Cardiomyopathies

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Abstract
The cardiomyopathies are a heterogeneous collection of heart muscle disorders with diverse genetic and non-genetic aetiologies. The advent of molecular genetics and next-generation sequencing has transformed understanding of the mechanisms of disease underlying many forms of cardiomyopathy, and unlocked the prospect of personalized medicine based on knowledge of an individual's genetic variants. Current management of patients with inherited cardiomyopathies is beginning to integrate knowledge of individual genomic profiles with advances in cardiovascular imaging. This has enhanced surveillance potential for high-risk individuals and begun to facilitate diagnosis, appropriate risk stratification and prognostication. This review provides an introduction to the cardiomyopathies, focusing on hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic cardiomyopathy and left ventricular non-compaction, giving an overview of their aetiological complexity, diagnosis and contemporary clinical management.

Key points

•Hypertrophic cardiomyopathy is the most common monogenic cardiac disorder. It is defined by the presence of unexplained left ventricular hypertrophy and is genetically primarily a disease of sarcomeric and associated myofilament proteins

•Dilated cardiomyopathy (DCM) has a broad clinical spectrum ranging from genotype-positive, phenotype-negative disease identified on cascade screening, to the hypokinetic, non-dilated phenotype to classical DCM with biventricular dilatation and systolic impairment

•Restrictive cardiomyopathy is rare and characterized by diastolic impairment from restrictive ventricular filling but with preserved systolic function. It results from a diverse range of infiltrative, non-infiltrative and storage disorders, whose clinical presentation is largely that of heart failure

•Arrhythmogenic cardiomyopathy is a phenotypic response to disruption of desmosomal function. It is characterized pathologically by myocyte loss and progressive fibro-fatty replacement that can involve either or both ventricles, and clinically by a high frequency of ventricular arrhythmias and propensity to sudden cardiac death

•Left ventricular non-compaction (LVNC) is characterized by abnormal trabeculations of the left ventricle. It can be associated with neuromuscular disease and chromosomal defects, or isolated. LVNC can be complicated by thromboembolism, heart failure and sudden cardiac death

Cardiomyopathies – definition and classification

Cardiomyopathies are a group of heart muscle disorders defined by structural and functional abnormalities of the ventricular myocardium not explained by obstructive coronary artery disease or abnormal loading conditions.[1] Traditional taxonomies have classified cardiomyopathies first as primary or secondary disorders, and then based on gross morpho-functional appearances[1] into hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy and, more recently, left ventricular non-compaction (LVNC). However, the practical distinction between primary and secondary cardiomyopathy can be challenging and not reflect the complexity of clinical presentation. In contrast, subdivision of the major phenotypes into familial (genetic) and non-familial (non-genetic) types informs diagnosis and management (Figure 1).[1] Familial cardiomyopathies are largely monogenic disorders, reflecting a single-gene defect whose ultimate phenotypic expression reflects a complex interaction with modifier genes and environmental exposures.

A more comprehensive genotype–phenotype nosology has been advocated, in particular the MOGE(S) nomenclature, endorsed by the World Heart Federation.[2] The MOGE(S) descriptive classification emulates the TNM grading systems for tumours, integrating morphofunctional phenotype (M), organ/system involvement (O), genetics (inheritance pattern) (G), aetiological annotation (E) and an optional stage (S) reflecting American Heart Association stage (A–D) and New York Heart Association (NYHA) functional class.

Hypertrophic cardiomyopathy

With a prevalence of 1:500, HCM is the most common inherited cardiomyopathy.(Table 1) It is defined in adults by ≥15 mm ventricular wall thickening in any left ventricle (LV) myocardial segment on cardiac imaging (not explained solely by loading conditions).[3] The LV hypertrophy (LVH) is characteristically asymmetrical and should be differentiated from acquired causes of LVH, such as systemic hypertension, aortic stenosis, infiltrative disorders and athlete's heart.

Molecular genetics and pathogenesis

HCM is inherited as an autosomal dominant trait with variable penetrance, and demonstrates substantial locus and allelic heterogeneity. Molecular genetic screening can detect pathogenic genetic variants in around 60% of individuals diagnosed clinically with HCM (Figure 2). Sporadic cases can reflect true *de novo* mutations, incomplete penetrance in a parent or, uncommonly, non-dominant modes of genetic transmission. Genetic testing is recommended for those fulfilling the diagnostic criteria for HCM, to enable – if positive – cascade genetic screening for the specific variant in family members, followed by clinical evaluation with or without long-term follow-up or discharge as appropriate. Of individuals with known mutations, 70% harbour mutations within either the β-myosin heavy chain (*MYH7*) or myosin-binding protein C (*MYBPC3*) gene.[4] *MYH7 is* associated with high disease penetrance and moderate to severe LVH, while *MYBPC3* manifests in mid to late adulthood with mild to moderate LVH and a relatively good prognosis. Troponin T2 gene (*TNNT2*) mutations account for around 5% of disease, with a high incidence of sudden cardiac death (SCD) even with minimal LVH.

Importantly, lack of a sarcomeric mutation does not exclude familial HCM. Functional analysis of mutant sarcomeres and clinical ^{31}P-magnetic resonance spectroscopy data have revealed profligate ATP usage by mutant sarcomeres and consequent energetic compromise in HCM hearts, irrespective of the degree of LVH, leading to the concept of HCM as primarily a disease of myocardial energy deficiency.[5] A number of disorders not involving mutations in sarcomeric protein genes – ranging from rare inherited metabolic/storage disorders, primary mitochondrial disease, neuromuscular disorders and genetic syndromic disorders, to non-genetic infiltrative disorders (amyloidosis) or endocrinopathies (acromegaly or phaeochromocytoma) – can also present with unexplained LVH. Prompt recognition of these and the presence of non-cardiac symptoms/signs (muscle weakness, retinopathy, gait disturbance, cutaneous lesions such as angiokeratomas or café-au-lait spots) can for some disorders enable aetiology-specific/genotype-guided management ..

