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LMNA-Related Dilated Cardiomyopathy

Ray E Hershberger, MD[1] and Elizabeth Jordan, MMSc, CGC[2]

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Summary

Clinical characteristics

LMNA-related dilated cardiomyopathy (DCM) is characterized by left ventricular enlargement and/or reduced systolic function preceded (sometimes by many years) by or accompanied by conduction system disease and/or arrhythmias. *LMNA*-related DCM usually presents in early to mid-adulthood with symptomatic conduction system disease or arrhythmias, or with symptomatic DCM including heart failure or embolus from a left ventricular mural thrombus. Sudden cardiac death can occur, and in some instances is the presenting manifestation; sudden cardiac death may occur with minimal or no systolic dysfunction.

Diagnosis/testing

The diagnosis of *LMNA*-related DCM is established in a proband with suggestive findings and a heterozygous pathogenic variant in *LMNA* identified by molecular genetic testing.

Management

Treatment of manifestations: Chronic atrial fibrillation is treated initially with attempts to restore normal sinus rhythm, anticoagulation, and rate control. Symptomatic supraventricular arrhythmias are usually treated with pharmacologic therapy or ablation; symptomatic bradyarrhythmias or significant heart block is treated with an electronic pacemaker. Symptomatic ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, and resuscitated sudden cardiac death are treated with an implantable cardioverter defibrillator (ICD) and drug therapy as needed. Because risk for sudden cardiac death in *LMNA*-related DCM accompanies heart block and bradyarrhythmias, ICD use (rather than just pacemaker use) has been recommended for all indications. Treatment of symptomatic DCM, including heart failure, is pharmacologic with ACE inhibitors, beta blockers, and other conventional approaches. Progressive deterioration in left ventricular function is treated with an ICD. Cardiac transplantation or other advanced therapies may be considered for refractory disease in persons receiving comprehensive care from cardiovascular disease experts.

Author Affiliations: 1 Professor of Medicine, Divisions of Human Genetics and Cardiovascular Medicine The Ohio State University Columbus, Ohio; Email: ray.hershberger@osumc.edu. 2 Assistant Professor, Division of Human Genetics The Ohio State University Columbus, Ohio; Email: elizabeth.jordan@osumc.edu.

Surveillance: Individuals with an *LMNA* pathogenic variant who are found to have any EKG abnormality should undergo a cardiovascular evaluation for disease progression (EKG, 24-48 hour rhythm monitoring, LV function measurement) at least annually. Asymptomatic individuals with a pathogenic *LMNA* variant should undergo cardiovascular evaluation (medical history, physical examination, echocardiogram, and EKG) every one to two years and/or whenever new symptoms arise. In families with a known *LMNA* pathogenic variant, at-risk individuals for whom genetic testing is not possible should have yearly cardiovascular evaluation. At onset of new symptoms an immediate evaluation for evidence of DCM and/or conduction system disease is indicated regardless of genetic status.

Evaluation of relatives at risk: To facilitate prompt diagnosis, targeted *LMNA* genetic testing when the family-specific pathogenic variant is known; otherwise regular surveillance with cardiovascular screening tests.

Pregnancy management: Pregnancy is contraindicated in women with DCM. Pregnant women with DCM should be followed by a high-risk obstetrician. At-risk women with unknown genetic status should undergo a cardiovascular evaluation and be offered genetic counseling, ideally prior to pregnancy.

Genetic counseling

LMNA-related DCM is inherited in an autosomal dominant manner. Some individuals diagnosed with *LMNA*-related DCM have an affected parent; the proportion of individuals with *LMNA*-related DCM caused by a *de novo* pathogenic variant is unknown. Each child of an individual with *LMNA*-related DCM has a 50% chance of inheriting the pathogenic variant. Once an *LMNA* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

LMNA-related dilated cardiomyopathy (DCM) **should be considered** in individuals with the following clinical findings and family history.

