (13).

HCM often has a silent course. Nevertheless, a sizeable proportion of patients present with angina, dyspnea, palpitations, syncope, or sudden cardiac death (SCD). In hypertrophic obstructive cardiomyopathy, nearly 70% of all deaths are sudden (14). Mutations in the β-myosin heavy chain gene, *MYH7,* result in an earlier and more severe phenotype than other HCM forms (15). Patients with sarcomeric gene mutations are diagnosed at a younger age and have a

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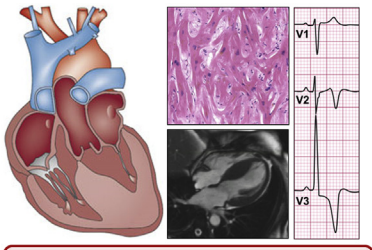
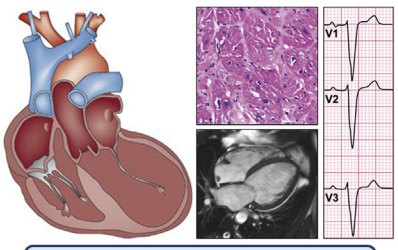
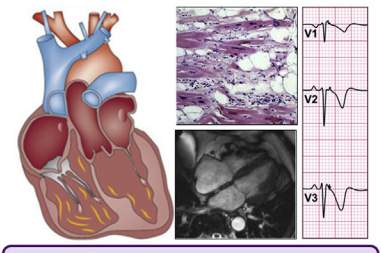
FIGURE 1 The Clinical and Genetic Characteristics of Hypertrophic, Dilated, and Arrhythmogenic Cardiomyopathies







	Hypertrophic cardiomyopathy	Dilated cardiomyopathy	Arrhythmogenic cardiomyopathy
Prevalence	≈1:500	≈1:250	≈1:5000 to 1:2000
Typical Clinical Presentation	**Age at presentation:** 25-40 years **Symptoms:** syncope, exercise intolerance palpitations, dyspnea, SCA or SCD	**Age at presentation:** 20-50 years **Symptoms:** fatigue, dyspnea, dizziness, exercise intolerance, SCA or SCD	**Age at diagnosis:** 20-45 years **Symptoms:** syncope, palpitations, dyspnea, SCA or SCD
Diagnosis	**Methods:** Echocardiography, CMR **Criteria:** LV wall thickness of ≥15 mm* LVOTO = peak LVOT pressure gradient ≥30 mm Hg	**Methods:** Echocardiography or CMR **Criteria:** unexplained LVEF <50%	**Methods:** ECG, Echocardiography, CMR SAECG, Holter monitoring, FHx, genetic test, EMB **Criteria:** revised Task Force criteria
Risk Factors for Sudden Cardiac Death	• unexplained syncope • LVH ≥30 mm • NSVT • extensive LGE • LVOTO ≥50 mm Hg • FHx of SCD <40 years and/or HCM-SCD	• ↓LVEF • LGE • ↓age at diagnosis • T-Wave alternans • *LMNA, FLNC, DSP, PLN,* or *RBM20* mutation	• male sex • ↑PVC count/24 hour • ↓age at diagnosis • NSVT • cardiac syncope • ↓RVEF • Number of leads with TWI
Mortality	**Annual SCD mortality:** ≈1% **Annual mortality:** ≈3%	**Annual SCD mortality:** ≈2–3% **Annual mortality:** ≈5–6%	**Annual rate of VT/VF/SCD:** ≈2–3% **Annual mortality:** ≈1%
Genetics	**Genetic test diagnostic yield:** ≈65% **Affected structures:** cardiac sarcomere **Common genes:** *MYH7, MYBPC3*	**Genetic test diagnostic yield:** ≈30-35% **Affected structures:** diverse structures **Common genes:** *TTN, LMNA, MYH6, SCN5A*	**Genetic test diagnostic yield:** ≈65% **Affected structures:** cardiac desmosome **Common genes:** *PKP2, DSP, DSG2, PLN*
Implications of Genetic Testing	**Diagnostic:** no **Risk stratification:** no **Management:** no **Presympt. diagnosis in the family:** yes	**Diagnostic:** no **Risk stratification:** yes **Management:** yes **Presympt. diagnosis in the family:** yes	**Diagnostic:** no **Risk stratification:** no **Management:** no **Presympt. diagnosis in the family:** yes
Management	**Drug therapy:** β-blockers or non-DHP CCB disopyramide **Interventional:** septal ablation (HOCM) **Surgery:** septal myectomy (HOCM) **Cardiac device:** ICD in high-risk patients	**Drug therapy:** standard therapy for HF **Cardiac device:** ICD or CRT-P/D in high-risk patients	**Drug therapy:** β-blockers HF therapy (if indicated) **Cardiac device:** ICD in high-risk patients

