Diseases of the Nuclear Envelope

Howard J. Worman, Cecilia Östlund, and Yuexia Wang

Department of Medicine and Department of Pathology and Cell Biology, College of Physicians and Surgeons, Columbia University, New York, New York 10032

Correspondence: hjw14@columbia.edu

In the past decade, a wide range of fascinating monogenic diseases have been linked to mutations in the *LMNA* gene, which encodes the A-type nuclear lamins, intermediate filament proteins of the nuclear envelope. These diseases include dilated cardiomyopathy with variable muscular dystrophy, Dunnigan-type familial partial lipodystrophy, a Charcot-Marie-Tooth type 2 disease, mandibuloacral dysplasia, and Hutchinson-Gilford progeria syndrome. Several diseases are also caused by mutations in genes encoding B-type lamins and proteins that associate with the nuclear lamina. Studies of these so-called laminopathies or nuclear envelopopathies, some of which phenocopy common human disorders, are providing clues about functions of the nuclear envelope and insights into disease pathogenesis and human aging.

Mutations in *LMNA* encoding the A-type lamins cause a group of human disorders often collectively called laminopathies. The major A-type lamins, lamin A and lamin C, arise by alternative splicing of the *LMNA* pre-mRNA and are expressed in virtually all differentiated somatic cells. Although the A-type lamins are widely expressed, *LMNA* mutations are responsible for at least a dozen different clinically defined disorders with tissue-selective abnormalities. Mutations in genes encoding B-type lamins and lamin-associated proteins, most of which are similarly expressed in almost all somatic cells, also cause tissue-selective diseases.

Research on the laminopathies has provided novel clues about nuclear envelope function. Recent studies have begun to shed light on how alterations in the nuclear envelope could

explain disease pathogenesis. Along with basic research on nuclear structure, the nuclear lamins, and lamina-associated proteins, clinical research on the laminopathies will contribute to a complete understanding of the functions of the nuclear envelope in normal physiology and in human pathology.

LMNA: ONE GENE, MANY DISEASES

George Beadle and Edward Tatum (Beadle and Tatum 1941) proposed what became known as the “one gene-one enzyme” hypothesis and was later modified to the “one gene-one polypeptide” hypothesis. The premise underlying this hypothesis was that genes act through the production of polypeptides, with each gene producing a single polypeptide functioning in

Editors: Tom Misteli and David Spector

Additional Perspectives on The Nucleus available at www.cshperspectives.org

Copyright © 2010 Cold Spring Harbor Laboratory Press; all rights reserved; doi: 10.1101/cshperspect.a000760

Cite this article as *Cold Spring Harb Perspect Biol* 2010;2:a000760

H.J. Worman, C. Östlund, and Y. Wang

a particular step in a metabolic pathway or other cellular process. A corollary of this hypothesis, which formed the foundation of most early studies using positional cloning to identify disease genes, was the “one gene-one disease” principle. We now know that this is not correct and perhaps the best example that disproves this principle is *LMNA*.

LMNA encoding the A-type lamins was characterized in 1993 and subsequently mapped to chromosome 1q21.2-q21.3 (Lin and Worman 1993; Wydner et al. 1996). The first human disease identified by positional cloning to be caused by *LMNA* mutations was autosomal dominant Emery-Dreifuss muscular dystrophy (Bonne et al. 1999). Rare compound heterozygous mutations in *LMNA* causing recessively inherited Emery-Dreifuss muscular dystrophy were described shortly thereafter (Raffaele di Barletta et al. 2000). Patients with Emery-Dreifuss muscular dystrophy classically have early contractures of the elbows, Achilles tendons, and posterior neck, rigidity of the spine, slowly progressive muscle weakness in the upper arms and lower legs, and dilated cardiomyopathy with an early onset atrio-ventricular conduction block (Emery 2000; Muchir and Worman 2007).

Soon after *LMNA* mutations were shown to cause Emery-Dreifuss muscular dystrophy, mutations in this gene were shown to cause other dominantly inherited diseases affecting primarily striated muscle, including dilated cardiomyopathy 1A (Fatkin et al. 1999) and limb girdle muscular dystrophy type 1B (Muchir et al. 2000). Like Emery-Dreifuss muscular dystrophy, these conditions have a predominant dilated cardiomyopathy with early onset atrio-ventricular conduction block. In dilated cardiomyopathy 1A, skeletal muscle is minimally affected or unaffected. In limb-girdle muscular dystrophy, the distribution of skeletal muscle involvement is primarily around the shoulders and hips with sparing of the distal extremities. Most subjects with limb-girdle muscular dystrophy do not have joint contractures characteristic of classical Emery-Dreifuss muscular dystrophy. It was originally proposed that Emery-Dreifuss muscular dystrophy, dilated

cardiomyopathy 1A, and limb-girdle muscular dystrophy type 1B resulted from different mutations in *LMNA*. However, the phenotypic variability is most likely because of the influence of modifier genes or environmental factors. This is suggested by intrafamilial variability and phenotypic overlap in patients with *LMNA* mutations and muscle disease (Bonne et al. 2000). Within a single family, one affected individual can be diagnosed with isolated cardiomyopathy, another with Emery-Dreifuss muscular dystrophy, and others with limb-girdle muscular dystrophy (Brodsky et al. 2000). Based on the combined phenotypic and genetic data, dilated cardiomyopathy with variable skeletal muscle involvement, a phrase used by Brodsky et al. (2000), is a very appropriate descriptor of the striated muscle disease caused by *LMNA* mutations.

Although most *LMNA* mutations causing muscle disorders present during childhood or early adulthood, rare subjects present with congenital muscular dystrophy (Quijano-Roy et al. 2008). Congenital muscular dystrophy has an earlier onset and more severe phenotype than the later-onset muscle disorders caused by *LMNA* mutations. Most cases of *LMNA*-associated congenital muscular dystrophy are caused by de novo mutations but cases of germinal mosaicism have also been identified (Makri et al. 2009). Although some of the *LMNA* mutations causing congenital muscular dystrophy appear to be unique, others have been reported in patients with the later-onset myopathies. A unique *LMNA* splice site mutation has also been associated with a heart-hand syndrome, which is characterized by the association of congenital cardiac disease and limb deformities (Renou et al. 2008).

After *LMNA* mutations were shown to cause striated muscle diseases, a surprising discovery was made regarding another monogenic disease affecting different tissues. In 1998, the genetic locus for Dunnigan-type familial partial lipodystrophy had been mapped using positional cloning to chromosome 1q21-22 (Jackson et al. 1998; Peters et al. 1998). Lipodystrophies are a group of disorders characterized by the absence or reduction of subcutaneous adipose

tissue. Patients with Dunnigan-type familial partial lipodystrophy, a dominantly inherited disorder, are born with normal fat distribution but after the onset of puberty there is regional loss of fat from the extremities associated with insulin resistance and frequently diabetes mellitus (Dunnigan et al. 1974). Knowing that the genetic locus for this disease was at chromosome 1q21-22, Cao and Hegele (2000) hypothesized that the analogy between the regional muscle wasting in autosomal dominant Emery-Dreifuss muscular dystrophy and the regional adipocyte degeneration in this disease made *LMNA* a candidate gene. They identified a novel missense mutation in exon 8 leading to a R482Q amino-acid substitution, which cosegregated with the lipodystrophy phenotype in five Canadian families. At around the same time, the two groups that had mapped the disease to chromosome 1q21-22 performed finer mapping and identified the *LMNA* R482Q and other mutations in exon 8 leading to amino-acid substitutions (Shackleton et al. 2000; Speckman et al. 2000). Missense mutations in exon 11 of *LMNA* leading to R582H and R584H amino-acid substitutions in lamin A, but not lamin C, were further identified in some atypical cases (Speckman et al. 2000; Vigouroux et al. 2000). Subsequently, there have been a few reports of patients with other *LMNA* mutations with atypical lipodystrophy syndromes, sometimes in combination with muscle abnormalities (Vigouroux and Capeau 2005).

By 2000, the positional cloners had clearly shown that mutations in *LMNA* cause two quite different diseases: dilated cardiomyopathy with variable muscular dystrophy and partial lipodystrophy. However, the situation soon became more complicated when just a couple of years later De Sandre-Giovannoli et al. (2002) performed homozygosity mapping in inbred Algerian families with an autosomal recessive form of Charcot-Marie-Tooth disease type 2, linked it to chromosome 1q21.2-q21.3, and identified a *LMNA* mutation leading to the R298C amino-acid substitution. Subjects with Charcot-Marie-Tooth disease type 2 diseases, including the subtype caused by *LMNA* mutation, have slight or absent reduction of nerve

conduction velocities, loss of large myelinated fibers, and axonal degeneration (Chaouch et al. 2003). Affected individuals with the R298C mutation have variable severity and progression of disease, suggesting that modifier genes influence the phenotype of peripheral neuropathy caused by *LMNA* mutation (Tazir et al. 2004). Later in 2002, Novelli et al. (2002) hypothesized that *LMNA* mutations might cause mandibuloacral dysplasia, a rare autosomal recessive disorder in which subjects have an undersized jaw, underdeveloped clavicles, other congenital bone abnormalities, and partial lipodystrophy. They studied five consanguineous Italian families and identified a homozygous *LMNA* missense mutation causing a R527H amino-acid substitution that was shared by all affected patients. Subsequent subjects have been described with homozygous *LMNA* mutations causing R527C or A529V amino-acid substitutions (Agarwal et al. 2008; Garg et al. 2005). A compound heterozygous subject for the *LMNA* R527H and a V440M mutation with some features of mandibuloacral dysplasia, lack of muscle strength, and decreased muscle tone has also been reported (Lombardi et al. 2007).

