Familial Dilated Cardiomyopathy

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G. Aernout Somsen, G. Kees Hovingh, I.I. Tulevski, Jon Seidman, and Christine E. Seidman

4.1 Introduction

Dilated cardiomyopathy (DCM) is a disorder of the ventricular myocardium characterized by normal or thinned walls, enlarged chamber volumes, and diminished systolic function. Clinically, DCM gives rise to fatigue, shortness of breath, and increased morbidity and mortality. DCM occurs in response to underlying pathologies including valvular dysfunction, hypertension, or myocarditis, or as an idiopathic disorder of the myocardium. Among patients with idiopathic DCM, approximately 25–30% have affected first-degree family members, implying a genetic etiology.[16] However, a pathogenic mutation is found in a minority of cases of familial DCM upon molecular analyses. A number of candidate genes have been identified, and these encode for proteins of the myocyte contractile apparatus, the myocyte cytoskeleton, and nuclear envelope, as well as proteins involved in calcium homeostasis. In addition, the function of a number of proteins encoded by candidate genes is still unknown. To date, over 20 genes have been shown to play a pivotal role in the origin of DCM. This diversity of genetic etiologies in DCM explains why patients sometimes exhibit additional clinical manifestations, including defects in the conduction system resulting in arrhythmias, skeletal muscle abnormalities, deafness, and endocrinologic disease.

Current molecular testing strategies allow us to identify mutations in DCM patients. In addition to confirmation of the diagnosis in these patients with clinical signs of the disease, genetic testing also holds great value in the identification of carriers of the disease-causing mutation in family members. Molecular screening of these individuals does not only result in a potential strategy to diminish disease-related complications (arrhythmias and thromboembolism) in a very early phase, but will also greatly enhance our knowledge about the exact role of a mutated gene in the course of disease.

The list of genes is not deemed to be complete and more genes involved will be identified in the future. Knowledge of the full repertoire of key-role genes is indispensable for our understanding of pathways involved in the process of the failing heart.

4.2 Epidemiology and Prevalence

DCM (without coronary artery disease) has a prevalence of 40 per 100,000 in the USA and a reported incidence of 5–8 in 100,000 in the USA and Europe.[15]

Among 1,230 patients that were categorized as having primary or secondary DCM, 50% were defined as idiopathic (IDC) (Table 4.1)[13] Before the widespread application of echocardiography, assessment of the prevalence of DCM among family members was troublesome, likely resulting in an underestimation of the heritability. In recent years, however, more accurate numbers have been published. In their study, Grunig and colleagues showed that 35% of the cases of IDC were familial DCM, indicating that a substantial proportion of all DCM patients may have a genetic etiology.[16] While the prevalence and incidence of genetic disorders may vary between populations and geographic regions, the true prevalence of genetic DCM may even be higher, due to the age-dependent expression of the disease. An increased awareness among

G.A. Somsen (✉)
Department of Cardiology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands and
Cardiologie Centra Nederland / Cardiology Centers of The Netherlands, Amsterdam, The Netherlands
e-mail: a. somsen@cardiokliniek.nl

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Table 4.1 Prevalence of DCM specified for cause[13]

Cause of DCM	# of patients	Prevalence (%)
Idiopathic	616	50.1
Peripartum	51	4.1
Myocarditis	111	9.0
Ischemic heart disease	91	7.4
Infiltrative	59	4.8
Hypertension	49	4.0
HIV	45	3.7
Connective tissue disease	39	3.2
Substance abuse	37	3.0
Doxorubicine	15	1.2
Other	117	9.5
Total	1,230	100.0

physicians of the heritability of DCM, in concert with improved imaging modalities that enable the early detection of the disease, may further increase the disease prevalence.

4.2.1 Diagnosis and Clinical Course of Familial DCM

The age of onset of symptoms differs between DCM disease genes. For example, clinical manifestations occur, in general, at young age in individuals with mutations in sarcomere protein genes or in the calcium-handling gene encoding the protein phospholamban, while in individuals with lamin A/C mutations, symptoms of the disease may become overt only after the fourth decade of life.

Presenting symptoms are often nonspecific and include exertional dyspnea, fatigue, and palpitations. Sudden death is a rare initial presentation of DCM.

Findings at physical examination are often unremarkable or subtle in DCM patients. On examination, the heart may be enlarged and the ictus cordis may be displaced. On auscultation, the heart sounds can be normal, but a S3 and S4 gallop due to reduced ventricular compliance may be present. With advanced ventricular dilation, a pansystolic blowing murmur due to mitral regurgitation may be audible at the apex. In addition, signs of heart failure, such as rales and peripheral edema, may be present. Irregular heart rhythms are common in DCM and initially include atrial or ventricular premature complexes and atrial fibrillation. In addition, ventricular arrhythmias may be present.

Diagnosis of DCM is based upon identification of ventricular dilation and impaired function. This can either be assessed by means of echocardiography, bloodpool scintigraphy, or magnetic resonance imaging (MRI). Typically, the left ventricular fractional shortening, as measured by echocardiography, is less than 25% percent. Bloodpool scintigraphy and MRI can be used to measure the end-diastolic and end-systolic volumes, from which the left ventricular ejection fraction (LVEF) can be calculated. DCM is diagnosed if LVEF is less than 40% (Table 4.2).

