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# Genetics of Dilated Cardiomyopathy

Ramone Eldemire,[1] Luisa Mestroni,[1,2] and Matthew R.G. Taylor[2,3]

[1]Division of Cardiology, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA; email: luisa.mestroni@cuanschutz.edu

[2]Cardiovascular Institute, University of Colorado, Aurora, Colorado, USA

[3]Adult Medical Genetics Program, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

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## Keywords

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## Abstract

Dilated cardiomyopathy (DCM) is defined as dilation and/or reduced function of one or both ventricles and remains a common disease worldwide. An estimated 40% of cases of familial DCM have an identifiable genetic cause. Accordingly, there is a fast-growing interest in the field of molecular genetics as it pertains to DCM. Many gene mutations have been identified that contribute to phenotypically significant cardiomyopathy. DCM genes can affect a variety of cardiomyocyte functions, and particular genes whose function affects the cell–cell junction and cytoskeleton are associated with increased risk of arrhythmias and sudden cardiac death. Through advancements in next-generation sequencing and cardiac imaging, identification of genetic DCM has improved over the past couple decades, and precision medicine is now at the forefront of treatment for these patients and their families. In addition to standard treatment of heart failure and prevention of arrhythmias and sudden cardiac death, patients with genetic cardiomyopathy stand to benefit from gene mechanism–specific therapies.

## EPIDEMIOLOGY AND PATHOGENESIS OF DILATED CARDIOMYOPATHY

**HCM:** hypertrophic cardiomyopathy

**ACM:** arrhythmogenic cardiomyopathy

The cardiomyopathies are defined as myocardial disorders with abnormal structure or function of the heart. Broadly, these can be subdivided into dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), arrhythmogenic cardiomyopathy (ACM), and left ventricular noncompaction cardiomyopathy. DCM is characterized by dilation and loss of function of one or both ventricles and can be due to secondary causes such as infiltrative disease, metabolic derangements, valvular disease, toxins, medication, and many more. Although ischemic cardiomyopathies are more common in the United States (59% versus 41%) (1), patients with nonischemic DCM are more likely to be women, nonwhite, and younger than those with ischemic cardiomyopathies. The true prevalence of nonischemic DCM is not fully identified but is likely underestimated. An epidemiological study performed in Olmsted County, MN, from 1975 to 1984 using autopsy data, echocardiography, and angiography found a DCM prevalence of 36.5 in 100,000 patients and a man-to-woman ratio of 3:4 (2). This differs from several other studies performed in various regions, a difference that may reflect geographical and ethnic contributions to the frequency of DCM (3–6). Up to 50% of nonischemic DCM is genetic or idiopathic (7). Familial DCM is defined as (*a*) the presence of two or more relatives with DCM or (*b*) the presence of one relative with DCM and sudden cardiac death (SCD) prior to the age of 35 years. An estimated 40% of cases of familial DCM have an identifiable genetic cause (8). As such, there is a fast-growing interest in the field of molecular genetics as it pertains to DCM. Many genes have been identified that may contribute to phenotypically significant cardiomyopathy (9).

A significant portion (20–38%) of DCM may have an oligogenic basis; multiple rare variants from different unlinked loci and inconstant penetrance may cause a similar phenotype of DCM. The effects of environmental insults such as myocarditis, chemotherapy, and alcohol on the phenotypic expression of DCM in patients with genetic mutations are termed gene–environment interactions (GxE) and have also been studied (10, 11). In contrast, HCM and ACM fit more classically into a Mendelian model due to few highly penetrant rare variants affecting the sarcomere or desmosome, respectively. In fact, for HCM and ACM, a single mutation may explain most genetic causes in individual families (12–14). As with HCM, variants in the sarcomere genes are a frequent cause of DCM. For example, truncating mutations in the giant sarcomeric protein Titin (TTN) are the most common cause of DCM in adults but may also cause HCM (15–18) in rare cases. Mechanistically, the distinction from HCM is that DCM variants of the sarcomere gene are generally a loss-of-function mutation resulting in impaired force generation and decreased systolic function of the ventricle. DCM-causing mutations are not limited to the sarcomere. They may affect force transmission, mechanical stress, signaling, desmosomal proteins, nuclear structure and function, ion channel activity, protein turnover, and calcium hemostasis (19).