Clinical presentation

HCM presentations include aborted sudden death and incidental identification on imaging or through cascade screening. However up to 80% of patients remain asymptomatic. When present, symptoms include dyspnoea, fatigue, chest pain, palpitations and presyncopal/syncopal episodes. The pathophysiological mechanisms responsible for these include impaired cardiac filling/diastolic function and/or emptying, microvascular dysfunction

and arrhythmia. SCD is the most feared complication of HCM, with an annual event rate of 1–2% in children/adolescents and 0.5–1% in adults. Up to 20% of patients experience early-onset heart failure (HF), at a median age of 48±19 years. HF in HCM is broadly attributable to: (1) HF with preserved ejection fraction; (2) systolic dysfunction induced by LV outflow tract obstruction (LVOTO); or (3) 'burnt-out' HCM characterized by progressive LV dilatation, wall thinning and systolic dysfunction. One in five patients also experiences atrial fibrillation, associated with a high risk of embolic stroke.

Clinical assessment

Clinical assessment aims to identify high-risk features of HCM associated with adverse outcomes, including: (1) unexplained syncope; (2) first-degree family history of SCD at a young age (or any age if HCM was confirmed); (3) non-sustained ventricular tachycardia (VT; ≥3 consecutive ventricular extrasystoles at ≥120 beats per minute); (4) abnormal blood pressure responses during exercise; and (5) maximal LV wall thickness >30 mm. Other factors influencing risk profile include age, left atrial diameter, LVOTO and extent of late gadolinium enhancement on cardiac magnetic resonance (CMR) imaging.[6] Clinical examination can be unremarkable, particularly in individuals with minimal LVOTO. Those with resting LVOTO can exhibit specific findings, including a bisferiens pulse, forceful and sustained apical impulse, audible fourth heart sound (S4) and classical crescendo–decrescendo systolic murmur at the lower left sternal edge that increases with the Valsalva manoeuvre (because of reduced preload, reducing LV filling and worsening LVOTO).

Investigations

Non-invasive imaging of cardiac structure and function with transthoracic and Doppler echocardiography is widely available and plays a central role in diagnosis and evaluation. This includes detection of unexplained LVH (most commonly in the basal anterior septum; other variants include apical HCM), assessment for LVOTO (defined as a peak Doppler LV outflow tract gradient ≥30 mmHg), mitral leaflet and papillary muscle abnormalities (including systolic anterior motion leading to dynamic LVOTO) and evaluation of LV diastolic dysfunction. LVOT gradients ≥5 mmHg mark the level for intervention. CMR imaging enables identification of subtle features (e.g. myocardial crypts, papillary muscle abnormalities) or very localized hypertrophy in difficult cases, myocardial characterization for prognostic assessment and pre-intervention planning.[6] Myocardial fibrosis with late gadolinium enhancement can aid diagnosis of specific causes in some cases. Thus, CMR has been recommended for consideration in all HCM patients at baseline.[6]

The electrocardiogram (ECG) is abnormal in most patients at presentation and can show atrial fibrillation, pathological Q waves, left atrial abnormalities, LVH by voltage criteria and/or associated ST–T wave changes. Further relevant investigations include ambulatory ECG monitoring as part of risk stratification of SCD, exercise testing to quantify functional capacity or assess for inducible arrhythmia or dynamic LVOTO in the setting of symptoms, genetic testing, and selected laboratory blood testing for non-sarcomeric causes, complications or treatment monitoring (Table 2).

Management

Current European Society of Cardiology guidelines stratify treatment based on the presence of LVOTO, HF and anginal symptoms.[3] In symptomatic patients with LVOTO, therapy with β-adrenoceptor blockers and/or non-dihydropyridine calcium channel blockers (e.g. verapamil) is indicated. This uses the negatively inotropic properties of these agents to reduce LVOTO, prolong diastole (hence ventricular filling) and reduce anginal symptoms. Disopyramide can be used alone or in combination with the above, with attention to QTc and anticholinergic adverse effects. Vasodilators and diuretics are generally avoided as they can increase LVOTO, provoking syncope. Consideration of invasive treatment to reduce LVOTO is considered only in symptomatic patients (NYHA class III/IV and/or recurrent exertional syncope) despite maximally tolerated pharmacotherapy using ventricular septal myectomy or septal alcohol ablation, both of which carry a risk of atrioventricular (AV) block. Insertion of an implantable cardioverter-defibrillator (ICD) is guided by SCD risk stratification, with individualized decision-making aided by a validated risk prediction model, the HCM Risk-SCD Calculator (www.doc2do.com/hcm/webHCM.html). Other specific considerations include advice on sports participation, pre-conception counselling and management of atrial arrhythmia.[3] Importantly, patients with HCM and AF exhibit a high incidence of thromboembolic stroke, highlighting the importance of long-term oral anticoagulation (unless contraindicated) for

thromboprophylaxis in any form of AF and regardless of CHA_2DS_2-VASc score (which is not recommended in this population) (see Figure 1).

Dilated cardiomyopathy

DCM is a common phenotype resulting from diverse inherited or acquired injuries impairing cardiomyocyte systolic function. It is traditionally defined by left or bi-ventricular dilatation and impaired systolic function (i.e. abnormal ejection fraction) unexplained by loading conditions or coronary artery disease. In practice, its clinical spectrum is broad, ranging from pre-clinical/early phase (including isolated LV dilatation or arrhythmogenic manifestations) to phenotypic expression of systolic dysfunction with HF. The latter constitutes DCM (i.e. LV dilatation + hypokinesis), but now also encompasses a new proposed category of hypokinetic non-dilated cardiomyopathy.[7] DCM has an estimated prevalence of 1:2500 and represents the most frequent cause of heart transplantation.[8](Table 1)

Aetiology and genetics

The aetiology of DCM is grouped into genetic and non-genetic aetiologies (Table 3). Evidence of familial disease is present in around 20–30% patients, largely autosomal dominant inheritance but also including X-linked (dystrophinopathies – Duchenne/Becker), recessive (desminopathies) and mitochondrial variants. These include mutations in genes encoding components of the sarcomere, nuclear envelope and cytoskeleton. These are most frequently (around 25% of familial DCM) truncating mutations in *TTN*, which encodes titin, the largest human protein; this spans half the sarcomere and is involved in sarcomere stabilization and passive force enhancement.[9] Collectively, these mutations identify an impairment in force generation (sarcomere), force mechano-transduction (cytoskeleton/sarcolemma), force activation (calcium cycling) and energy generation (mitochondria) as critical factors leading to a common DCM phenotype. Non-genetic causes include anti-cancer drugs, toxins, nutritional deficiency, iron overload, electrolyte abnormalities, endocrinopathies and pregnancy.

