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MYOCARDIAL DISEASE (A ABBATE AND G SINAGRA, SECTION EDITORS)

Lamin A/C Cardiomyopathy: Implications for Treatment

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Abstract

Purpose of Review The purpose of this review is to provide an update on lamin A/C (*LMNA*)-related cardiomyopathy and discuss the current recommendations and progress in the management of this disease. *LMNA*-related cardiomyopathy, an inherited autosomal dominant disease, is one of the most common causes of dilated cardiomyopathy and is characterized by steady progression toward heart failure and high risks of arrhythmias and sudden cardiac death.

Recent Findings We discuss recent advances in the understanding of the molecular mechanisms of the disease including altered cell biomechanics, which may represent novel therapeutic targets to advance the current management approach, which relies on standard heart failure recommendations. Future therapeutic approaches include repurposed molecularly directed drugs, siRNA-based gene silencing, and genome editing.

Summary *LMNA*-related cardiomyopathy is the focus of active in vitro and in vivo research, which is expected to generate novel biomarkers and identify new therapeutic targets. *LMNA*-related cardiomyopathy trials are currently underway.

Keywords Lamin A/C gene · Laminopathy · Heart failure · Arrhythmias · Mechanotransduction · P53 · CRISPR–Cas9 therapy

Introduction

Mutations in the lamin A/C gene (*LMNA*) cause *laminopathies*, a heterogeneous group of inherited disorders including muscular dystrophies and cardiomyopathy [1, 2], the latter characterized by progressive heart failure (HF), complicated by life-threatening arrhythmias, which eventually leads to death or heart transplant [3, 4, 5•]. *LMNA* encodes a nucleoskeletal intermediate filament dimerizing protein with complex cellular functions, including maintaining nuclear structural integrity, regulating gene expression, mechanosensing, and mechanotransduction through the lamina-associated proteins [6–11]. In humans, *LMNA* mutations frequently lead to a signature dysrhythmia that includes conduction disease, ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation), and sudden cardiac death [4, 12], and indeed, *LMNA* is a major cause of *arrhythmogenic cardiomyopathy* (ACM) [13••].

A series of investigations have independently shown that defects of nuclear lamina due to *LMNA* mutations [7, 8, 14] affect mechanotransduction and mechanosensing in cardiomyocytes [15] leading to altered gene expression and cell dysregulation spanning from the nuclear lamina to the cell-cell junction. These mechanisms and the link to cardiac pump dysfunction are still incompletely understood, but their elucidation is critical for the development of novel therapies. In fact, currently, there are no specific therapies for *LMNA*-related cardiomyopathy, and the guidelines for cardiac dysfunction follow general recommendations for treatment of heart failure and prevention of ventricular arrhythmias and sudden cardiac death [16]. However, as discussed below, active research is ongoing to develop novel treatments though high-throughput drug discovery, repurposed molecularly directed drugs for mutation-specific altered gene pathways, siRNA-based gene silencing for malignant gene mutations, and genome editing.

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Molecular Mechanisms Involved in the Pathogenesis of *LMNA* Cardiomyopathy

The paucity of human heart tissue from dilated cardiomyopathy (DCM) patients with identified *LMNA* mutations has hindered research discovery of the molecular mechanisms responsible for the pathogenesis of DCM. Subsequently, the lack of cellular targets has hampered the development of effective drug treatments for DCM patients with *LMNA* mutations. Therefore, several murine models with *LMNA* mutations (Table 1) have been generated to bridge the gap between genotype and phenotype and are aimed to unravel the pathogenic signaling pathways affecting DCM patients with *LMNA* mutations in order to facilitate the development of therapeutic treatments for *LMNA*-related DCM.

In Vivo LMNA Mouse Models Thus far, majority of the molecular mechanisms associated with *LMNA* cardiomyopathy were discovered using the $Lmna^{H222P/H222P}$ mice [17]. Studies from hearts of male $Lmna^{H222P/H222P}$ mice at early stages before the onset of cardiac disease showed upregulation of mitogen-activated protein kinase (c-Jun N-terminal kinase (JNK), p38α and extracellular signal-regulated kinases 1 and 2 (ERK1 and 2), protein kinase B (AKT)/mammalian target of rapamycin complex 1 (mTORC1), and transforming growth factor-β (TGF-β) signaling. However, WNT/β-catenin signaling was downregulated in the hearts of $Lmna^{H222P/H222P}$ mice at a later age. The findings from $Lmna^{H222P/H222P}$ mice, where ERK1/2, AKT/mTORC1, TGF-β, and WNT/β-catenin signaling were involved in the pathogenesis of DCM, have been corroborated in human heart samples diagnosed with *LMNA* cardiomyopathy [18–20].