Clinical findings

- **A clinical diagnosis of idiopathic DCM** (etiology not attributed to coronary artery disease, structural heart disease, or other established clinical conditions that may cause DCM; see Dilated Cardiomyopathy Overview), almost always in the setting of conduction system disease and/or supraventricular or ventricular arrhythmias. The diagnosis of DCM is based on the principal findings of left ventricular enlargement and/or reduced systolic function (other causes excluded):
  - **Left ventricular enlargement** is most commonly identified with two-dimensional echocardiography, optimally assessed by a height- and sex-based approach [Vasan et al 1997], or by cardiac magnetic resonance (CMR) imaging.
  - **Reduced systolic function** is described clinically as a reduction in left ventricular ejection fraction, which can be measured by two-dimensional echocardiography, angiography, radioisotope scanning, or MRI of left ventricular function. An ejection fraction of less than 50% is considered systolic dysfunction [Bozkurt et al 2021].
- **The key distinguishing characteristic of *LMNA*-related DCM** is that conduction system disease and/or arrhythmias almost always occur prior to or in association with the evolution of DCM and commonly before the development of heart failure (see Clinical Description).

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). A detailed three- to four-generation family history looking for heart failure, DCM, cardiac transplantation, pacemakers or implantable cardiac defibrillators, unexplained sudden death, unexplained

cardiac conduction system disease and/or arrhythmia, or unexplained stroke or other thromboembolic disease in relatives is indicated to assess the possibility of *LMNA*-related DCM. Conduction system disease, particularly with pacemakers, is particularly suggestive of *LMNA*-related DCM.

Establishing the Diagnosis

The diagnosis of *LMNA*-related DCM **is established** in a proband with suggestive findings and a heterozygous pathogenic variant in *LMNA* identified on molecular genetic testing (see Table 1).

Note: Identification of a heterozygous *LMNA* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

Because the phenotype of *LMNA*-related DCM is indistinguishable from many other inherited disorders with DCM and DCM with a highly arrhythmic presentation, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *LMNA*, followed by gene-targeted deletion/duplication analysis) for suspected *LMNA*-related DCM is rarely useful and typically NOT recommended.

- **A comprehensive cardiomyopathy multigene panel** that includes *LMNA* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. When prominent arrhythmia with minimal DCM phenotype is present, **a combined cardiomyopathy and arrhythmia multigene panel** should be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *LMNA*-Related Dilated Cardiomyopathy

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
LMNA	Sequence analysis [3]	>99% [4]
	Gene-targeted deletion/duplication analysis [5]	<1% [4, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. At least three reports have identified *LMNA*-related DCM resulting from deletions [van Tintelen et al 2007, Gupta et al 2010, Cirino et al 2020].

Clinical Characteristics

Clinical Description

LMNA-related dilated cardiomyopathy (DCM) is characterized by left ventricular enlargement and/or reduced systolic function frequently preceded or accompanied by significant conduction system disease.

Age of onset. While *LMNA*-related DCM usually presents in adulthood either with conduction system disease commonly accompanied by arrhythmias or with symptomatic DCM (including heart failure or embolus from a left ventricular mural thrombus), it may also be present in asymptomatic individuals: conduction system disease, arrhythmia, or DCM may be discovered during a medical evaluation conducted for another reason (e.g., a routine preoperative EKG) or clinical screening of at-risk relatives [Kumar et al 2016].

Presenting signs, timing, and progression. Family studies suggest that conduction system disease commonly precedes the development of DCM by a few years to a decade or more. In a study involving 64 individuals with an *LMNA* pathogenic variant, the median time differential from EKG abnormalities to observed left ventricular dysfunction was seven years [Brodt et al 2013]. In another retrospective study of 122 individuals with *LMNA* pathogenic variants, of those who had preserved left ventricular function and no heart failure at the time of presentation, new-onset left ventricular dysfunction or heart failure was observed in ~24% and 7% of individuals, respectively, after seven years [Kumar et al 2016].

- **Conduction system involvement** usually starts with disease of the sinus node and/or atrioventricular node that can manifest as sinus bradycardia, sinus node arrest with junctional rhythms, or heart block (commonly first-degree heart block that progresses to second- and third-degree block). The following are also common:
  - Symptomatic bradyarrhythmias requiring cardiac pacemakers
  - Supraventricular arrhythmias including atrial flutter, atrial fibrillation, supraventricular tachycardia, and the sick sinus syndrome (i.e., tachycardia-bradycardia syndrome)
  - Ventricular arrhythmias including frequent premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation
- **Sudden cardiac death** may occur with progressive disease. Although more malignant, life-threatening arrhythmias may occur with longstanding and usually previously symptomatic DCM, sudden cardiac

death can also be the presenting manifestation of *LMNA*-related DCM, with minimal or no left ventricular dysfunction [Meune et al 2006].