Clinical assessment and family screening

In addition to assessing for evidence of HF, arrhythmia (including syncope), thromboembolism and family history, clinical evaluation should include a systematic search for features (‘red flags’) suggestive of uncommon non-cardiac symptoms and signs. These include muscle weakness, retinopathy, gait disturbance and clinically important DCM aetiologies, integrating findings from the personal/family history, physical examination, ECG and imaging.[7] If present, these should be followed up by further diagnostic testing as appropriate (e.g. biochemical analysis, endomyocardial biopsy, genetic testing). Initial testing in all patients includes laboratory testing and exclusion of coronary artery disease in those aged >35 years (or younger if there are significant risk factors)[7] (see Table 2). CMR is valuable in accurately assessing morphology, function and tissue characterization, which can aid recognition of specific aetiologies (e.g. myocarditis, sarcoidosis, iron overload),[10] as well as assisting risk stratification through quantification of late gadolinium enhancement associated with increased risk of SCD. Cardiac screening of first-degree relatives of an affected individual is recommended regardless of family history, with genetic testing generally reserved for those with familial disease or red flags suggestive of a specific genetic aetiology. As with HCM, identification of a causative mutation enables cascade screening of first-degree relatives If there is familial DCM but no causative mutation, first-degree relatives should be followed up for cardiac screening (echocardiogram, ECG ± Holter monitoring).

Management

Identification of a specific aetiology of DCM pragmatically informs all aspects of clinical management: proband genetic counselling, lifestyle advice, family screening, advice on contraception and risks of pregnancy, disease-specific drug therapy, threshold for device therapy (e.g. considering early primary prevention ICD in *LMNA* mutations) or transplantation referral and follow-up. General management of chronic HF is central across aetiologies and includes consideration of β-adrenoceptor blockade, renin–angiotensin–aldosterone system (RAAS)/neutral endopeptidase system inhibition, I_f current inhibition, diuretic therapy, management of arrhythmia, device therapy (including cardiac resynchronization and/or ICD implantation) and, in certain cases, cardiac transplantation (see Figure 1).

Restrictive cardiomyopathy

RCM comprises a heterogeneous group of disorders resulting in restrictive ventricular physiology, and is regarded as the least common subtype of cardiomyopathy. It is

characterized by restrictive ventricular physiology (impaired ventricular filling usually resulting from increased myocardial stiffness) with normal or near-normal ventricular size.[1,11] Systolic function is generally normal until late in the disease process.

Aetiology

RCM can result from underlying systemic or familial disorders, or be idiopathic (Table 4). Causes include infiltrative, non-infiltrative, storage and endomyocardial disorders, the latter reflecting endocardial pathology (fibrosis, fibroelastosis, thrombosis) that impairs diastolic function.[1]

Diagnosis

Clinical presentation varies by underlying aetiology, with cardiac manifestations largely those of left- or right-sided HF, arrhythmia or conduction disease. Diagnosis requires a high index of suspicion and relies heavily on echocardiography; this typically demonstrates significant diastolic dysfunction with a restrictive filling pattern, bi-atrial enlargement and non-dilated ventricles. An echocardiogram may highlight features suggestive of specific aetiologies while aiding differentiation from pericardial constriction. Determining specific aetiology usually requires careful integration of clinical findings, laboratory testing, cardiac/other imaging (which can include CMR and fluorodeoxyglucose positron emission tomography scanning, e.g. suspected cardiac sarcoidosis) and, in some cases, genetic testing and tissue histology (e.g. bone marrow, endomyocardial biopsy).[10,11]

Management

Management of RCM is that of HF (which can include device therapy or orthotopic cardiac transplantation) and, where available, specific aetiology-directed therapy. This should take into account individual patient tolerability (e.g. therapeutic phlebotomy/iron chelation in cardiac haemochromatosis, chemotherapy/autologous stem cell transplantation in AL cardiac amyloidosis).[11]

Arrhythmogenic cardiomyopathy (AC)

AC is an inherited disease of cell-to-cell junctions resulting in electrical instability and risk of SCD. AC is characterized by progressive fibro-fatty replacement in the ‘triangle of dysplasia’ between the inflow, outflow and apical portions of the right ventricle (RV), and is associated with prominent ventricular arrhythmia, HF and SCD. Phenotypes characterized by predominant LV (left-dominant AC) or bi-ventricular involvement are now well recognized, prompting transition from use of the terms arrhythmogenic RV cardiomyopathy or historical dysplasia to AC, to more accurately reflect its breadth of phenotypic expression. AC has a prevalence of 1:1000–1:5000 and is a prominent cause of SCD in young individuals (constituting around 15% of SCD in athletes).[12](Table 1) AC has both a higher incidence and severity of disease in male patients.

Genetics

AC is genetically heterogeneous and demonstrates autosomal dominant inheritance with variable penetrance and expressivity. About 50–60% of patients have mutation in genes encoding for cardiac desmosomes (adhesion complexes linking neighbouring cellular cytoskeletons); this includes plakophilin 2 (*PKP2*, most common), desmoplakin (*DSP*), junction plakoglobin (*JUP*), desmocollin 2 (*DSC2*) and desmoglein 2 (*DSG2*). Non-desmosomal mutations involving the area composita (*CTNNA3*, *CDH2*) and nuclear envelope (e.g. *TMEM43*, *LMNA*), and in other genes (e.g. *TGFB3*, SCN5A), have been described.[12] Recessive forms of AC also occur in association with desmosomal cardiocutaneous syndromes, namely Naxos disease and Carvajal’s syndrome, caused by mutations in plakoglobin and desmoplakin, respectively, with associated woolly hair and palmoplantar keratoderma.

