

LMNA cardiomyopathy: cell biology and genetics meet clinical medicine

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Mutations in the *LMNA* gene, which encodes A-type nuclear lamins (intermediate filament proteins expressed in most differentiated somatic cells), cause a diverse range of diseases, called laminopathies, that selectively affect different tissues and organ systems. The most prevalent laminopathy is cardiomyopathy with or without different types of skeletal muscular dystrophy. *LMNA* cardiomyopathy has an aggressive clinical course with higher rates of deadly arrhythmias and heart failure than most other heart diseases. As awareness among physicians increases, and advances in DNA sequencing methods make the genetic diagnosis of *LMNA* cardiomyopathy more common, cardiologists are being faced with difficult questions regarding patient management. These questions concern the optimal use of intracardiac cardioverter defibrillators to prevent sudden death from arrhythmias, and medical interventions to prevent heart damage and ameliorate heart failure symptoms. Data from a mouse model of *LMNA* cardiomyopathy suggest that inhibitors of mitogen-activated protein kinase (MAPK) signaling pathways are beneficial in preventing and treating cardiac dysfunction; this basic research discovery needs to be translated to human patients.

LMNA and the laminopathies

The *LMNA* gene encodes nuclear lamin A and nuclear lamin C, intermediate filament proteins that are components of the nuclear lamina (Lin and Worman, 1993). These A-type lamins are expressed in virtually all differentiated somatic cells. In the latter part of the 20th century, those who studied lamins were mainly cell biologists interested in fundamental processes such as nuclear envelope structure and mitosis. In 1999, however, a positional cloning study showed that mutations in *LMNA* cause the autosomal dominant form of Emery-Dreifuss muscular dystrophy, an inherited disorder that selectively affects heart and skeletal muscle (Bonne et al., 1999). Since then, geneticists have discovered that mutations in *LMNA* cause more than a dozen previously defined clinical entities that are now often referred to as laminopathies (Box 1).

Understanding the pleiotropic effects – which can be grouped primarily on the basis of phenotypes that selectively involve striated muscle, adipose tissue, peripheral nerve or multiple systems with features of accelerated aging (progerias) (Box 1) – of mutations in this single gene is one of the most exciting clinical puzzles facing basic scientists and clinicians today.

Most disease-causing *LMNA* mutations affect the heart, causing a dilated cardiomyopathy, with or without skeletal muscle involvement. Although a relatively rare disease, clinical cardiologists are becoming increasingly aware of *LMNA* cardiomyopathy because of its particularly aggressive course compared with most other inherited cardiomyopathies. Advances in DNA sequencing technology are also making the genetic diagnosis of what were formerly classified as ‘idiopathic’ cardiomyopathies part

of the clinical routine. These facts, combined with recent data obtained from studies of model mice suggesting a novel possible treatment, make *LMNA* cardiomyopathy a timely topic for the physician-scientist as well as the clinical cardiologist.

Lamins and the nuclear lamina

LMNA, located on human chromosome 1q21.2-21.3, encodes the A-type nuclear lamins. Lamin A (664 amino acids) and lamin C (574 amino acids) are the major A-type lamins expressed in somatic cells. They arise via alternative splicing of pre-mRNA encoded by exon 10 (Lin and Worman, 1993). Lamins A and C are identical for the first 566 amino acids. Lamin A is synthesized as a precursor, prelamin A, which has 98 unique C-terminal amino acids. Prelamin A protein has the amino acids CSIM (Cys-Ser-Ile-Met) at its C-terminus, which triggers a series of enzymatic reactions that lead to farnesylation and carboxymethylation of the cysteine and endoproteolytic cleavage of the SIM peptide. The farnesylated prelamin A is then recognized by the endoprotease ZMSTE24, which cleaves 15 amino acids up from the cysteine residue at the C-terminus to yield lamin A (Davies et al., 2009). By contrast, lamin C has six unique C-terminal amino acids and is not post-translationally modified by farnesylation. Two other genes in the mammalian genome, *LMNB1* and *LMNB2*, encode lamins B1 and B2, respectively. Lamins A and C are widely expressed in the majority of differentiated somatic cells but are lacking from early embryos and from some undifferentiated cells, whereas lamins B1 and B2 are expressed in all or most somatic cells. There are little data and no systemic studies on the differences in the relative amount of lamins A, C, B1 and B2 expression.

