Published in final edited form as:

Prog Pediatr Cardiol. 2014 December ; 37(1-2): 13–18. doi:10.1016/j.ppedcard.2014.10.003.

GENETIC CAUSES OF DILATED CARDIOMYOPATHY

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Abstract

Dilated cardiomyopathy is a disease of the myocardium characterized by left ventricular dilatation and/or dysfunction, affecting both adult and pediatric populations. Almost half of cases are genetically determined with an autosomal pattern of inheritance. Up to 40 genes have been identified affecting proteins of a wide variety of cellular structures such as the sarcomere, the nuclear envelope, the cytoskeleton, the sarcolemma and the intercellular junction. Novel gene mutations have been recently identified thanks to advances in next-generation sequencing technologies. Genetic screening is an essential tool for early diagnosis, risk assessment, prognostic stratification and, possibly, adoption of primary preventive measures in affected patients and their asymptomatic relatives. The purpose of this article is to review the genetic basis of DCM, the known genotype-phenotype correlations, the role of current genetic sequencing techniques in the discovery of novel pathogenic gene mutations and new therapeutic perspectives.

Keywords

Dilated cardiomyopathy; gene; prognosis; screening; pediatrics; heart failure

INTRODUCTION

Dilated cardiomyopathy (DCM) represents an important health issue both in the in adult and pediatric population, with high rates of morbidity, mortality and hospital admissions. DCM is a severe disease of the heart muscle that is characterized by dilatation of the left ventricle and reduced left ventricular systolic function (1). Genetic forms of DCM account for approximately 40 % of cases (2), whereas the etiology of a wide portion of cases remains

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The authors report that they have no relationship to disclose.

Conflict of Interest Disclosures:

No conflict of interest to disclose.

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still unknown and it is considered idiopathic. In this group, the possibility to identify novel genetic mutations represents an intriguing challenge for the current advanced techniques of high-throughput genetic sequencing. Genetic screening for rare specific variants is an essential diagnostic tool not only in affected subjects but also in their asymptomatic relatives, including at risk siblings and children of affected patients, in order to improve early diagnosis, risk assessment for prognostic stratification and to identify patients who may benefit from primary prevention strategies such as regular cardiac monitoring, early institution of heart failure medications, and consideration of implantable cardioverter-defibrillators in those with a genetic-related increased risk of life threatening malignant arrhythmias.

The purpose of this article is to review the genetic basis of DCM, the known genotype-phenotype correlations and the role of current genetic sequencing techniques in the discovery of novel pathogenic gene mutations. Finally, we will discuss future developments including novel therapeutic perspectives.

Epidemiology of DCM in the adult and pediatric populations

DCM is a heart-muscle disorder characterized by systolic dysfunction and dilatation of the left ventricle with normal left ventricular wall thickness. DCM may present with biventricular involvement (Figures 1A and 1B), even though the presence of a dilated and dysfunctional right ventricle is neither necessary nor sufficient for the diagnosis. Systolic dysfunction may lead to cardiac thrombus formation (Figure 1C) that confers a risk of systemic embolization. DCM represents an important health issue both in the adult and pediatric population, with high rates of morbidity, mortality and hospital admissions: DCM can lead to progressive heart failure and represents the most frequent indication for heart transplantation (3).

The prevalence of DCM in the general population remains undefined. This disorder develops at any age, in either sex, and in people of any ethnic origin (4). It is among the most common causes of cardiomyopathy with an estimated prevalence of 1:2,500, and incidence of 7:100,000. In adults, males are more frequently affected than females with an approximately 3:1 ratio of males to females (5) (6). More recent estimates suggest a substantially higher prevalence of approximately 1 in 250 individuals (2). In the pediatric population, DCM is the predominant type of cardiomyopathy (7) and its incidence is higher in the first year of life (8). The majority of cases are idiopathic, followed by familial forms (4), which, in 6.8% of cases, are due to inborn errors of metabolism mainly regarding metabolic disorders, oxidative phosphorylation defects and systemic carnitine deficiency (9).