A second *LMNA* mouse line, homozygous for the $Lmna^{N195K/N195K}$ mutation, develops cardiac arrhythmias resembling DCM patients with conduction system disease [21]. The LMNA N195K mutation was identified from autosomal dominant Emery-Dreifuss muscular dystrophy (EDMD) patient, but the $Lmna^{N195K/WT}$ mice have indistinguishable phenotype as wild-type mice. Interestingly, when bred to homozygosity, the homozygous $Lmna^{N195K/N195K}$ mice die postnatally at 12 weeks old due to cardiac arrhythmia with minimal involvement of skeletal muscle. The cause of death of the mutant $Lmna^{N195K/N195K}$ mice was due to the mislocalization of CX43, CX40 and Hf1b/Sp4 in the heart of these mice. Moreover, expression levels of desmin were reduced at the intercalated disc and z-lines. Collectively, findings from the $Lmna^{N195K/N195K}$ mouse model are suggestive of defective mechanosignaling caused by the mutant $LMNA^{N195K}$ in the heart.

Recently, a cardiac-specific inducible transgenic mouse model expressing $Lmna^{D300N}$, a mutation identified from a patient with DCM, has been generated and identified the activation of the DNA damage response/TP53 pathways as the causative mechanisms of the disease [22•]. In this mouse model, cell cycle, apoptosis, and senescence-associated secretory phenotype were dysregulated and echoed the activation of TGF-β resulting in increased myocardial fibrosis in the heart. Moreover, retinoblastoma expression was significantly downregulated resulting in dysregulation of E2F/CDKN2A/MDM2 to activate DDR/TP53 pathways. Therefore, the DDR/TP53 pathways could potentially be therapeutic targets for LMNA cardiomyopathy.

Other LMNA mouse models have been investigated [23–25]: *Myh6-*$Lmna^{E82K}$ and $Lmna^{L530P/L530P}$ showed cardiac remodeling [26]. The *LMNA* E82K is a DCM causing variant and involved in the activation of Fas and mitochondrial pathways responsible for apoptosis. Although the $Lmna^{L530P/L530P}$ mice showed enlarged heart and fibrosis, molecular mechanisms responsible for the cardiac phenotype remain to be determined.

In Vitro LMNA Models Several in vitro studies on *LMNA* mutations (ΔK32, E161K, R190W, N195K and M371K) showed defective structural assembly and restoration after stress, but no molecular mechanisms have been provided to explain the observed phenotype [27, 28].

In summary, the data from *LMNA* mouse models and in vitro cellular models strongly suggests that mutant LMNA causes gene expression and structural defects in the heart (Fig. 1). However, the direct molecular mechanisms

Table 1 Human *LMNA* mutations and associated transgenic mouse models

Mutations	Human disease	Mouse model	Observed phenotype
ΔK32	L-CMD	$Lmna^{\Delta K32/C}$ [24]	Late postnatal death with DCM
E82K	DCM	*Myh6-*$Lmna^{E82K}$ [25]	DCM with cardiac remodeling
N195K	DCM	$Lmna^{N195K/N195K}$ [22]	Postnatal death with DCM
H222P	EDMD	$Lmna^{H222P/H222P}$ [18]	Postnatal death with DCM
D300N	Atypical Werner syndrome/DCM	*Myh6-tTAe;tetO-*$Lmna^{D300N}$ [23•]	Postnatal death with DCM
M371K	EDMD	*Myh6-*$Lmna^{M371K}$ [26]	Early postnatal death with acute and subacute cardiac damage
L530P	EDMD	$Lmna^{L530P/L530P}$ [27]	Progeria with cardiac remodeling
G608G	HGPS	$Lmna^{G609G/G698G}$ [73]	Progeria, LQT and arrhythmia

caused by *LMNA* mutations remained largely unknown. Moreover, the fact that LMNA regulates transcription factors such as Wnt and Hf1b/Sp4, the involvement of LMNA in cardiac development particularly in determining cell fate is yet to be determined.