Lamins are intermediate filament proteins (Fisher et al., 1986; McKeon et al., 1986). Like all intermediate filament proteins, lamins contain a highly conserved α -helical core of approximately 350 amino acid residues flanked by globular N-terminal head and C-

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Box 1. Clinical entities caused by LMNA mutations

Mutations in the single *LMNA* gene cause several defined clinical entities that can be grouped primarily into those with phenotypes selectively involving striated muscle, adipose tissue (lipodystrophy syndromes), peripheral nerve (peripheral neuropathy) or multiple systems with features of accelerated aging (progerias).

Diseases of striated muscle (see also Fig. 1)

- Autosomal Emery-Dreifuss muscular dystrophy
- Cardiomyopathy dilated 1A
- Limb-girdle muscular dystrophy type 1B
- Congenital muscular dystrophy

Lipodystrophy syndromes

- Dunnigan-type familial partial lipodystrophy
- Lipodystrophy with diabetes and other features of insulin resistance
- Insulin resistance without lipodystrophy
- Mandibuloacral dysplasia^a

Peripheral neuropathy

- Charcot-Marie-Tooth disorder type 2B1

Accelerated aging disorders (progerias)

- Hutchinson-Gilford progeria syndrome
- Atypical Werner syndrome
- Restrictive dermopathy
- Variant progeroid disorders
- Mandibuloacral dysplasia^a

^aDiseases with features of both lipodystrophy and progeria

terminal tail domains. Lamins polymerize within the nucleus to form the nuclear lamina, a meshwork of intermediate filaments (Aebi et al., 1986). The nuclear lamina is attached to the inner nuclear membrane by the binding of lamins to integral proteins of the membrane, among other factors (Wilson and Foisner, 2010).

Most cell biologists agree that one function of the lamina is to provide structural support to the nucleus, and many have argued that defects in this function can lead to disease. Indeed, deficiency of A-type lamins leads to defective nuclear mechanics and defective mechanotransduction in cultured fibroblasts (Lammerding et al., 2004). Nuclear lamins have also been implicated in processes such as chromatin organization, gene regulation, DNA replication and RNA splicing (Dechat et al., 2008). However, the specific mechanistic roles of lamins in these processes, particularly in a cell- or tissue-type-specific context, remain obscure.

LMNA cardiomyopathy

In 1999, Bonne et al. identified *LMNA* mutations that cause the autosomal

dominant form of Emery-Dreifuss muscular dystrophy (Bonne et al., 1999), which is characterized by a triad of muscle weakness and wasting in a humeroperoneal distribution, early tendon contractures and dilated cardiomyopathy. Early-onset conduction system disease, particularly heart block, is a feature of the cardiomyopathy of Emery-Dreifuss muscular dystrophy. Subsequently to this study, Fatkin et al. reported that *LMNA* mutations can cause dilated cardiomyopathy and conduction system disease with minimal to no skeletal muscle involvement (Fatkin et al., 1999). Soon after, Muchir et al. reported that *LMNA* mutations cause limb-girdle muscular dystrophy type 1B, a muscular dystrophy affecting more-proximal skeletal muscles than Emery-Dreifuss muscular dystrophy but with a similar dilated cardiomyopathy featuring prominent conduction system disease (Muchir et al., 2000). The age of onset of cardiac manifestations in these diseases is widely variable. According to data compiled by meta-analysis of 299 patients (van Berlo et al., 2005), arrhythmias occur relatively early in life in *LMNA* carriers (18% before age 10 years) and are highly penetrant (92% in those >30 years of age). Heart failure manifests later, and is found in 10% of patients by age 30 years and in 64% of patients by age 50 years.

Autosomal dominant Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy type 1B and dilated cardiomyopathy with minimal skeletal muscle involvement are traditionally

classified separately on the basis of clinical criteria. However, they can all clearly be caused by mutations in the *LMNA* gene, even by the same mutations within the same family (Bonne et al., 2000; Brodsky et al., 2000). Overlapping phenotypes have also been described. Mutations in *LMNA* have also been associated with congenital muscular dystrophy, affecting infants, with frequent heart involvement (Quijano-Roy et al., 2008). Although the classical phenotypic distinctions are of clinical utility, from a genetic and cell biological basis it might be most appropriate to regard these conditions as a single disease: *LMNA* cardiomyopathy with or without different types of skeletal muscular dystrophy (Fig. 1).