Hutchinson-Gilford progeria syndrome, first described over a century ago, is a rare disease with features of accelerated or premature aging (Hutchinson 1886; Gilford 1904; McKusick 1952; DeBusk 1972). Individuals with this autosomal dominant sporadic syndrome generally die in the second decade of life from myocardial infarction or stroke (DeBusk 1972; Merideth et al. 2008). Other prominent phenotypic features are sclerotic skin, joint contractures, prominent eyes, an undersized jaw, decreased subcutaneous fat, alopecia, skin dimpling and mottling, prominent vasculature in the skin, fingertip tufting, and growth impairment (Merideth et al. 2008). In 2003, Francis Collins and colleagues localized the responsible gene to chromosome 1q by observing two cases in which this chromosomal region was from the same parent and one case with a six-megabase paternal interstitial deletion (Eriksson et al. 2003). They then showed that 18 out of 20 classical cases of Hutchinson-Gilford progeria

H.J. Worman, C. Östlund, and Y. Wang

had a de novo G608G (nucleotide 1824 C>T) mutation within exon 11 of *LMNA* and another case with a G608S (nucleotide 1822 G>A) mutation (Eriksson et al. 2003), a finding that was simultaneously reported by De Sandre-Giovannoli et al. (2003) and then confirmed by Cao and Hegele (2003). These mutations activate a cryptic splice donor site resulting in the synthesis of a protein with 50 amino acids deleted near the carboxyl terminus of prelamin A. This truncated prelamin A variant is not appropriately processed to lamin A (see below). Other *LMNA* missense mutations not generating abnormal RNA splicing within exon 11 have also been reported in variant progeroid syndromes (Chen et al. 2003; Csoka et al. 2004; Verstraeten et al. 2006). Mandibuloacral dysplasia caused by *LMNA* mutations, as discussed previously, also has progeroid features.

In summary, genetic studies since the late 1990s have shown that mutations in *LMNA* cause about a dozen clinical disorders with different names (Table 1). These can more broadly

be classified into diseases affecting predominantly (1) striated muscle, (2) adipose tissue, (3) peripheral nerve, or (4) multiple tissues resulting in progeroid phenotypes. These mostly tissue-selective disorders occur even though A-type lamins are intermediate filament protein components of the nuclear lamina in virtually all differentiated somatic cells.

OTHER LAMINOPATHIES/NUCLEAR ENVELOPATHIES

Monogenic diseases resulting from mutations in genes encoding B-type lamins and proteins that are directly or indirectly associated with the nuclear lamina are also sometimes referred to as laminopathies or nuclear envelopathies (Table 2). Emery-Dreifuss muscular dystrophy was shown to be inherited in an X-linked manner years before autosomal inheritance was described (Emery and Dreifuss 1966). In its classical presentation, the X-linked inherited disease phenocopies the autosomal form. In 1994, Daniella Toniolo and colleagues reported that the gene responsible for X-linked Emery-Dreifuss muscular dystrophy encoded a monogenic transmembrane protein expressed in virtually all cells that the authors named emerin (Bione et al. 1994). They extended their initial findings to more patients (Bione et al. 1995). Soon after, emerin was shown to be a protein of the inner nuclear membrane (Manilal et al. 1996; Nagano et al. 1996). Emerin was further shown to depend on A-type lamins for its localization to the nuclear envelope and to directly interact with lamins (Clements et al. 2000; Fairley et al. 1999; Sullivan et al. 1999). The clinical spectrum of disease resulting from mutations in *EMD* encoding emerin is actually wider than the classical Emery-Dreifuss phenotype and includes a limb-girdle muscular dystrophy, cardiomyopathy with minimal muscle or joint involvement, and various intermittent forms (Astejada et al. 2007).

Lamin B receptor is an integral protein of the inner nuclear membrane that binds to B-type lamins (Worman et al. 1988). It has a basically charged, nucleoplasmic, amino-terminal domain that binds to lamins, DNA, and

Table 1. Mutations in *LMNA* cause several distinct clinical diseases predominantly affecting striated muscle, adipose, and peripheral nerve, or give a progeria phenotype

Striated Muscle

Autosomal dominant (and rarely recessive)
Emery-Dreifuss muscular dystrophy
Cardiomyopathy dilated 1A
Limb-girdle muscular dystrophy type 1B
Congenital muscular dystrophy
“Heart-hand” syndrome

Adipose Tissue

Dunnigan-type familial partial lipodystrophy
Lipodystrophy with diabetes and other features of insulin resistance
Atypical lipodystrophy syndromes
Mandibuloacral dysplasia*

Peripheral Nerve

Charcot-Marie-Tooth disease type 2B1

Progeria Phenotype

Hutchinson-Gilford progeria syndrome
Atypical Werner Syndrome
Variant progeroid disorders
Mandibuloacral Dysplasia*

*Mandibuloacral dysplasia has features of lipodystrophy and progeria

Table 2. Diseases caused by mutations in genes encoding B-type lamins or proteins associated with the nuclear lamina

Gene	Protein	Disease
<i>EMD</i>	emerin	cardiomyopathy with muscular dystrophy
<i>LBR</i>	lamin B receptor	Pelger-Huët anomaly (heterozygous) Greenberg skeletal dysplasia (homozygous)
<i>LEMD3</i>	MAN1	Sclerosing bone dysplasias
<i>SYNE1</i>	nesprin-1	cerebellar ataxia
<i>TMPO</i>	lamina-associated polypeptide 2	cardiomyopathy*
<i>TOR1A</i>	torsinA	DYT1 dystonia
<i>LMNB1</i>	lamin B1	adult-onset autosomal dominant leukodystrophy
<i>LMNB2</i>	lamin B2	acquired partial lipodystrophy
<i>ZMPSTE24</i>	prelamin A endoprotease	restrictive dermopathy and progeroid disorders

*Reported in two affected individuals in a single family without gene sequencing from unaffected individuals in the same family.

chromatin proteins followed by a stretch of eight putative transmembrane segments that has high sequence similarity to sterol reductases (Worman et al. 1990; Ye and Worman 1994, 1996; Holmer et al. 1998). Heterozygous mutations in *LBR* that lead to reduced expression of the protein cause Pelger-Huët anomaly, a benign autosomal dominant disorder characterized by abnormal nuclear shape and chromatin organization in blood neutrophils (Hoffmann et al. 2002). In contrast, homozygous *LBR* mutations lead to severe developmental abnormalities or are lethal in utero (Hoffmann et al. 2002; Oosterwijk et al. 2003). In one case, a homozygous mutation leading to production of a truncated protein lacking the carboxyl-terminal 82 amino acids was reported to cause hydrops-ectopic calcification-“moth-eaten” or Greenberg skeletal dysplasia, a lethal disorder, which was associated with loss of detectable sterol $\Delta 14$ -reductase activity (Waterham et al. 2003). It appears that depending on the amount of expression and the affected functional domains of the protein, the phenotypes resulting from mutations in *LBR* can range from a benign alteration in neutrophil nuclear morphology to death in utero.

MAN1 is an integral inner nuclear membrane protein with two transmembrane segments and two nucleoplasmic domains (Lin et al. 2000). The nucleoplasmic domain preceding the first transmembrane segment has been

reported to bind to A-type lamins, B-type lamins, and emerin (Mansharamani and Wilson, 2005). The nucleoplasmic domain following the second transmembrane segment binds to regulatory-Smads and DNA (Hellemans et al. 2004; Lin et al. 2005; Pan et al. 2005; Caputo et al. 2006). Heterozygous loss-of-function mutations in *LEMD3* encoding MAN1 cause osteopoikilosis, Buschke-Ollendorff syndrome, and nonsporadic melorheostosis, sclerosing bone dysplasias that sometimes have hyperproliferative skin abnormalities. These phenotypes are likely associated with enhanced transforming growth factor- β and bone morphogenic protein signaling, the effects of which are mediated by regulatory-Smads.

SYNE1 encodes nesprin-1, a protein with several isoforms that arise by alternative RNA splicing. Depending on their size, nesprin-1 isoform may localize to the inner or outer nuclear membrane. Larger nesprin-1 isoforms localize to the outer nuclear membrane and interact in the perinuclear space with Sun proteins, integral proteins of the inner nuclear membrane that bind to lamins, forming a complex connecting the nucleus to the cytoskeleton (Crisp et al. 2006). Homozygous mutations in *SYNE1* have been shown to cause an autosomal recessive cerebellar ataxia specifically affecting a part of the brain (Gros-Louis et al. 2007). In one large family, however, a *SYNE1* mutation was shown to cosegregate with autosomal

H.J. Worman, C. Östlund, and Y. Wang

recessive arthrogryposis, a disease characterized by bilateral clubfoot, decreased fetal movements, and delayed motor milestones with progressive motor decline after the first decade (Attali et al. 2009).

Mutations in genes encoding other proteins that interact directly or indirectly with lamins also cause tissue-selective human diseases. Polymorphisms in the gene encoding lamina-associated polypeptide 2 have been identified in two individuals with cardiomyopathy in a single family; however, sequencing of the gene in unaffected family members was not reported (Taylor et al. 2005). DYT1 dystonia is a central nervous system movement disorder in which sustained muscle contractions lead to twisting and repetitive movements or abnormal postures; it is caused by an in-frame deletion in *TOR1A* encoding torsinA that leads to loss of a glutamic acid residue ($\Delta E302/3$) from the protein (Ozelius et al. 1997). TorsinA is an AAA+ ATPase of the endoplasmic reticulum that interacts with the luminal domain of lamina-associated polypeptide 1, an integral inner nuclear membrane protein that interacts with lamins (Goodchild and Dauer 2005). The torsinA $\Delta E302/3$ variant concentrates in the perinuclear space relative to the bulk endoplasmic reticulum (Gonzalez-Alegre and Paulson 2004; Goodchild and Dauer 2004; Naismith et al. 2004), where it appears to selectively disrupt the structure of the nuclear envelopes of neurons (Goodchild et al. 2005).

Mutations in genes other than *LMNA* but directly affecting lamins also cause diseases. ZMPSTE24 is an endoprotease responsible for the processing of prelamin A to lamin A (see later). Loss-of-function mutations in *ZMPSTE24* cause autosomal recessive restrictive dermopathy, a neonatal lethal progeroid disorder (Navarro et al. 2005). Compound heterozygous mutations in *ZMPSTE24* also cause progeroid disorders with some cases being diagnosed as mandibuloacral dysplasia (Agarwal et al. 2003; Shackleton et al. 2005). Duplication of *LMNB1* encoding lamin B1 leading to increased expression of the protein causes adult onset autosomal dominant leukodystrophy, a slowly progressive neurological disorder characterized

by symmetrical widespread myelin loss in the central nervous system (Padiath et al. 2006). Heterozygous mutations or polymorphisms in *LMNB2* encoding lamin B2 have been also reported in patients with acquired partial lipodystrophy (Hegele et al. 2006).

Overall, a number of human disorders have been described that are caused by mutations in genes encoding lamins and associated nuclear envelope proteins. This number is likely to continue to grow over time. Achalsia-Addisonianism-alacrima syndrome, familial atrial fibrillation, infantile bilateral striatal necrosis, and infection-triggered acute necrotizing encephalopathy have also been shown to result from mutations in genes encoding proteins of the nuclear pore complex, a major component of the nuclear envelope that mediates nucleocytoplasmic transport (Tullio-Pelet et al. 2000; Cronshaw and Matunis 2003; Basel-Vanagaite et al. 2006; Zhang et al. 2008; Neilson et al. 2009).