Biophysical and Biomechanical Characteristics of *Laminopathies*

In 1999, it was realized for the first time that a mutation in the nuclear lamin A/C was causing (EDMD) [29]. Since then, more than 450 disease-associated lamin mutations have been discovered. Why are lamins, type V intermediate filaments specific to the nucleus, so important for their contribution in these diseases? Undoubtedly, lamins (i) provide structural support to the nucleus (indeed, they are called molecular shock absorber) and control nuclear size and stiffness [30–32]. (ii) They also contribute to cytoskeletal/nucleus coupling (through the LINC protein complex) [33], (iii) chromatin organization [34], (iv) DNA replication [35], and (v) transcriptional regulation [34]. As far as their mechanical roles are concerned, lamins control nuclear elasticity and deformation, and they play major role in mechanotransduction and mechanosignaling, i.e., the cell ability to react to mechanical stimuli. Being alpha-helix-based intermediate filament, lamins, in contrast to actin filaments and microtubules, withstand much larger strains of up to several hundred percent and therefore, they offer structural support under rapid, large and severe deformation. Furthermore, Ackbarow et al. [36] have shown that in the presence of a *macroscopic* defect, the structure and properties of the lamin alpha-helix allow shape changes which effectively protect the protein network against catastrophic failure. However, at the *nano* scale, the mechanisms of the damaging effects of LMNA pathogenic mutations on the lamin network are incompletely understood [37, 38].

Recently, it has been envisioned that the nucleus itself could be seen as a mechanosensor, which modulates gene expression in response to mechanical disturbances [39]. Therefore, external forces that are transferred through the cytoskeleton to the nucleus create a deformation but at the same time, based on lamin composition, can modify chromatin organization and transcriptional activity. For instance, the physical organization and location of heterochromatin inside the nucleus can change, such as the highly condensed heterochromatin normally positioned at the outer nucleus border and mostly silent is moved toward the inside increasing gene activation. Other effects might be triggered since the mechanical properties of the nucleus are primarily determined by the nuclear interior and the nuclear lamina. The elastic nuclear lamina is the major load-bearing element; however, the nuclear interior also plays a role. Chromatin is more viscoelastic in nature but any modifications in chromatin structure and organization can also affect the mechanical properties of the nucleus. At the same time, characteristic mechanical stresses can induce altered phosphorylation in nuclear envelope proteins [40]. Reduced tension leads to an increased lamin A/C phosphorylation, while increased tension produces decreased lamin A/C phosphorylation. An example is the application of shear stresses to isolated nuclei which caused the immunoglobulin (Ig) domain of lamin A to unfold, exposing a previously buried cysteine residue [41].

Force-induced stretching of nuclear membranes might be another mechanism triggered by impaired mechanotransduction. Since the nuclear lamina is much stiffer than the nuclear membrane, it protects the nuclear membrane from experiencing large mechanical forces. This "shock-absorber" function can therefore significantly modulate the stretch response of the nuclear membrane altering the distribution and organization of membrane-bound proteins [40, 42]. The aforementioned results demonstrate the relevance and the direct role of nuclear lamins in modulating transcriptional activity, nuclear and cytoskeletal organization.

In the presence of LMNA mutations, not only the nucleus and cell mechanical properties might change but also the adhesion properties at the level of outer cell membrane can be altered. For example, atomic force microscopy (AFM) and

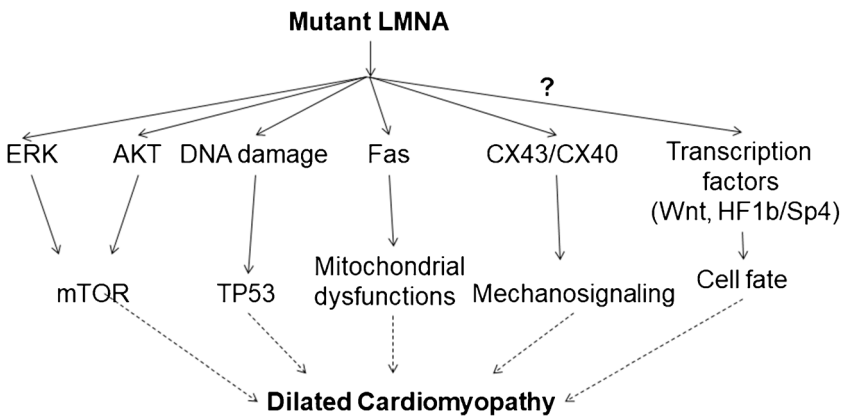

Fig. 1 Signaling pathways affected by LMNA mutations

Table 2 Genotype-phenotype correlations and current guidelines for the treatment of *LMNA*-related DCM