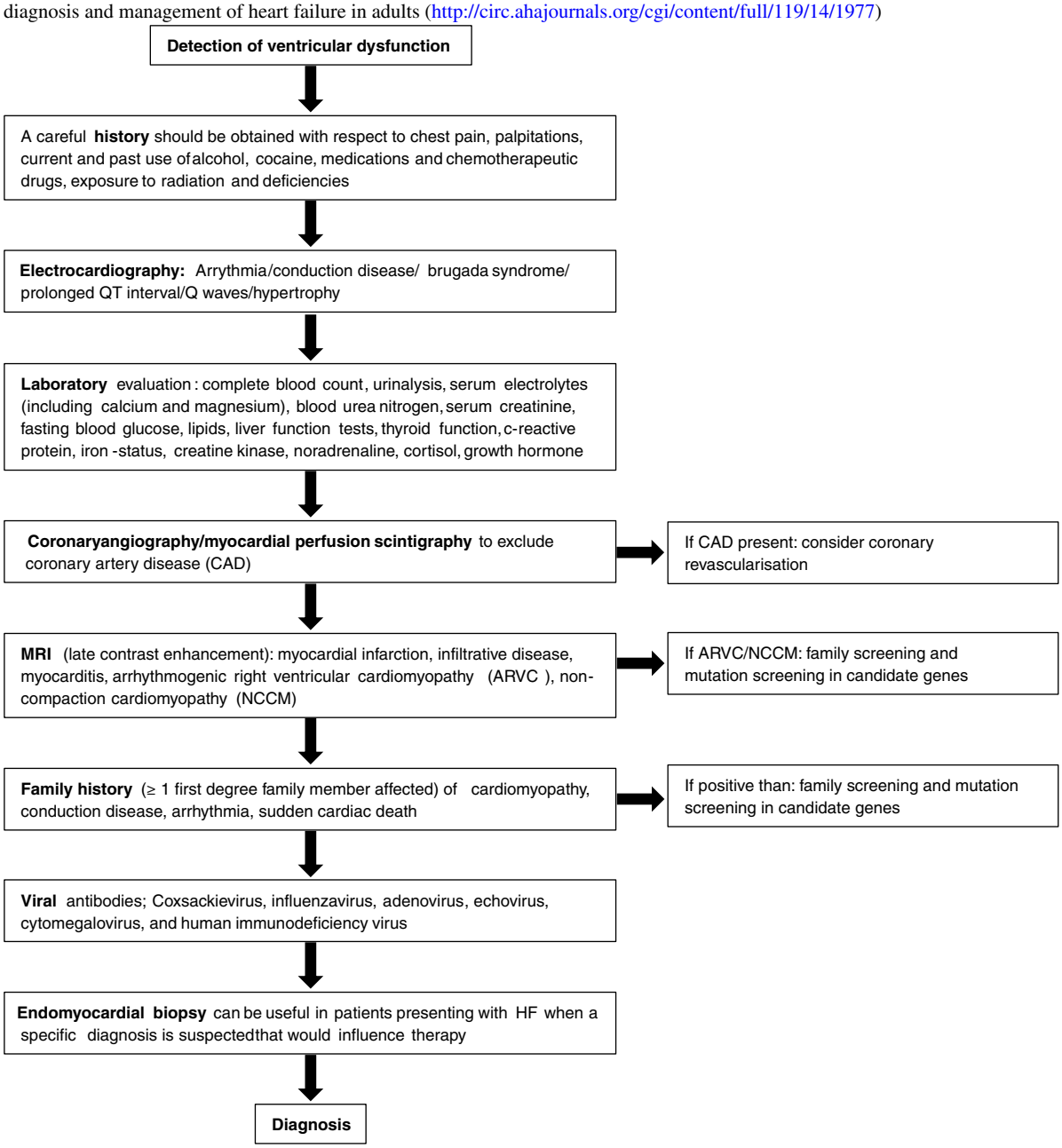
The end stage of the natural course of DCM is heart failure. The rate of progression toward heart failure due to DCM varies considerably – ranging from slow, indolent decline to rapid deterioration of ventricular function. An appreciation of the expected course can be gleaned from the family history. Increased morbidity and mortality in DCM is also attributed to thromboembolic events and sudden death due to arrhythmias. Although different mutations may affect myocyte function in different ways, there seems to be a common final pathway resulting in myocyte hypertrophy, premature myocyte death, and increased myocardial fibrosis. These histopathologic features are identified in virtually all postmortem and explanted cardiac tissues of genetic DCM patients.

4.2.2 Genetic Background

Familial DCM is most frequently inherited as an autosomal dominant trait, a pattern of transmission that implies considerable risk that offspring will also develop DCM. Other forms of inheritance, that is, autosomal recessive, X-linked, and matrilineal, are less common in DCM and convey different risks to offspring (Table 4.3). Mitochondrial mutations produce matrilineal inheritance, in which, all offspring from an affected mother, but no offspring from an affected father are at risk for DCM.

DCM gene mutations are known to exhibit variable penetrance, a genetic term that indicates the discrepancy between the presence of a mutation and clinical manifestation of disease. Some individuals who carry a DCM gene mutation (genotype) lack

Table 4.2 Proposed diagnostic workup of DCM patients (Modified from the 2009 Focused Update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults (http://circ.ahajournals.org/cgi/content/full/119/14/1977)



clinical manifestations of ventricular dysfunction (phenotype). The proportion of individuals with a gene mutation who express disease are called penetrants, whereas mutation carriers without clinical disease are called nonpenetrants. Many factors contribute to the variable penetrance of DCM mutations, including age, interacting genes, and environmental modifying factors. These parameters need to be considered when screening the relatives of individuals with DCM. The presence of a disease causing mutation can most often not be excluded based on clinical examination at a single point in time, and especially young, clinically unaffected relatives of a DCM patient may transmit a disease causing mutation to children. An appreciation of the penetrance of DCM can be obtained from large families with one specific underlying genetic defect. This information can help to define appropriate screening strategies for LV dysfunction in specific individuals at risk for developing DCM (Fig. 4.1)