NUCLEAR ENVELOPE FUNCTION AND DISEASE PATHOGENESIS

Studies of laminopathies have provided insights into novel functions of the nuclear envelope. Perhaps most significantly, these studies strongly suggest that the intermediate filament nuclear lamina, although serving as a structural support for the nuclear membranes, must have additional functions. Because very different disease phenotypes can result from alterations in lamins, the nuclear lamina likely has cell-type and tissue-selective properties.

Like all intermediate filament proteins, A-type lamins have a relatively small head domain, a conserved α -helical rod domain, and a tail domain. Lamins A and C are identical for the first 566 amino acids, sharing the head, rod, and first portion of the tail domain, with lamin C having six unique carboxy-terminal amino acids and prelamin A having 98 unique carboxy-terminal residues. Examination of the predominant genotype-phenotype correlations for alterations in lamin A structure strongly suggests that different domains of the proteins have different tissue-selective functions (Fig. 1). Most mutations that cause striated muscle

Figure 1. Schematic diagram of a prelamin A molecule with mutations causing laminopathies indicated. Mutations causing Dunnigan-type familial partial lipodystrophy (FPLD, dark blue asterisks), Charcot-Marie-Tooth disease (CMT, orange asterisk), mandibuloacral dysplasia (MAD, light blue asterisks), or Hutchinson-Gilford progeria syndrome (HGPS, purple asterisk) are found in specific areas of the molecule, whereas mutations causing myopathies (red asterisks) are found throughout. Mutation data are from Leiden Muscular Dystrophy pages (http://www.dmd.nl/lmna_home.html). Photographs are reproduced with permission from Elsevier (Chaouch et al. 2003; Emery 2000; Novelli et al. 2002), Macmillan Publishers Ltd (Peters et al. 1998; Towbin and Bowles 2002), and the American Association for the Advancement of Science (De Sandre-Giovannoli et al. 2003).

diseases lead to amino-acid substitutions, small deletions, splice site alterations, or truncations throughout lamins A and C. Approximately 90% of the mutations that cause Dunnigan-type familial partial lipodystrophy generate amino-acid substitutions within an immunoglobulin-type fold in the tails of lamins A and C. Most mutations causing peripheral neuropathy lead to the R298C substitution in the rod domain and most mutations causing mandibuloacral dysplasia generate amino-acid substitutions at or very near amino-acid residue 527 in the

immunoglobulin-type fold. Classical Hutchinson-Gilford progeria syndrome is caused by mutations within exon 11 of *LMNA*, leading to an in frame deletion of 50 amino acids from the tail of prelamin A.

The distribution of *LMNA* mutations causing striated muscle diseases suggests that these lead to a defect in overall lamina structure in cells. Homozygous *Lmna* knockout mice develop regional skeletal and cardiac muscle abnormalities within the first 2 months of life and their heterozygous littermates develop

H.J. Worman, C. Östlund, and Y. Wang

cardiomyopathy with conduction block at much older ages (Sullivan et al. 1999; Wolf et al. 2008). Heterozygous mutations leading to significant lamin truncations in humans also cause striated muscle disease (Bonne et al. 1999; Jakobs et al. 2001; MacLeod et al. 2003). Expression of missense lamin A variants that cause muscle disease disrupts the structure of the nuclear lamina and leads to morphological alterations similar to those in cells from which A-type lamins are depleted (Östlund et al. 2001; Raharjo et al. 2001). Transgenic expression of a lamin A variant encoded by a *LMNA* mutation that causes cardiomyopathy and muscular dystrophy in humans alters lamina structure and induces severe heart disease in mice (Wang et al. 2006). These observations suggest that muscle disease results either from a partial loss of A-type lamins or expression of variants that “dominantly interfere” with the overall structure and function of the nuclear lamina.

It remains generally accepted that one function of the lamina is to provide structural support to the nuclear envelope. One hypothesis for the pathogenesis of striated muscle disease is that a defective lamina fails to properly carry out this support function. Fibroblasts from *Lmna* knockout mice, transfected cells that express lamin A variants and fibroblasts from human subjects with *LMNA* mutations and muscle diseases, all have abnormal nuclear morphology at the light microscopy level (Sullivan et al. 1999; Östlund et al. 2001; Raharjo et al. 2001; Muchir et al. 2004). Fibroblasts from *Lmna* knockout mice also have decreased mechanical stiffness (Broers et al. 2004; Lammerding et al. 2004; Lee et al. 2007). Abnormalities in the nuclear lamina could even potentially affect cytoskeleton functions, as the lamina is connected to cytoplasmic actin via the nesprin isoforms and Sun proteins that span the perinuclear space (Crisp et al. 2006). Depletion of A-type lamins indeed disrupts cytoskeletal processes such as cellular migration and nuclear positioning (Lee et al. 2007; Houben et al. 2009).

In hearts and to a lesser extent in skeletal muscle from *Lmna* H222P knockin mice, a model of Emery-Dreifuss muscular dystrophy,

there is abnormal activation of the MAP kinases ERK1/2 and JNK (Muchir et al. 2007b). These MAP kinases are activated by mechanical stress in cardiomyocytes (Baines and Molkenkin 2005). Chronically increased ERK and JNK activation is detrimental to hearts and treatment of *Lmna* H222P knockin mice with an inhibitor of ERK signaling prevents development of cardiomyopathy (Muchir et al. 2009). Altered nuclear envelope elasticity is also caused by loss of emerin, which binds to A-type lamins, and this could contribute to increased nuclear fragility in humans subjects with mutations in *EDM* and striated muscle disease (Rowat et al. 2006). ERK is also abnormally activated in hearts of mice lacking emerin (Muchir et al. 2007a). Structural alterations in the nuclear envelope and connected cytoskeleton resulting from *LMNA* or *EDM* mutations may therefore make cells such as cardiomyocytes highly susceptible to damage by recurrent mechanical stress, leading to the activation of stress-response pathways that are further detrimental to cells over time.

Data from subjects with Dunnigan-type familial partial lipodystrophy suggest that the immunoglobulin-type fold in the tail of A-type lamins has specific functions in adipose cells. *LMNA* mutations responsible for approximately 90% of cases lead to amino-acid substitutions that decrease the positive charge of a solvent-exposed surface on the immunoglobulin-type fold but are not predicted to alter the three-dimensional structure of lamins (Dhe-Paganon et al. 2002; Krimm et al. 2002). However, they affect the ability of the immunoglobulin-type fold of A-type lamins to bind to DNA (Stierlé et al. 2003) and could potentially alter binding of a protein important in adipocyte differentiation or survival. These mutations have in fact been shown to decrease an interaction between lamin A and SREBP1 (Lloyd et al. 2002); however, the physiological consequences of this interaction remain to be shown. *LMNA* mutations that cause Dunnigan-type familial partial lipodystrophy may result in a “gain of function,” as overexpression of either lamin A with a causative amino-acid change or wild-type lamin A both block differentiation of preadipocytes in adipocytes in vitro

(Boguslavsky et al. 2006) and deficiency of A-type lamins does not cause lipodystrophy in mice (Cutler et al. 2002). The immunoglobulin-type fold of A-type lamins may therefore negatively regulate adipocyte differentiation, or survival “gain of function” may cause partial lipodystrophy. Mandibuloacral dysplasia, which has partial lipodystrophy as a predominant feature, also results from amino-acid substitutions in the immunoglobulin-type fold; however, there are other abnormalities affecting different tissues in this autosomal recessive disease requiring inheritance of two mutant *LMNA* alleles.

Perhaps the best example of a laminopathy providing insights into nuclear envelope protein function is what progeroid disorders have taught us about the need for proper prelamin A processing. Since the early 1980s, it has been recognized that lamin A is synthesized as a precursor molecule prelamin A (Gerace et al. 1984). Prelamin A contains a CaaX motif at its carboxyl terminus, a sequence known to initiate three sequential chemical reactions (Clarke 1992; Zhang and Casey 1996; Young et al. 2005). In the first reaction, the cysteine of the carboxy-terminal CaaX motif is farnesylated

by protein farnesyltransferase. In the second reaction, the –aaX is clipped off. In the third, the farnesylcysteine is methylated by isoprenylcysteine carboxyl methyltransferase. The role of these three reactions in prelamin A processing is shown in Figure 2.

Initially, the groups of Klaus Weber and Michael Sinensky showed that processing of prelamin A resulted from cleavage of an isoprenylated, specifically farnesylated, polypeptide 15 amino acids away from the carboxy-terminal cysteine (Weber et al. 1989; Beck et al. 1990; Sinensky et al. 1994). Sinensky’s group then characterized a farnesylation-dependent prelamin A endoprotease activity in cells (Kilic et al. 1997). In 2002, the groups of Stephen Young and Carlos López-Otín reported that mice deficient in zinc metalloproteinase ZMPSTE24 were defective in the processing of prelamin A to lamin A (Bergo et al. 2002; Pendás et al. 2002). In 2005, Sinensky’s group confirmed in vitro using recombinant ZMPSTE24 that this endoprotease clips the –aaX from prelamin A and catalyzes the second cleavage that removes the remaining 15 carboxyl-terminal amino acids (Corrigan et al. 2005). Removal of the –aaX from prelamin A is likely

Figure 2. Processing of prelamin A to mature lamin A in wild-type (WT) cells occurs in several steps, described in the text (*middle column*). In restrictive dermopathy (RD), the ZMPSTE24 enzyme is nonfunctioning, resulting in accumulation of farnesylated prelamin A (*left column*). In Hutchinson-Gilford progeria syndrome (HGPS), the second cleavage site for ZMPSTE24 is deleted, resulting in accumulation of a truncated form of farnesylated prelamin A (*right column*).

H.J. Worman, C. Östlund, and Y. Wang

redundantly catalyzed by the enzyme RCE1 (Young et al. 2005).