Diagnosis

The diagnosis of early AC can be challenging. It should be suspected in survivors of SCD, especially if this occurred during exercise, and in patients lacking concomitant heart disease with asymptomatic VT of left bundle branch block configuration indicating an RV origin. Formal diagnostic criteria (2010 revised International Task Force Criteria) require integration of clinical, ECG (including Holter monitoring), genetic, imaging (particularly CMR) and, in selected cases, histopathological findings.[13] This is based on six categories: (1) global or regional dysfunction and structural alterations on imaging; (2) tissue characterization of wall from endomyocardial biopsy; (3) repolarization abnormalities on ECG; (4) repolarization/conduction abnormalities on

ECG; (5) arrhythmias on ambulatory Holter monitoring; and (6) first-degree family history or identified pathogenic mutation. Each category consist of major and minor criteria; the presence of two major, or one major and two minor, or four minor criteria constitutes a definite diagnosis of AC. In borderline cases, myocardial biopsy can aid distinction from differential diagnoses such as sarcoidosis, myocarditis or endomyocardial fibrosis, but is limited by the patchy nature of the disease.

Notably, the 12-lead ECG demonstrates repolarization and depolarization abnormalities in most patients with definite AC. This is most commonly anterior precordial T wave inversion, but can also feature right bundle branch block (usually incomplete), prolonged right precordial QRS duration and epsilon waves, reflecting regions of slowed intraventricular conduction.[12]

Disease course

Original descriptions of the natural history (of classical right-sided AC) have highlighted several phases: (1) an initial subclinical 'concealed' phase with minimal symptoms and subtle/absent findings on imaging (but nevertheless a risk of SCD, particularly on extreme exertion); (2) an overt RV electrical phase with a range of arrhythmias of RV origin (ranging from frequent ventricular ectopy to sustained VT or ventricular fibrillation (VF)), associated with palpitations, syncope or cardiac arrest, and detectable RV wall motion or structural abnormalities; and (3) diffuse RV involvement producing isolated RV failure; with subsequent progression to (4) significant LV involvement resulting in bi-ventricular failure resembling DCM.[12] The latter 'phase' has attendant risks of systemic or pulmonary thromboembolism as a result of *in situ* thrombus formation and can require cardiac transplantation for intractable HF or untreatable ventricular arrhythmias. SCD results from sustained VT or VF.

Management

Management of AC focuses largely on SCD risk stratification (highest risk in those with previous cardiac arrest, sustained VT or severe RV/LV dysfunction) and prevention (see Figure 1). ICDs are the only proven therapy to affect prognosis, but are associated with significant cumulative morbidity, necessitating appropriate patient selection. Lifestyle changes are important and require avoidance of competitive sports and endurance physical training (which result in RV distension/volume overload and acute sympathetic stimulatory surges, and accelerate disease progression). Specific interventions include β-blockers and/or class III antiarrhythmics, catheter ablation (not an alternative to ICD and usually reserved for incessant VT or frequent VT triggering ICD shocks unresponsive to drug therapy), ICD primary/secondary prevention of VT/VF and (with significant ventricular dysfunction) standard treatment of HF, including cardiac transplantation.[12]

Left ventricular non-compaction

LVNC is characterized by prominent trabeculation (most frequently at the LV apex), deep intra-trabecular recesses and a bi-layered myocardium consisting of a spongy, non-compacted endocardium and a thin compacted epicardial layer.[14] Its prevalence varies by population, with an estimated 0.01–0.3% in adults undergoing echocardiography to 4% in patients with HF, and by age at presentation, ranging from infancy to late adult life (median adult age 40–50 years).[15]

Aetiology

LVNC can be classified according to onset (congenital/acquired), presence of additional cardiac structural abnormalities (non-isolated LVNC, e.g. associated with LV outflow tract abnormalities or Ebstein anomaly), symptomatic status, familial status, presence/absence of another form of cardiomyopathy and genetic aetiology (frequent association with chromosomal defects and neuromuscular disease).[15] This range reflects the limited understanding of LVNC aetiology, with its pathogenesis variably speculated to reflect *in utero* developmental failure of myocardial compaction, activation of a common developmental programme in response to congenital heart disease, or an adaptive process to physiological (volume overload, e.g. pregnancy, or athletic training) or acquired systolic dysfunction.[15]

Genetics

LVNC has been associated with mutations in >40 genes and a number of chromosomal defects.[15] The former includes genes involved in muscular dystrophies (e.g. *DMD*, *LMNA*, *DMPK*), congenital and hereditary myopathies (e.g. *MYH7*, *RYR1*, *TPM1*, *TAZ*) and metabolic/mitochondrial disorders (e.g. *LAMP2*, *GBE1*, *SDHD*, *HADHB*). Notably, mutations in

sarcomere genes (e.g. *MYH7*, *MYBPC3*) are identifiable in a significant proportion (around 30%) of isolated LVNC.[14] However, causation has yet to be established, with attendant variable recommendations for genetic testing. LVNC is familial in 30–50% of cases, with autosomal dominant (e.g. *MYH7*), autosomal recessive, X-linked (e.g. the multisystem Barth syndrome resulting from a mutation in *TAZ*) and maternal (mitochondrial) inheritance patterns described. In view of this, first-degree relatives of index patients should undergo echocardiographic screening.[14,15]