Table 4.3 Known modes of inheritance of DCM[16]

Inheritance mode	% of familial DCM	Risk to offspring	Risk to sibs
Autosomal dominant	56	50%[a]	%50%[a, b]
Autosomal recessive	~16	<1%	25%
X-linked recessive[c]	~10	Dependent on sex of the index[d]	Dependent on whether or not mother is a carrier of the mutation[e]
Matrilineal (tRNA mutations in mtDNA)	?	Males and females may be equally affected. Only females will transmit mtDNA mutations to offspring. The chance of transmission may be close to 100%. Still only a proportion of offspring will be affected. Because as a result of heteroplasmy (see Chap. 2) the mutation threshold required for disease expression to occur may never be reached	

mtDNA mitochondrial DNA
[a]May be a little less in clinical practice as a result of reduced penetrance
[b]Only if one parent is carrier of the causative mutation
[c]In classical X-linked recessive disease females are asymptomatic carriers, however in the most common X-linked recessive disorders associated with DCM (Duchenne and Becker muscular dystrophy), females may develop DCM, and should remain under cardiac surveillance
[d]Affected males will transmit the mutation to none of their sons and all of their daughters
[e]Mutations in X-linked recessive disorders that are associated with DCM arise quite often de novo. If the mother is a mutation carrier, both sons and daughters have 50% chance of inheriting the mutation

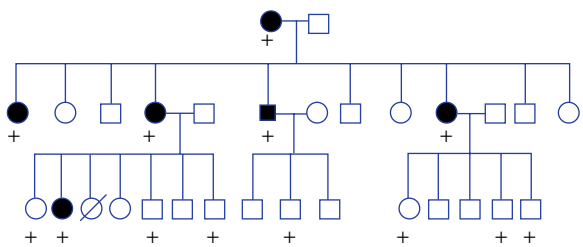


Fig. 4.1 An example of age-dependent penetrance within a dilated cardiomyopathy (*DCM*) family. Plus (+) refers to a positive genotype (carrier of a genetic defect, associated with DCM), filled symbols refer to phenotypically defined DCM

4.2.3 Genes and Mutations in DCM

Molecular studies have identified many genes and mutations that can cause DCM and more will undoubtedly be discovered. In some instances, investigations have identified only the chromosome region (or locus) that likely contains a DCM gene. Table 4.4 provides an illustration of this expanding knowledge of genes that are mutated in DCM. Many of these genes encode cytoskeletal and sarcomere proteins or proteins involved in ion homeostasis. In addition, DCM genes encode

Table 4.4 Loci and gene mutations associated with DCM as registered in the Online Mendelian Inheritance in Man (OMIM) database

Locus	Gene	Phenotype (other than DCM)	Reference
1p1–q21	LMNA	Sudden cardiac death, LBBB, SVT, sinus bradycardia, AV-conduction block. NCCM; EDMD;LGMD type 1b;partial LD; HGP;AO	12
1q31–q42	PSEN 2	Alzheimer	25
1q32	TNNT 2	NCCM; HCM	11, 32
1q42–q43	ACTN 2	HCM	33
2q31	TTN	HCM	14
2q35	DES	Progressive distal-onset skeletal myopathy, respiratory insufficiency	26
3p21	SCN5A	Sinus node dysfunction, SVT, progressive atrial and intraventricular conduction delay; lqts3;BS	30

Table 4.4 (continued)

Locus	Gene	Phenotype (other than DCM)	Reference
3p21.3–p14.3	TNNC 1	Myocyte hypertrophy, increased interstitial fibrosis, endocardial thickening, SCD	32
4q12	SGCB	LGMD type 2e	3
5q33	SGCD	LGMD type 2f (absence of skeletal muscular dystrophy)	57
6q22.1	PLN	SCD, ventricular tachycardia/fibrillation	50
6q23–q24	EYA4	Sensorineural hearing loss	51, 52
6q24	DSP	Wooly hair, keratoderma, ARVC	6
9q31	FKTN	Mild limb-girdle muscle involvement, Fukuyama muscular dystrophy, Walker–Warburg syndrome	39
10q21–23	LDB3suffices	NCCM	62
10q22.1–q23	VCL	HCM	43
11p11.2	MYBPC3	HCM	34
11p15.1	CSRP3	HCM	23
11q22.3–q23.1	CRYAB	Skeletal myopathy	49
12p12.1	ABCC9	Ventricular arrhythmia	5
12q22	LAP2	TMPO	56
13q12	SGCG	LGMD2c	42
14q12	MYH7	NCCM	22
14q24	TGFB3	Arrhythmogenic right ventricular cardiomyopathy	4
15q11–14	ACTC1	NCCM	45
15q22.1	TPM1	SCD	44
17q12	TCAP	LLGMD type 2g	23
17q21	JUP	Palmoplantar keratoderma, arrhythmogenic right ventricular cardiomyopathy (Naxos disease)	29
18q12.1	DSC2	Arrhythmogenic right ventricular cardiomyopathy	53
18q12.1	DTNA	NCCM	19
19q13.4	TNNI3	Myofibrillar loss, hyperchromatic nuclei, and myocyte hypertrophy; HCM	40
Xp21.2	DMD	Skeletal dystrophy, high serum creatine kinase, mental retardation (DMD, BMD)	38
Xq24	LAMP2	Skeletal myopathy, high serum creatine kinase, mild cognitive impairment in males, pigmentary retinopathy (Danon disease)	55
Xq28	TAZ	NCCM, death in early infancy, Barth syndrome	8

AO and others, *BMD* Becker muscular dystrophy, BS Brugada syndrome *DCM* dilated cardiomyopathy, *DMD* Duchenne muscular dystrophy, EDMD Emmery-Dreifus muscular dystrophy, *HCM* hypertrophic cardiomyopathy, *HGP* Hutchinson-Gilford progeria, *LBBB* left bundle *LD* lipodystrophy, *LGMD* limb girdle muscular dystrophy, *LQTS* long *QT* syndrome branch block, muscular dystrophy, *NCCM* noncompaction cardiomyopathy

proteins involved in the nuclear membrane and in mitochondrial functions.