The *LMNA* mutation causing Hutchinson-Gilford progeria syndrome that activates a cryptic splice site in exon 11 leads to an in frame deletion of 50 amino acids that contains the second ZMPSTE24 endoproteolytic site in prelamin A (De Sandre-Giovannoli et al. 2003; Eriksson et al. 2003). As a result, a farnesylated, truncated prelamin A variant that cannot be properly processed accumulates in cells (Fig. 2). Loss of ZMPSTE24 activity leads to accumulation of unprocessed, farnesylated prelamin A (Fig. 2), which causes restrictive dermopathy and other progeroid disorders that have clinical overlap with Hutchinson-Gilford progeria syndrome. *Zmpste24* knockout mice have progeroid features that overlap with mice having a targeted knockin mutation of *Lmna* that causes Hutchinson-Gilford progeria syndrome (Yang et al. 2006). Blocking farnesylation of the truncated prelamin A or unprocessed prelamin A in these mice with chemical inhibitors improves the mouse phenotypes (Fong et al. 2006; Yang et al. 2006; Varela et al. 2008). Similarly, heterozygosity for *Lmna* deficiency eliminates the progeria-like phenotypes in *Zmpste24* knockout mice (Fong et al. 2004). These results indicate that accumulation of farnesylated prelamin A or the truncated variant plays a key role in the pathogenesis of the progeroid phenotype.

It is less clear how accumulation of farnesylated prelamin A polypeptides lead to progeria phenotypes. Cultured cells expressing these proteins have microscopic abnormalities in nuclear morphology and blocking protein farnesyltransferase activity significantly reverses these abnormalities (Eriksson et al. 2003; De Sandre-Giovannoli et al. 2003; Bridger and Kill 2004; Goldman et al. 2004; Paradisi et al. 2005; Yang et al. 2005; Capell et al. 2005; Glynn and Glover 2005; Mallampalli et al. 2005; Toth et al. 2005; Young et al. 2005; Wang et al. 2008). These nuclear morphological abnormalities are associated with reduced deformability of the lamina and increased stiffness of the nucleus (Dahl et al. 2006; Verstraeten et al. 2008). However, alterations in nuclear morphology and nuclear mechanics are not unique to progeroid

syndromes and occur as a result of *LMNA* mutations that cause other laminopathies. Expression of farnesylated prelamin A or the truncated variant in Hutchinson-Gilford progeria syndrome perturb DNA damage response and repair, leading to genomic instability (Liu et al. 2005), but inhibition of protein farnesylation does not appear to reduce DNA double-strand breaks or damage checkpoint signaling (Liu et al. 2006). Cells accumulating these isoprenylated A-type lamins also have altered signaling pathways involved in regulating stem cell behavior (Espada et al. 2008; Scaffidi and Misteli 2008).

Although accumulation of isoprenylated prelamin A polypeptides is important in progeria pathogenesis, genetic studies show that it is not the entire explanation. Some atypical progeroid disorders resulting from *LMNA* mutations are not associated with accumulation of prelamin A (Verstraeten et al. 2006). Furthermore, Yang et al. (2008) elegantly showed that expression in mice of a nonfarnesylated variant of the truncated prelamin A in Hutchinson-Gilford progeria syndrome nonetheless causes a progeroid-like phenotype, albeit less severe than that in mice expressing the farnesylated protein. Hence, alterations in A-type lamins other than accumulation of isoprenylated forms can lead to the same cellular defects that give rise to progeroid phenotypes.

CONCLUDING REMARKS

Are studies of the rare monogenic laminopathies relevant to common human diseases and physiological aging? Some data suggest that this might indeed be the case. As patients with familial dilated cardiomyopathies have been screened for genetic causes at some medical centers, *LMNA* mutations have been shown to be responsible for approximately ten percent of all cases and a third with atrioventricular conduction block (Arbustini et al. 2002; Taylor et al. 2003; van Tintelen et al. 2007; Parks et al. 2008). Compared with other dilated cardiomyopathies, those caused by *LMNA* mutations are associated with the rapid development of heart failure, early life-threatening arrhythmias, and

sudden death (Bécane et al. 2000; Taylor et al. 2003; van Berlo et al. 2005; Pasotti et al. 2008). Hence, screening for *LMNA* mutations as part of the clinical routine could provide information that leads to early placement of a pacemaker and an implantable cardioverter defibrillator to prevent sudden death (Meune et al. 2006).

Given that mutations in genes encoding nuclear envelope proteins cause rare monogenic diseases, it is possible that polymorphic variants of the same genes predispose or contribute quantitatively to the development of common diseases. As *LMNA* mutations cause rare lipodystrophy disorders, several groups have examined if *LMNA* polymorphisms contribute to the development of common disorders. Although not completely conclusive, some studies suggest that polymorphic variations in *LMNA* may predispose to insulin resistance, diabetes mellitus, and metabolic syndrome (Duesing et al. 2008; Steinle et al. 2004; Wegner et al. 2007; Owen et al. 2007; Mesa et al. 2007; Murase et al. 2002). Hence, subtle alterations in A-type lamins may contribute to the pathogenesis of diseases that are endemic in the developed world. One could similarly hypothesize that polymorphisms in genes encoding other nuclear envelope proteins could contribute to other common diseases. For example, subtle alterations in *MAN1*, loss of function of which causes sclerosing bone dysplasias, could hypothetically contribute to the development of osteoporosis.

The involvement of A-type lamins in the pathogenesis of progeroid syndromes has raised interest about their role in physiological aging. The abnormal RNA splicing occurring as a result of the *LMNA* mutations that cause Hutchinson-Gilford progeria syndrome takes place at very low levels in normal cells (McClintock et al. 2007; Scaffidi and Misteli 2006). One study has shown that the truncated prelamin A that results from this RNA splicing event accumulates in dermal fibroblasts and keratinocytes in older individuals (McClintock et al. 2007). Fibroblasts from older normal subjects have also been reported to show defects similar to those in cells from subjects with Hutchinson-Gilford progeria syndrome, such as abnormal nuclear morphology, increased

DNA damage, and changes in histone modifications (Scaffidi and Misteli 2006). These findings support a hypothesis that low-level expression of the truncated prelamin A generated as a result of the *LMNA* mutation that causes Hutchinson-Gilford progeria syndrome may contribute to aspects of physiological aging.

In closing, a word of caution is warranted about extrapolating data from laminopathies to common diseases. For example, children with Hutchinson-Gilford progeria syndrome have normal cognitive and other brain functions, whereas central nervous system degeneration is a major feature of normal human aging. Elevated blood levels of total cholesterol, C-reactive protein, and low density lipoprotein do not appear to contribute to the accelerated vascular occlusive disease in Hutchinson-Gilford progeria syndrome (Gordon et al. 2005) and affected vessels show pathological features that are unusual for typical atherosclerosis (Stehbens et al. 1999). Hence, Hutchinson-Gilford progeria syndrome may not be a perfectly accurate model to understand some of the major complications of physiological human aging. Similarly, other laminopathies that share phenotypic features with common human disorders may have different underlying pathogenic mechanisms. Nonetheless, research on this fascinating group of rare diseases is clearly providing clues about fundamental functions of the nuclear envelope as well as relevant insights into cellular processes that must be at least partly involved in certain aspects of common diseases and aging.

ACKNOWLEDGMENTS

The authors were supported by grants from the National Institutes of Health (AR048997, NS059352, and AG025240) and a grant from the Muscular Dystrophy Association (MDA4287) to H.J. Worman.

REFERENCES

- Agarwal AK, Fryns JP, Auchus RJ, Garg A. 2003. Zinc metalloproteinase, ZMPSTE24, is mutated in mandibuloacral dysplasia. *Hum Mol Genet* 12: 1995–2001.