The inheritance pattern of *LMNA* cardiomyopathy is primarily autosomal dominant, although autosomal recessive and sporadic cases have been reported (di Barletta et al., 2000). Penetrance is high and data suggest that 100% of mutation carriers are affected by the age of 60 years (Pasotti et al., 2008). Most *LMNA* mutations causing striated muscle diseases are missense mutations distributed throughout all of the exons of the gene (http://www.dmd.nl/lmna_seqvar.html). Mutations causing RNA splicing abnormalities and small deletions, as well as nonsense mutations leading essentially to haploinsufficiency of A-type lamins, have also been documented. One homozygous *LMNA* missense mutation (H222Y) has been reported to be associated with Emery-Dreifuss muscular dystrophy (di Barletta et al., 2000), and an *LMNA* mutation leading to truncation of lamins A and C (Y259X), which causes a

Clinical terms

Arrhythmia: abnormal heart rhythm; can be too fast (tachyarrhythmia) or too slow (bradyarrhythmia).

Cardiomyopathy: disease or dysfunction of heart muscle.

Conduction block: abnormal slowing of electrical signal through the specialized conduction system within the heart.

Dyspnea: breathlessness.

Echocardiogram: ultrasound of the heart, allowing one to directly visualize pumping function, chamber size and velocity of blood flow of the heart.

Ejection fraction: percentage of blood pumped out from the heart chamber with each beat.

Electrocardiogram: electrical activity of the heart recorded by electrodes attached to the surface of the skin.

Intracardiac cardioverter defibrillator (ICD): an internal device that delivers electrical shocks to the heart when it senses dangerous, abnormal heart rhythms.

PR interval: the time between the onset of atrial depolarization (contraction) and the beginning of ventricular depolarization (contraction).

QRS interval: the time taken for depolarization (contraction) of the ventricles.

QT interval: the time between the start of ventricular depolarization (contraction) and the end of ventricular repolarization (relaxation).

Syncope: loss of consciousness.

Tachycardia: more rapid than normal heart rate.