*In the presence of family history of HCM, left ventricular wall thickness of ≥13 mm is diagnostic for HCM. CCB = calcium channel blocker; CMR = cardiac magnetic resonance imaging; CRT-P/D = cardiac resynchronization therapy pacemaker/ defibrillator; CT = computed tomography; DHP = *dihydropyridine;* ECG = electrocardiogram; EMB = endomyocardial biopsy; FHx = family history; HCM = hypertrophic cardiomyopathy; HF = heart failure; HOCM = hypertrophic obstructive cardiomyopathy; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LV = left ventricle; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; LVOTO = left ventricular outflow tract obstruction; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular contraction; RVEF = right ventricular ejection fraction; SAECG = single averaged electrocardiogram; SCA = sudden cardiac arrest; SCD = sudden cardiac death; TWI = T-wave inversion; VF = ventricular fibrillation; VT = ventricular tachycardia.

higher rate of familial SCD (16,17). The risk stratification in patients with HCM is based on a prediction model, which quantifies the risk of life-threatening arrhythmias during the following 5 years based on clinical variables (18). However, precision treatment of patients with HCM is only in its early days. Drugs that alter the myofilament calcium sensitivity and calcium homeostasis such as blebbistatin, diltiazem, and ranolazine, modifiers of myocardial energetic substrates, inhibitors of mitogen-activated protein kinase and mammalian target of rapamycin pathways, as well as genome editing and gene transfer technologies are currently under investigation and may enable precision therapy for treatment of HCM in the near future.

ARVC is genetic heart disease with a progressive course and a risk of SCD. In the advanced stages, it is characterized histopathologically by necrosis and fibrofatty replacement of the right ventricular myocardium, which may lead to progressive heart failure and increased susceptibility to SCD (19). However, ARVC may be manifest with life-threatening ventricular arrhythmias before the development of clinical structural heart disease (19). Due to its variable phenotype, there is no single gold standard for the diagnosis of ARVC. Therefore, the Task Force diagnostic criteria were proposed in 1994, and then revised in 2010 to improve the sensitivity but maintaining diagnostic specificity (19). During the past decade, ARVC has been increasingly recognized as a biventricular disease with involvement of the left ventricle to a lesser extent. Also, left-dominant forms of disease have been reported. These observations have resulted in a broader term, arrhythmogenic cardiomyopathy, to reflect the spectrum of arrhythmogenic cardiomyopathies (20). Recently, a prediction model has been proposed to stratify the risk of life-threatening arrhythmias in patients with ARVC, and tailor the therapy according to an individual patient's needs (21).

Most cardiomyopathies are not rare and are often seen by cardiologists, molecular geneticists, and pathologists. Because the phenotype in cardiomyopathies appears to be influenced by a variety of genetic and environmental factors, it is not uncommon to be faced with both a diagnostic and challenging therapeutic situation in patients with cardiomyopathies. The ultimate need for improved care of patients mandates the reporting of such rare experiences in case reports or case series to enable the transfer of knowledge between clinical specialists.

For the purpose of promoting the understanding, recognition, and precision management of patients with cardiomyopathies, *JACC: Case Reports* launched this issue on inherited cardiomyopathies. Carreras-Mora et al. (22) describe a case of cardiogenic shock caused by right ventricular Takotsubo syndrome. The authors emphasize the importance of recognizing this rare condition because patients with shock might benefit more from phosphodiesterase-3 inhibitors than treatment with dobutamine, which can exacerbate the condition. Binder et al. (23) describe a new mutation in the *FHL1* gene, which segregated with a phenotype of HCM, neuromuscular disease, and/or SCD, and underscore the implications of *FHL1* screening in patients and families with HCM. Gi et al. (24) report a large atrial myxoma in a patient with apical HCM. Concomitant occurrence of myxoma and HCM is characterized in LEOPARD syndrome, a rare multiple congenital anomaly predominantly

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affecting the skin, face, and heart. The authors have excluded LEOPARD syndrome because of the absence of extracardiac manifestations. Based on this patient and the previous 6 reports of atrial myxoma in patients with HCM, the authors raise the hypothesis that there may be a link between the 2 conditions, particularly based on the shared pathogenetic activation of RAS/MASK pathway in LEOPARD syndrome and HCM, and the fact that *RAS* is the most common oncogene in humans. Ali et al. (25) describe a case of a patient with hypertrophic obstructive cardiomyopathy and accompanying aortic valve stenosis. In this patient, percutaneous coronary intervention in the proximal left-anterior descending coronary artery, associated with occlusion of the first septal coronary artery, resulted in substantial reduction in the left ventricular outflow tract gradient and improvement in the left ventricular function. These observations illustrate the expanding spectrum of cardiomyopathies. The evolving knowledge of the genetics, mechanisms of disease, and determinants of phenotype in cardiomyopathies will result in better risk stratification and improve the outcome in patients with cardiomyopathy.

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