Diagnosis	Key elements	References
Phenotype red flags		
Muscle involvement	• High serum creatine kinase • Emery-Dreifuss muscular dystrophy • Limb-Girdle muscular dystrophy • Joint/tendon contractures	Captur et al. Heart 2018 [45] Paldino et al. Curr Cardiol Rep 2018 [46]
Cardiac involvement	• Sinus node dysfunction, atrioventricular blocks, intraventricular conduction delays • Supraventricular and ventricular arrhythmias, SCD • Left and right ventricular systolic and diastolic dysfunction • Atrial dilatation	Captur et al. Heart 2018 [45] Paldino et al. Curr Cardiol Rep 2018 [46]
Other organs possible involvement	• Spinal rigidity • Insulin resistance • Lipodystrophy • Accelerated aging	Captur et al. Heart 2018 [45]
LMNA Genetics		
Family History	• Sudden cardiac death • Cardiac conduction disease • DCM • Arrhythmia • Skeletal myopathy	2018 Genetic Evaluation of Cardiomyopathy—HFSA Practice Guideline, and ACMG Clinical Practice Resource [47, 48]
Genotype	• Missense and loss of function • Young age of onset and high penetrance	2018 Genetic Evaluation of Cardiomyopathy—HFSA Practice Guideline, and ACMG Clinical Practice Resource [47, 48]
Genetic testing	Recommended	2018 Genetic Evaluation of Cardiomyopathy—HFSA Practice Guideline, and ACMG Clinical Practice Resource [47, 48]
Therapy		
Ventricular dysfunction	• Heart failure GDMT • Heart transplantation	2013 ACCF/AHA Guideline for the Management of Heart Failure [49]
Supraventricular arrhythmias	• Beta-Blockers • Amiodarone • Catheter ablation	Captur et al. Heart 2018 [45] 2019 HRS Expert Consensus Statement on Evaluation, Risk Stratification, and Management of ACM [13]
Prevention of SCD	Class IIa—level of evidence B for ICD implantation in presence of two or more risk factors: • NSVT • LVEF < 45% • Male sex • Non-missense mutations[a]	2017 AHA/ACC/HRS Guideline for Management of Patients With VA and the Prevention of SCD [50]* 2019 HRS Expert Consensus Statement on Evaluation, Risk Stratification, and Management of ACM [13••]

ACM arrhythmogenic cardiomyopathy, *DCM* dilated cardiomyopathy, *GDMT* guideline-directed medical therapy, *ICD* implantable cardioverter-defibrillator; *LVEF* left ventricular ejection fraction, *NSVT* non-sustained ventricular tachycardia, *SCD* sudden cardiac death

[a] Criterion only in the 2017 AHA/ACC/HRS guideline

steered molecular dynamics (SMD) have been used to study three lamin mutations: Glu161Lys (E161K, rs28933093), Asp192Gly (D192G, rs57045855), and Asn195Lys (N195K, rs28933091) [32, 43•, 44•]. All three mutations cause a profound change in cardiomyocytes biomechanics leading to (i) increased nuclear stiffness, (ii) altered cellular viscoelasticity associated with modifications of the actin microfilaments network but also (iii) nearly complete loss of cell membrane work of adhesion. These findings indicate that lamins and lamina-associated proteins form a unique functional mechanical and mechanosensing entity that extends from the nucleo-skeleton to the cell membrane and which becomes destabilized by changes in any of its component elements. Furthermore, these biomechanical experiments predict that LMNA D192G will be the most damaging, followed by N195K and E161K. Remarkably, these biomechanical findings are in good agreement with clinical findings and even though genotype-phenotype correlation was evaluated in an extremely limited population, data suggest that the most severe outcome is associated with the D192G variant, while the mildest with the E161K [43•].

The aforementioned evidence indicates that nuclear configuration and deformability, as well as force transmission between the cytoskeleton and nucleus, play critical roles in activating or modulating cellular mechanotransduction signaling. These properties are particularly important in the cardiac and skeletal muscle, tissues exposed to high levels of mechanical stresses. The identification of quantifiable biomechanical

alterations in laminopathies and the possibility to rescue them with therapeutic compounds make cell biomechanics and attractive biomarker for drug developments.

LMNA Phenotypes *LMNA* mutations can cause a variety of different diseases that may present in a variety of combinations (Table 2) [45]. In the heart, *laminopathies* may cause DCM or cardiac conduction disease, and these two disorders can be present independently or overlap. *LMNA*-related DCM is typically characterized by left ventricular enlargement, systolic and diastolic dysfunction, and can involve the right ventricle mimicking arrhythmogenic right ventricular cardiomyopathy [51]. Conduction disease can range from atrioventricular block to atrial standstill. Supraventricular arrhythmias are frequent [52], as are ventricular arrhythmias which associate with increased risk of sudden cardiac death [4, 5•]. Thromboembolism may also be associated with LMNA-DCM [53].