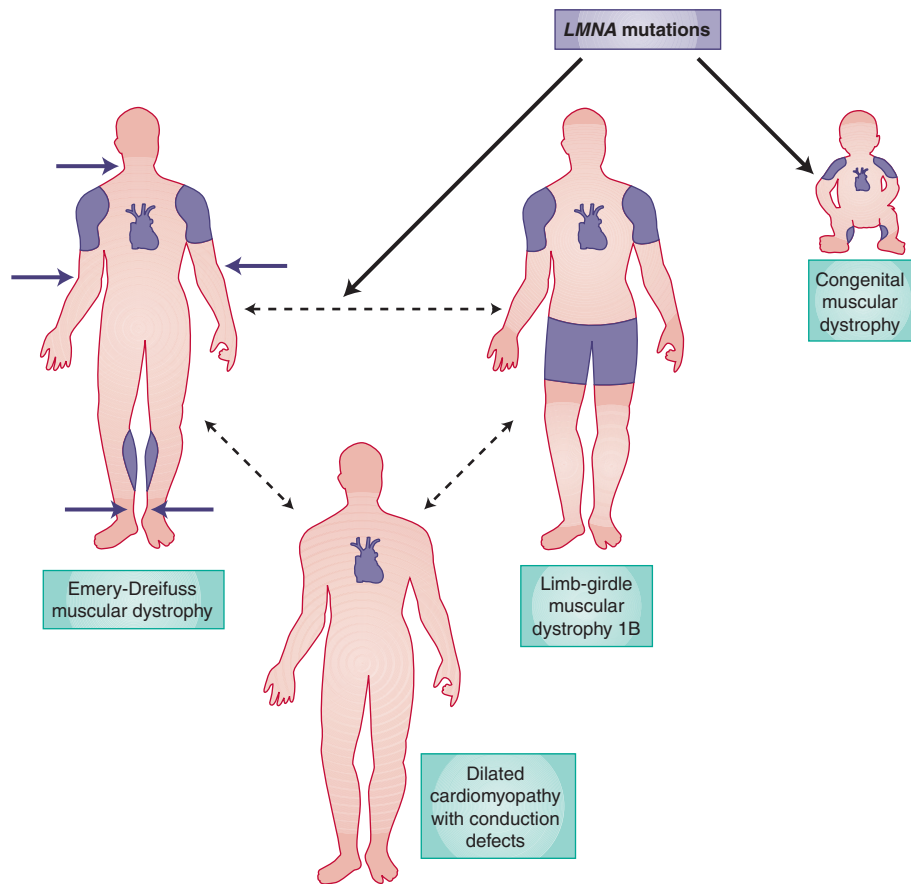


Fig. 1. Laminopathies affecting striated muscles. Classically defined distinct clinical disorders that present in childhood or adulthood (Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy 1B and isolated cardiomyopathy with conduction defects) are shown with affected muscle groups indicated in purple. The adult-onset diseases are actually a spectrum of the same disease that can have overlapping phenotypes and be caused by the same *LMNA* mutation (indicated by dashed arrows); note that the heart is always affected. These laminopathies affecting striated muscle can therefore be defined as *LMNA* cardiomyopathy with or without different types of skeletal muscular dystrophy. Mutations in *LMNA* can also present in infants as congenital muscular dystrophy, usually with heart involvement. Purple arrows indicate the location of contractures (permanent shortening) in the elbows, Achilles and the back of the neck that are characteristic of Emery-Dreifuss muscular dystrophy.

limb-girdle muscular dystrophy phenotype when heterozygous, caused a neonatal lethal phenotype with severe generalized muscular dystrophy in a reported case of homozygous inheritance (van Engelen et al., 2005). The presence of cardiomyopathy and muscular dystrophy in *Lmna*-null mice suggests that a partial loss of function of A-type lamins underlies the pathogenesis of *LMNA* cardiomyopathy (Sullivan et al., 1999). This hypothesis is further supported by experiments in genetically modified mice showing that compound heterozygous mice carrying one cardiomyopathy-associated mutation and one null mutation in *Lmna* have a more severe phenotype than homozygous mice with two cardiomyopathy-associated

mutations. By contrast, gain-of-function mutations in A-type lamins might underlie the progeria phenotype, because compound heterozygous mice carrying one progeria-associated mutation and one null mutation have a less severe phenotype than mice carrying two progeria-associated mutations (Davies et al., 2011).

***LMNA* cardiomyopathies versus other diseases caused by *LMNA* mutations**

Although genotype-phenotype relationships of laminopathies are incompletely understood, there are some clear differences between *LMNA* mutations that cause cardiomyopathy versus diseases that primarily affect tissues

other than striated muscle (see Box 1). Mandibuloacral dysplasia and Charcot-Marie-Tooth type 2 are always recessively inherited and are caused by amino acid substitutions at specific residues (De Sandre-Giovannoli et al., 2002; Novelli et al., 2002). Autosomal dominant Hutchinson-Gilford progeria syndrome is caused by de novo mutations leading to expression of a truncated prelamin A protein that retains its farnesylated C-terminal cysteine (De Sandre-Giovannoli et al., 2003; Eriksson et al., 2003). Mutations causing autosomal dominant Dunnigan-type familial partial lipodystrophy generally cluster in *LMNA* exon 8 and lead to amino acid substitutions that alter the surface charge but do not affect the overall structure of an immunoglobulin-like fold in the tail domains of lamins A and C (Dhe-Paganon et al., 2002; Krimm et al., 2002). By contrast, mutations in the same region of the *LMNA* gene that cause striated muscle disease lead to disruption of the tertiary structure of this fold. There has also been a report of several patients with mutations leading to amino acid substitutions outside of the immunoglobulin-like fold who lack the typical lipodystrophy of Dunnigan-type familial partial lipodystrophy but suffer from insulin resistance, altered glucose tolerance and hypertriglyceridemia (Decaudo et al., 2007).

Clinical features and differential diagnosis of *LMNA* cardiomyopathy

There are currently no clinical criteria that can reliably distinguish *LMNA* cardiomyopathy from other forms of idiopathic dilated cardiomyopathy. Similar to other dilated cardiomyopathies, *LMNA* cardiomyopathy is characterized by chamber enlargement and systolic dysfunction of one or both ventricles. When first approaching a patient, it is obligatory to rule out the more common acquired etiologies by comprehensive clinical evaluation, including history, physical examination, laboratory testing, imaging studies and perhaps invasive evaluation in the catheterization laboratory. Family history is crucial in determining a possible genetic cause of dilated cardiomyopathy.

