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Familial Dilated Cardiomyopathy: Risk Stratification for Sudden Cardiac Death

Gustav Mattsson and Peter Magnusson

Abstract

Heart failure implies a considerable burden for patients and resources for the health care system. Dilated cardiomyopathy is defined as left ventricular dilation and reduced systolic function, not solely explained by ischemic heart disease or abnormal loading conditions. Numerous genes have been identified in familial cases of dilated cardiomyopathy. Heart failure with reduced ejection fraction increases the risk for sudden cardiac death. Implantable cardioverter defibrillator therapy can provide a means of preventing sudden cardiac death in those deemed to be at high risk. Health care providers are in need of better tools in order to improve risk stratification. This chapter aims to provide an overview of the current knowledge about risk of arrhythmia and sudden death in patients with familial dilated cardiomyopathy, in particular for those patients with a specific mutation.

Keywords: arrhythmia, cardiology, cardiomyopathy, genetic, heart failure, sudden cardiac death

1. Introduction

The prevalence of heart failure is approximately 1–2% in the adult population and is 10% for those above the age of 70 years [1]. Dilated cardiomyopathy (DCM) is a common form of heart failure defined by dilatation of the left ventricle and reduced ejection fraction [2]. In later phases, dilation of the right ventricle and both atria is often seen, although this is not required for diagnosis. The disease confers a reduction in left ventricular ejection fraction but in early stages dilatation of the left ventricle can be seen with only minimal reduction of systolic function. Definitions vary, sometimes a distinction is made between ischemic and nonischemic DCM; however more often DCM refers to a disease that is not explained by coronary artery disease or abnormal loading conditions due to hypertension or valve defects [2]. With this definition the prevalence is at the least 1 in 2500 in the general population, which is likely an underestimation and some estimates refer the prevalence as high as 1 in 250 [3, 4]. In more than 20% of these patients a known disease causative mutation is found [3, 5]. Mutations in more than 50 different genes have been associated to DCM and some of the most common are the genes encoding for lamin A/C, titin, and desmin [1, 6]. Often the phenotype is the similar regardless of the causative mutation, therefore broad gene panels are used in genetic testing. Some genes however affect the conduction system and have been linked to an increase in sudden cardiac death.

2. Definitions

2.1 Cardiomyopathies

Definitions of cardiomyopathies differ over time and between clinical traditions. While in the future cardiomyopathies might be classified after causative mutations, they have traditionally been classified by phenotype and cardiac morphology, e.g. DCM or hypertrophic cardiomyopathy (HCM). This system of classification has the advantage that the phenotype is most often known prior to the genotype.

Originally, cardiomyopathies were considered distinct primary myocardial disorders of unknown etiology, whereas heart muscle disorders of known etiology or caused by systemic disease were classified as secondary or specific heart muscle disease. In 2006 the American Heart Association proposed a classification that defined cardiomyopathies either as primary or secondary, referring either to a disease where the heart is the sole or primarily affected organ, alternatively where myocardial involvement is part of a systemic disease [7]. However, in 2008, the European Society of Cardiology (ESC) proposed an alternate classification in which a cardiomyopathy is defined as “a myocardial disorder in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality”. Furthermore, the ESC subdivides cardiomyopathies depending on morphology and function as well as based upon inheritance pattern; distinguishing between familial or genetic forms versus non-familial or non-genetic forms of cardiomyopathy (Figure 1) [2].

2.2 Dilated cardiomyopathy

DCM is a distinct cardiomyopathy and a common cause of heart failure defined by dilatation of the left ventricle and reduced ejection fraction [2]. In later phases dilation of the right ventricle and the atria is often seen, however this is not required for diagnosis. For the diagnosis of DCM, the reduction in global systolic function should not solely be attributable to coronary artery disease or abnormal loading conditions (hypertension, valve disease) [2].