4.3 Molecular Pathophysiology

Our current understanding of the mechanisms by which mutations result in DCM is predicted on the function of these molecules and cardiac biology. The sarcomere is the fundamental structural and functional unit of cardiac muscle that consists of an interdigitating system of thick and thin filaments (Fig. 4.2). Force is generated from the sliding movement of thick filaments relative to thin filaments, which is achieved by cyclical attachment and detachment of myosin crossbridges to actin. Hydrolysis of ATP by myosin provides energy for the detachment and subsequent reattachment of the crossbridges and results in a step-like displacement of thin filament relative to the thick filament. The troponin–tropomyosin complex provides a Ca^{2+}-sensitive switch that regulates this process. Troponin I is an inhibitory component of the troponin–tropomyosin complex which binds actin and inhibits actomyosin ATPase activity in the absence of Ca^{2+}. Ca^{2+} binding to troponin C causes the troponin–tropomyosin complex to release the myosin binding domain of actin, permitting the interaction of actin and myosin heads. The myosin light chains maintain optimal speed and efficiency of crossbridge cycling. Myosin binding protein C contributes to the organization and assembly of thick filaments and modulates crossbridge function by regulating the position of the myosin head relative to the thin filament.

DCM mutations in sarcomere proteins clearly perturb these processes. Diminished force may occur in myosin mutations that alter actin-binding residues involved in initiating the power stroke of contraction. Impaired contractile force may also occur in DCM troponin mutations that alter residues implicated in tight binary troponin interactions. Because Troponin molecules modulate calcium-stimulated actinomyosin ATPase activity, these defects may cause inefficient ATP hydrolysis and therein decrease contractile power.

Other DCM mutations may impair force transmission. Cytoskeletal proteins as desmin, dystrophin, and sarcoglycans are responsible for propagating force generated in the sarcomere to the plasma membrane and to the extracellular matrix. Mutations in cytoskeletal proteins may destabilize protein-protein interactions and compromise or cause ineffectual force propagation/force transmission throughout the myocyte.

Nuclear envelope proteins are proposed to provide structural support for the nucleus and to play an important role in chromosome organization, gene regulation, and nuclear protein handling. Mutations in these genes may cause DCM by altering the myocyte toward more susceptibility for mechanical stress.

Although mutations have long been considered to contribute specifically to the development of DCM, recent studies have shown that some of these "DCM mutations" can also cause hypertrophic cardiomyopathy (HCM) when present in a different part of the gene or in a different family.

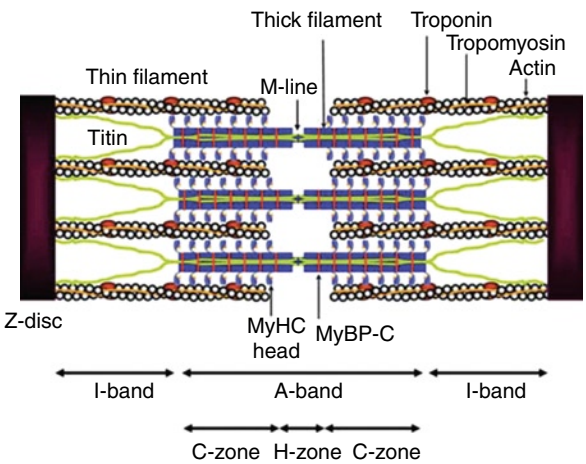


Fig. 4.2 Schematic drawing of the sarcomere structure[36]

4.3.1 Sarcomere Proteins

4.3.1.1 Actin

Actin participates in force generation by the sarcomere and also provides interaction with Z-bands and the intercalated discs (Fig. 4.2). These structures are the scaffold onto which myosin proteins generate force to support muscle contraction.

Mutations in actin and in all other sarcomere proteins can cause either hypertrophic cardiomyopathy or DCM, depending on the precise location of the mutation. DCM caused by actin mutations can be due to a failure in force generation or due to ineffectual force propagation.

Actin mutations are not associated with extracardiac manifestations. Although actin mutations are a rare cause of DCM, several reports indicate that these mutations can cause early onset, childhood disease.

4.3.1.2 Metavincullin

Metavincullin interacts with actin and links thin filaments to the plasma membrane. This muscle-specific isoform of vinculin is essential for force transmission during muscular contraction.[61] Metavincullin was analyzed as a candidate gene and rare mutations were identified in two patients with sporadic DCM.[43] Electron microscopy of myocytes from a DCM patient with a metavincullin mutation showed irregular and fragmented intercalated discs. Mutations in functionally distinct regions of metavincullin have also been associated with HCM.