As with adults, genetic testing has become integral to the diagnosis, prognostication, and treatment of the pediatric population. Although DCM variants that directly disturb aspects of cardiomyocyte function are also present in younger patients, many genes associated with inborn errors of metabolism cause DCM (20, 21). Interestingly, a genetic cause in a pediatric patient is identified more commonly than in an adult patient (54% versus 27%) (22, 23). The 5-year survival in pediatric DCM that is familial is 94%, but this same cohort of patients has a relatively high 5-year transplantation rate of 38% (24, 25). These trends differ in idiopathic DCM and myocarditis, emphasizing the importance of genetic testing in all pediatric patients with DCM (26).

## DIAGNOSIS AND IMAGING

When evaluating for genetic DCM, it is essential to perform a detailed medical history. In addition, clinicians should obtain baseline hematologic and metabolic data, as well as a baseline

electrocardiogram, which may be abnormal in HCM, ACM, or DCM. Furthermore, patients should undergo ambulatory cardiac monitoring to evaluate arrythmia burden for further risk stratification. Building a detailed three-generation family history is crucial for determining risk factors for disease progression and SCD as well as classifying cases as familial or sporadic DCM (27). Echocardiography should be included in the initial work-up and screening for patients with suspected DCM. Cardiac magnetic resonance imaging (CMRI) can also be useful in characterization of cardiomyopathy and is frequently utilized in the diagnosis of genetic DCM.

The imaging diagnosis of DCM on echocardiogram is defined as the presence of fractional shortening of <25%, left ventricular ejection fraction (LVEF) of <45%, and left ventricular end diastolic diameter of >2.7 cm/m$^2$ or >117% predicted when corrected for age and body surface area (>2 standard deviations from the upper limits of normal values) (28). Any known secondary cause of myocardial disease must be excluded prior to making a diagnosis of genetic or idiopathic DCM (29). Phenotype-negative individuals who have confirmed variant mutations for DCM may undergo screening by echocardiography every 1–5 years.

## Echocardiography

On 2D echocardiography, the LVEF is assessed using the biplane Simpson method with the use of contrast agents to opacify the left ventricular endocardium in the case of poor image quality (30). Linear measurements for estimation of LVEF (Teichholz method) should be avoided due to inaccuracy. Also useful in the estimation of LVEF is 3D echocardiography, which has shown greater reproducibility, accuracy, and inter- and intra-reader consistency when compared to conventional 2D echocardiography techniques (31, 32). This improvement is likely due to several factors, including geometric assumptions with 2D echocardiography in which the heart is modeled as an ellipsoid shape, multiple acquisitions with 2D that can introduce more error, and foreshortening that can affect 2D calculation. Compared to CMRI, a 3D echocardiogram underestimates left ventricular volumes due to overall lower spatial resolution.

Aside from the imaging definition of DCM, other associated findings may be present on a DCM patient's echocardiogram. As DCM progresses, the left ventricle continues to remodel, becoming more spherical. This change is directly measured by an increased ratio of the short axis to the long axis (33). Functional mitral regurgitation results from dilation of the mitral valve annulus and consequent tethering of the mitral valve leaflets. Careful attention should be given to evaluate for left ventricular thrombus, pulmonary hypertension, and right ventricular dysfunction or dilation.

## Cardiac Magnetic Resonance Imaging

CMRI is currently the gold standard for assessment of biventricular volumes and function (34). In addition, the main strength of CMRI is the enhanced ability for tissue characterization and scar pattern analysis (35–38). It is a useful additional test in conjunction with echocardiography to further characterize the phenotype of DCM, as well as to rule out secondary causes of DCM (39). For instance, postischemic DCM with severe myocardial hypoperfusion or scarring may have a similar phenotype of ventricular dilation with reduced function but have distinctive findings on CMRI compared with nonischemic DCM, associated with different prognosis and treatment (40).