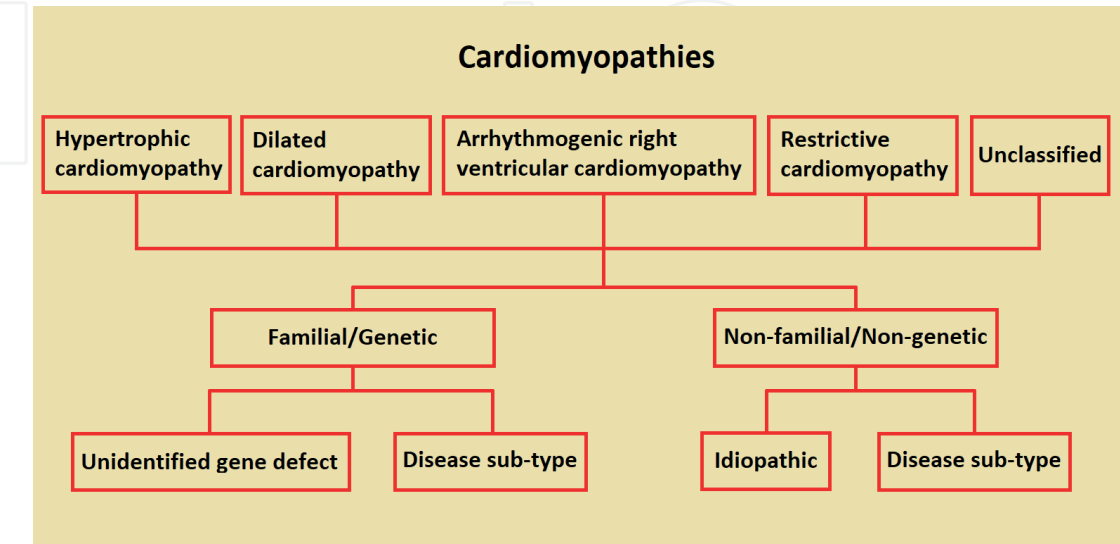


Figure 1. Classification of cardiomyopathies proposed by the European Society of Cardiology [2]. Cardiomyopathies are primarily classified according to morphology and function, then based on whether the disease is familial or non-familial, and lastly depending on either known disease causing mutation or pathophysiological mechanism.

2.3 Familial dilated cardiomyopathy

Familial DCM is diagnosed when at least two relatives (first-degree or second-degree) meet the diagnostic criteria for DCM [8].

3. Diagnostic evaluation of dilated cardiomyopathy

3.1 Echocardiography

Diagnostic evaluation for suspected heart failure should be managed in accordance with guidelines, such as those of the ESC [1]. Echocardiography constitutes a cornerstone of the evaluation and is readily available. For the diagnosis of DCM both left ventricular systolic dysfunction, as well as dilatation of the left ventricle, needs to be present and not explained by coronary artery disease or abnormal loading conditions (hypertension, valve disease) [9]. Left ventricular systolic dysfunction is defined as abnormal left ventricular systolic ejection fraction measured with any modality, preferentially echocardiography or cardiac magnet resonance tomography. Left ventricular dilatation (**Figure 2**) is defined as left ventricular end-diastolic volumes or diameters >2 standard deviations according to nomograms ($Z > 2$ standard deviations) after correction for body surface area and age, or body surface area and sex [9].

3.2 Cardiac magnetic resonance tomography

Cardiac magnetic resonance tomography is valuable as a complement to echocardiography. It allows for a better evaluation of the whole myocardium including the right ventricle and septum which provides aid in ruling out other cardiomyopathies such as arrhythmogenic right ventricular cardiomyopathy (ARVC) and HCM. Myocarditis has been identified as a cause of acquired forms of DCM [10]. Cardiac magnetic resonance can be used to assess the presence of active myocarditis as well as scar tissue that could indicate previous episodes of myocarditis. Cardiac magnetic resonance imaging is, according to the ESC, indicative of active myocarditis if it, in the setting of clinically suspected myocarditis, fulfills 2 out of 3 Lake Louise criteria [11]. These criteria include; high signaling on T2-weighted images (indicative of edema), early gadolinium enhancement (indicative of increased blood flow), and late gadolinium enhancement (indicative of scar tissue) [11].