H.J. Worman, C. Östlund, and Y. Wang

- Agarwal AK, Kazachkova I, Ten S, Garg A. 2008. Severe mandibuloacral dysplasia-associated lipodystrophy and progeria in a young girl with a novel homozygous Arg527Cys LMNA mutation. *J Clin Endocrinol Metab* **93**: 4617–4623.
- Arbustini E, Pilotto A, Repetto A, Grasso M, Negri A, Diegoli M, Campana C, Scelsi L, Baldini E, Gavazzi A, Tavazzi L. 2002. Autosomal dominant dilated cardiomyopathy with atrioventricular block: A lamin A/C defect-related disease. *J Am Coll Cardiol* **39**: 981–990.
- Astejada MN, Goto K, Nagano A, Ura S, Noguchi S, Nonaka I, Nishino I, Hayashi YK. 2007. Emerinopathy and laminopathy clinical, pathological and molecular features of muscular dystrophy with nuclear envelopopathy in Japan. *Acta Myol* **26**: 159–164.
- Attali R, Warwar N, Israel A, Gurt I, McNally E, Puckelwartz M, Glick B, Nevo Y, Ben-Neriah Z, Melki J. 2009. Mutation of SYNE-1, encoding an essential component of the nuclear lamina, is responsible for autosomal recessive arthrogryposis. *Hum Mol Genet* **18**: 3462–3469.
- Baines CP, Molkentin JD. 2005. STRESS signaling pathways that modulate cardiac myocyte apoptosis. *J Mol Cell Cardiol* **38**: 47–62.
- Basel-Vanagaite L, Muncher L, Straussberg R, Pasmanik-Chor M, Yahav M, Rainshtein L, Walsh CA, Magal N, Taub E, Drasinover V, et al. 2006. Mutated nup62 causes autosomal recessive infantile bilateral striatal necrosis. *Ann Neurol* **60**: 214–222.
- Beadle GW, Tatum EL. 1941. Genetic control of biochemical reactions in Neurospora. *Proc Natl Acad Sci* **27**: 499–506.
- Bécane HM, Bonne G, Varnous S, Muchir A, Ortega V, Hammouda EH, Urtizberea JA, Lavergne T, Fardeau M, Eymard B, et al. 2000. High incidence of sudden death with conduction system and myocardial disease due to lamins A and C gene mutation. *Pacing Clin Electrophysiol* **23**: 1661–1666.
- Beck LA, Hosick TJ, Sinensky M. 1990. Isoprenylation is required for the processing of the lamin A precursor. *J Cell Biol* **110**: 1489–1499.
- Bergo MO, Gavino B, Ross J, Schmidt WK, Hong C, Kendall LV, Mohr A, Meta M, Genant H, Jiang Y, et al. 2002. Zmpste24 deficiency in mice causes spontaneous bone fractures, muscle weakness, and a prelamin A processing defect. *Proc Natl Acad Sci* **99**: 13049–13054.
- Bione S, Maestrini E, Rivella S, Mancini M, Regis S, Romeo G, Toniolo D. 1994. Identification of a novel X-linked gene responsible for Emery-Dreifuss muscular dystrophy. *Nat Genet* **8**: 323–327.
- Bione S, Small K, Aksmanovic VM, D'Urso M, Ciccodicola A, Merlini L, Morandi L, Kress W, Yates JR, Warren ST, et al. 1995. Identification of new mutations in the Emery-Dreifuss muscular dystrophy gene and evidence for genetic heterogeneity of the disease. *Hum Mol Genet* **4**: 1859–1863.
- Boguslavsky RL, Stewart CL, Worman HJ. 2006. Nuclear lamin A inhibits adipocyte differentiation: Implications for Dunnigan-type familial partial lipodystrophy. *Hum Mol Genet* **15**: 653–663.
- Bonne G, Di Barletta MR, Varnous S, Bécane HM, Hammouda EH, Merlini L, Muntoni F, Greenberg CR, Gary F, Urtizberea JA, et al. 1999. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. *Nat Genet* **21**: 285–288.
- Bonne G, Mercuri E, Muchir A, Urtizberea A, Bécane HM, Recan D, Merlini L, Wehnert M, Boor R, Reuner U, et al. 2000. Clinical and molecular genetic spectrum of autosomal dominant Emery-Dreifuss muscular dystrophy due to mutations of the lamin A/C gene. *Ann Neurol* **48**: 170–180.
- Bridger JM, Kill IR. 2004. Aging of Hutchinson–Gilford progeria syndrome fibroblasts is characterised by hyperproliferation and increased apoptosis. *Exp Gerontol* **39**: 717–724.
- Brodsky GL, Muntoni F, Miocic S, Sinagra G, Sewry C, Mestroni L. 2000. Lamin A/C gene mutation associated with dilated cardiomyopathy with variable skeletal muscle involvement. *Circulation* **101**: 473–476.
- Broers JL, Peeters EA, Kuijpers HJ, Endert J, Bouten CV, Oomens CW, Baaijens FP, Ramaekers FC. 2004. Decreased mechanical stiffness in LMNA-/- cells is caused by defective nucleo-cytoskeletal integrity: Implications for the development of laminopathies. *Hum Mol Genet* **13**: 2567–2580.
- Cao H, Hegele RA. 2000. Nuclear lamin A/C R482Q mutation in Canadian kindreds with Dunnigan-type familial partial lipodystrophy. *Hum Mol Genet* **9**: 109–112.
- Cao H, Hegele RA. 2003. LMNA is mutated in Hutchinson–Gilford progeria (MIM 176670) but not in Wiedemann–Rautenstrauch progeroid syndrome (MIM 264090). *J Hum Genet* **48**: 271–274.
- Capell BC, Erdos MR, Madigan JP, Fiordalisi JJ, Varga R, Conneely KN, Gordon LB, Der CJ, Cox AD, Collins FS. 2005. Inhibiting farnesylation of progerin prevents the characteristic nuclear blebbing of Hutchinson–Gilford progeria syndrome. *Proc Natl Acad Sci* **102**: 12879–12884.
- Caputo S, Couprie J, Duband-Goulet I, Kondé E, Lin F, Braud S, Gondry M, Gilquin B, Worman HJ, Zinn-Justin S. 2006. The carboxyl-terminal nucleoplasmic region of MAN1 exhibits a DNA binding winged helix domain. *J Biol Chem* **281**: 18208–18215.
- Chaouch M, Allal Y, De Sandre-Giovannoli A, Vallat JM, Amer-el-Khedoud A, Kassouri N, Chaouch A, Sindou P, Hammadouche T, Tazir M, et al. 2003. The phenotypic manifestations of autosomal recessive axonal Charcot-Marie-Tooth due to a mutation in Lamin A/C gene. *Neuromuscul Disord* **13**: 60–67.
- Chen L, Lee L, Kudlow BA, Dos Santos HG, Sletvold O, Shafeghati Y, Botha EG, Garg A, Hanson NB, Martin GM, et al. 2003. LMNA mutations in atypical Werner's syndrome. *Lancet* **362**: 440–445.
- Clarke S. 1992. Protein isoprenylation and methylation at carboxyl-terminal cysteine residues. *Annu Rev Biochem* **61**: 355–386.
- Clements L, Manilal S, Love DR, Morris GE. 2000. Direct interaction between emerin and lamin A. *Biochem Biophys Res Commun* **267**: 709–714.
- Corrigan DP, Kuszczak D, Rusinol AE, Thewke DP, Hrycyna CA, Michaelis S, Sinensky MS. 2005. Prelamin A endoproteolytic processing in vitro by recombinant Zmpste24. *Biochem J* **387**: 129–138.

- Crisp M, Liu Q, Roux K, Rattner JB, Shanahan C, Burke B, Stahl PD, Hodzic D. 2006. Coupling of the nucleus and cytoplasm: Role of the LINC complex. *J Cell Biol* **172**: 41–53.
- Cronshaw JM, Matunis MJ. 2003. The nuclear pore complex protein ALADIN is mislocalized in triple A syndrome. *Proc Natl Acad Sci* **100**: 5823–5827.
- Csoka AB, Cao H, Sammak PJ, Constantinescu D, Schatten GP, Hegele RA. 2004. Novel lamin A/C gene (LMNA) mutations in atypical progeroid syndromes. *J Med Genet* **41**: 304–308.
- Cutler DA, Sullivan T, Marcus-Samuels B, Stewart CL, Reitman ML. 2002. Characterization of adiposity and metabolism in Lmna-deficient mice. *Biochem Biophys Res Commun* **291**: 522–527.
- Dahl KN, Scaffidi P, Islam ME, Yodh AG, Wilson KL, Misteli T. 2006. Distinct structural and mechanical properties of the nuclear lamina in Hutchinson-Gilford progeria syndrome. *Proc Natl Acad Sci* **103**: 10271–10276.
- DeBusk FL. 1972. The Hutchinson-Gilford progeria syndrome. *J Pediatr* **80**: 697–724.
- De Sandre-Giovannoli A, Bernard R, Cau P, Navarro C, Amiel J, Boccaccio I, Lyonnet S, Stewart CL, Munnich A, Le Merrer M, et al. 2003. Lamin A truncation in Hutchinson-Gilford progeria. *Science* **300**: 2055.
- De Sandre-Giovannoli A, Chaouch M, Kozlov S, Vallat JM, Tazir M, Kassouri N, Szepietowski P, Hammadouche T, Vandenberghe A, Stewart CL, et al. 2002. Homozygous defects in LMNA, encoding lamin A/C nuclear-envelope proteins, cause autosomal recessive axonal neuropathy in human (Charcot-Marie-Tooth disorder type 2) and mouse. *Am J Hum Genet* **70**: 726–736.
- Dhe-Paganon S, Werner ED, Chi YI, Shoelson SE. 2002. Structure of the globular tail of nuclear lamin. *J Biol Chem* **277**: 17381–17384.
- Duesing K, Charpentier G, Marre M, Tichet J, Hercberg S, Froguel P, Gibson F. 2008. Evaluating the association of common LMNA variants with type 2 diabetes and quantitative metabolic phenotypes in French Europids. *Diabetologia* **51**: 76–81.
- Dunnigan MG, Cochrane MA, Kelly A, Scott JW. 1974. Familial lipotrophic diabetes with dominant transmission. A new syndrome. *Q J Med* **43**: 33–48.
- Emery AE. 2000. Emery-Dreifuss muscular dystrophy—a 40 year retrospective. *Neuromuscul Disord* **10**: 228–232.
- Emery AE, Dreifuss FE. 1966. Unusual type of benign x-linked muscular dystrophy. *J Neurol Neurosurg Psychiatry* **29**: 338–342.
- Eriksson M, Brown WT, Gordon LB, Glynn MW, Singer J, Scott L, Erdos MR, Robbins CM, Moses TY, Berglund P, et al. 2003. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. *Nature* **423**: 293–298.
- Espada J, Varela I, Flores I, Ugalde AP, Cadiñanos J, Pendás AM, Stewart CL, Tryggvason K, Blasco MA, Freije JM, et al. 2008. Nuclear envelope defects cause stem cell dysfunction in premature-aging mice. *J Cell Biol* **181**: 27–35.
- Fairley EA, Kendrick-Jones J, Ellis JA. 1999. The Emery-Dreifuss muscular dystrophy phenotype arises from aberrant targeting and binding of emerin at the inner nuclear membrane. *J Cell Sci* **112**: 2571–2582.
- Fatkin D, MacRae C, Sasaki T, Wolff MR, Porcu M, Frenneaux M, Atherton J, Vidaillet HJ Jr, Spudich S, De Girolami U, et al. 1999. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. *N Engl J Med* **341**: 1715–1724.
- Fong LG, Frost D, Meta M, Qiao X, Yang SH, Coffinier C, Young SG. 2006. A protein farnesyltransferase inhibitor ameliorates disease in a mouse model of progeria. *Science* **311**: 1621–1623.
- Fong LG, Ng JK, Meta M, Coté N, Yang SH, Stewart CL, Sullivan T, Burghardt A, Majumdar S, Reue K, et al. 2004. Heterozygosity for Lmna deficiency eliminates the progeria-like phenotypes in Zmpste24-deficient mice. *Proc Natl Acad Sci* **101**: 18111–18116.
- Garg A, Cogulu O, Ozkinay F, Onay H, Agarwal AK. 2005. A novel homozygous Ala529Val LMNA mutation in Turkish patients with mandibuloacral dysplasia. *J Clin Endocrinol Metab* **90**: 5259–5264.
- Gerace L, Comeau C, Benson M. 1984. Organization and modulation of nuclear lamina structure. *J Cell Sci Suppl* **1**: 137–160.
- Gilford H. 1904. Ateleiosis and progeria: Continuous youth and premature old age. *Brit Med J* **2**: 914–918.
- Glynn MW, Glover TW. 2005. Incomplete processing of mutant lamin A in Hutchinson-Gilford progeria leads to nuclear abnormalities, which are reversed by farnesyltransferase inhibition. *Hum Mol Genet* **14**: 2959–2969.
- Goldman RD, Shumaker DK, Erdos MR, Eriksson M, Goldman AE, Gordon LB, Gruenbaum Y, Khuon S, Mendez M, Varga R, et al. 2004. Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson-Gilford progeria syndrome. *Proc Natl Acad Sci* **101**: 8963–8968.
- Gonzalez-Alegre P, Paulson HL. 2004. Aberrant cellular behavior of mutant torsinA implicates nuclear envelope dysfunction in DYT1 dystonia. *J Neurosci* **24**: 2593–2601.
- Goodchild RE, Dauer WT. 2004. Mislocalization to the nuclear envelope: An effect of the dystonia-causing torsinA mutation. *Proc Natl Acad Sci* **101**: 847–852.
- Goodchild RE, Dauer WT. 2005. The AAA+ protein torsinA interacts with a conserved domain present in LAP1 and a novel ER protein. *J Cell Biol* **168**: 855–862.
- Goodchild RE, Kim CE, Dauer WT. 2005. Loss of the dystonia-associated protein torsinA selectively disrupts the neuronal nuclear envelope. *Neuron* **48**: 923–932.
- Gordon LB, Harten IA, Patti ME, Lichtenstein AH. 2005. Reduced adiponectin and HDL cholesterol without elevated C-reactive protein: Clues to the biology of premature atherosclerosis in Hutchinson-Gilford Progeria Syndrome. *J Pediatr* **146**: 336–341.
- Gros-Louis F, Dupré N, Dion P, Fox MA, Laurent S, Verreault S, Sanes JR, Bouchard JP, Rouleau GA. 2007. Mutations in SYNE1 lead to a newly discovered form of autosomal recessive cerebellar ataxia. *Nat Genet* **39**: 80–85.
- Hegele RA, Cao H, Liu DM, Costain GA, Charlton-Menys V, Rodger NW, Durrington PN. 2006. Sequencing of the reannotated LMNB2 gene reveals novel mutations in patients with acquired partial lipodystrophy. *Am J Hum Genet* **79**: 383–389.