Clinical phenotypes and diagnosis

Clinical presentation varies from identification on imaging in an asymptomatic patient to thromboembolism, syncope, end-stage HF or SCD.[14] Individuals with associated neuromuscular disease can have associated symptoms (e.g. muscle weakness, myalgia, exercise intolerance, myotonia, malignant hyperthermia during general anaesthesia).[15] A significant proportion of patients progress to HF (two-thirds) or SCD (18% in adults, up to 13% in children).[15] Reflecting the breadth of presentation, multiple clinical phenotypes are recognized, including 'benign' LVNC (normal LV size, systolic function and wall thickness), LVNC with arrhythmia, dilated LVNC, hypertrophic LVNC (usually asymmetrical septal hypertrophy), hypertrophic dilated LVNC, restrictive LVNC (rare with a poor prognosis), RV or bi-ventricular non-compaction, and LVNC with congenital heart disease.[14] Although there is no current consensus on a single set of diagnostic criteria, echocardiographic and CMR algorithms focus on the ratio of the non-compacted to compacted layer (e.g. Petersen CMR criteria: non-compacted/compacted >2.3 in diastole). To prevent overdiagnosis, other findings have been incorporated, including total burden of trabeculations and presence of scar on CMR, and advanced echocardiographic modalities assessing LV strain and torsion. Abnormalities on 12-lead ECG include hypertrophy by voltage, ST segment changes, T wave inversion, altered axis, pre-excitation and QT prolongation.[14] ECG monitoring is recommended annually in those without an ICD[15], as it frequently reveals atrial or ventricular tachyarrhythmias, and less commonly bradyarrhythmias Specific evaluation for frequently associated neuromuscular disease and chromosomal defects has been recommended in all LVNC patients.[15]

Management and prognosis

Management of LVNC focuses on standard therapy for HF, risk assessment and prophylaxis of thromboembolism and ventricular arrhythmia (including VT ablation and ICD implantation), in addition to screening of first-degree family members (see Figure 1). Overall mortality is estimated at 5–12%/year in adults, with adverse outcomes strongly dominated by the presence of HF, thromboembolism and ventricular arrhythmia.

Table 1 Summary of key findings for inherited cardiomyopathies

	HCM	AC	DCM
Prevalence	1:500	1:1000–1:2000	7–12:100,000
Histological findings	Interstitial fibrosis Cardiomyocyte enlargement and disarray Abnormal intramural coronary arterioles	Fibro-fatty infiltration Patchy fibrosis Inflammation Cardiomyocyte death Wall thinning Aneurysm formation	Cardiomyocyte hypertrophy Loss of myofibrils Interstitial fibrosis
Range of ECG findings	• Left axis deviation • Repolarization changes • Abnormal Q waves in infero-lateral territories • Deep T wave inversion	• QRS prolongation (V1–V6) • Incomplete or complete RBBB • Prolonged S wave upstroke • Epsilon wave • T wave inversion (V1, V2, V3, V4)	• Left or bi-atrial enlargement • Atrial fibrillation • Abnormal Q waves • Left bundle branch block • Ventricular ectopy, bigeminy or VT
Range of echo findings	• LV wall thickness ≥15 mm • Typically asymmetrical septal hypertrophy • Systolic anterior motion of the mitral valve • LVOTO • Left atrial enlargement • Diastolic dysfunction on Doppler imaging	• Regional RV akinesia, dyskinesia or aneurysm • Increased RVOT dimensions • Reduced RV fractional area change	• LV dilatation • Wall thinning • Global LV hypokinesia and systolic impairment • LV diastolic dysfunction • Functional mitral regurgitation • Left atrial enlargement • LV mechanical dyssynchrony • LV mural thrombus
Key disease genes	**Sarcomeric** • β-Myosin, heavy chain 7 (*MYH7*) • Myosin-binding protein C (*MYBPC3*) • Troponin T type 2 (*TNNT2*) • Troponin I type 3 (*TNNI3*) • Tropomyosin 1 (*TPM1*) • Myosin, light chain 2 (*MYL2*) • Myosin, light chain 3 (*MYL3*) • α-Actin, cardiac muscle (*ACTC1*) **Non-sarcomeric** • Cysteine and glycine-rich protein 3 (*CSRP3*) **HCM phenocopies** • γ2 regulatory subunit of AMP-activated protein kinase (*PRKAG2*) • Lysosomal-associated membrane protein 2 (*LAMP2*) • α-Galactosidase alpha (GLA) • Four-and-a-half LIM domains 1 (FHL1)	**Desmosomal** • Plakophilin 2 (*PKP2*) • Desmocollin 2 *DSC2*) • Desmoglein 2 (*DSG2*) • Desmoplakin (*DSP*) • Junction plakoglobin (*JUP*) **Extradesmosomal** • Transforming growth factor-β 3 (*TGFB3)* • Transmembrane protein 43 (*TMEM43*)	**Force generation/regulation** • α-Actin, cardiac muscle (*ACTC1*) • β-Myosin heavy chain 7 (*MYH7*) • Troponin T type 2 (*TNNT2*) • Troponin I type 3 (*TNNI3*) • Troponin C type 1 (*TNNC1*) • Phospholamban (*PLN*) **Force transduction/mechano-sensing** • Titin (*TTN*) • Dystrophin (*DMD*) • Sarcoglycan-δ (*SGCD*) • Desmin (*DES*) **Nuclear proteins/transcription** • Lamin A/C (*LMNA*) **Other** • RNA-binding motif protein 20 (RBM20)

RBBB, Right bundle branch block; RVOTO, RV outflow tract obstruction. For other abbreviations, see text.

Table 2 Suggested tests to be performed in all ('first level') and selected ('second level') patients with cardiomyopathy

	HCM	DCM	RCM
First level	CK Renal function Proteinuria Liver function tests	CK Renal function Proteinuria Liver function tests Haemoglobin and white blood cell count Serum iron, ferritin Calcium, phosphate, thyroid stimulating hormone	CK; Renal function; Proteinuria Liver function tests Haemoglobin and white blood cell count Serum iron, Ferritin Urine and plasma protein immunofixation,[a] free light chains[a]
Second level	alpha-Galactosidase A levels (or DNA for AFD suspected in women) Lactic acid[b]; myoglobinuria[b] Urine and plasma protein immunofixation,[a] free light chains[a]	Organ and non-organ specific serum autoantibodies; Titres for suspected infection: coxsackievirus, echovirus, influenza virus; HIV; Borrelia bugdorferi (suspected Lyme disease), Chagas disease (geographic exposure). Thiamine (alcohol abuse, nutritional deficiency). Urinary/plasma catecholamines (suspected phaeochromocytoma) Serum angiotensin converting enzyme (sarcoidosis)	Serum angiotensin converting enzyme (sarcoidosis) Organ and non-organ specific serum autoantibodies

AFD, Anderson–Fabry disease; CK, creatine kinase; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy; TTR, transthyretin.
[a]AL amyloidosis.
[b]Mitochondrial diseases.