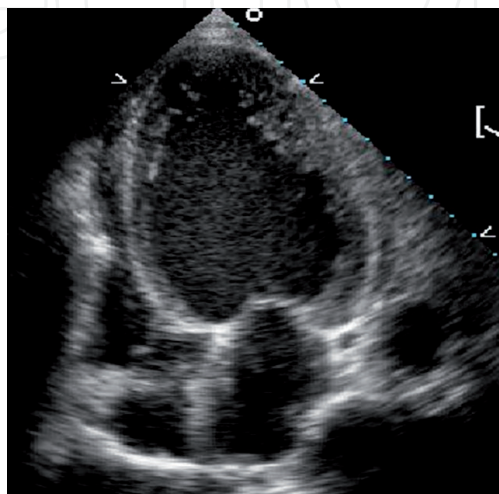


Figure 2.
Echocardiography with apical four chamber view showing spherical dilatation of the left ventricle. Image adapted from Jamil et al. [12]. Published by IntechOpen under open access <https://creativecommons.org/licenses/by/3.0/>.

3.3 Family history

Of particular importance is a family history of cardiomyopathy, arrhythmia or sudden cardiac death. If another family member also fulfills the criteria for DCM the patient can be said to have familial DCM [8]. A pedigree, a family tree, could be drawn to visualize what family members are affected by the disease or certain symptoms as well as how they are related to each other. By doing this the type of inheritance pattern can often be discerned, see Section 5.1. Inheritance patterns.

3.4 Genetic testing

Genetic testing requires knowledge about genetics, the disease in question, as well as legal and ethical considerations. It is important that the patient is the one who makes an informed decision about if a gene test should be performed [13]. It is also important to be aware of what the benefits and potential detriments of a genetic test are. The current ESC Heart failure guidelines from 2016 recommend that genetic testing should be performed in accordance with the ESC position statement on genetic counseling and testing in cardiomyopathies from 2010 [1, 13]. Most genotypes cannot be distinguished from each other by evaluation of the phenotype. Due to this broad gene panels are required that incorporate most known definite and putative DCM genes. The ESC states that the main role of genetic testing is in patients with an already confirmed diagnosis of idiopathic DCM (where acquired causes has been ruled out) to enable genetic testing of first degree-relatives and possibly cascade screening, see Section 5.2. Family screening. They caution against the use of genetic testing to establish the diagnosis of a cardiomyopathy in borderline cases except for in the setting of expert teams after detailed clinical and family assessment. In definite DCM most often, the exact gene affected do not change the clinical management of that individual patient. However, in some cases of DCM with red flags such as simultaneous conduction disorders indicative of a specific phenotype, genetic testing can be used to establish a specific genetic diagnosis. In patients with mutations in LMNA that causes DCM, genetic diagnosis might affect the clinical management. It should be noted that negative genetic tests do not rule out that the cardiomyopathy is familial or genetic. The interpretation of genetic tests is time consuming, complicated, and often not conclusive. When the ESC position statement was written in 2010 genetic tests had been mainly used for research purposes and had recently become available for clinicians. Genetic tests have today become more affordable and available. The current trend is towards more genetic evaluations being conducted and it is our opinion that this trend should continue. More patients with DCM receiving a genetic diagnosis will over time improve knowledge of the different genotypes. In order to offer equal health care genetic testing must be conducted even outside the setting of tertiary centers.

4. Clinical management of dilated cardiomyopathy

4.1 Heart failure

Heart failure management should be in accordance with guidelines, such as those of the ESC, which are summarized below [1]. An angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) is indicated in left ventricular systolic dysfunction. If symptomatic, i.e. New York Heart Association functional classification (NYHA-class) 2 or above, a beta-blocker should be added to treatment with the ACEi/ARB. In patients who remain symptomatic with systolic

ejection fraction $\leq 35\%$ despite the highest tolerable evidence-based doses of ACEi or ARB as well as a beta-blocker, a mineral receptor antagonist is recommended with maximum tolerated evidence-based dose. If the patient is still symptomatic with systolic ejection fraction $\leq 35\%$ it is recommended to initiate treatment with an angiotensin receptor neprilysin inhibitor that replaces the ACEi/ARB [1]. Further treatment modalities that should be considered include the addition of ivabradine in patients with sinus rhythm ≥ 70 beats per minute, or the implantation of a cardiac device to allow for cardiac resynchronization therapy in those with left bundle branch block and QRS ≥ 130 ms or without left bundle branch block but QRS ≥ 150 ms. These mentioned treatment modalities have shown increased survival in randomized controlled trials [1]. Digoxin could be considered if symptoms remain, however reduced mortality has not been shown but rather reduced need for hospitalization. The small therapeutic window of digoxin should be kept in mind, most commonly digoxin is used for rate control in atrial fibrillation that is common in heart failure. Loop-diuretics such as furosemide should be considered in patients with heart failure to relieve symptoms and signs of congestion, but this has not been shown to reduce mortality. The dosage of diuretics should be kept as low as possible and cessation of treatment might often be possible. In end-stage heart failure, transplant might be considered or mechanical left ventricular assist devices that can be used as destination therapy, bridge-to-decision, or bridge to transplant [1].