To date, mutations in more than 30 genes have been identified as the genetic etiology for dilated cardiomyopathies. Only two primarily occur combined with conduction block: those caused by *LMNA* and *SCN5A* mutations (Fatkin et al., 1999; McNair et al., 2004). Of these, *LMNA* cardiomyopathy is far

Case study

N.A. is a 28-year-old woman who was referred to the cardiac electrophysiology service. She suffered from syncope three times as a teenager. Circumstances surrounding all three episodes were similar: she was traveling abroad during summer vacations and had little to eat or drink on those days. With each episode, she felt lightheaded but did not have palpitations, chest pain or dyspnea. She has no other significant past medical history, takes only oral contraceptives and has no allergies. Her physical and routine laboratory examinations were normal. Electrocardiogram showed normal sinus rhythm with PR interval of 160 milliseconds, narrow QRS interval and heart rate corrected QT interval of 400 milliseconds. Echocardiogram revealed a normal ejection fraction of 65% without chamber thickening or dilatation. A Holter monitor documented short runs of supraventricular tachycardia. The patient's father is 55 years old and developed atrial fibrillation, left bundle branch block and non-sustained ventricular tachycardia in his late 40s. Sick sinus syndrome required implantation of a dual chamber pacemaker at 51 years of age. He underwent electrophysiology studies prior to pacemaker implantation, which showed that he had delayed sinus node recovery time but was negative for inducible ventricular arrhythmia. His echocardiogram revealed a normal ejection fraction with mild left ventricular hypertrophy. The patient's father's younger brother is 53 years old and has atrial fibrillation, atrioventricular conduction block and dilated cardiomyopathy with an ejection fraction of 25% and abnormally dilated left and right ventricles. He has a history of ventricular tachycardia and has a biventricular intracardiac cardioverter defibrillator implanted. He more recently required the placement of left and right ventricular assist devices to aid in the management of his worsening heart failure and has been listed for heart transplantation. Given the family history, a panel of 30 genes known to be associated with dilated cardiomyopathy was analyzed in the patient's uncle. This identified an *LMNA*-E191K mutation that was subsequently found in the patient as well as her father. Another paternal uncle and a paternal aunt who are healthy do not have this mutation. The issue of whether to implant a primary prevention intracardiac cardioverter defibrillator was raised with the patient.

cardiomyopathy. Ventricular arrhythmias most often occur in the presence of systolic dysfunction but can be the first manifestation of the disease. In the meta-analysis of 299 *LMNA* mutation carriers, sudden death was highly prevalent, occurring in 46% of patients compared with death due to heart failure in 12% of patients (van Berlo et al., 2005). Among patients who died suddenly, 43% had a pacemaker implanted, suggestive of malignant ventricular arrhythmia as a major cause of fatality. Given these findings, some cardiologists recommend that, if a known *LMNA* carrier requires pacemaker implantation owing to conduction disease, an intracardiac cardioverter defibrillator should be placed even if the degree of systolic dysfunction does not meet the generally accepted criteria for primary prophylaxis (Meune et al., 2006). A more difficult issue, as illustrated in the Case Study, is whether and when a primary prevention intracardiac cardioverter defibrillator is indicated in healthy *LMNA* mutation carriers.

Genetic diagnosis of *LMNA* cardiomyopathy

Because diagnosis of *LMNA* cardiomyopathy is ultimately made genetically, the molecular pathology laboratory has grown to play an important role. Sequencing of the exons and intron-exon junctions of the *LMNA* gene is available in several research and commercial laboratories if the clinical suspicion is extremely high or if a family member is known to have an *LMNA* mutation. However, classical methods such as Sanger DNA sequencing are slow and become prohibitively expensive for the analysis of more than one or a few candidate genes. By contrast, currently available high-throughput sequencing technologies make the sequencing of up to 40 genes in samples from hundreds of individuals simultaneously technically feasible (Voelkerding et al., 2010). In this regard, it is now possible to simultaneously search for mutations in the approximately 30 genes known to cause dilated cardiomyopathy, including *LMNA*, in a given patient at a reasonable cost.