Source: Reproduced from Rapezzi et al.[10]

Table 3 Aetiology of DCM

Group	Subtype disease or agent	Comments
Genetics		
Main genes associated with predominant cardiac phenotype:		
	Titin (TTN)	~20–25% of familial DCM; autosomal-dominant (AD) mode
	Lamin A/C (LMNA)	~6%; AD mode; associated with AVB and VA; can also cause Limb-Girdle myopathy
	Myosin heavy chain (MYH7)	~4%; AD mode
	Troponin T (TNNT2)	~2%; AD mode
	Myosin-binding protein C (MYBPC3)	~2%; AD mode
	RNA-binding Motif-20 (RBM20)	~2%; AD mode
	Myopalladin (MYPN)	~2%; AD mode
	Sodium channel alpha unit (SCN5A)	~2%; AD mode
	BaCl2-associated athanogene 3 (BAG3)	~2%; AD mode
	Phospholamban (PLN)	~1%; AD mode; low QRS voltage on ECG
Neuromuscular disorders		
	Duchenne muscular dystrophy (DMD)	X-linked mode; CK elevation; paediatric patients
	Becker muscular dystrophy (BMD)	X-linked mode; CK elevation; paediatric or adult patients
	Myotonic dystrophy or Steinert (MD)	AD mode; AV block
Syndromic diseases		
	Mitochondrial diseases	Mitochondrial inheritance syndromic expression including skeletal myopathy
	Tafazin (TAZ/G4.5)	X-linked mode; paediatric patients; Barth syndrome
Drugs		
	Antineoplastic drugs	Anthracyclines; antimetabolites; alkylating agents; Taxol; hypomethylating agent; monoclonal antibodies; tyrosine kinase inhibitors; immunomodulating agents
	Psychiatric drugs	Clozapine, olanzapine; chlorpromazine, risperidone, lithium; methylphenidate; tricyclic antidepressants;
	Other drugs	Chloroquine; all-trans retinoic acid; antiretroviral agents; phenothiazines
Toxic and overload		
	Ethanol	Risk proportional to entity and duration of alcohol intake. Frequent good response after withdrawal
	Cocaine, amphetamines, ecstasy	Chronic users
	Other toxic	Arsenic; cobalt; anabolic/androgenic steroids
	Iron overload	Transfusions; haemochromatosis
Nutritional deficiency		
	Selenium deficiency	Rare, high frequency in some regions in China (Keshan disease)
	Thiamine deficiency (Beri-Beri)	Favoured by malnutrition, alcohol abuse. High-output dilated cardiac failure
	Zinc and copper deficiency	Possible contributors to DCM
	Carnitine deficiency	Paediatric patients
Electrolyte disturbance		
	Hypocalcemia, hypophosphatemia	
Endocrinology		
	Hypo- and hyper-thyroidism	
	Cushing/addison disease	
	Phaeocromocytoma	
	Acromegaly	
	Diabetes mellitus	
Infection		
	Viral (including HIV), bacterial (including Lyme disease), mycobacterial, fungal, parasitic (Chagas disease)	DCM caused by infectious myocarditis. Atrio-ventricular block (AVB) in Lyme disease. Chagas' disease: DCM develops after a long latent infection
Auto-immune diseases		
Organspecific		
	Giant-cell myocarditis (GCM)	Multinucleated giant cell; frequent AV block and ventricular arrhythmia
	Inflammatory DCM	DCM caused by biopsy-proven, non-infectious myocarditis
Not organ specific		
	Polymyositis/dermatomyositis; Churg–Strauss syndrome; Wegener's granulomatosis; systemic lupus erythematosus, sarcoidosis	In cardiac sarcoidosis there is granulomatous myocarditis; AV block is frequent DCM is possible but uncommon in these diseases
Peripartum		Risk factors: multiparity, African descent, familial DCM, autoimmunity

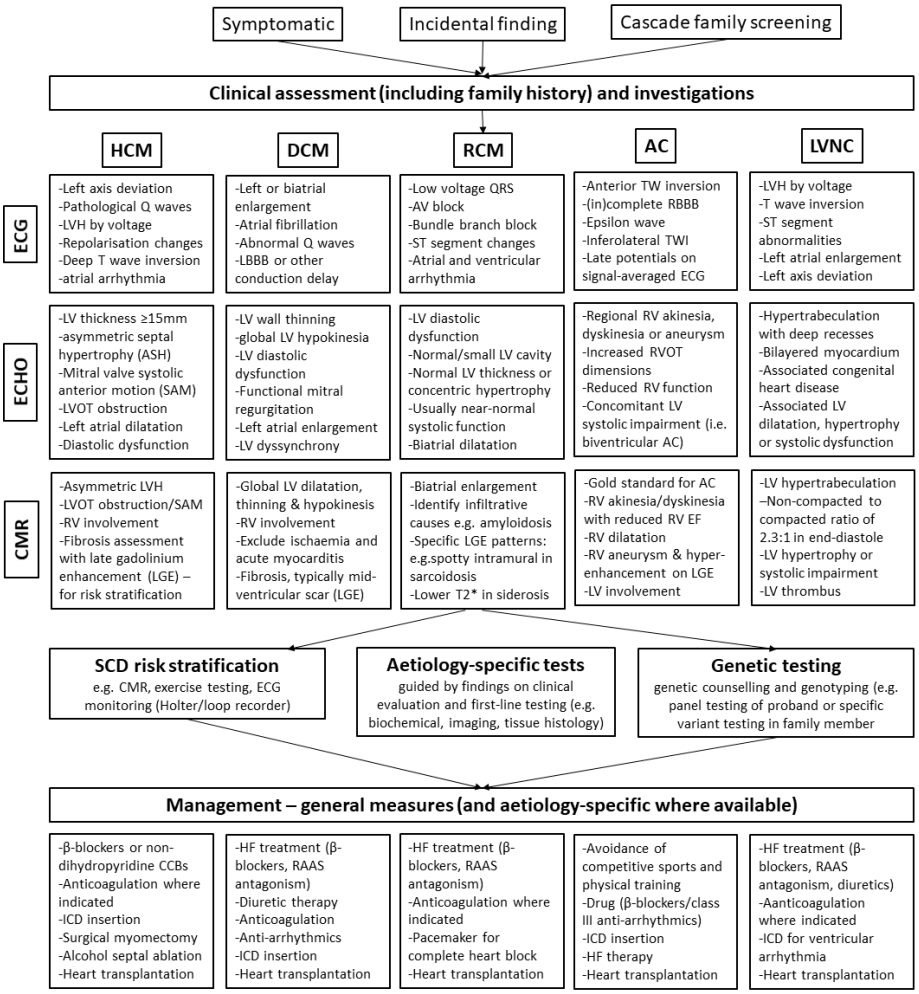
AV, atrio-ventricular; CK, creatine kinase; ECG, electrocardiogram; HIV, human immunodeficiency virus.
Source: Reproduced from Pinto et al.[7]