H.J. Worman, C. Östlund, and Y. Wang

- Hellemans J, Preobrazhenska O, Willaert A, Debeer P, Verdonk PC, Costa T, Janssens K, Menten B, Van Roy N, Vermeulen SJ, et al. 2004. Loss-of-function mutations in LEMD3 result in osteopoikilosis, Buschke-Ollendorff syndrome and melorheostosis. *Nat Genet* **36**: 1213–1238.
- Hoffmann K, Dreger CK, Olins AL, Olins DE, Shultz LD, Lucke B, Karl H, Kaps R, Müller D, Vayá A, et al. 2002. Mutations in the gene encoding the lamin B receptor produce an altered nuclear morphology in granulocytes (Pelger-Huët anomaly). *Nat Genet* **31**: 410–414.
- Holmer L, Pezhman A, Worman HJ. 1998. The human lamin B receptor/sterol reductase multigene family. *Genomics* **54**: 469–476.
- Houben F, Willems CH, Declercq IL, Hochstenbach K, Kamps MA, Snoeckx LH, Ramaekers FC, Broers JL. 2009. Disturbed nuclear orientation and cellular migration in A-type lamin deficient cells. *Biochim Biophys Acta* **1793**: 312–324.
- Hutchinson J. 1886. Case of congenital absence of hair, with atrophic condition of the skin and its appendages, in a boy whose mother had been almost wholly bald from alopecia areata from the age of six. *Lancet* **I**: 923.
- Jackson SN, Pinkney J, Bargiotta A, Veal CD, Howlett TA, McNally PG, Corral R, Johnson A, Trembath RC. 1998. A defect in the regional deposition of adipose tissue (partial lipodystrophy) is encoded by a gene at chromosome 1q. *Am J Hum Genet* **63**: 534–540.
- Jakobs PM, Hanson EL, Crispell KA, Toy W, Keegan H, Schilling K, Icenogle TB, Litt M, Hersherberger RE. 2001. Novel lamin A/C mutations in two families with dilated cardiomyopathy and conduction system disease. *J Card Fail* **7**: 249–256.
- Kilic F, Dalton MB, Burrell SK, Mayer JB, Patterson SD, Sinensky M. 1997. In vitro assay and characterization of the farnesylation-dependent prelamin A endoprotease. *J Biol Chem* **272**: 5298–5304.
- Krimm I, Östlund C, Gilquin B, Couprie J, Hossenlopp P, Mornon JP, Bonne G, Courvalin JC, Worman HJ, Zinn-Justin S. 2002. The Ig-like structure of the C-terminal domain of lamin A/C, mutated in muscular dystrophies, cardiomyopathy, and partial lipodystrophy. *Structure* **10**: 811–823.
- Lammerding J, Schulze PC, Takahashi T, Kozlov S, Sullivan T, Kamm RD, Stewart CL, Lee RT. 2004. Lamin A/C deficiency causes defective nuclear mechanics and mechanotransduction. *J Clin Invest* **113**: 370–378.
- Lee JS, Hale CM, Panorchan P, Khatau SB, George JB, Tseng Y, Stewart CL, Hodzic D, Wirtz D. 2007. Nuclear lamin A/C deficiency induces defects in cell mechanics, polarization, and migration. *Biophys J* **93**: 2542–2552.
- Lin F, Worman HJ. 1993. Structural organization of the human gene encoding nuclear lamin A and nuclear lamin C. *J Biol Chem* **268**: 16321–16326.
- Lin F, Blake DL, Callebaut I, Skerjanc IS, Holmer L, McBurney MW, Paulin-Levasseur M, Worman HJ. 2000. MAN1, an inner nuclear membrane protein that shares the LEM domain with lamina-associated polypeptide 2 and emerin. *J Biol Chem* **275**: 4840–4847.
- Lin F, Morrison JM, Wu W, Worman HJ. 2005. MAN1, an integral protein of the inner nuclear membrane, binds Smad2 and Smad3 and antagonizes transforming growth factor- β signaling. *Hum Mol Genet* **14**: 437–445.
- Liu Y, Rusinol A, Sinensky M, Wang Y, Zou Y. 2006. DNA damage responses in progeroid syndromes arise from defective maturation of prelamin A. *J Cell Sci* **119**: 4644–4649.
- Liu B, Wang J, Chan KM, Tjia WM, Deng W, Guan X, Huang JD, Li KM, Chau PY, Chen DJ, et al. 2005. Genomic instability in laminopathy-based premature aging. *Nat Med* **11**: 780–785.
- Lloyd DJ, Trembath RC, Shackleton S. 2002. A novel interaction between lamin A and SREBP 1: Implications for partial lipodystrophy and other laminopathies. *Hum Mol Genet* **11**: 769–777.
- Lombardi F, Gullotta F, Columbaro M, Filaretto A, D'Adamo M, Vielle A, Guglielmi V, Nardone AM, Azzolini V, Grosso E, et al. 2007. Compound heterozygosity for mutations in LMNA in a patient with a myopathic and lipodystrophic mandibuloacral dysplasia type A phenotype. *J Clin Endocrinol Metab* **92**: 4467–4471.
- MacLeod HM, Culley MR, Huber JM, McNally EM. 2003. Lamin A/C truncation in dilated cardiomyopathy with conduction disease. *BMC Med Genet* **4**: 4.
- Makri S, Clarke NF, Richard P, Maugeenre S, Demay L, Bonne G, Guicheney P. 2009. Germinal mosaicism for LMNA mimics autosomal recessive congenital muscular dystrophy. *Neuromuscul Disord* **19**: 26–28.
- Mallampalli MR, Huyer G, Bendale P, Gelb MH, Michaelis S. 2005. Inhibiting farnesylation reverses the nuclear morphology defect in a HeLa cell model for Hutchinson-Gilford progeria syndrome. *Proc Natl Acad Sci* **102**: 14416–14421.
- Manilal S, Nguyen TM, Sewry CA, Morris GE. 1996. The Emery-Dreifuss muscular dystrophy protein, emerin, is a nuclear membrane protein. *Hum Mol Genet* **5**: 801–808.
- Mansharamani M, Wilson KL. 2005. Direct binding of nuclear membrane protein MAN1 to emerin in vitro and two modes of binding to barrier-to-autointegration factor. *J Biol Chem* **280**: 13863–13870.
- McClintock D, Ratner D, Lokuge M, Owens DM, Gordon LB, Collins FS, Djabali K. 2007. The mutant form of lamin A that causes Hutchinson-Gilford progeria is a biomarker of cellular aging in human skin. *PLoS One* **2**: e1269.
- McKusick VA. 1952. The clinical observations of Jonathan Hutchinson. *Am J Syph Gonorrhea Vener Dis* **36**: 101–126.
- Merideth MA, Gordon LB, Clauss S, Sachdev V, Smith AC, Perry MB, Brewer CC, Zaleski C, Kim HJ, Solomon B, et al. 2008. Phenotype and course of Hutchinson-Gilford progeria syndrome. *N Engl J Med* **358**: 592–604.
- Mesa JL, Loos RJ, Franks PW, Ong KK, Luan J, O'Rahilly S, Wareham NJ, Barroso I. 2007. Lamin A/C polymorphisms, type 2 diabetes, and the metabolic syndrome: Case-control and quantitative trait studies. *Diabetes* **56**: 884–889.
- Meune C, Van Berlo JH, Anselme F, Bonne G, Pinto YM, Duboc D. 2006. Primary prevention of sudden death in patients with lamin A/C gene mutations. *N Engl J Med* **354**: 209–210.
- Muchir A, Bonne G, van der Kooij AJ, van Meegen M, Baas F, Bolhuis PA, de Visser M, Schwartz K. 2000. Identification of mutations in the gene encoding lamins A/C in