LMNA mutations can cause multisystem involvement including neuromuscular, metabolic, and aging processes. Moreover, different types of muscular dystrophies are associated with *LMNA*, such as Emery-Dreyfuss muscular dystrophy (the autosomal dominant form EDMD2, and the recessive form EDMD3), limb-girdle muscular dystrophy (LGMD1B), and the pediatric LMNA-related congenital muscular dystrophy. *LMNA*-related metabolic disorders include partial lipodystrophy, insulin resistance, and hypertriglyceridemia (FPLD2) and the Malouf syndrome. Other disorders include the axonal Charcot-Marie-Tooth neuropathy (CMT2B1), skeletal abnormalities, such as brachydactyly, short stature, and heart-hand syndrome-Slovenian type. Finally, *LMNA* mutations can cause the premature aging Hutchinson–Gilford progeria syndrome (HGPS) and the adult-onset progeria Atypical Werner's syndrome [45].

The understanding of the pleomorphic features of laminopathies is important from the diagnostic standpoint. In evaluating a patient with DCM, the possibility of multisystem involvement, in particular neuromuscular disease, due to *LMNA* mutations must be considered. An accurate skeletal muscle evaluation (CK elevation, rigidity of the spine, contractures of the elbows and Achilles tendons [54]) and the presence of atrioventricular block, supraventricular and ventricular arrhythmias, insulin resistance, and lipodystrophy can raise the clinical suspicion of a *laminopathy*.

Genetics of Laminopathies *LMNA* mutations are inherited in an autosomal dominant manner, seen as multiple affected family members across generations, with age-related penetrance. The evaluation of DCM starts with an accurate family history, which by current guidelines should include three or more generations [13••, 47, 48]. Genetic testing should be offered to patients with DCM, in particular patients with family history of DCM, conduction disease, or sudden cardiac death, and patients with a "red flag" phenotype suspicious for *laminopathies*. Family cascade screening should include clinical testing with ECG and echocardiogram. If a *LMNA* pathogenic or likely pathogenic variant is identified according to current genetic guidelines [55], at-risk first-degree relatives should be tested to allow appropriate management. The pathogenic role of a novel *LMNA* variant may be difficult to assess, and in this case, the availability of the family for segregation analysis may add significant informativity [56]. The pre-test probability for a *LMNA* mutation rises from 5 to 8% in the DCM population to 33% when the DCM phenotype is associated with family history of DCM and conduction disease [52, 57, 58].

The type of *LMNA* mutation may modify the risk disease progression and arrhythmias. Non-missense mutations (insdel/truncating, or mutations affecting splicing) are an established risk factor for malignant ventricular arrhythmias and risk of sudden cardiac death: Heterozygous truncating *LMNA* mutations appear to have a higher arrhythmia risk than missense variants [4, 59]; indeed, they are considered among the criteria for ICD for prevention of SCD in the AHA/ACC guidelines [50]. However, in laminopathies, the majority of reported variants are missense mutations, and their association with the prognosis is still poorly defined. In a recent analysis of LMNA mutation reported in the literature, Captur et al. [60•] found that missense mutations upstream of the nuclear localization sequence were associated with a worse prognosis.

While some of the *LMNA* missense variant are recurrent and therefore more frequent, such as p.Glu161Lys, providing some insights into their pathogenic effect, most of the missense variants are "private" and unique to a patient or a family, therefore very rare, making the assessment of genotype-phenotype association difficult. Another challenge in assessing the pathogenic effect of *LMNA* missense variants is the significant phenotype variability found even within families carrying the same mutation, probably due to the modifier effect that environmental and epigenetic factors can have on *LMNA* gene expressivity.

Management of *LMNA*-Related Cardiomyopathy

Lifestyle Modifications Highly dynamic competitive sports for 10 years or more were found to be independent predictors of sudden cardiac death and equivalents in patients with *LMNA* mutations in a small series [61]. In general, there is lack of information in this regard, and the current guidelines, based on expert opinion (class III; level of evidence C), recommend that symptomatic athletes with DCM (without specifying the cause of DCM) should not participate in most competitive sports, with the possible exception of low-intensity (class 1A) sports [62].