In the pediatric cohort, a comprehensive clinical evaluation is important to exclude secondary causes of cardiomyopathies. In some cases, such as cardiomyopathy related to anomalous coronary connections to the pulmonary artery and tachycardia-induced cardiomyopathy, surgical treatment in the former and ablation in the latter may be curative (10) (11). Furthermore, hormonal and nutritional causes should be excluded, as it was observed that vitamin D deficiency is associated with reversible pediatric dilated cardiomyopathy (12).

Diagnostic criteria of idiopathic and familial dilated cardiomyopathy

Criteria for the diagnosis of DCM are the presence of left ventricular fractional shortening <25% and/or left ventricular ejection fraction <45%, and left ventricular end-diastolic dimensions >117% of the predicted value by the Henry formula (1) (13). The diagnosis of familial dilated cardiomyopathy is made in the presence of two or more affected individuals in a single family or in the presence of a first-degree relative of a dilated cardiomyopathy patient, with well-documented unexplained sudden death at <35 years of age (1). In idiopathic DCM and familial DCM, the exclusion of potential secondary causes of ventricular dilatation and dysfunction (systemic arterial hypertension, coronary artery disease, valvular diseases, active myocarditis, chronic excess of alcohol consumption, sustained and rapid supraventricular arrhythmias, systemic disease, pericardial diseases, cor pulmonale, congenital heart diseases) is needed before reaching a DCM diagnosis. There are not significant clinical differences between idiopathic and familial forms of DCM except for the earlier age of onset and slight higher left ventricular ejection fraction in the latter group (14). Notably, also idiopathic DCM can have a genetic cause and lack the familial transmission due to small family size, lack of information, low penetrance, or *de novo* mutations.

Genetic determinants of dilated cardiomyopathy and genotype-phenotype correlations

Genetic forms of DCM account for nearly half of cases and are characterized by profound genetic heterogeneity, as about 40 causative genes have been identified so far (2) (15). These genes encode for a wide variety of proteins of the sarcomere, cytoskeleton, nuclear envelope, sarcolemma, ion channels and intercellular junctions. Specific mutations of these genes alter various pathways and cellular structures and negatively affect the mechanism of muscle contraction, functioning and sensitivity of ion channels to electrolytes, calcium homeostasis and generation-transmission of mechanic force in the myocardium. The fact that this genetic heterogeneity results in a common phenotype has been explained by Bowles and Towbin with the “Final Common Pathway” hypothesis: different mutations alter various proteins involved in a common pathway whose disruption leads to DCM, even the arrhythmogenic form (16) (17).

The main pattern of inheritance in pediatric genetic forms of DCM is the autosomal recessive. In adult population, familial genetic forms of DCM account for 30–48% of cases, their main pattern of inheritance is autosomal dominant (56%) (14) and they are usually characterized by incomplete and age-related penetrance, and variable expression. The clinical phenotype, in terms of age of presentation, clinical characteristics and severity, is heterogeneous not only among different families, but also among members of the same family. Patients may be asymptomatic for several years before the development of overt progressive heart failure requiring transplantation. Arrhythmias, conduction system disorders and sudden death are often the first manifestation of the disease (18).

Sarcomeric genes

The sarcomere is the basic contractile unit of both skeletal and cardiac muscle. Mutations of genes encoding sarcomeric proteins account for 5–10% of cases and are associated with defects in force generation and transmission in some cases (19) (20). Sarcomeric mutations are an important cause of DCM, but also of hypertrophic cardiomyopathy where the prevalence is approximately 60% (21). Sometimes, sarcomeric gene mutations may lead to overlapping phenotypes.

In DCM sarcomeric mutations are hypothesized to reduce sarcomeric contractile function (with systolic dysfunction detected even in subclinical forms), while in hypertrophic cardiomyopathy different sarcomeric mutations are believed to augment force generation thorough a gain of function mechanisms (22) (23). Mutations of genes encoding myosin proteins (*MYH6*, *MYH7* and *MYBPC3*) actin proteins (*ACTC1* and *ACTC2*) and tropomyosin protein (*TPM1*), result in alterations of the correct coupling-uncoupling of actin to/from myosin (24) (25) (26) (27).