4.3.1.3 Telethonin

Telethonin is localized in the Z disc of the skeletal and cardiac myocyte and undergoes dynamic phosphorylation following calcium/calmodulin binding. Telethonin interacts with titin, which serves as docking sites for multiple proteins and regulators of contraction and provides machinery for sensing myocyte stretch. Telethonin mutations are a rare cause of DCM[23]

4.3.1.4 Troponin-T

Cardiac troponin T participates in modulating calcium-stimulated actinomyosin ATPase activity. DCM mutations in troponin T alter residues that are involved in tight binary troponin interactions and may decrease the calcium sensitivity of force generation and therein decrease contractile power. Mutations in troponin T usually cause HCM, but DCM mutations have also been described.[37]

4.3.1.5 Troponin-I

Cardiac troponin I binds actin and inhibits actomyosin ATPase activity in the absence of calcium. The functional consequences of troponin I mutation were impairment of interactions with cardiac troponin-T but not with troponin-C. As such, this defect is presumed to function similar to troponin T mutations, and to perturb force generation. Troponin-I mutations are a rare cause of DCM – only 1 mutation was identified in 235 DCM patients. Troponin I mutations may be transmitted as recessive mutations in DCM.[40]

4.3.1.6 Troponin C

Cardiac troponin-C regulates calcium uptake in the sarcomere and promotes interaction of actin with myosin, the hydrolysis of ATP, and the generation of tension. Functional studies of mutated troponin C indicate that these disrupt normal interactions with troponin-T and I.

To date, few troponin C mutations have been defined in DCM patients,[32] but notably, the DCM phenotype was severe in these patients.

4.3.1.7 Tropomyosin

Both, alpha- and beta tropomyosin-1 mutations can cause DCM by decreasing the calcium sensitivity of the contractile apparatus or by destabilizing actin interactions. These abnormalities compromise force transmission to neighboring sarcomeres. Electron microscopy of heart tissue from a DCM patient with a tropomyosin-1 mutation revealed an abnormal sarcomere structure in which the thin filaments were irregular and fragmented, sarcomeres were also contracted with decreased distance between Z bands, and the sarcolemma had a scalloped appearance.[44] The prevalence of tropomyosin mutations is low.[63]

4.3.1.8 Beta-Myosin Heavy Chain

Beta-myosin heavy chain (beta-MHC) is the principle myosin expressed in the adult human ventricle, whereas alpha-MHC is the primary myosin isoform found in the atria. Beta-MHC is also expressed in slow skeletal muscle, type I fibers. Human myosin mutations that alter actin-binding residues cause DCM by diminishing the power stroke of contraction. Other myosin mutations that are located within the flexible fulcrum that

transmits movement from myosin to the thick filament could reduce transmitted force and cause DCM.[22]

The contribution of myosin mutations to DCM has been increasingly appreciated and may account for 10% of DCM. The clinical manifestations of these mutations are restricted to cardiac disease that can present early in life or be quiescent until middle age. Symptoms and left ventricular dysfunction appear to be mild to moderate. In one report, slow progressive AV and ventricular conduction defects were found.[9]

4.3.1.9 Titin

Mutations in the giant protein titin (also known as connectin) cause DCM. Titin contributes to passive muscle stiffness and myofilament calcium sensitivity and serves as a scaffold for many molecules that regulate cardiac contraction. DCM mutations in titin decrease binding affinities of titin to Z-line proteins like T-cap/telethonin and alpha-actinin.[20] Due to its extremely large size, genetic analyses of titin have been limited. Two DCM families with titin mutations had only cardiac disease, and no skeletal muscle involvement.[14]

Other genes that encode sarcomeric proteins have been associated with familial and sporadic cases of DCM. These genes are Cypher gene (LDB3), alfa-actinin gene (ACTN2), and the CSRP3[36]

4.3.2 Nuclear Envelope Proteins

4.3.2.1 Lamin A/C

Lamin A/C encodes an inner nuclear membrane protein that interacts with emerin and other molecules. Lamin A/C is essential for maintenance of nuclear stability and human mutations in this protein may render cells more susceptible to mechanical forces. Given the constancy of myocardial contraction, lamin A/C mutations may be particularly deleterious to myocytes.

Lamin A/C mutations cause DCM that is characterized by high penetrance, adult onset, heart failure, conduction defects, arrhythmias, sudden cardiac death, and substantial premature mortality.[46] These mutations cause dominant DCM and account for at least 33% of the familial DCM and 0.5–5% of all DCM with conduction disease and bradycardia in the western populations.[2,58] Lamin A/C mutations can also cause Emery–Dreifuss muscular dystrophy, which has its onset in childhood and is characterized by joint abnormalities, conduction disease, and arrhythmias.

A distinct histopathology is found in hearts with lamin A/C mutations. There is fibrofatty degeneration of the myocardium and marked involvement of the atrioventricular node and conducting cells. A similar situation is found in skeletal muscles in patients with Emerin mutations. The marked atrioventricular node pathology in lamin A/C mutations accounts for the presence of electrophysiologic deficits (progressive atrioventricular block and atrial arrhythmias) found in these patients.

Due to the high prevalence of lamin A/C mutations in idiopathic DCM and the poor prognosis of symptomatic carriers, systematic mutation screenings have been recommended.[17,54] It has recently been confirmed that prophylactic therapy with an implantable cardioverter-defibrillator prevents sudden death in these patients more efficiently than pacemaker implantation. This might also hold for asymptomatic carriers of the mutation.

4.3.2.2 Thymopoietin

Thymopoietin is also known as lamina-associated protein (LAP2), and like lamin, contributes to the maintenance of nuclear integrity and nuclear functions. In a family with DCM, a mutation was found, which altered interaction with LAP2 and lamin A.[56] Some patients with a mutation in the thymopoietin gene have severe DCM without signs of skeletal muscle disease. The finding that thymopoietin mutation results in DCM underlines the pivotal role of nuclear functions in the pathogenesis leading to myocardial dysfunction.