The total length of the exons corresponding to 30 known cardiomyopathy genes is approximately 200,000 base pairs. If sequencing of exons and intron-exon junctions of these known genes does not identify a mutation, copy-number-variation studies can be performed to exclude the possibility of larger genomic rearrangements

more common. In prevalence studies of dilated cardiomyopathy, *LMNA* mutations were found in up to 7.5% of cases that had a positive family history and in 3.6–11% of sporadic cases (Taylor et al., 2003; Parks et al., 2008). In one study of patients with familial dilated cardiomyopathy and conduction block as a prominent feature, 33% were found to have *LMNA* mutations (Arbustini et al., 2002). The presence of premature conduction system disease in combination with unexplained dilated cardiomyopathy should therefore lead cardiologists to strongly consider *LMNA* mutation as a cause. The clinical suspicion should be even higher in patients with dilated cardiomyopathy, conduction block and any evidence of skeletal muscle disease.

The presence of *LMNA* mutations can affect all levels of the conduction system, manifesting as sick sinus syndrome, atrioventricular block or bundle branch blocks. The conduction disease often necessitates the implantation of a permanent pacemaker in patients with *LMNA* mutation. Classically, this is thought to occur prior to the development of chamber dilatation. Both atrial and ventricular arrhythmias are common among *LMNA* mutation carriers. In young healthy *LMNA* carriers, arrhythmias including atrial ectopy, atrial fibrillation, non-sustained ventricular tachycardia and

ventricular arrhythmias can be the earliest clinical expression of the mutation prior to, or independent of, chamber dilatation (Arbustini et al., 2002; van Berlo et al., 2005).

The natural course of *LMNA* cardiomyopathy is aggressive, often leading to premature death or cardiac transplant (Taylor et al., 2003; van Berlo et al., 2005; Pasotti et al., 2008). By an age of 60 years, 55% of *LMNA* mutation carriers die of cardiovascular death or receive a heart transplant, compared with 11% of patients with idiopathic cardiomyopathy without *LMNA* mutation (Taylor et al., 2003). Once dilated cardiomyopathy is detected clinically, the management for *LMNA* cardiomyopathy follows the standard of care for heart failure. Standard medical therapy includes angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics and aldosterone antagonists, depending on the patient's New York Heart Association functional class (<http://www.americanheart.org/presenter.jhtml?identifier=4569>). It is unclear whether early institution of these therapeutic agents prior to detectable cardiac dysfunction can modify the aggressive nature of *LMNA* cardiomyopathy.

The prominence of tachyarrhythmias and bradyarrhythmias probably contributes to the aggressive nature of the *LMNA*

Clinical and basic research opportunities

- Connect specific alterations in nuclear lamins to signaling pathways or other cellular processes that can explain the pathogenesis of diseases caused by *LMNA* mutations.
- Translate to human subjects the recent discovery that treatment with inhibitors of ERK or JNK signaling is beneficial in a mouse model of *LMNA* cardiomyopathy.
- Obtain data to determine the optimal timing of intracardiac cardioverter defibrillator implantation to prevent sudden death in patients with *LMNA* cardiomyopathy.

that are not detectable by exon sequencing. Full exome sequencing is now available on a research basis to identify unknown pathogenic mutations, and declining costs might ultimately enable this method to become routine in the clinical diagnostic laboratory.

Insights into novel treatments from a mouse model

There is currently no specific therapy available for human patients that targets the molecular pathophysiology of *LMNA* cardiomyopathy. However, recent findings in animal models of the disease have yielded promising results that might translate into novel pharmacological therapy. This novel therapy has the potential of modifying the aggressive natural course of *LMNA* cardiomyopathy prior to the onset of significant clinical disease.

Several mouse models of *LMNA* cardiomyopathy that recapitulate the human disease have been generated (Stewart et al., 2007). Microarray analysis of gene expression in hearts from one of these models, *Lmna*-H222P knock-in mice, has revealed abnormal activation of the extracellular signal-regulated kinase 1/2 (ERK1/2) and Jun N-terminal kinase (JNK) signaling pathways, which are both branches of the mitogen-activated protein kinase (MAPK) cascade (Muchir et al., 2007b). Abnormal activation of ERK1/2 and JNK signaling occurs prior to the appearance of significant echocardiographic and histopathological abnormalities in the heart. The ERK1/2 and JNK signaling pathways are composed of serine/threonine-specific protein kinases that respond to stress stimuli, regulate a wide range of cellular activities, and have been implicated in various aspects of cardiac function and pathology.