Late gadolinium enhancement (LGE) imaging comprises a standard sequence with CMRI to evaluate for focal myocardial fibrosis. A majority (58%) of DCM patients have no LGE, while up to 28% may have a characteristic midmyocardial pattern of enhancement (41, 42). The presence or absence of LGE has large prognostic implications. A study following 472 patients with DCM for 5.3 years noted that those with midmyocardial LGE had a threefold increase in all-cause

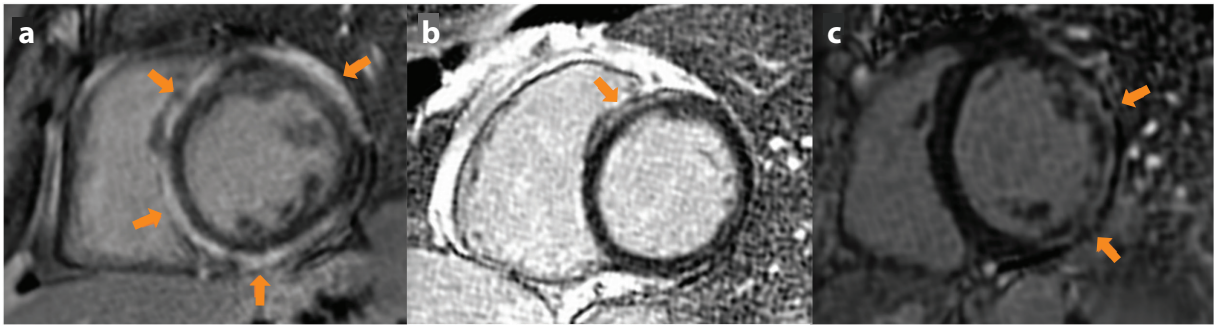


**Figure 1**

Phase-sensitive inversion recovery MRI sequences showing examples of nonischemic patterns of LGE in DCM (*arrows*). (*a*) Characteristic ring-like subepicardial LGE in patient with DCM and *DSP* mutation. (*b*) Anteroseptal midmyocardial LGE in a patient with idiopathic DCM. (*c*) Patient with Duchenne's muscular dystrophy demonstrating subepicardial LGE of the anterolateral and inferolateral walls. Abbreviations: DCM, dilated cardiomyopathy; LGE, late gadolinium enhancement; MRI, magnetic resonance imaging.

mortality and fivefold increase in a composite end point of SCD and aborted SCD. A smaller study with 65 patients also showed worse prognosis for DCM patients with midmyocardial LGE, reporting an eightfold increase in heart failure, appropriate internal defibrillator (ICD) firing, and cardiac death (43).

There is overlap between ACM and DCM. Specific genes such as *LMNA*, *SCN5A*, *FLNC*, *RBM20*, *PLN*, *DSP*, *DES*, and *TMEM43* can cause an arrhythmogenic DCM and may require ICD outside of the traditional primary prevention criteria (44–49). CMRI is also used clinically in DCM patients for additional SCD risk stratification. For example *DSP* and *FLNC* mutations may have a characteristic extensive ring-shaped LGE, which is a midmyocardial or subepicardial LGE pattern in three contiguous walls on the short axis view (50). Other forms of DCM do not typically present with this ring-shaped enhancement and can have heterogeneous scar patterns (**Figure 1**).

## Genetics

There have been remarkable achievements in the field of genetics due to advancements in next-generation sequencing, and now a person's entire genome can be evaluated with a single test. Many gene variants have been identified in the pathogenesis of DCM (**Table 1**). Most of the DCM genes are inherited in an autosomal dominant pattern and have variable penetrance (51). Autosomal recessive, X-linked, mitochondrial inheritance patterns and de novo mutations also occur (52). As discussed, DCM genes encode a wide variety of cellular functions.

### *TTN*

The giant protein TTN forms the "elastic" filament of the sarcomere, essential for the mechanical compliance of the heart muscle (53). TTN is the largest macromolecule in the human body, composed of 27,000–33,000 amino acids, and is encoded by the gene *TTN*, which contains 363 exons. It is heavily expressed in striated muscle tissue including cardiac myocytes (54). Modifications at the genetic, transcriptional, and post-translational levels can lead to loss or gain of function and present as HCM, ACM, or DCM. Truncating *TTN* variants (*TTNtv*) are the most common causes of genetic DCM, accounting for 20–25% of all cases. Interestingly, at least a subset of peripartum cardiomyopathy cases are attributable to *TTNtv* (55, 56). Greater than 60,000 missense variants of *TTN* have been identified, but the clinical significance of missense variations in *TTN* remains unknown (9).