Lately inhibition of sodium-glucose transporter protein 2 (SGLT2i) has proved an interesting treatment modality for heart failure with reduced ejection fraction. In the EMPA-REG trial in 2015, the SGLT2i empagliflozin showed reduced cardiovascular mortality, reduction in all-cause mortality, and reduced need for hospitalization for heart failure in patients with type 2 diabetes mellitus [14]. In 2019 the results of the DAPA-HF trial showed that the SGLT2i dapagliflozin reduced cardiovascular and all-cause mortality as well as risk of worsening heart failure in patients with heart failure with reduced ejection fraction even if they did not have diabetes mellitus [15].

4.2 Arrhythmia

There is an increased risk for both brady- and tachyarrhythmia in DCM, these arrhythmias can also be a contributing factor worsening heart failure. In symptomatic sinus node disease or in high-degree atrioventricular (AV)-block without a reversible cause a pacemaker is indicated in order to relieve symptoms and/or increase survival [3]. Beta-blockers are often indicated for the treatment of symptomatic heart failure but also have antiarrhythmic properties making it useful for both rhythm and rate control. With the exception of beta-blockers currently available antiarrhythmic drugs have not consistently been shown in randomized clinical trials to improve survival in the primary management of arrhythmia. Amiodarone have shown some positive results and is highly useful to control symptoms, to terminate tachyarrhythmia and prevent recurrence [3]. In heart failure with reduced ejection fraction most other antiarrhythmic agents are contraindicated, this includes flecainide and dronedarone otherwise frequently used for rhythm control in atrial fibrillation [3].

4.3 Prevention of sudden cardiac death

An implantable cardioverter defibrillator (ICD) is an effective way to prevent sudden cardiac death in those at risk for developing ventricular tachycardia or ventricular fibrillation [3]. An ICD offers both antitachycardia pacing, rapid ventricular pacing (preferably bursts), that can terminate ventricular tachycardia, as well as

cardioversion that effectively terminate ventricular tachycardia and ventricular fibrillation. In addition, an ICD also functions as a bradycardia pacemaker and in combination with a left-ventricular lead it can offer cardiac resynchronization therapy.

The ESC recommends a primary prophylactic ICD for patients with symptomatic heart failure (NYHA-class II-III), left ventricular systolic ejection fraction $\leq 35\%$ despite at least three months of optimal medical therapy and a life expectancy of at least 1 year [3]. The recommendation is class I (is recommended) for both heart failure due to ischemic heart disease as well as nonischemic cardiomyopathy. The level of evidence is considered stronger for heart failure with ischemic etiology (level A) than for nonischemic etiology (level B) [3]. In the SCD-HeFT trial an ICD reduced all-cause mortality as well as sudden cardiac death in patients with reduced ejection fraction [16]. In the DEFINITE trial, with a study population of patients with heart failure due to nonischemic etiology, sudden cardiac death was reduced by 80%, however reduction in all-cause mortality did not reach statistical significance (hazard ratio 0.65, $p = 0.08$) [17]. In 2016, the DANISH trial randomized participants with heart failure of nonischemic origin to either an ICD or otherwise optimal medical management (both groups were eligible for cardiac resynchronization therapy), after 5 years there was a significant reduction in sudden cardiac death (HR; 0.50, $p = 0.005$) [18]. For the whole group no significant reduction was seen in all-cause mortality (HR; 0.87, $p = 0.28$), however subgroup analysis of patients younger than 68 years showed a reduction all-cause mortality (hazard ratio 0.64; $p = 0.01$) [18]. This caused uncertainty about whether patients with heart failure of nonischemic etiology should receive ICDs on the same indications as those with ischemic etiology. Since then, a meta-analysis of six trials, that included DANISH, has showed that ICD on primary-prevention indication in patients with heart failure of nonischemic etiology reduced all-cause mortality (hazard ratio 0.76, $p = 0.001$) [19]. An analysis of the Swedish Heart Failure Registry revealed a 27% relative risk reduction in all-cause mortality after 1 year, this was consistent in both the subgroup with ischemic and with nonischemic etiology [20]. We have previously published a retrospective observational study of our ICD-cohort [21]. In our study 236 patients with primary prevention ICD due to heart failure of ischemic (61.9%) or nonischemic (38.1%) etiology were included, there was no difference in cumulative risk for appropriate therapy between the groups (Mantel-Cox $p = 0.985$) [21]. The guidelines of the ESC recommending implantation of a primary prevention ICD should therefore be followed in patients with heart failure with both ischemic etiology as well as nonischemic DCM [3].