4.3.3 Cytoskeletal Proteins

4.3.3.1 Desmin

Desmin is a muscle-specific intermediate filament protein that participates in maintaining the structural and mechanical integrity of the contractile apparatus in muscle tissues.[47] Mutations in the gene encoding desmin may impair normal force transmission during muscular contraction. Mutations that are found in the

tail domain of the molecule may disrupt intercalated discs, whereas mutations found in the head domain may cause defects in Z-disc binding.[28]

Patients with desmin mutations have both cardiac and extracardiac manifestations. In addition to DCM, patients may develop progressive distal-onset skeletal myopathy and respiratory insufficiency.[10] The histopathology of skeletal or cardiac tissue with these mutations may show cytoplasmic aggregates of desmin, which may suggest the diagnosis.

4.3.3.2 Dystrophin

The dystrophin gene is located on chromosome X and encodes a protein that is crucial for the formation of the cytoskeleton. Dystrophin and related proteins including sarcoglycans and laminin-2 make up the dystrophin-associated glycoprotein complex, which plays a crucial role in the transmission of force from the sarcomere and the plasma membrane to the extracellular matrix.[24] Dystrophin mutations produce Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD) in male subjects. In addition to these skeletal myopathies, patients also develop delayed onset of cardiomyopathy. In a minority of cases, mental retardation can be found. Severity of the disease due to these mutations is variable as DMD has a high mortality rate in young patients, whereas BMD is a milder disease. The onset of DMD usually occurs before the age of 3 years and results in physical impairment necessitating a wheelchair by the age of 10 and death in the second decade, when a DCM is present. The onset of BMD is often in the20s and30s and survival to a relatively advanced age is frequent. The incidence of DMD/BMD is 21.7/3.2 per 100,000 male live births.[41] In the Netherlands, the prevalence of DMD at birth was estimated to be 1:4.215 male live births.[59]

Both, DMD and BMD are X-linked inherited diseases and are characterized by DCM and progressive proximal muscular dystrophy with pseudohypertrophy of the calves. High plasma levels of creatine kinase, myopathic changes by electromyography, and myofiber degeneration with fibrosis and fatty infiltration and absence of dystrophin fibers on (heart) muscle biopsy can be found in these patients. On the electrocardiogram specific abnormalities can be found (Fig. 4.3). Even in female carriers of DMD en BMD, electrocardiographic abnormalities have been found in 41% and 27%, respectively (E.M.[18])

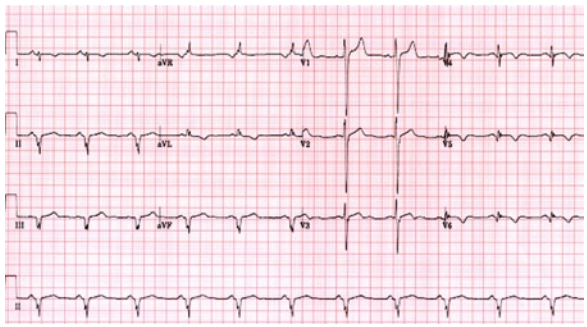


Fig. 4.3 ECG from a patient with Duchenne's muscular dystrophy (*DMD*) characterized by short PR interval, Q waves in inferior and lateral leads, and inverted T waves in the lateral leads. The extreme QRS axis is not specific for DMD (Courtesy of W.G. de Voogt, M.D., Ph.D.)

In female mutation carriers, muscle weakness and DCM can be found in 20%.[18] Left ventricular dilatation was present in 18% of these carriers.

In another study, it was shown that approximately 10% of the heterozygous females develop cardiomyopathy even in the absence of muscular weakness.[31] Therefore, screening for left ventricular dilatation and dysfunction is recommended in the female carriers of these diseases.

Therapy in DMD/BMD patients consists of corticosteroids for skeletal muscle weakness, standard pharmacologic treatment for heart failure, and noninvasive ventilation in case of respiratory failure. Currently, new therapies are studied which focus on increase of dystrophin expression, increase of muscle growth, and regeneration.

4.3.3.3 Sarcoglycans and Dystrophin-Associated Glycoproteins

The dystrophin-associated glycoprotein complex (composed of dystroglycans, delta- sarcoglycans, caveolin-3, syntrophin, and dystrobrevin) provides stability to the sarcomere and transmits force to the extracellular matrix. Recessive mutations in a subset of these genes cause DCM that is most often accompanied by skeletal myopathy.

Mutations in the delta-sarcoglycan gene (SGCD) cause mitochondrial aggregation resulting in pathological vascular smooth muscle cell proliferation and apoptosis.[27] Patients with delta-sarcoglycan mutations develop cardiomyopathy that is usually, but not

invariably, accompanied by skeletal muscular dystrophy.[57] In contrast, mutations in the beta- and gamma-sarcoglycan cause both cardiomyopathy and skeletal muscular dystrophy.

4.3.4 Mitochondrial DNA Mutations

Mitochondria are crucial for the energy metabolism of the myocyte and mitochondrial mutations (which are encountered in larger quantities due to inefficient repair mechanisms in mitochondrial DNA) result in syndromes characterized by multiorgan dysfunction such as myopathy, encephalopathy, diabetes mellitus, and lactic acidosis.

4.3.4.1 Genes Involved in Electrolyte Homeostasis

SCN5A

SCN5A gene encodes the cardiac sodium channel. SCN5A mutations lead to a loss in channel function and may cause Brugada syndrome, the long QT syndrome, idiopathic ventricular fibrillation, and sick sinus syndrome. In addition, other loss-of-function mutations in SCN5A have been associated with ventricular dilatation and dysfunction accompanied by sinus bradycardia and atrial fibrillation.[1,30]

The linked molecular etiology of these different clinical disorders is presumed to reflect the essential role for ion homeostasis in ventricular function and the notion that arrhythmias can directly remodel the myocardium. The mechanisms by which similar or identical mutations in SCN5A lead to a variable expression of heart disease, even within the same family, are still unknown.