- autosomal dominant limb girdle muscular dystrophy with atrioventricular conduction disturbances (LGMD1B). *Hum Mol Genet* **9**: 1453–1459.
- Muchir A, Medioni J, Laluc M, Massart C, Arimura T, van der Kooi AJ, Desguerre I, Mayer M, Ferrer X, Briault S, et al. 2004. Nuclear envelope alterations in fibroblasts from patients with muscular dystrophy, cardiomyopathy, and partial lipodystrophy carrying lamin A/C gene mutations. *Muscle Nerve* **30**: 444–450.
- Muchir A, Worman HJ. 2007. Emery-Dreifuss muscular dystrophy. *Curr Neurol Neurosci Rep* **7**: 78–83.
- Muchir A, Pavlidis P, Bonne G, Hayashi YK, Worman HJ. 2007a. Activation of MAPK in hearts of EMD null mice: Similarities between mouse models of X-linked and autosomal dominant Emery Dreifuss muscular dystrophy. *Hum Mol Genet* **16**: 1884–1895.
- Muchir A, Pavlidis P, Decostre V, Herron AJ, Arimura T, Bonne G, Worman HJ. 2007b. Activation of MAPK pathways links LMNA mutations to cardiomyopathy in Emery-Dreifuss muscular dystrophy. *J Clin Invest* **117**: 1282–1293.
- Muchir A, Shan J, Bonne G, Lehnart SE, Worman HJ. 2009. Inhibition of extracellular signal-regulated kinase signaling to prevent cardiomyopathy caused by mutation in the gene encoding A-type lamins. *Hum Mol Genet* **18**: 241–247.
- Murase Y, Yagi K, Katsuda Y, Asano A, Koizumi J, Mabuchi H. 2002. An LMNA variant is associated with dyslipidemia and insulin resistance in the Japanese. *Metabolism* **51**: 1017–1021.
- Nagano A, Koga R, Ogawa M, Kurano Y, Kawada J, Okada R, Hayashi YK, Tsukahara T, Arahata K. 1996. Emerin deficiency at the nuclear membrane in patients with Emery-Dreifuss muscular dystrophy. *Nat Genet* **12**: 254–259.
- Naismith TV, Heuser JE, Breakefield XO, Hanson PI. 2004. TorsinA in the nuclear envelope. *Proc Natl Acad Sci* **101**: 7612–7617.
- Navarro CL, Cadiñanos J, De Sandre-Giovannoli A, Bernard R, Courrier S, Boccaccio I, Boyer A, Kleijer WJ, Wagner A, Giuliano F, et al. 2005. Loss of ZMPSTE24 (FACE-1) causes autosomal recessive restrictive dermopathy and accumulation of Lamin A precursors. *Hum Mol Genet* **14**: 1503–1513.
- Neilson DE, Adams MD, Orr CM, Schelling DK, Eiben RM, Kerr DS, Anderson J, Bassuk AG, Bye AM, Childs AM, et al. 2009. Infection-triggered familial or recurrent cases of acute necrotizing encephalopathy caused by mutations in a component of the nuclear pore, RANBP2. *Am J Hum Genet* **84**: 44–51.
- Novelli G, Muchir A, Sangiulio F, Helbling-Leclerc A, D'Apice MR, Massart C, Capon F, Sbraccia P, Federici M, Lauro R, et al. 2002. Mandibuloacral dysplasia is caused by a mutation in LMNA-encoding lamin A/C. *Am J Hum Genet* **71**: 426–431.
- Oosterwijk JC, Mansour S, van Noort G, Waterham HR, Hall CM, Hennekam RC. 2003. Congenital abnormalities reported in Pelger-Huët homozygosity as compared to Greenberg/HEM dysplasia: highly variable expression of allelic phenotypes. *J Med Genet* **40**: 937–941.
- Östlund C, Bonne G, Schwartz K, Worman HJ. 2001. Properties of lamin A mutants found in Emery-Dreifuss muscular dystrophy, cardiomyopathy and Dunnigan-type partial lipodystrophy. *J Cell Sci* **114**: 4435–4445.
- Owen KR, Groves CJ, Hanson RL, Knowler WC, Shuldiner AR, Elbein SC, Mitchell BD, Froguel P, Ng MC, Chan JC, et al. 2007. Common variation in the LMNA gene (encoding lamin A/C) and type 2 diabetes: Association analyses in 9,518 subjects. *Diabetes* **56**: 879–883.
- Ozelius LJ, Hewett JW, Page CE, Bressman SB, Kramer PL, Shalish C, de Leon D, Brin MF, Raymond D, Corey DP, et al. 1997. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. *Nat Genet* **17**: 40–48.
- Padiath QS, Saigoh K, Schiffmann R, Asahara H, Yamada T, Koeppen A, Hogan K, Ptáček LJ, Fu YH. 2006. Lamin B1 duplications cause autosomal dominant leukodystrophy. *Nat Genet* **38**: 1114–1123.
- Pan D, Estévez-Salmerón LD, Stroschein SL, Zhu X, He J, Zhou S, Luo K. 2005. The integral inner nuclear membrane protein MAN1 physically interacts with the R-Smad proteins to repress signaling by the transforming growth factor- β superfamily of cytokines. *J Biol Chem* **280**: 15992–16001.
- Paradisi M, McClintock D, Boguslavsky RL, Pedicelli C, Worman HJ, Djabali K. 2005. Dermal fibroblasts in Hutchinson–Gilford progeria syndrome with the lamin A G608G mutation have dysmorphic nuclei and are hypersensitive to heat stress. *BMC Cell Biol* **6**: 27.
- Parks SB, Kushner JD, Nauman D, Burgess D, Ludwigsen S, Peterson A, Li D, Jakobs P, Litt M, Porter CB, et al. 2008. Lamin A/C mutation analysis in a cohort of 324 unrelated patients with idiopathic or familial dilated cardiomyopathy. *Am Heart J* **156**: 161–169.
- Pasotti M, Klersy C, Pilotto A, Marziliano N, Rapezzi C, Serio A, Mannarino S, Gambarin F, Favalli V, Grasso M, et al. 2008. Long-term outcome and risk stratification in dilated cardiomyopathies. *J Am Coll Cardiol* **52**: 1250–1260.
- Pendás AM, Zhou Z, Cadiñanos J, Freije JM, Wang J, Hultenby K, Astudillo A, Wernerson A, Rodríguez F, Tryggvason K, et al. 2002. Defective prelamin A processing and muscular and adipocyte alterations in Zmpste24 metalloproteinase-deficient mice. *Nat Genet* **31**: 94–99.
- Peters JM, Barnes R, Bennett L, Gitomer WM, Bowcock AM, Garg A. 1998. Localization of the gene for familial partial lipodystrophy (Dunnigan variety) to chromosome 1q21–22. *Nat Genet* **18**: 292–295.
- Quijano-Roy S, Mbieleu B, Bönnemann CG, Jeannet PY, Colomer J, Clarke NF, Cuisset JM, Roper H, De Meirleir L, D'Amico A, et al. 2008. De novo LMNA mutations cause a new form of congenital muscular dystrophy. *Ann Neurol* **64**: 177–186.
- Raharjo WH, Enarson P, Sullivan T, Stewart CL, Burke B. 2001. Nuclear envelope defects associated with LMNA mutations cause dilated cardiomyopathy and Emery-Dreifuss muscular dystrophy. *J Cell Sci* **114**: 4447–4457.
- Raffaele di Barletta M, Ricci E, Galluzzi G, Tonali P, Mora M, Morandi L, Romorini A, Voit T, Orstavik KH, Merlini L, et al. 2000. Different mutations in the LMNA gene cause autosomal dominant and autosomal recessive Emery-Dreifuss muscular dystrophy. *Am J Hum Genet* **66**: 1407–1412.

H.J. Worman, C. Östlund, and Y. Wang

- Renou L, Stora S, Yaou RB, Volk M, Sinkovec M, Demay L, Richard P, Peterlin B, Bonne G. 2008. Heart-hand syndrome of Slovenian type: A new kind of laminopathy. *J Med Genet* **45**: 666–671.
- Rowat AC, Lammerding J, Ipsen JH. 2006. Mechanical properties of the cell nucleus and the effect of emerin deficiency. *Biophys J* **91**: 4649–4664.
- Scaffidi P, Misteli T. 2006. Lamin A-dependent nuclear defects in human aging. *Science* **312**: 1059–1063.
- Scaffidi P, Misteli T. 2008. Lamin A-dependent misregulation of adult stem cells associated with accelerated ageing. *Nat Cell Biol* **10**: 452–459.
- Shackleton S, Lloyd DJ, Jackson SN, Evans R, Niermeijer MF, Singh BM, Schmidt H, Brabant G, Kumar S, Durrington PN, et al. 2000. LMNA, encoding lamin A/C, is mutated in partial lipodystrophy. *Nat Genet* **24**: 153–156.
- Shackleton S, Smallwood DT, Clayton P, Wilson LC, Agarwal AK, Garg A, Trembath RC. 2005. Compound heterozygous ZMPSTE24 mutations reduce prelamin A processing and result in a severe progeroid phenotype. *J Med Genet* **42**: e36.
- Sinensky M, Fantle K, Trujillo M, McLain T, Kupfer A, Dalton M. 1994. The processing pathway of prelamin A. *J Cell Sci* **107**: 61–67.
- Speckman RA, Garg A, Du F, Bennett L, Veile R, Arioglu E, Taylor SI, Lovett M, Bowcock AM. 2000. Mutational and haplotype analyses of families with familial partial lipodystrophy (Dunnigan variety) reveal recurrent missense mutations in the globular C-terminal domain of lamin A/C. *Am J Hum Genet* **66**: 1192–1198.
- Stehbens WE, Wakefield SJ, Gilbert-Barness E, Olson RE, Ackerman J. 1999. Histological and ultrastructural features of atherosclerosis in progeria. *Cardiovasc Pathol* **8**: 29–39.
- Steinle NI, Kazlauskaitė R, Imumori IG, Hsueh WC, Pollin TI, O'Connell JR, Mitchell BD, Shuldiner AR. 2004. Variation in the lamin A/C gene: Associations with metabolic syndrome. *Arterioscler Thromb Vasc Biol* **24**: 1708–1713.
- Stierlé V, Couprie J, Östlund C, Krimm I, Zinn-Justin S, Hossenlopp P, Worman HJ, Courvalin JC, Duband-Goulet I. 2003. The carboxyl-terminal region common to lamins A and C contains a DNA binding domain. *Biochemistry* **42**: 4819–4828.
- Sullivan T, Escalante-Alcalde D, Bhatt H, Anver M, Bhat N, Nagashima K, Stewart CL, Burke B. 1999. Loss of A-type lamin expression compromises nuclear envelope integrity leading to muscular dystrophy. *J Cell Biol* **147**: 913–920.
- Taylor MR, Fain PR, Sinagra G, Robinson ML, Robertson AD, Carniel E, Di Lenarda A, Bohlmeier TJ, Ferguson DA, Brodsky GL, et al. 2003. Natural history of dilated cardiomyopathy due to lamin A/C gene mutations. *J Am Coll Cardiol* **41**: 771–780.
- Taylor MR, Slavov D, Gajewski A, Vlcek S, Ku L, Fain PR, Carniel E, Di Lenarda A, Sinagra G, Boucek MM, et al. Familial Cardiomyopathy Registry Research Group. 2005. Thymopoietin (lamina-associated polypeptide 2) gene mutation associated with dilated cardiomyopathy. *Hum Mutat* **26**: 566–574.
- Tazir M, Azzedine H, Assami S, Sindou P, Nouioua S, Zemmouri R, Hamadouche T, Chaouch M, Feingold J, Vallat JM, et al. 2004. Phenotypic variability in autosomal recessive axonal Charcot-Marie-Tooth disease due to the R298C mutation in lamin A/C. *Brain* **127**: 154–163.
- Toth JI, Yang SH, Qiao X, Beigneux AP, Gelb MH, Moulson CL, Miner JH, Young SG, Fong LG. 2005. Blocking protein farnesyl transferase improves nuclear shape in fibroblasts from humans with progeroid syndromes. *Proc Natl Acad Sci* **102**: 12873–12878.
- Towbin JA, Bowles NE. 2002. The failing heart. *Nature* **415**: 227–233.
- Tullio-Pelet A, Salomon R, Hadj-Rabia S, Mugnier C, de Laet MH, Chaouachi B, Bakiri F, Brottier P, Cattolico L, Penet C, et al. 2000. Mutant WD-repeat protein in triple-A syndrome. *Nat Genet* **26**: 332–335.
- van Berlo JH, de Voogt WG, van der Kooij AJ, van Tintelen JP, Bonne G, Yaou RB, Duboc D, Rossenbacker T, Heidebüchel H, de Visser M, et al. 2005. Meta-analysis of clinical characteristics of 299 carriers of LMNA gene mutations: Do lamin A/C mutations portend a high risk of sudden death? *J Mol Med* **83**: 79–83.
- van Tintelen JP, Hofstra RM, Katerberg H, Rossenbacker T, Wiesfeld AC, du Marchie Sarvaas GJ, Wilde AA, van Langen IM, Nannenberg EA, van der Kooij AJ, et al. 2007. High yield of LMNA mutations in patients with dilated cardiomyopathy and/or conduction disease referred to cardiogenetics outpatient clinics. *Am Heart J* **154**: 1130–1139.
- Varela I, Pereira S, Ugalde AP, Navarro CL, Suárez ME, Cau P, Cadiñanos J, Osorio FG, Foray N, Cobo J, et al. 2008. Combined treatment with statins and aminobisphosphonates extends longevity in a mouse model of human premature aging. *Nat Med* **14**: 767–772.
- Verstraeten VL, Broers JLV, Steensel MAM, Zinn-Justin S, Ramaekers FCS, Steijlen PM, Kamps M, Kuipers HJH, Merckx D, Smeets HJM, et al. 2006. Compound heterozygosity for mutations in LMNA causes a progeria syndrome without prelamin A accumulation. *Hum Mol Genet* **15**: 2509–2522.
- Verstraeten VL, Ji JY, Cummings KS, Lee RT, Lammerding J. 2008. Increased mechanosensitivity and nuclear stiffness in Hutchinson-Gilford progeria cells: Effects of farnesyltransferase inhibitors. *Aging Cell* **7**: 383–393.
- Vigouroux C, Capeau J. 2005. A-type lamin-linked lipodystrophies. *Novartis Found Symp* **264**: 166–177.
- Vigouroux C, Magré J, Vantghem MC, Bourut C, Lascols O, Shackleton S, Lloyd DJ, Guerci B, Padova G, Valensi P, et al. 2000. Lamin A/C gene: Sex-determined expression of mutations in Dunnigan-type familial partial lipodystrophy and absence of coding mutations in congenital and acquired generalized lipodystrophy. *Diabetes* **49**: 1958–1962.
- Wang Y, Herron AJ, Worman HJ. 2006. Pathology and nuclear abnormalities in hearts of transgenic mice expressing M371K lamin A encoded by an LMNA mutation causing Emery-Dreifuss muscular dystrophy. *Hum Mol Genet* **15**: 2479–2489.
- Wang Y, Panteleyev AA, Owens DM, Djabali K, Stewart CL, Worman HJ. 2008. Epidermal expression of the truncated prelamin A causing Hutchinson-Gilford progeria syndrome: Effects on keratinocytes, hair and skin. *Hum Mol Genet* **17**: 2357–2369.