5. Familial dilated cardiomyopathy

5.1 Inheritance patterns

Most genetic mutations that cause familial DCM have an autosomal dominant inheritance pattern with variable penetrance [22]. However, autosomal recessive, X-linked recessive and mitochondrial inheritance patterns have been described [22]. Sometimes a mutation is found that does not occur in any of the parents, this is called a *de novo* mutation.

5.1.1 Autosomal dominant

Autosomal inheritance is related to a mutation in an autosome, i.e. any chromosome that is not a sex chromosome. Dominant inheritance pattern implies that it is enough with only one mutant allele for the disease to be expressed. This means that

the effect of a mutation in a gene masks or overrides the effect of a normal variation of the same gene on the other copy of the same chromosome. Those who have only a mutation in one of their two gene copies are said to be heterozygous. Due to a complex interplay with other genes and with the environment the disease is not always expressed, this is called varying penetrance. Men and women are equally as likely to inherit a mutated gene from a parent that carries it, regardless if it is the father or mother. If one parent carries one copy of the mutated gene, the offspring has a 50% risk of inheriting it. If both parents carry one copy of the gene, the offspring has a 75% risk of inheriting at least one copy.

5.1.2 Autosomal recessive

Autosomal recessive inheritance is caused by mutation in a gene situated on an autosome but requires both the copy inherited from the father and the copy from the mother to be mutated. For the mutation to cause the disease to be expressed the carrier needs to be homozygous for the mutation. This inheritance pattern requires both parents to carry at least one gene affected by the mutation. Men and women are equally as likely to inherit two affected gene copies from a certain pair of parents. If both parents carry one mutated gene, the offspring has a 25% risk of inheriting two mutated gene copies.

5.1.3 X-linked recessive

X-linked recessive inheritance pattern is caused by a mutation in a gene situated on the X chromosome. Since the X chromosome is a sex chromosome and females have two copies while males have only one copy, if the inheritance pattern is recessive, males will be affected, while females need to inherit a mutated gene from both their father and mother in order to be affected. Since men never inherit their X-chromosome from their father, the mutated gene can never pass to a son from his father. Daughters have always inherited one of their X-chromosomes from their father, thus an affected father will always have passed the mutated gene on to his daughters. This daughter will only be a carrier and not affected by the disease, unless she also has inherited the mutated gene from her mother. It is therefore common for X-linked recessive diseases to skip generations of daughters. A female that carry one mutated gene copy have a 50% risk of passing this on to both their sons and daughters.

5.1.4 Mitochondrial inheritance

In humans, mitochondria, and also mutations affecting mitochondrial DNA, is inherited from the mother. Both males and female can be affected by mitochondrial disease but only females can pass on the mutation to their offspring.

5.2 Family screening

5.2.1 Family screening in case of a known mutation

In many European countries including Sweden, the physician has no legal right to contact or inform first-degree relatives about the results of a genetic test. Instead the patient must be equipped with sufficient knowledge, both verbally and in written form to inform relatives about the genetic aspect of the disease, although usually there is no legal obligation for the patient to do this.

If the proband, the first identified individual with DCM in a family, has a known disease-causing mutation it is possible to screen all first-degree relatives

for this single mutation [13]. If the inheritance pattern is autosomal dominant, children each have 50% risk of carrying the mutation. A simple genetic test could with certainty confirm or reject that an individual carries the mutation, this has large implications. If the individual is not a carrier of the mutated gene, no further follow-up is required, no cascade screening is needed of this individual's children, and the individual have a better chance of living a normal life.