The finding that ERK1/2 and JNK are abnormally activated in hearts of *Lmna*-H222P mice led to the hypothesis that inhibiting these signaling pathways could prevent or improve cardiac function. Male *Lmna*^{H222P/H222P} mice develop significant left ventricular dilatation and decreased ejection fraction by 16 weeks of age (Arimura et al., 2005). *Lmna*^{H222P/H222P} mice treated with a small-molecule inhibitor of MEK1/2, the kinase that activates ERK1/2, have normal cardiac ejection fraction and left ventricular diameters at 16 weeks of age (Muchir et al., 2009). The same is true if these mice are treated with a small-molecule inhibitor of JNK (Wu et al., 2010). If treatment with these drugs is initiated in *Lmna*^{H222P/H222P} mice at 16 weeks of age, when cardiac dysfunction is already detectable, there are significant increases in ejection fraction and decreases in left ventricular diameters and cardiac fibrosis at 20 weeks of age (Wu et al., 2011). Hence, presymptomatic treatment with MEK1/2 or JNK inhibitors might prevent or delay the development of *LMNA* cardiomyopathy, and initiation of treatment later in the course of the disease might improve symptoms and similarly slow progression. Because MEK1/2 inhibitors have been tested in humans during clinical trials for other indications, their efficacy and safety in *LMNA* cardiomyopathy are worthy of human clinical investigation.

Unresolved issues and goals for future research

How do different mutations in a single gene, *LMNA*, cause so many different disease phenotypes (Box 1)? Why are alterations in A-type lamins – which are expressed in virtually all differentiated somatic cells – associated with relatively tissue-selective abnormalities? These two questions have challenged a growing number of cell biologists and geneticists over the past decade, and will probably remain unresolved issues and the subject of research for many years to come. How specific alterations in A-type lamins are associated with the different laminopathies is only starting to be understood. Future studies should attempt to connect such alterations in lamin proteins, and possibly associated changes in nuclear envelope structure, to signaling pathways or other cellular processes that can rationally explain the pathology of these different diseases. More broadly, emerging evidence suggests that the nuclear envelope functions

as a crucial signaling node in development and disease (Dauer and Worman, 2009).

Mutations in genes encoding different nuclear envelope proteins can sometimes cause the same or similar phenotypes. This is best demonstrated by the fact that mutations in the gene encoding emerin cause X-linked Emery-Dreifuss muscular dystrophy (Bione et al., 1994), a disease that phenocopies the autosomal dominantly inherited form of Emery-Dreifuss muscular dystrophy caused by *LMNA* mutations. Emerin is an integral protein of the inner nuclear membrane that binds to A-type lamins (Wilson and Foisner, 2010). Evidence further suggests that deficiency of emerin, similar to *LMNA* mutations that cause cardiomyopathy, leads to abnormal activation of ERK signaling in the heart (Muchir et al., 2007a). Hence, scientists might have to look at the nuclear envelope as a whole to understand the pathogenic mechanisms of laminopathies. Moreover, although laminopathies are rare diseases, their phenotypes mimic those of more common disorders, including to some extent the aging process itself. This suggests that cellular abnormalities ‘downstream’ of nuclear envelope alterations are commonly affected in diseases other than laminopathies.

The ultimate goal of medical research is to discover new diagnostic and therapeutic modalities of clinical utility. Because *LMNA* mutations have been shown to cause cardiomyopathy, several retrospective studies have provided information about the clinical features associated with them. We now know that *LMNA* cardiomyopathy has an aggressive clinical course compared with most other cardiomyopathies. However, because prospective clinical studies are lacking, crucial practical issues – such as when to implant an intracardiac cardioverter defibrillator for prevention of sudden death, as in the accompanying Case Study – remain unresolved. Similarly, there is no information on whether early implementation of standard medical interventions could potentially slow or prevent heart damage or the development of symptomatic heart failure. The puzzle of *LMNA* cardiomyopathy highlights the need to foster the education and training of physician-scientists who can translate basic discoveries based on cell biology, genetics and animal model research into treatments for human patients.

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COMPETING INTERESTS

A.M. and H.J.W. are inventors on a pending PCT patent application on methods for treating and/or preventing cardiomyopathies by ERK and JNK inhibition filed by the trustees of Columbia University in New York, NY.

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