Recent studies have shown that the sarcomeric gene most frequently involved in DCM is titin (*TTN*), as protein truncating mutations are detected in 25% of familial DCM and 18% of idiopathic DCM (28). Titin is the largest-known human protein, highly expressed in the heart and extending from the Z line to the M line of the sarcomere (29). *TTN* provides both passive force and elasticity to preserve diastolic and systolic function, respectively. Furthermore, it regulates the assembly and length of the sarcomere. While the role of truncation mutations in DCM is accepted, the pathogenic and prognostic role of missense variants is still debated and under investigation.

Despite the limited availability of longitudinal prognostic data on the impact of sarcomere variants, a recent study by Merlo et al. observed that sarcomeric rare variant carriers showed a more rapid progression toward death or heart transplantation compared to non-carriers, particularly after 50 years of age (30).

Nuclear proteins

The nuclear proteins lamin A and C are intermediate filaments which form the lamina of the nuclear envelope. They are two isoforms encoded by the same *LMNA* gene mapping on chromosome 1. These proteins have structural/mechanical functions in the nucleus and regulate the replication and transcription of DNA (31).

LMNA mutations are associated with a variety of phenotypes including DCM with arrhythmias and conduction disease, Limb-Girdle Muscular Dystrophy, Emery-Dreifuss Muscular Dystrophy and autosomal dominant partial lipodystrophy. The reported prevalence of *LMNA* mutations among DCM patients is about 8% (32) with an autosomal dominant pattern of inheritance. From a clinical point of view, DCM patients carrying a *LMNA* mutation show an early onset of disease, have cardiac conduction disturbances (33), skeletal muscle involvement with high creatinine kinase levels and are at a high risk for life threatening or malignant ventricular arrhythmias and sudden death (34). Other proteins of the nuclear envelope interacting with *LMNA* may cause a DCM phenotype. Thymopoietin is a protein that interacts with Lamin A/C encoded by *TMPO* (*LAP2*) gene on chromosome 12:

a mutation in *LAP2* has been associated with DCM with a low prevalence of approximately 1% (35).

Ion Channels proteins

Among ion channels proteins involved in DCM, sodium channel (*SCN5A*) and phospholamban (*PLN*) mutations have been described (36) (37) (38). *SCN5A* mutations account for 1.7% of DCM families and are associated with an arrhythmogenic phenotype characterized by early onset of disease, arrhythmias such as atrial fibrillation or ventricular tachycardia, sinus node dysfunction and conduction disease (39). *SCN5A* mutations are related also to other arrhythmic disturbances such as Long QT Syndrome and Brugada Syndrome.

PLN mutations are thought to lead to DCM through inhibition of calcium pump (SERCA2a). Furthermore, it has been reported that a specific mutation of *PLN* gene (R14del) is associated with high risk for malignant ventricular arrhythmias and end-stage heart failure from late adolescence and can cause either a DCM phenotype or arrhythmogenic right ventricular cardiomyopathy (40).

Cytoskeletal proteins

Desmin (*DES*) mutations can cause a spectrum of phenotypes including skeletal myopathy, mixed skeletal-cardiac disease (“desmin-related myopathy”), and cardiomyopathy (DCM as well as hypertrophic or restrictive cardiomyopathies). DCM is typically preceded by skeletal myopathy and can be associated with conduction defects. The reported prevalence of *DES* mutations in DCM is about 1–2% of DCM cases (41)

Cypher/*ZASP* (*LDB3*) mutations were identified by Vatta et al in 2003 (42) and are thought to be related to pure DCM or DCM with left ventricular non-compaction, with or without skeletal involvement and are found more commonly in pediatric populations (43) (44).

Mutations of the gene encoding dystrophin (*DMD*) cause Duchenne muscular dystrophy, its milder, later onset form Becker muscular dystrophy, and X-linked DCM where the muscular involvement is absent or subclinical (45). The *DMD* genes maps on chromosome X, therefore the pattern of inheritance is X-linked (45). Dystrophin, in conjunction with the dystrophin glycoprotein complex, functions as a link between the cytoskeleton and the extracellular matrix and, therefore, its mutations result in altered force transmission and progressive cell death. DCM, with supraventricular arrhythmias, atrio-ventricular blocks and right bundle branch block, characterizes X-linked DCM and occurs as a late complication in Duchenne muscular dystrophy, whereas it is less frequent in Becker muscular dystrophy.