If instead the gene test confirms that an individual carries the mutated gene, so called cascade screening should be considered of this individual's first-degree relatives. Carrying a known disease-causing mutation implies that cardiologic evaluation should be conducted consisting of at least 12-lead ECG and echocardiography. If this evaluation results in a diagnosis of DCM life-long follow-up is required. If this cardiologic evaluation is inconclusive or finds no signs of DCM continued follow-up is still required. The penetrance of familial DCM is most often age-dependent, age at diagnosis of DCM is most often seen during or after puberty up until 60 years of age [13]. Therefore, renewed assessment with at least ECG and echocardiography should be conducted every year between the ages of 10 and 20 and then every 1–3 years.

5.2.2 Family screening in case of no known mutation

In idiopathic DCM, in a setting where genetic testing is not available, negative, or inconclusive, familial DCM can still not be ruled out. All first-degree relatives of the proband should undergo cardiologic evaluation with at least 12-lead ECG and echocardiography [13]. If they are diagnosed with DCM life-long follow-up is required and all their first-degree relatives should undergo cardiologic evaluation as well. If instead the cardiologic evaluation is negative for DCM, the relative should be followed-up with repeat cardiologic evaluations; every 1–3 years for those younger than 10 years of age, every 1–2 years between the age of 10 and 20, and every 2–5 years from 20 years of age up until 50–60 years of age. The reason for this continued evaluation during life is the age-dependent penetrance. For those affected, penetrance is almost complete at 60 years of age, therefore repeated evaluation is not necessary after this [13].

6. Causative gene mutations

Many genes have been linked to DCM, some with a definite and some with a putative link. For definite DCM genes see **Table 1**, adapted from McNally et al. [22]. It is often difficult to determine if a mutation in a gene is causative of cardiomyopathy, sometimes mutations are determined to be so called variants of unknown significance. Most genes implicated in the pathogenesis of DCM are highly conserved with few *de novo* mutations occurring, making new mutations, found in a known DCM gene that alters the encoded protein, likely to be pathogenic.

Mutations that have been linked to DCM affect genes related to diverse cell structures such as; ion channels, dystrophin complexes, sarcoplasmic reticulum, nuclear lamina, desmosomes, mitochondria, cytoskeleton, z-disc, and sarcomeres. For an image visualizing different cellular structures related to definite DCM genes see **Figure 3**.

6.1 Genes associated with sudden cardiac death

The general consensus is that risk of arrhythmia in DCM scales with the degree of left ventricular systolic dysfunction. Most genotypes cannot be distinguished from each other by evaluation of the phenotype. Due to this broad gene panels are required. However, some genotypes have been shown to be prone to arrhythmia and in some

Gene	Protein	Frequency and overlapping phenotypes
Sarcomere	Force generation/transmission	
MYH7	Beta-myosin heavy chain	3–4% of DCM; HCM, LVNC
TPM1	Alpha-tropomyosin	1–2% of DCM; HCM, LVNC
ACTC1	Alpha cardiac actin	HCM, LVNC
TNNT2	Cardiac troponin T	3% of DCM; HCM, LVNC
TNNC1	Cardiac troponin C	HCM, LVNC
TNNI3	Cardiac troponin 1	HCM
TTN	Titin	12–25% of DCM; HCM, tibial muscle dystrophy
TNNI3K	Troponin 1 interacting kinase	Conduction defect, atrial fibrillation
Z-disc	Mechanosensing/mechanosignaling	
ACTN2	Alpha-actinin 2	LVNC
BAG3	BCL2 Associated Athanogene 3	Myofibrillar myopathy
CRYAB	Alpha-B-crystallin	Protein aggregation myopathy
TCAP	Titin-cap/telethonin	LGMD2G
CSRFP3	Muscle LIM protein	HCM
ANKRD1	Cardiac ankyrin repeat protein	Congenital heart disease
LDB3	Cipher/ZASP	LVNC
NEBL	Nebulette	LVNC, HCM
Dystrophin complex	Sarcolemma, structural integrity	
DMD	Dystrophin	Duchenne/Becker muscular dystrophy
SGCA	Alpha-sarcoglycan	LGMD2D
SGCB	Beta-sarcoglycan	LGMD2E
SGCD	Delta-sarcoglycan	LGMD2F
Cytoskeleton	Mechanotransduction/mechanosignaling/structural integrity	
DES	Desmin	<1% of DCM; desminopathies, myofibrillar myopathy
VCL	Metavinculin	1% of DCM
FLNC	Filamin C	1% of DCM; myofibrillar myopathy, HCM, RCM
Desmosomes	Cell–cell adhesion/mechanotransmission/mechanosignaling	
DSP	Desmoplakin	2% of DCM; ARVC
Sarcoplasmic reticulum and cytoplasm Ca homeostasis, contractility modulation, signaling		
PLN	Phospholamban	ARVC, HCM
Nuclear envelope	Nuclear structural integrity, mechanotransduction, mechanosignaling	
LMNA	Lamin A/C	4–8% of DCM; multiple phenotypes, LGMD1B, EDMD, progeria
EMD	Emerin	EDMD
Nucleus	Transcription cofactors, gene expression	
RBM20	RNA-binding protein 20	2% of DCM; RNA-binding protein of spliceosome of TTN and other proteins
Ion channels	Transportation of ions	
SCN5A	Type V voltage-gated cardiac Na channel	2–3% of DCM; LQTS, Brugada, atrial fibrillation, conduction defects