There is little information concerning the risk of pregnancy in *LMNA* carriers. A small study reported a favorable outcome in early stages of cardiomyopathy and in absence of heart failure [63]. In limited studies on symptomatic DCM and in patients with family history of DCM, the prognosis appears to be poor, although some benefit has been reported with the "BOARD therapy regime" (prolactin blocker bromocriptine (BR), oral heart failure drugs, anticoagulation, diuretics) [64, 65]. A multicenter study on pregnancy in DCM is currently in progress to evaluate the risks and prognosis question in this patient population (ClinicalTrials.gov Identifier: NCT03235063).

Medical Therapy for Myocardial Dysfunction The current management of LMNA-related cardiomyopathy follows general recommendations for the treatment of heart failure, including beta-blockers, ACE inhibitors, or angiotensin-receptor blockers, although the specific efficacy in this population is unknown (Table 2) [49, 66]. In terminal stages of heart failure, *LMNA* carriers may require advanced therapies such as heart transplantation or ventricular assist devices.

Therapy for Arrhythmias and Prevention of Sudden Cardiac Death The frequent occurrence of conduction disease may require permanent pacing. The recent AHA/ACC/HRS guidelines for the prevention of sudden cardiac death [50] and the new 2019 HRS guidelines on arrhythmogenic cardiomyopathy [13••] identify the *LMNA* carrier status as a high-risk condition and recommend an implantable cardioverter-defibrillator even in absence of significant left ventricular dysfunction (left ventricular ejection fraction < 45%) when other predictors of life-threatening ventricular arrhythmias are present (non-sustained ventricular tachycardia, male gender, truncation mutation). For supraventricular and ventricular arrhythmias refractory to medical management, catheter ablation may be used in experienced centers (Table 2).

Recent Advances in *LMNA* Therapy Advanced strategies to develop novel treatments include high-throughput drug discovery and repurposed molecularly directed drugs. Indeed, activation of the mTOR pathway was reported in *LMNA*-associated DCM, and, in animal models, inhibition of mTOR by temsirolimus or rapamycin was shown to rescue the DCM phenotype [67, 68]. Mitogen-activated protein kinase (MAPK) signaling is increased in *LMNA*-associated DCM, leading to the discovery of compounds aimed at reducing this signaling, such as Selumetinib (Array BioPharma) [69]. Recently, encouraging results were reported from a phase 2 registrational trial on A797 (Array Biopharma), an oral, selective p38 MAPK inhibitor in *LMNA*-associated DCM [70], and this compound is now in phase 3 clinical trial. Remarkably, there is a significant overlap in the activation of important signaling pathways (MAPK and p38, Wnt/β-catenin and mTOR, Cx43, TGFB) in *LMNA*, which offers opportunities for the development of novel treatments.

Other novel experimental strategies include antisense oligonucleotide therapy (siRNAs) targeting exon 11 for the treatment of progeria which aims at reducing prelamin A/progerin in favor of the alternative splicing of lamin C [71].

Finally, two recent papers report favorable results in vitro and in vivo of genome editing by CRISPR/Cas9-technology for Hutchinson–Gilford progeria syndrome, which is caused by a *LMNA* point mutation, in most cases a c.1824C > T; p.Gly608Gly, which activates a cryptic splice site in exon 11. Santiago-Fernández et al. Beyret et al. independently showed progerin reduction and improved the progeria phenotype in a HGPS mice model by introducing frameshift mutations with CRISPR/Cas9 technology using an adeno-associated virus 9 (AAV9) delivery vectors [72•, 73•]. Advantage of genome editing technology is the persistence of the effect compared to antisense oligonucleotides. Although off-target effects need still to be addressed, it is noteworthy to emphasize that genome editing therapies for other diseases have now entered in clinical trials, and that the HGPS gene editing model could be recapitulated in other malignant *LMNA* missense variants.

Conclusion

LMNA-related cardiomyopathy is one of the most common causes of dilated cardiomyopathy and is characterized by progression toward heart failure and high risk of arrhythmias and sudden cardiac death. The possible multiorgan involvement should prompt a careful examination of potential carriers and raise red flags suspicious of *LMNA* mutation carriers. While the current therapies are aiming at containing the progression of myocardial remodeling and the risk of life-threatening arrhythmias, investigators are exploring novel technologies to correct the gene defect or the molecular mechanisms causing the disease phenotype.

Compliance with Ethical Standards

Conflict of Interest Suet Nee Chen, Orfeo Sbaizero, and Luisa Mestroni declare that they have no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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