**ICD:** internal defibrillator

**Table 1 Genes causing dilated cardiomyopathy**

| Gene | Gene symbol | Mode of inheritance | Classification[a] |
|---|---|---|---|
| ATP Binding Cassette Subfamily C Member 9 | *ABCC9* | AD | Limited |
| Actin Alpha Cardiac Muscle 1 | *ACTC1* | AD | Moderate |
| Ankyrin Repeat Domain 1 | *ANKRD1* | AD | Limited |
| BAG Cochaperone 3 | *BAG3* | AD | Definitive |
| Cysteine And Glycine Rich Protein 3 | *CSRP3* | AD | Limited |
| Cardiotrophin 1 | *CTF1* | AD | Limited |
| Desmin | *DES* | AD | Definitive |
| Desmoglein 2 | *DSG2* | AD | Limited |
| Desmoplakin | *DSP* | AD | Definitive[b] |
| Dystrobrevin Alpha | *DTNA* | AD | Limited |
| EYA Transcriptional Coactivator And Phosphatase 4 | *EYA4* | AD | Limited |
| Filamin C | *FLNC* | AD | Definitive |
| GATA Zinc Finger Domain Containing 1 | *GATAD1* | AR | Limited |
| Integrin Linked Kinase | *ILK* | AD | Limited |
| Junctophilin 2 | *JPH2* | AR | Moderate |
| Laminin Subunit Alpha 4 | *LAMA4* | AD | Limited |
| LIM Domain Binding 3 | *LDB3* | AD | Limited |
| Lamin A/C | *LMNA* | AD | Definitive |
| Leucine Rich Repeat Containing 10 | *LRRC10* | AR | NKDR/AMO |
| MIB E3 Ubiquitin Protein Ligase 1 | *MIB1* | AD | NKDR/AMO |
| Myosin Binding Protein C 3 | *MYBPC3* | AD | Limited |
| Myosin Heavy Chain 6 | *MYH6* | AD | Limited |
| Myosin Heavy Chain 7 | *MYH7* | AD | Definitive |
| Myosin Light Chain 2 | *MYL2* | AD | Limited |
| Myosin Light Chain 3 | *MYL3* | AD | Disputed |
| Myopalladin | *MYPN* | AD | Limited |
| Nebulette | *NEBL* | AD | Limited |
| Nexilin F-Actin Binding Protein | *NEXN* | AD | Moderate |
| NK2 Homeobox 5 | *NKX2–5* | AD | Limited |
| Natriuretic Peptide A | *NPPA* | AR | NKDR |
| Obscurin | *OBSCN* | AD | Limited |
| PDZ And LIM Domain 3 | *PDLIM3* | AD | Disputed |
| Phospholamban | *PLN* | AD | Moderate[b] |
| Plakophillin 2 | *PKP2* | AD | Disputed |
| Pleckstrin Homology And RUN Domain Containing M2 | *PLEKHM2* | AR | Limited |
| PR/SET Domain 16 | *PRDM16* | AD | Limited |
| Presenilin 1 | *PSEN1* | AD | Disputed |
| Presenilin 2 | *PSEN2* | AD | Limited |
| RNA Binding Motif Protein 20 | *RBM20* | AD | Definitive |
| Sodium Voltage-Gated Channel Alpha Subunit 5 | *SCN5A* | AD | Definitive |
| Sarcoglycan Delta | *SGCD* | AD | Limited |
| T-Box Transcription Factor 20 | *TBX20* | AD | Limited |
| Titin-Cap | *TCAP* | AD | Limited |

(*Continued*)

**Table 1 (*Continued*)**

| Gene | Gene symbol | Mode of inheritance | Classification[a] |
|---|---|---|---|
| Transmembrane Protein 43 | *TMEM43* | AD | Definitive[b] |
| Troponin C1, Slow Skeletal And Cardiac Type | *TNNC1* | AD | Definitive |
| Troponin I3, Cardiac Type | *TNNI3* | AD | Moderate |
| TNNI3 Interacting Kinase | *TNNI3K* | AD | Limited |
| Troponin T2, Cardiac Type | *TNNT2* | AD | Definitive |
| Tropomyosin 1 | *TPM1* | AD | Moderate |
| Titin | *TTN* | AD | Definitive |
| Vinculin | *VCL* | AD | Moderate |

[a]**https://www.clinicalgenome.org/**.

[b]In arrhythmogenic right ventricular cardiomyopathy.

Abbreviations: AD, autosomal dominant; AMO, animal model only; AR, autosomal recessive; NKDR, no known disease relationship.