Gene	Protein	Frequency and overlapping phenotypes
ABCC9	Component of ATP-sensitive potassium channel	Atrial fibrillation, osteochondrodysplasia
KCNQ1	Potassium channel	Atrial fibrillation, LQTS1, short QT1, Jervell and Lange-Nielsen syndrome
Mitochondria	Supply and/or regulation of energy metabolism	
DNAJC19	HSP40 homolog, C19	3-methylglutaconic aciduria type V
TAZ/G4.5	Tafazzin	LVNC, Barth syndrome, endocardial fibroelastosis 2

ARVC: arrhythmogenic right ventricular cardiomyopathy; DCM: dilated cardiomyopathy; EDMD: Emery Dreifuss muscular dystrophy; HCM: hypertrophic cardiomyopathy; LGMD: limb-girdle muscular dystrophy; LVNC: left ventricular non-compaction cardiomyopathy; LQTS: long QT-syndrome; RCM: restrictive cardiomyopathy. Adapted from McNally et al. [22].

Table 1.
Definite dilated cardiomyopathy genes.

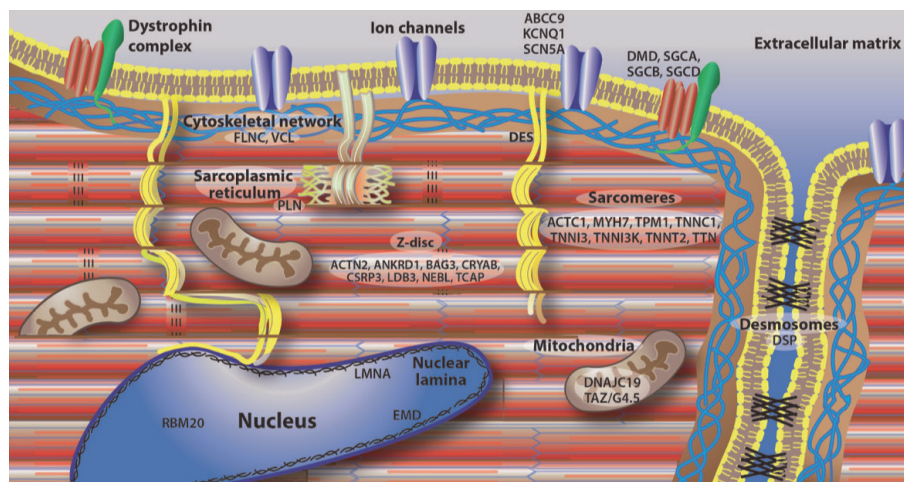


Figure 3. Cross section of two cardiomyocytes that connect to each other with desmosomes at the intercalated disc. Definite DCM genes and important cellular structures pertaining to them are named. Image by Todd Cooper.

cases sudden cardiac death. Some genes are very rare, or only putative and not definitively linked to DCM. Out of the genes that regularly are found to cause DCM, LMNA and SCN5A stand out for their propensity to cause arrhythmia. Mutations in both of these genes can cause a phenotype with atrial fibrillation, conduction system disease or ventricular tachyarrhythmia as the presenting symptom [22]. Guidelines from the ESC give specific indications for the implantation of an ICD in patients with DCM and LMNA mutation, these are described below [3]. For SCN5A no specific guidelines are given [3]. However, it is reasonable to adapt clinical management for patients with mutation in this gene to account for the known risk for arrhythmia. This also holds true for patients with other or unknown mutations, but with a family history indicative of a high risk of arrhythmia and sudden cardiac death. Such adaptations might include more frequent ambulatory ECG-monitoring or the use of insertable cardiac monitors to screen for potentially life-threatening arrhythmias.