Phospholamban

Phospholamban is a critical regulator of cardiac relaxation. After contraction, calcium reuptake into the SR is mediated by the Ca^{2+}-ATPase pump (SERCA2a). Phospholamban inhibits SERCA2 activity. Phosphorylation of phospholamban relieves this inhibition and accelerates ventricular relaxation. Several human mutations in phospholamban have been defined that functionally cause constitutive inhibition of SERCA, and delayed myocardial relaxation. Phospholamban mutations cause severe DCM with rapid progression to heart failure. In addition, these patients have significant ventricular arrhythmias due to altered calcium homeostasis.[50]

4.3.5 Cardiac ATP-Sensitive Potassium Channels

Cardiac ATP-Sensitive Potassium (KATP) channels are protein complexes, which ensure the maintenance of cellular and metabolic homeostasis such that the reaction to stress is not harmful to the organism itself. During high sympathetic stimulation, KATP channels increase outward potassium current to offset the resulting calcium influx, thereby reducing the energy-demanding myocardial calcium overload and avoiding contractile dysfunction.

KATP channels contain an inwardly rectifying potassium channel pore (Kir6.2), a regulatory SUR2A subunit, and an ATPase-harboring ATP-binding cassette protein. Human mutations in the regulatory SUR2A subunit (encoded by ABCC9) cause DCM and heart failure.[5] These mutations directly result in calcium overload and contraction band necrosis. The clinical manifestations of human KATP mutations are DCM and arrhythmias such as ventricular tachycardias.

4.3.6 DCM and Ventricular Noncompaction Cardiomyopathy

Noncompaction Cardiomyopathy (NCCM) is a rare form of DCM, characterized by incomplete compaction of the left ventricle that occurs late in cardiac embryogenesis. As a result, ventricular trabeculation persists. These blood-filled deep intratrabecular recesses impair ventricular function and predispose to thrombosis. NCCM is associated with heart failure, ventricular arrhythmias, and arterial thromboembolism, and produces increased morbidity and mortality.

NCCM can be associated with other congenital heart anomalies, including ventricular septal defects, pulmonic stenosis, and atrial septal defects.[19] The clinical criteria for diagnosis in NCCM are subject to

Table 4.5 Specific morphologic criteria for noncompaction cardiomyopathy (NCCM) by echocardiography and cardiac magnetic resonance imaging (MRI)

Diagnostic modality	Diagnostic criteria
General	Absence of coexisting cardiac abnormalities
Echocardiography[21]	1. Two layer structure (compacted thin epicardial band and a much thicker noncompacted endocardial layer of trabecular meshwork)
	2. Maximum ratio of noncompacted to compacted myocardium > 2:1
	3. Noncompaction predominantly localized in midlateral wall of left ventricle
	4. Deep perfused intertrabecular recesses (color Dopplerand/contrast echocardiography)
	5. Reduced global left ventricular systolic and diastolic function
	6. Left ventricular thrombi
	7. Abnormal papillary muscle structure
Cardiac magnetic resonance[48]	1. Noncompaction in the apical and lateral segments
	2. Ratio of noncompacted to compacted myocardium >2.3 during diastole (sensitivity 0.86/specificity 0.99)

debate. Recently, criteria have been proposed for different diagnostic modalities as shown in Table 4.5.

NCCM can arise from defects in several different genes, including genes that encode sarcomere protein (beta-MHC, alpha cardiac actin, and cardiac troponin-T) and in genes that encode G4.5 (Tafazzin), alpha-dystrobrevin, FKBP-12-, lamin A/C- and LBD3/Cypher gene.[35] In addition, a locus (chromosome 6p24.3–21.2) has been associated with the NCCM phenotype. Due to the large number of genes that are related to NCCM, screening for mutations in NCCM families is labor intensive.

Treatment of NCCM includes management of heart failure and arrhythmias, with particular attention to the potential for thromboembolic events. Since the genetics of NCCM have been diverse, the clinical importance of the screening of first-degree relatives of affected patients is high.[7]

4.4 Therapy

At present, specific therapies for the different genetic causes of DCM have not been evaluated in clinical trials. Patients with asymptomatic and symptomatic ventricular dysfunction due to an underlying gene mutation should be treated according to the AHA/ACC/ESC guidelines for heart failure treatment. As DCM patients progress to heart failure, standard therapies are used. These include beta-receptor blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor blockers, diuretics, anticoagulants when indicated, implantable cardiac defibrillator, biventricular pacing to obtain cardiac resynchronization, and surgical interventions as valvular reconstruction and heart transplantation.

Recognition of the genetic basis for DCM has led to the identification of mutation carriers who lack clinical signs of ventricular dilatation. Serial evaluations on a regular basis depending on severity and family history of these individuals are warranted to prevent sudden death and to initiate pharmacologic interventions when ventricular dilatation emerges. A more provocative issue is whether mutation carriers without clinical manifestations might benefit from prophylactic therapies to retard ventricular remodeling. While this consideration remains a research question, knowledge of genetic status poses the first clinical opportunity to intervene early in DCM and to potentially limit ventricular dysfunction and progression to heart failure.

4.5 Prognosis and Risk Stratification

The prognosis of DCM strongly depends on the precise gene mutation and interacting factors, including modifying genes and environments. Our current understanding of these interacting factors is incomplete. As such, prognosis and risk stratification are based upon

Table 4.6 Gene mutations associated with high risk of sudden cardiac death

Lamin A/C	12
Phospholamban	50
Tropomyosin-1	44
Tafazzin	8
Slow troponin-C	32

the clinical course of other affected family members and clinical parameters.