	Acquisition mode	Genetic Perturbations
Infiltrative		
Amyloidosis	Acquired/ inherited	*TTR* gene variants (V122I; I68L; L111M; T60A; S23N; P24S; W41L; V30M; V20I), *APOA1*
Sarcoidosis	Acquired	
Primary hyperoxaluria	Inherited	*AGXT (type 1), GRHPR (type 2), HOGA1 (type 3)*
Storage diseases		
Fabry disease	Inherited	*GLA*
Gaucher disease	Inherited	*GBA*
Hereditary hemochromatosis	Inherited	*HAMP, HFE, HFE2, HJV, PNPLA3, SLC40A1, TfR2*
Glycogen storage disease	Inherited	Per specific type
Mucopolysaccharidosis type I (Hurler syndrome)	Inherited	*IDUA*
Mucopolysaccharidosis type II (Hunter syndrome)	Inherited	IDS
Niemann–Pick disease	Inherited	NPC1, NPC2, SMPD1
Noninfiltrative		
Idiopathic	Acquired	
Diabetic cardiomyopathy	Acquired	
Scleroderma	Acquired	
Myofibrillar myopathies	Inherited	*BAG3, CRYAB, DES, DNAJB6, FHL1, FLNC, LDB3, MYOT*
Pseuxanthoma elasticum	Inherited	ABCC6
Sarcomeric protein disorders	Inherited	*ACTC, β-MHC, TNNT2, TNNI3, TNNC1, DES, MYH, MYL3, CRYAB*
Werner's syndrome	Inherited	*WRN*
Endomyocardial		
Carcinoid heart disease	Acquired	
Endomyocardial fibrosis		
Idiopathic	Acquired	
Hypereosinophilic syndrome	Acquired	
Chronic eosinophilic leukemia	Acquired	
Drugs (serotonin, methysergide, ergotamine, mercurial agents, busulfan)	Acquired	
Endocardial fibroelastosis	Inherited	*BMP5, BMP7, TAZ*
Consequence of cancer/ cancer therapy		
Metastatic cancer	Acquired	
Drugs (anthracyclines)	Acquired	
Radiation	Acquired	

Table 4 Aetiology of RCM

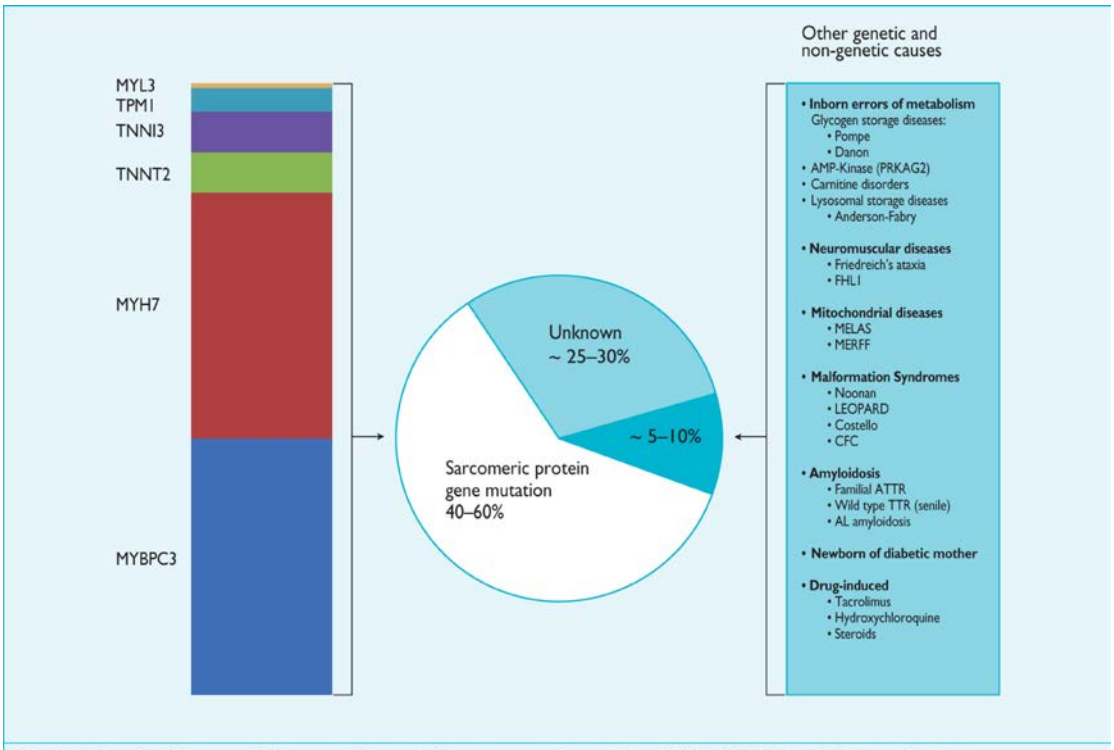
Source: Reproduced from Muchtar et al.[11] Muchtar E, Blauwet LA, Gertz MA. Restrictive Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. *Circulation research* 2017; **121**(7): 819-37.