- **Variable DCM**. Only mild-to-moderate left ventricular dilatation despite progressive disease has been noted by some investigators. Therefore, *LMNA*-related DCM may be an appropriate diagnosis in those with an *LMNA* pathogenic variant who have clinical conduction system disease and/or arrhythmia prior to the left ventricular enlargement or with minimal or no systolic dysfunction.
- **Skeletal muscle disorder**. Occasionally, individuals with *LMNA*-related cardiomyopathy also manifest signs or symptoms of skeletal myopathy, which may be associated with elevated serum creatine kinase concentration.

Large prospective longitudinal studies to define the range of natural history of individuals with *LMNA* pathogenic variants have not yet been published.

Genotype-Phenotype Correlations

No specific genotype-phenotype correlations have been established for *LMNA*-related DCM.

A few studies focusing on pathogenic variant type suggest a correlation between splice site variants and increased risk for sudden cardiac death [van Rijsingen et al 2012], and between non-missense variants (indel, truncating, splice site) and risk for malignant ventricular arrhythmias.

Penetrance

LMNA-related DCM demonstrates age-related penetrance with onset in the third and fourth decades, so that by the seventh decade penetrance is considered greater than 90%-95%.

Prevalence

Second to *TTN*, *LMNA* is the most common genetic cause of nonsyndromic DCM. Estimates of the frequency of *LMNA*-related DCM in persons with DCM of unknown cause (also referred to as idiopathic dilated cardiomyopathy) ranges from 5% to 13% [Morales et al 2020, Rosenbaum et al 2020].

Genetically Related (Allelic) Disorders

Pathogenic variants in *LMNA* have been reported in individuals with a phenotype consistent with arrhythmogenic right ventricular cardiomyopathy – although after gene curation by ClinGen, the relationship with ARVC meeting the 2010 ARVC clinical Task Force Criteria was limited [James et al 2021].

Pathogenic variants have also been identified in several disorders of striated muscle, nerve, adipose, and vascular tissue, collectively referred to as the **laminopathies.** Laminopathies result primarily from pathogenic missense variants, with occasional nonsense and splice-site variants, as well as short insertions or deletions. A remarkable exception is the synonymous variant (a nucleotide change that does not alter the amino acid) in *LMNA* codon 608 (GGC changed to GGT that does not change the Gly608 residue) causing Hutchinson-Gilford progeria.

Table 2 reviews selected *LMNA* allelic disorders; for other phenotypes associated with pathogenic variants in *LMNA*, see OMIM 150330.

Table 2. Selected *LMNA* Allelic Disorders

Disorder	MOI	Clinical Characteristics / Comment
Arrhythmogenic right ventricular cardiomyopathy / Arrhythmogenic cardiomyopathy	AD	Progressive fibrofatty replacement of the myocardium that predisposes to ventricular tachycardia & sudden death. While initially described as primarily affecting the right ventricle, biventricular involvement has been observed w/ occasional presentations mimicking DCM.

Table 2. continued from previous page.

Disorder	MOI	Clinical Characteristics / Comment
Charcot-Marie-Tooth hereditary neuropathy type 2B1	AR	Chronic motor & sensory polyneuropathy
Dunnigan-type familial partial lipodystrophy (FPLD2) (OMIM 151660)	AD	Adipocytes degenerate during puberty, followed by abnormal fat deposition, glucose intolerance, & late-onset diabetes mellitus. Most FPLD2-causing *LMNA* pathogenic variants involve arginine at amino acid residue 482.
Emery-Dreifuss muscular dystrophy	AD AR	Humero-peroneal muscular dystrophy (See also Differential Diagnosis.)
Heart-hand syndrome, Slovenian type (OMIM 610140)	AD	DCM w/conduction system disease & variable degrees of brachydactyly
Hutchinson-Gilford progeria syndrome	AD	Clinical features that typically develop in childhood & resemble some features of accelerated aging