- Waterham HR, Koster J, Mooyer P, Noort Gv G, Kelley RI, Wilcox WR, Wanders RJ, Hennekam RC, Oosterwijk JC. 2003. Autosomal recessive HEM/Greenberg skeletal dysplasia is caused by 3 β -hydroxysterol δ 14-reductase deficiency due to mutations in the lamin B receptor gene. *Am J Hum Genet* **72**: 1013–1017.
- Weber K, Plessmann U, Traub P. 1989. Maturation of nuclear lamin A involves a specific carboxy-terminal trimming, which removes the polyisoprenylation site from the precursor; implications for the structure of the nuclear lamina. *FEBS Lett* **257**: 411–414.
- Wegner L, Andersen G, Sparso T, Grarup N, Glümer C, Borch-Johnsen K, Jørgensen T, Hansen T, Pedersen O. 2007. Common variation in LMNA increases susceptibility to type 2 diabetes and associates with elevated fasting glycemia and estimates of body fat and height in the general population: Studies of 7,495 Danish whites. *Diabetes* **56**: 694–698.
- Wolf CM, Wang L, Alcalai R, Pizard A, Burgon PG, Ahmad F, Sherwood M, Branco DM, Wakimoto H, Fishman GI, et al. 2008. Lamin A/C haploinsufficiency causes dilated cardiomyopathy and apoptosis-triggered cardiac conduction system disease. *J Mol Cell Cardiol* **44**: 293–303.
- Worman HJ, Evans CD, Blobel G. 1990. The lamin B receptor of the nuclear envelope inner membrane: A polytopic protein with eight potential transmembrane domains. *J Cell Biol* **111**: 1535–1542.
- Worman HJ, Yuan J, Blobel G, Georgatos SD. 1988. A lamin B receptor in the nuclear envelope. *Proc Natl Acad Sci* **85**: 8531–8534.
- Wydner KL, McNeil JA, Lin F, Worman HJ, Lawrence JB. 1996. Chromosomal assignment of human nuclear envelope protein genes LMNA, LMNB1, and LBR by fluorescence in situ hybridization. *Genomics* **32**: 474–478.
- Yang SH, Andres DA, Spielmann HP, Young SG, Fong LG. 2008. Progerin elicits disease phenotypes of progeria in mice whether or not it is farnesylated. *J Clin Invest* **118**: 3291–3300.
- Yang SH, Bergo MO, Toth JL, Qiao X, Hu Y, Sandoval S, Meta M, Bendale P, Gelb MH, Young SG, et al. 2005. Blocking protein farnesyltransferase improves nuclear blebbing in mouse fibroblasts with a targeted Hutchinson–Gilford progeria syndrome mutation. *Proc Natl Acad Sci* **102**: 10291–10296.
- Yang SH, Meta M, Qiao X, Frost D, Bauch J, Coffinier C, Majumdar S, Bergo MO, Young SG, Fong LG. 2006. A farnesyltransferase inhibitor improves disease phenotypes in mice with a Hutchinson–Gilford progeria syndrome mutation. *J Clin Invest* **116**: 2115–2121.
- Ye Q, Worman HJ. 1994. Primary structure analysis and lamin B and DNA binding of human LBR, an integral protein of the nuclear envelope inner membrane. *J Biol Chem* **269**: 11306–11311.
- Ye Q, Worman HJ. 1996. Interaction between an integral protein of the nuclear envelope inner membrane and human chromodomain proteins homologous to *Drosophila* HP1. *J Biol Chem* **271**: 14653–14656.
- Young SG, Fong LG, Michaelis S. 2005. Prelamin A, Zmpste24, misshapen cell nuclei, and progeria—New evidence suggesting that protein farnesylation could be important for disease pathogenesis. *J Lipid Res* **46**: 2531–2558.
- Zhang FL, Casey PJ. 1996. Protein prenylation: Molecular mechanisms and functional consequences. *Annu Rev Biochem* **65**: 241–269.
- Zhang X, Chen S, Yoo S, Chakrabarti S, Zhang T, Ke T, Oberti C, Yong SL, Fang F, Li L, et al. 2008. Mutation in nuclear pore component NUP155 leads to atrial fibrillation and early sudden cardiac death. *Cell* **135**: 1017–1027.

Cold Spring Harbor Perspectives in Biology

Diseases of the Nuclear Envelope

Howard J. Worman, Cecilia Östlund and Yuexia Wang

Cold Spring Harb Perspect Biol 2010; doi: 10.1101/cshperspect.a000760

Subject Collection [The Nucleus](#)

Nuclear Compartments: An Incomplete Primer to Nuclear Compartments, Bodies, and Genome Organization Relative to Nuclear Architecture

Andrew S. Belmont

Uncovering the Principles of Genome Folding by 3D Chromatin Modeling

Asli Yildirim, Lorenzo Boninsegni, Yuxiang Zhan, et al.

3D or Not 3D: Shaping the Genome during Development

Juliane Glaser and Stefan Mundlos

The Impact of Space and Time on the Functional Output of the Genome

Marcelo Nollmann, Isma Bennabi, Markus Götz, et al.

Chromatin Mechanisms Driving Cancer

Berkley Gryder, Peter C. Scacheri, Thomas Ried, et al.

Liquid–Liquid Phase Separation in Chromatin

Karsten Rippe

Mechanical Forces in Nuclear Organization

Yekaterina A. Miroshnikova and Sara A. Wickström

Imaging Organization of RNA Processing within the Nucleus

Jeetayu Biswas, Weihai Li, Robert H. Singer, et al.

Mechanisms of Chromosome Folding and Nuclear Organization: Their Interplay and Open Questions

Leonid Mirny and Job Dekker

Epigenetic Reprogramming in Early Animal Development

Zhenhai Du, Ke Zhang and Wei Xie

Essential Roles for RNA in Shaping Nuclear Organization

Sofia A. Quinodoz and Mitchell Guttman

The Molecular and Nuclear Dynamics of X-Chromosome Inactivation

François Dossin and Edith Heard

Structure, Maintenance, and Regulation of Nuclear Pore Complexes: The Gatekeepers of the Eukaryotic Genome

Marcela Raices and Maximiliano A. D'Angelo

The Nuclear Lamina

Xianrong Wong, Ashley J. Melendez-Perez and Karen L. Reddy

The Nuclear Pore Complex as a Transcription Regulator

Michael Chas Sumner and Jason Brickner

Physical Nature of Chromatin in the Nucleus

Kazuhiro Maeshima, Shiori Iida and Sachiko Tamura

For additional articles in this collection, see <http://cshperspectives.cshlp.org/cgi/collection/>

**All Modifications and
Oligo Types Synthesized**

Long Oligos • Fluorescent • Chimeric • DNA • RNA • Antisense

Oligo Modifications?
Your wish is our command.

For additional articles in this collection, see <http://cshperspectives.cshlp.org/cgi/collection/>

**All Modifications and
Oligo Types Synthesized**

Oligo Modifications?
Your wish is our command.

Long Oligos • Fluorescent • Chimeric • DNA • RNA • Antisense