Other genes and proteins

A number of other genes and mechanisms can lead to the DCM phenotype (2). Among the most recent discoveries on genetic basis of DCM is the *BAG3* gene, encoding for BCL2-associated athanogene 3, a co-chaperone protein with anti-apoptotic function, which localizes at Z-disc in the striated muscles. The estimated prevalence of *BAG3* mutations is 2.8% of Japanese familial DCM patients (46). It is thought to cause DCM by interfering

with Z-disc assembly and inducing apoptotic cell death under the metabolic stress (46) (47) (48). However, functional abnormalities caused by mutations in this gene are not fully understood. Furthermore, extracellular matrix proteins such as Lamin alpha-4 (*LAMA4*) and Fukutin (*FKT*) has been described and related to DCM: they may lead to the DCM phenotype by disrupting signaling pathways and modifying cell-surface molecules respectively (49) (50).

Genetic testing: progress and novel problems

Genetic screening is indicated in familial forms of DCM and it is a useful tool for risk stratification and prognostic assessment in affected subjects and their relatives who may benefit from early diagnosis. Family screening can effectively identify DCM patients at an earlier stage of disease and improve survival (51). However, the relatively low sensitivity of genetic testing (40%) (2) and the difficulties in distinguishing disease-causing from non-pathogenic mutations (52) are critical issues that should be taken into consideration. One of the problems is that presumably several DCM genes remain to be discovered and added to the more than 40 causative genes have been identified. Secondly, older techniques of genetic screening such as denaturing high performance liquid chromatography were not be able to detect all types of genetic variations. In this contest, new deoxyribonucleic acid (DNA) sequencing techniques with multi-genes panels (53) together with progress in next-generation sequencing technologies may have improved the sensitivity of genetic screening. To be certain, next-generation sequencing has allowed for broader research screening of genes and this should presumably translate into the discovery of additional DCM genes. On the other hand, the population frequency of genetic variants linked to DCM phenotypes is greater than expected (2) (54) possibly because of reduced penetrance of DCM-causing mutations, or higher than previously estimated prevalence of DCM, but also because non-causal variants may have been erroneously assigned causality. Furthermore, like in other forms of cardiomyopathy, the genetic basis of DCM is likely to be more complex than previously thought, including the presence of multiple (double or more) pathogenic variations contributing to the phenotype. This higher level of complexity requires expert management, as discussed in the next section.

Genetic counseling in dilated cardiomyopathy

All family members that are identified as carriers or first-degree relatives of affected family members potentially at risk of disease should receive lifestyle modification advice, e.g. avoidance of alcohol excess, regular moderate exercise, etc. Female family members who are at risk and are considering pregnancy should have initial cardiac exam and regular follow-up during pregnancy, since familial DCM may be unmasked or accelerated in the peri-partum period, especially in the last trimester and first six months postpartum. The diagnosis of a genetic disorder in a family and the possibility of testing for carriers of the disease gene variant raises a number of clinical and social issues that are best addressed by experienced cardiovascular genetic counselors (55).

Medical management

According to American Heart Association guidelines (56), treatment of left ventricular dysfunction in adults is stratified by four stages of heart failure: stage A, patients at risk without symptoms or structural heart disease; stage B, presence of structural heart disease without symptoms; stage C, structural heart disease with present or past heart failure symptoms; and stage D, refractory heart failure. Angiotensin-converting enzyme (ACE) inhibitors represent class 1 indication for stages B and C heart failure (56) (57) as they reduce morbidity and mortality in asymptomatic-to-moderate symptomatic heart failure (58) (59) (60) (61). Similarly, beta-blockers have been demonstrated to reduce mortality and morbidity in heart failure and their use is a class 1 indication for stage C heart failure (62) (63) (64) (65).