AD = autosomal dominant; AR = autosomal recessive; DCM = dilated cardiomyopathy; MOI = mode of inheritance

Differential Diagnosis

The genetic differential diagnosis of idiopathic dilated cardiomyopathy (DCM) should include all genes known to be associated with nonsyndromic DCM. Particular attention can be focused on nonsyndromic DCM-related genes that have been associated with arrhythmia and conduction system disease phenotypes (see Dilated Cardiomyopathy Overview, Table 2. Nonsyndromic Dilated Cardiomyopathy Genes: **Distinguishing Features**).

For individuals with a clinical diagnosis of idiopathic DCM and/or conduction disease/arrhythmias in whom molecular genetic testing fails to identify a pathogenic variant in *LMNA* or another gene associated with nonsyndromic DCM, physical examination to evaluate for extra-cardiac features (especially neuromuscular issues) or additional study of the cardiovascular findings may lead to a diagnosis of other disorders causing DCM and conduction system disease or other cardiomyopathies with or without neuromuscular disease that may resemble a DCM phenotype such as arrhythmogenic right ventricular cardiomyopathy / arrhythmogenic cardiomyopathy, *DES*-related myopathy (OMIM 601419), limb-girdle muscular dystrophy (see OMIM Autosomal Dominant Limb-Girdle Muscular Dystrophy [LGMD] and Autosomal Recessive LGMD Phenotypic Series), and Emery-Dreifuss Muscular Dystrophy.

Management

Guidelines for the clinical evaluation and surveillance of individuals with *LMNA*-related DCM and other genetic cardiomyopathies have been published [Hershberger et al 2018]. Additional guidance regarding the management of arrhythmic disease in *LMNA*-related DCM is also available [Towbin et al 2019].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *LMNA*-related DCM, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *LMNA*-Related DCM

System/Concern	Evaluation	Comment
Conduction system disease & arrhythmia	Comprehensive cardiovascular eval incl clinical cardiovascular history & physical exam. Review history of presyncope, syncope, resuscitated sudden cardiac death, palpitations, & other symptoms of conduction system disease & arrhythmia	
	EKG	Follow up of abnormalities w/addl testing as indicated; e.g., 24-hr monitoring or event monitors, exercise EKG, or invasive electrophysiologic eval for conduction system disease [Towbin et al 2019]
Left ventricular dysfunction & DCM	Review history of shortness of breath, dyspnea on exertion, paroxysmal nocturnal dyspnea, chest pain.	
	Assessment of left ventricular enlargement & function by 2-dimensional echocardiography or cardiac MRI	Radionuclide ventriculography is an alternative measure of the ejection fraction.
Skeletal myopathy	• Assessment for skeletal muscle weakness • Serum CK level	If skeletal muscle weakness or ↑ CK, neuromuscular eval is indicated.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *LMNA*-related DCM in order to facilitate medical & personal decision making

CK = creatine kinase; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Management guidelines for genetic cardiomyopathies have been published [Hershberger et al 2018, Towbin et al 2019]. Elements of the guidelines include the following:

- Because of the complexity of treatment interventions in *LMNA*-related DCM in symptomatic and asymptomatic individuals, referral to centers with special expertise in cardiovascular genetic medicine should be considered.
- Consider therapy based on cardiac phenotype (i.e., DCM or arrhythmia).
- With an established arrhythmia or known risk of arrhythmia, consider ICD implantation before the ejection fraction falls below 35%. Note that this recommendation was included in the Heart Failure Society guidelines in large part because of the risk for lethal arrhythmias in persons with an *LMNA* pathogenic variant who have systolic function well above a left ventricular ejection fraction of 35%, the usual measure of systolic dysfunction below which ICDs are indicated in most US guidelines.

The management of *LMNA*-related DCM is focused on treatment of **conduction system disease**, **arrhythmia**, and **DCM**.

Table 4. Treatment of Manifestations in Individuals with *LMNA*-related DCM

Manifestation/Concern	Treatment
Cardiac conduction system disease & arrhythmias	For chronic atrial fibrillation unresponsive to cardioversion: • Anticoagulants • Agents for ventricular rate control

Table 4. continued from previous page.