Figure 1 Overview of assessment and management of cardiomyopathies



CCB, calcium channel blocker; CMR, cardiac magnetic resonance; EF, ejection fraction; ICD, internal cardiac defibrillator; HF, heart failure; LBBB, left bundle branch block; LVOT, LV outflow tract; RAAS, Renin-angiotensin aldosterone system; RBBB, right bundle branch block; RVOT, RV outflow tract; TWI, t-wave inversion.

Figure 2 Aetiology of HCM



The majority of cases in adolescents and adults are caused by mutations in sarcomere protein genes. AL = amyloid light chain; ATTR=amyloidosis, transthyretin type. CFC = cardiofaciocutaneous; FHL-1=Four and a half LIM domains protein 1; LEOPARD = lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF = myoclonic epilepsy with ragged red fibres; MYL3 = myosin light chain 3; MYBPC3 = myosin-binding protein C, cardiac-type; MYH7 = myosin, heavy chain 7; TNNI3 = troponin I, cardiac; TNNT2 = troponin T, cardiac: TPM1 = tropomyosin 1 alpha chain; TTR = transthyretin.

Figure 2 Aetiology of HCM
Source: Reproduced from Elliott et al.[6]

Key References

1. Elliott P, Andersson B, Arbustini E, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2008; **29**(2): 270-6.
2. Arbustini E, Narula N, Tavazzi L, et al. The MOGE(S) classification of cardiomyopathy for clinicians. *J Am Coll Cardiol* 2014; **64**(3): 304-18.
3. Authors/Task Force m, Elliott PM, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *European heart journal* 2014; **35**(39): 2733-79.
4. Maron BJ, Maron MS. Hypertrophic cardiomyopathy. *Lancet* 2013; **381**(9862): 242-55.
5. Watkins H, Ashrafian H, Redwood C. Inherited cardiomyopathies. *The New England journal of medicine* 2011; **364**(17): 1643-56.
6. Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *European heart journal* 2014; **35**(39): 2733-79.
7. Pinto YM, Elliott PM, Arbustini E, et al. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. *European heart journal* 2016; **37**(23): 1850-8.
8. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* 2006; **113**(14): 1807-16.
9. Herman DS, Lam L, Taylor MR, et al. Truncations of titin causing dilated cardiomyopathy. *The New England journal of medicine* 2012; **366**(7): 619-28.
10. Rapezzi C, Arbustini E, Caforio AL, et al. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. *European heart journal* 2013; **34**(19): 1448-58.
11. Muchtar E, Blauwet LA, Gertz MA. Restrictive Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. *Circulation research* 2017; **121**(7): 819-37.
12. Corrado D, Basso C, Judge DP. Arrhythmogenic Cardiomyopathy. *Circulation research* 2017; **121**(7): 784-802.
13. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. *European heart journal* 2010; **31**(7): 806-14.
14. Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. *Lancet (London, England)* 2015; **386**(9995): 813-25.
15. Finsterer J, Stollberger C, Towbin JA. Left ventricular noncompaction cardiomyopathy: cardiac, neuromuscular, and genetic factors. *Nat Rev Cardiol* 2017; **14**(4): 224-37.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 35-year-old man presented with syncope. He had a family history of sudden cardiac death. On clinical examination, there was a soft ejection systolic murmur.

Investigation

•Echocardiogram showed asymmetrical hypertrophy

Which of the following is a poor prognostic feature?

A. Atrial fibrillation on ambulatory ECG monitoring
B. Widespread T wave inversion on ECG
C. Breathless on exertion
D. Maximal left ventricular wall thickness of 2 cm
E. Abnormal blood pressure response to exercise

Correct answer: E. As per European Society of Cardiolgy and American Heart Association guidelines, Risk factors of poor prognosis include non-sustained ventricular tachycardia, maximal LV wall thickness ≥3cm, family history of sudden cardiac death, unexplained syncope, and abnormal blood pressure response to exercise.

Question 2

A 50-year-old woman presented with a 3-month history of progressively worsening breathlessness and ankle swelling.
On clinical examination, there was ankle oedema., Heart rate was 86 beats/minute, blood pressure 110/68 mmHg and jugular venous pressure raised 7 cm. Heart sounds were normal, and lung fields appeared clear.

Investigations

•Chest X-ray showed small bilateral effusions
•Serum B-natriuretic peptide 210 pg/ml (normal <100 pg/ml)
•Urate 6.3 mmol/litre (2.5–7.0)
•Creatine 90 micromol/litre (60–110)
•CT coronary angiogram 1 month previously had shown no significant coronary artery disease

Initial management was of congestive heart failure.

Which of the following investigations is most useful in further prognostic assessment?

A. Echocardiogram with Doppler to assess diastolic function
B. Invasive coronary angiogram
C. Cardiac magnetic resonance with gadolinium contrast
D. 6-Minute walk test
E. Genetic testing

Correct answer: C. Imaging with cardiac magnetic resonance (CMR) helps to establish a diagnosis of dilated cardiomyopathy. Myocardial fibrosis assessed by late gadolinium enhancement on CMR is associated with poor prognosis in dilated cardiomyopathy. Genetic testing and invasive coronary angiogram are useful to elicit the aetiology but a recent negative CT coronary angiogram make ischaemic cardiomyopathy less likely. The prognostic value of diastolic dysfunction on echocardiogram and 6-minute walk test are less well established.

Question 3

A 15-year-old boy was referred for genetic testing after the sudden cardiac death of his brother.

On clinical examination, he had woolly hair, with hyperkeratosis on the palms and soles. Cardiac examination was normal.

Investigation
•ECG showed anterior T wave inversion and incomplete right bundle branch block

Which of the following is the most likely diagnosis?
A. Hypertrophic cardiomyopathy
B. Dilated cardiomyopathy
C. Restrictive cardiomyopathy
D. Arrhythmogenic cardiomyopathy
E. Left ventricular non-compaction

Correct answer: D. Desmosomal cardiocutaneous syndromes, such as Naxos disease and Carvajal's syndrome, caused by mutations in plakoglobin and desmoplakin, respectively, with associated woolly hair, palmoplantar keratoderma and arrhythmogenic cardiomyopathy.