### *LMNA*

*LMNA* missense and truncating mutations account for up to 8% of genetic DCM cases. Proteins Lamin A and Lamin C are encoded by the *LMNA* gene via differential splicing. Mutations in *LMNA* lead to phenotypic expressions including premature aging, myopathies, and DCM (57). *LMNA* mutations also lead to conduction abnormalities, atrial and ventricular arrythmias, and SCD, which usually precede DCM and have nearly complete penetrance by the seventh decade of life (58, 59).

### *PLN*

The gene *PLN* encodes phospholamban, a small, 52–amino acid transmembrane protein that inhibits sarcoplasmic reticulum $Ca^{2+}$ATPase in its unphosphorylated form. The R14del mutation of *PLN* is a founder mutation in the Netherlands and Germany, associated with ACM and DCM. Although, as with other DCM genes, mutations in *PLN* have variable penetrance, lethal arrythmias have been described (60, 61).

### *RBM20*

The gene *RBM20* encodes the RNA binding motif 20 protein, a 1,227–amino acid protein that is expressed in both the atria and the ventricles. Mutations in *RBM20* are responsible for 1–5% of genetic DCM (62). *RBM20* function regulates cardiac splicing including the splicing of *TTN*. Thus, given the downstream consequences of *RBM20* mutations, their presentation may be similar to those of *TTNtv*.

### *SCN5A*

The gene *SCN5A* encodes the alpha unit of the main cardiac sodium channel, $Na_v1.5$ (63). Mutations in this gene have been associated with ACM syndromes such as Brugada and long QT syndrome. Missense mutations in *SCN5A* have also been identified in DCM and carry a higher risk for arrythmias (46, 47).

## Cytoskeletal Genes

Various genes encode cardiac cytoskeletal proteins and are associated with DCM. Mutations in the dystrophin gene can lead to DCM in Duchenne's muscular dystrophy, which has an X-linked inheritance pattern (64). Mutations in the sarcoglycan genes can also produce cardiomyopathy

associated with muscular dystrophy from sarcolemmal instability. The gene *FLNC* encodes filamin C, and mutations have been described in both ACM and DCM. Filamin C has a critical function in cardiomyocytes, interacting with actin, Z-disk, the desmosome, and the dystrophin complex (65). Truncation mutations in *FLNC* cause DCM that is associated with a high rate of arrythmias and SCD (66).

## MANAGEMENT AND EMERGING THERAPIES

The current standard treatment of DCM with reduced LVEF (<40%) is directed toward heart failure, aiming to promote reverse remodeling, improve left ventricular dilation, and improve cardiac function. The current guidelines include a combination of four evidence-based therapies (67): (*a*) angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor/neprilysin inhibitor; (*b*) evidence-based beta-blockers; (*c*) aldosterone antagonists; and (*d*) SGLT2 (sodium-glucose transport protein 2) inhibitors. Reassessment of LVEF is typically performed after 3 months of uninterrupted medical therapy. Patients with persistently low LVEF (<35%) are at high risk for SCD and benefit from ICD (67), while those with a wide QRS (>150 ms), left bundle branch block, and NYHA (New York Heart Association) class II benefit from cardiac resynchronization therapy. Finally, patients who have refractory heart failure should be referred for advanced therapies including left ventricular assist device and transplant.

However, the heart failure guidelines concept of "one size fits all" does not fully apply to DCM. Patients who are carriers of ACM gene mutations, such as mutations of *FLNC*, *DSP*, *LMNA*, or *PLN*, may require ICD based on arrhythmic risk factors (68) rather than based on severe left ventricular dysfunction. Also, the understanding of the genetic cause provides novel treatment opportunities. Emerging treatments for DCM include gene therapy for gene replacement (as in regenerative medicine advanced therapy trials) or direct genome editing by CRISPR/Cas-9 technology (currently being tested in vitro and in vivo), signaling pathway modifiers [REALM-DCM trial (NCT03439514)], and modifiers of myofilament function (65, 69, 70).

## CONCLUSIONS

DCM is defined as dilation or loss of one or both ventricles and remains a common disease process worldwide. Through advancements in next-generation sequencing and cardiac imaging, identification of genetic DCM has improved over the past couple decades, and precision medicine is now at the forefront of treatment for these patients and their families. In addition to standard treatment of heart failure and prevention of SCD, patients with genetic cardiomyopathy stand to benefit from gene mechanism–specific therapies.

## DISCLOSURE STATEMENT

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