Manifestation/Concern	Treatment
	For other symptomatic supraventricular arrhythmias: • Pharmacologic agents • May be augmented with electrophysiologic intervention (e.g., atrial or atrioventricular node ablations)
	For symptomatic bradyarrhythmias or asymptomatic but significant heart block: • An implantable electronic pacemaker • Strongly consider an ICD (not an electronic pacemaker) due to risk of mortality from sudden cardiac death.
	For symptomatic ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, & resuscitated sudden cardiac death: • Use of an ICD • Drug therapy as needed
Dilated cardiomyopathy	ACE inhibitors, beta blockers, diuretics, & other conventional approaches, as summarized in Yancy et al [2013] (full text)
	When DCM is present & left ventricular ejection fraction is <35% (w/or w/o arrhythmia): use of an ICD
	For progressive deterioration in left ventricular function despite full medical & device therapy, consider: • Cardiac transplantation; • Durable mechanical circulatory support if cardiac transplantation is contraindicated.

ICD = implantable cardioverter defibrillator

Surveillance

Table 5. Recommended Surveillance for Individuals with *LMNA*-related DCM

System/Concern	Evaluation	Frequency
***LMNA* variant w/any EKG abnormality**	Cardiovascular eval for disease progression w/EKG, 24-48 hr rhythm monitoring, LV function measurement	Annually (at a minimum)
***LMNA* variant in an asymptomatic person**	Cardiovascular eval (medical history, physical exam, echocardiogram, & EKG)	Every 1-2 yrs &/or whenever new symptoms arise

Agents/Circumstances to Avoid

Drugs (beta blockers, calcium channel blockers, others) that exacerbate heart block, if present, should be avoided in *LMNA*-related DCM unless an electronic pacemaker or implantable cardioverter defibrillator is in place.

Evaluation of Relatives at Risk

Once a molecular diagnosis of *LMNA*-related DCM has been established in a family, molecular genetic testing for the familial *LMNA* pathogenic variant can be offered to relatives at risk in order to facilitate prompt diagnosis, surveillance, and treatment in those in whom the *LMNA* pathogenic variant has been detected.

The risk of DCM to family members who do not have the *LMNA* pathogenic variant identified in the proband is generally considered to be similar to that of the general population. However, because multiple variants in

DCM-associated genes have been observed in individuals with nonsyndromic DCM [Morales et al 2020] and because families may segregate pathogenic variants in more than one DCM-related gene [Liu et al 2015, Cowan et al 2018], thorough individualized risk assessment through clinical, genetic, and family history analysis is warranted to determine if discharge from high-risk cardiac surveillance is appropriate.

If molecular genetic testing is not possible, the first-degree relatives of a proband with *LMNA*-related DCM should be evaluated annually by medical history, physical examination, echocardiogram, and EKG to determine if any have detectable DCM and/or conduction system disease.

Note: Because the age of onset is variable and penetrance is reduced, a normal baseline echocardiogram and EKG in a first-degree relative who has not undergone molecular genetic testing does not rule out *LMNA*-related DCM in that individual, and the recommendations set forth in Surveillance should be followed.

Any abnormal cardiovascular test results in a relative of a proband with a known *LMNA* pathogenic variant should be followed up with a full cardiovascular assessment to evaluate for any acquired causes of disease (e.g., coronary artery disease). Results on screening tests that do not meet criteria for DCM but do show some abnormality (e.g., left ventricular enlargement but normal function; decreased ejection fraction but normal-sized left ventricle) may reflect variable expression of *LMNA*-related DCM in that relative. Targeted genetic testing to clarify the diagnosis as well as close surveillance (e.g., cardiovascular testing every 1-2 years) for progression of cardiovascular disease is recommended for such individuals.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnancy is contraindicated in women with DCM because of the significantly increased mortality with pregnancy in DCM. Women with DCM who become pregnant should be followed by a high-risk obstetrician. At-risk women with unknown genetic status should undergo a cardiovascular evaluation and be offered genetic counseling prior to pregnancy.