6.1.1 LMNA

LMNA, the gene encoding the proteins lamin A and C, is one of the most studied DCM genes. Lamin A/C form part of the nuclear lamina and have been implicated in several cellular processes, including regulation of gene expression [22]. DCM

associated with mutation in LMNA tend to have age-dependent penetrance but with disease onset early in life, often dysrhythmias mainly conduction disturbances and atrial fibrillation precede the development of heart failure. The risk for sudden cardiac death is also increased, even with only moderately reduced left ventricular ejection fraction [3]. Guidelines of the ESC state that an ICD should be considered (class of recommendation IIa) for patients with DCM and a confirmed disease-causing mutation in LMNA if any of the following clinical risk factors are present; non-sustained ventricular tachycardia, left ventricular ejection fraction $\leq 45\%$, male sex, or a non-missense mutation (insertion, deletion, truncation or mutation affecting splicing) [3]. This recommendation is based upon the results of a cohort study of 269 patients with LMNA-mutation and a median follow-up time of 43 months, 48 patients (18%) reached the composite endpoint of sudden cardiac death, appropriate ICD therapy, or aborted cardiac death [23]. In a review of published cohorts of patients with LMNA-associated cardiomyopathy, in total 299 patients, some sort of dysrhythmia was reported in 92% after the age of 30 years [24]. Dysrhythmias included sinus bradycardia, first-degree AV-block, and atrial or ventricular tachyarrhythmias [24]. Notably, almost half died from sudden cardiac death [24]. This high proportion of sudden cardiac death was also noted in those patients who had a pacemaker implanted, which implies that the mode of death in LMNA-associated cardiomyopathy may be caused by ventricular tachyarrhythmias [24].

6.1.2 SCN5A

Mutations in SCN5A, the gene that encodes the sodium voltage-gated channel alpha subunit 5 involved in the main cardiac sodium channel, has been linked to several diseases including Brugada syndrome, long QT-syndrome as well as DCM and ARVC [25]. Different kinds of mutations in SCN5A have been linked to DCM and the mechanism is still uncertain. Interestingly, the phenotype varies in families with the same genotype, indicating that environmental or other confounding factors are at play [25]. Mutations in SCN5A have also been linked to progressive conduction disorder and familial atrial fibrillation. Given this, it is not surprising that DCM due to SCN5A often presents with increased risk of arrhythmia [22].

7. Future perspectives

Currently, familial DCM is likely frequently underdiagnosed, and often genetic testing is not conducted. Increased awareness and availability of genetic evaluation might provide more knowledge and gene-specific therapies and management might become available. Increased identification of affected families will mean that more at-risk individuals will come into contact with health care providers prior to developing the phenotype. This means that future studies should focus on therapies aimed to prevent the development of DCM in these individuals. Further research into the different genotypes and their burden of arrhythmia is also warranted in order to improve risk stratification for sudden cardiac death. This includes the utilization of implantable cardiac monitors in those patients who have certain high-risk genotypes but have been judged not to fulfill criteria for the implantation of an ICD.

8. Conclusion

Reduced left ventricular systolic ejection fraction is the most common indication for the implantation of an ICD regardless of type of cardiomyopathy. In DCM some

genes have been linked to a propensity for arrhythmia, chief among them LMNA and SCN5A. A mutation in LMNA together with other clinical risk factors could warrant implantation of an ICD.

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Acronyms and abbreviations

ACEi: angiotensin converting enzyme inhibitor; ARVC: arrhythmogenic right ventricular cardiomyopathy; AV: atrioventricular; DCM: dilated cardiomyopathy; ESC: European Society of Cardiology; HCM: hypertrophic cardiomyopathy; ICD: implantable cardioverter defibrillator; NYHA: New York Heart Association; SGLT2i: sodium-glucose transporter protein 2.

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