In patients with genetic DCM the therapy follows the general heart failure guidelines, where significant clinical benefit, including increased survival, has been associated with the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β -adrenoreceptor blockers, aldosterone antagonists, and vasodilators. As described in consensus guidelines, these medications should be titrated to the dose used in clinical trials unless limited by side effect (66). Patients with DCM were included in the pivotal trials that established the survival benefit associated with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers use in a broad spectrum of patients with DCM, from severe (58) (67) to-moderate heart failure (68) (69) to asymptomatic LV systolic dysfunction (70) (71). The benefit conferred by aldosterone antagonists in patients with mild and severe heart failure was similar in patients with both non-ischemic and ischemic cardiomyopathy. Therapy with the vasodilator combination of hydralazine and isosorbide dinitrate improved survival in patients with DCM. However, not all vasodilators are beneficial, including doxazosin and dihydropyridine calcium channel blockers (72), which did not improve outcomes in DCM. The therapy of DCM in children follows the same guidelines and it is based on the use of beta-blockers and inhibition of the renin-angiotensin system. As with other forms of heart failure, patients with familial DCM are advised to limit excess dietary sodium and to avoid alcohol ingestion or exposure to other cardiotoxins—in particular, cocaine, amphetamines, and certain antineoplastic agents (anthracycline cardiomyopathy).

Future directions

The recent improvements in sequencing technology and better understanding of the *phenome* and genome of cardiomyopathies are starting to improve the diagnosis, prevention and therapy of genetic DCM. With next generation sequencing technology becoming more cost-effective and accurate, wider use of genetic testing will increase the number of DCM patients identified as well as asymptomatic carriers. Recent studies suggest that advances in mechanistic investigations may rapidly translate into effective therapies. Patients with overt disease will benefit from gene- and pathway-specific therapies (73) such as small molecule inhibitors of the extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) pathways to slow the progression of *LMNA* associated DCM to antisense oligonucleotides developed to treat Duchenne muscular dystrophy that have already shown promise in small clinical studies (74) (75) (76) (77).

Recently, Dhandapany et al. have reported the discovery of a novel gene associated with pediatric DCM, *RAFI*, in ~9% of childhood onset disease (78). The investigators found that *RAFI* mutants had AKT hyper activated. The investigators generated a mutant zebrafish model, which recapitulated the cardiomyopathy phenotype and showed AKT hyper-activation. The investigators were able to rescue the phenotype by inhibiting the AKT-mTOR pathway by inhibition with Rapamycin treatment.

Similarly, in *LMNA* associated adult-onset DCM, the mTOR pathway has also been found to be activated and, in animal models, the inhibition of the mTOR pathway by Temsirolimus or Rapamycin was able to rescue the DCM phenotype (79) (80). These novel findings are exciting and pave the way to novel therapeutic perspectives and trials in human disease.

Conclusions

DCM is a complex disease with a heterogeneous genetic etiology in almost half of cases. Progress in genetic screening, in particular with next-generation sequencing, will provide more insights into the wide variety of possible variants involved in the pathogenesis of DCM and help in understanding the molecular mechanisms leading to the disease. Future research will focus on expanding cohorts for genotype-phenotype studies and integrate phenome-genome data in order to provide more accurate information on diagnosis, prognosis, risk stratification and potential molecular therapies for affected subjects.

Acknowledgments

This study was supported by the NIH grants UL1 RR025780, UL1 TR001082 N01-HV-48194, R01 HL69071, R01 HL6906 to LM; K23 JLO67915 and R01HL109209 to MRGT; CRTrieste Foundation and GENERALI Foundation to GS.

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Figure 1. Echocardiographic findings in pediatric DCM

(A) Parasternal Long axis view in a 13 year-old patient with DCM and severe biventricular dysfunction showing enlargement of the cardiac chambers. (B) Four chamber echocardiogram shows biventricular dilation, biatrial enlargement and a marked trabecular meshwork in the lateral wall. (C) Echocardiography showing a large mobile thrombus (arrow).

Figure 2. Effect Temsirolimus, an inhibitor of the mTORC1 pathway, in *Lmna*^{H222P/H222P} mice vs. control

(from Choi et al. (79) with permission). Upper panels: representative hearts (scale bar 1 cm) and M-mode echocardiography showing improvement of dilatation and systolic dysfunction in Tg mice treated with Temsirolimus. Lower panels: left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), and fractional shortening (FS) showing significant improvement after Temsirolimus.