Therapies Under Investigation

Drugs aimed at reducing mitogen-activated protein (MAP) kinase signaling, a mechanism which has been shown to be increased in *LMNA*-associated DCM, are actively under investigation (ClinicalTrials.gov identifier NCT02351856) [Wu et al 2011, MacRae et al 2016].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

LMNA-related dilated cardiomyopathy (DCM) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with *LMNA*-related DCM have an affected parent.

  Note: Both sides of the family should be considered as possibly contributing. Families with DCM in both maternal and paternal lineages have been described [Liu et al 2015, Cowan et al 2018], and experience has shown that regardless of an apparent inheritance pattern in a family, assumptions regarding maternal or paternal inheritance of pathogenic variants in genes causing familial DCM in a given family may be unreliable and potentially misleading.

- Some individuals diagnosed with *LMNA*-related DCM have the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals with *LMNA*-related DCM caused by a *de novo* pathogenic variant is unknown.

- Recommendations for the evaluation of reportedly unaffected parents of a proband include:
  - Review of medical history, physical examination, echocardiogram, and EKG to determine if a parent has detectable DCM and/or conduction system disease. Evaluation of parents may determine that one is affected but has previously escaped diagnosis possibly because of a milder phenotypic presentation (e.g., evidence of DCM on echocardiogram without clinical heart failure symptoms).
  - Molecular genetic testing for the familial *LMNA* pathogenic variant. Because *LMNA*-related DCM demonstrates age-related penetrance, an asymptomatic parent may be found to be heterozygous for the familial *LMNA* pathogenic.

- If the *LMNA* pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If one parent of the proband has the *LMNA* pathogenic variant, the risk to the sibs of inheriting the variant is 50%. However, because of variable expression and reduced penetrance, no predictions can be made regarding age of onset, severity, or course of disease in sibs who inherit the pathogenic variant.
- Due to reduced penetrance, variable expression, and potentially subtle or unknown early cardiovascular phenotypes in the progression of *LMNA*-associated cardiomyopathy, the apparent absence of symptoms in parents who have not undergone molecular genetic testing should not be used to modify risk to sibs. Sibs should be considered to be at up to a 50% risk of developing features of *LMNA*-associated cardiomyopathy unless molecular genetic testing has confirmed that neither parent is heterozygous for the *LMNA* pathogenic identified in the proband. Recommendations for evaluation of sibs are included in Evaluation of Relatives at Risk.
- If the *LMNA* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent and parental identity testing has confirmed biological maternity and paternity, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- Sibs may be offered genetic testing for the familial *LMNA* pathogenic variant to help clarify risk. In general, sibs without the *LMNA* pathogenic variant identified in the proband are no longer considered to be at increased risk for DCM and thus may be discharged from cardiac surveillance. However, because multiple variants in DCM-associated genes have been observed in individuals with nonsyndromic DCM [Morales et al 2020] and because families may segregate pathogenic variants in more than one DCM-related gene [Liu et al 2015, Cowan et al 2018], thorough individualized risk assessment through clinical,

genetic, and family history analysis is warranted to determine if discharge from high-risk cardiac surveillance is appropriate.

Offspring of a proband. Each child of an individual with *LMNA*-related DCM has a 50% chance of inheriting the pathogenic variant identified in the proband. However, because of variable expression and reduced penetrance, no predictions can be made regarding age of onset, severity, or course of disease.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has an *LMNA* pathogenic variant, his or her family members may be at risk regardless of the clinical status of the parent.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *LMNA*-related DCM pathogenic variant has been identified in an affected family member.
- Testing of asymptomatic at-risk individuals is considered predictive testing for predisposition to *LMNA*-related DCM, not diagnostic testing.
- Predictive testing should only be performed in the context of formal genetic counseling, and is not useful in predicting age of DCM onset, severity, or rate of progression.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals age <18 years)

- Recent estimates of the likelihood of clinically detectable presentation of *LMNA*-related DCM in children is ~1.4% [Ware et al 2022]. Although relatively low, genetic testing should be offered as it can facilitate identification of at-risk children who may benefit from early treatment, potentially forestalling the development of advanced disease.
- In families with early-onset aggressive disease, identification of the familial pathogenic variant may guide more stringent clinical screening for asymptomatic but clinically detectable cardiovascular disease.
- See the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement for discussion of ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of *LMNA*-related DCM, it is appropriate to consider testing of symptomatic individuals regardless of age.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once an *LMNA* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing are possible.