Familial history and genetic data can provide information regarding disease penetrance, age of onset, and disease progression and severity. The presence of associated phenotypes, including conduction system, atrial- and ventricular arrhythmias, and thromboembolic events will help to guide management and therapeutic strategy.

Genotype-phenotype correlations in some DCM genes have demonstrated high prevalence of sudden cardiac death and progression to heart failure (Table 4.6). However, a publication bias should always be taken into account when interpreting these data. Genetic screening and counseling of families with these genetic etiologies is particularly important. Cardiac defibrillators may improve prognosis in a subset of these patients.

4.6 Family Screening

The diagnosis of idiopathic DCM should prompt family evaluation. When one or more first-degree relatives are recognized to have DCM, a genetic etiology should be considered. Construction of pedigrees will help to delineate those at risk for disease. In addition to cardiac findings, one should search for evidence for overt or subclinical skeletal myopathy, conduction system abnormalities, and arrhythmias. Drawing a pedigree, however, is time consuming, and the accuracy of medical and family history frequently questionable. Moreover, assessment of the family history and pedigree analysis does not seem to be routine for cardiologists. Van Langen and colleagues interviewed a cohort of 643 Dutch cardiologists and it was shown that their self-reported knowledge about cardiogenetics is low[60] and not even half of them gave genetic counseling to HCM patients (let alone DCM patients). A close collaboration between clinical geneticists and cardiologist probably adds great value to patient care.

Recognition of the considerable role for genetics in DCM has prompted recommendations for screening. These are reviewed in the AHA/ACC 2005 guidelines and in more recent guidelines provided by the Heart Failure Society of America. Both documents indicate the importance of referral to a center with genetic expertise for diagnosis and counseling. [http://circ.ahajournals.org/cgi/content/full/112/12/e154] and include the performance of echocardiography and ECG in all first-degree family members.

Gene-based diagnosis of DCM is now clinically available on http://www.ncbi.nlm.nih.gov/sites/GeneTests and http://www.eddnal.com. Genetic testing requires a peripheral blood sample from one affected individual. Comprehensive screening of multiple DCM genes is simultaneously accomplished. While this is costly, once a mutation is identified, family members can be rapidly screened for the presence or absence of a mutation at very low cost. Recently, a DCM CardioChip™ test has been developed for efficient mutation screening in DCM-related genes (Fig 4.4). This commercially available chip uses microarray-based sequencing technology and screens the coding sequence and splice sites of 19 genes. In addition, screening for gene mutations related to ARVC is also available. The clinical sensitivity of this test is expected to be greater than 30%.

Gene-based diagnosis precisely defines the etiology for DCM in patients with clinically evident disease. This knowledge may provide information about clinical course and help to define the risk for associated manifestations (such as development of conduction system disease). In addition, knowledge of the causal mutation in one affected individual provides the opportunity to accurately define the risk for DCM in all relatives. When gene-based assessment reveals that a family member has *not* inherited the DCM mutation, subsequent clinical follow-up is unnecessary.

4.7 Summary

Multiple genetic defects have been shown to cause DCM. DCM mutations occur in genes that encode proteins involved in force transmission, force generation,

DCM CHIP (19 genes) (>30%)	DCM Panel A	***MYBPC3***	DCM	HCM		LVNC	
		MYH7	DCM	HCM	RCM	LVNC	Laing Distal Myopathy
		TNNT2	DCM	HCM	RCM	LVNC	
		TNNI3	DCM	HCM	RCM		
		TPM1	DCM	HCM			
	DCM Panel B	***ACTC***	DCM	HCM			
		PLN	DCM	HCM			
		LDB3	DCM	HCM		LVNC	
		LMNA	DCM			Conduction system disease	Laminopathies*
		TAZ	DCM				Barth Syndrome
		ACTN2	DCM	HCM			
		VCL	DCM	HCM			
		CSRP3	DCM	HCM			
		TCAP	DCM	HCM			
		ABCC9	DCM			Arrythmias	
		CTF1	DCM				
		SGCD	DCM				Delta-Sarcoglycanopathy
		DES	DCM		RCM		Desminopathy
		EMD	DCM				Emery-Dreifuss muscular dystrophy (EDMD)
ARVC panel		***PKP2***			ARVC		
		DSP	DCM		ARVC		
		DSC2			ARVC		
		DSG2	DCM?		ARVC		
		TMEM43			ARVC		

Fig. 4.4 DCM CardioChipTM test (Laboratory for Molecular Medicine Partners Center for Personalized Genetic Medicine, http://www.hpcgg.org/lmm)

nuclear function, and calcium handling in the myocyte. Disease manifestations, severity, and prognosis depend on the precise disease gene mutation. However, the clinical phenotype is also influenced by unknown genes and environmental factors.

Genetic causes for DCM are common and should be sought in patients with unexplained ventricular dysfunction. Family history is the key to defining genetic DCM and warrants prompt screening of first-degree family members. With the availability of gene-based diagnosis, molecular testing can provide precise information that defines relatives at risk who require follow-up evaluations. Equally important, gene-based diagnosis can precisely define mutation-negative family members who are not at risk for developing DCM.

New DCM genes will undoubtedly be identified. As the full repertoire of gene mutations in DCM and the associated clinical information is compiled, the value of knowing precise molecular cause will increase. As translational research in DCM harnesses gene-based diagnosis to identify and treat preclinical patients, the opportunity to improve prognosis and to prevent heart failure is expected to increase.

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