Differences in perspective exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Heart Association**
  Dilated Cardiomyopathy (DCM)
- **Cardiomyopathy UK**
  United Kingdom
  Phone: 0800 018 1024 (UK only)
  Email: contact@cardiomyopathy.org
  www.cardiomyopathy.org
- **Children's Cardiomyopathy Foundation**
  Phone: 866-808-2873 (toll-free)
  Fax: 201-227-7016
  Email: info@childrenscardiomyopathy.org
  www.childrenscardiomyopathy.org
- **DCM Foundation**
  Phone: 833-DCM-HOPE (833-326-4673)
  Email: Info@DCMFoundation.org
  www.dcmfoundation.org
- **Dilated Cardiomyopathy Research Project**
  Phone: 877-800-8430
  Email: DCM.Research@osumc.edu
  www.dcmproject.com
- **MedlinePlus**
  Familial dilated cardiomyopathy
- **Sudden Arrhythmia Death Syndromes (SADS) Foundation**
  Phone: 801-948-0654
  www.sads.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. LMNA-Related Dilated Cardiomyopathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

LMNA	1q22	Prelamin-A/C	Human Intermediate Filament Database LMNA (lamin C1) Human Intermediate Filament Database LMNA (lamin A) Human Intermediate Filament Database LMNA (lamin C2) LMNA homepage - Leiden Muscular Dystrophy pages	LMNA	LMNA

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for LMNA-Related Dilated Cardiomyopathy (View All in OMIM)

115200	CARDIOMYOPATHY, DILATED, 1A; CMD1A
150330	LAMIN A/C; LMNA

Molecular Pathogenesis

LMNA encodes two proteins: lamin A and lamin C. Both lamins A and C are structural proteins of the inner nuclear membrane and are found in many different tissues. While the role and function of lamin proteins are clearly essential to several mechanical processes, the mechanism of cellular injury that causes *LMNA*-related DCM remains incompletely understood. Because lamin A/C is a structural protein of the nuclear membrane, it has been suggested that fragility of the nuclear membrane in the setting of repetitive contraction of skeletal or cardiac muscle may predispose to nuclear injury and cellular apoptosis. An alternative hypothesis suggests that an abnormal lamin A/C protein may disrupt the chromatin/lamin-associated protein complex, thereby disturbing gene expression [Chen et al 2019].

Mechanism of disease causation. *LMNA*-related DCM has been shown to occur via a loss-of-function mechanism associated with indel, splicing, or missense variants [Chen et al 2019], and to include both truncating and non-truncating variants in *LMNA* [Mazzarotto et al 2020].

NOTE: Curation of clinical and experimental evidence through the ClinGen DCM Gene Curation efforts resulted in a definitive classification for the relationship of *LMNA* variants with the DCM phenotype (see Gene-Disease Validity Classification Summary: LMNA - dilated cardiomyopathy) [Jordan et al 2021].

Chapter Notes

Author Notes

Website: Dilated Cardiomyopathy Research Project

The Dilated Cardiomyopathy Research Project, originally launched in 1993 by Dr. Ray Hershberger while at the Oregon Health & Science University, aims to advance our understanding of dilated cardiomyopathy genetics. Multiple studies including data from more than 1500 families affected by DCM across the country have contributed genetic and clinical information to this research program. This multi-institutional effort, still led by Dr Hershberger and now housed at The Ohio State University, leverages the many sites collaborating in the DCM Consortium to identify families eligible for studies within the DCM Research Project, including the recently completed DCM Precision Medicine Study and the ongoing DCM Discovery Study. More information about the DCM Project, affiliated research studies, and other information and resources can be found on the website (www.dcmproject.com) or by emailing dcm.research@osumc.edu.

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Author History

Jason Cowan, MS; University of Miami Miller School of Medicine (2008-2011)
Ray E Hershberger, MD (2008-present)
Ana Morales, MS, CGC; The Ohio State University (2008-2011; 2013-2021)
Elizabeth Jordan, MMSc, CGC (2022-present)

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