HHS Public Access

Author manuscript

Annu Rev Pathol. Author manuscript; available in PMC 2023 January 24.

Published in final edited form as:

Annu Rev Pathol. 2022 January 24; 17: 159–180. doi:10.1146/annurev-pathol-042220-034240.

Molecular Pathology of Laminopathies

Ji-Yeon Shin, **Howard J. Worman**

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

Abstract

The nuclear envelope is composed of the nuclear membranes, nuclear lamina, and nuclear pore complexes. Laminopathies are diseases caused by mutations in genes encoding protein components of the lamina and these other nuclear envelope substructures. Mutations in the single gene encoding lamin A and C, which are expressed in most differentiated somatic cells, cause diseases affecting striated muscle, adipose tissue, peripheral nerve, and multiple systems with features of accelerated aging. Mutations in genes encoding other nuclear envelope proteins also cause an array of diseases that selectively affect different tissues or organs. In some instances, the molecular and cellular consequences of laminopathy-causing mutations are known. However, even when these are understood, mechanisms explaining specific tissue or organ pathology remain enigmatic. Current mechanistic hypotheses focus on how alterations in the nuclear envelope may affect gene expression, including via the regulation of signaling pathways, or cellular mechanics, including responses to mechanical stress.

Keywords

cardiomyopathy; emerin; lamin; nuclear envelope; progeria

INTRODUCTION

In 1994, Daniela Toniolo and colleagues (1) reported that mutations in a novel gene caused X-linked Emery-Dreifuss muscular dystrophy. Two years later, the encoded transmembrane protein named emerin after Alan Emery was localized to the nuclear envelope, presumably the inner nuclear membrane (2, 3). In 1999, Ketty Schwartz and colleagues (4) reported that mutations in *LMNA* encoding lamin A and lamin C (lamin A/C), peripheral proteins of the inner nuclear membrane, cause the phenotypically identical autosomal dominant Emery-Dreifuss muscular dystrophy. Soon after, mutations in *LMNA* were reported to cause Dunnigan-type familial partial lipodystrophy (5-7), mandibuloacral dysplasia type A (8), an axonal peripheral neuropathy (9), and Hutchinson-Gilford progeria syndrome (HGPS) (10, 11). These initial studies led to the identification of a group of diseases caused by mutations

js3444@columbia.edu .

DISCLOSURE STATEMENT

J.Y.S. is a recipient of research funding (to Columbia University) from Gilead Sciences and Sarepta Therapeutics. H.J.W. serves on the scientific advisory board of and has an equity interest in AlloMek Therapeutics, has received consulting income from Eiger BioPharmaceuticals, and has received sponsored research funding (to Columbia University) from Navitor Pharmaceuticals and Sarepta Therapeutics.

in genes encoding proteins of the nuclear envelope, which are now often referred to as nuclear envelopathies or, more often, laminopathies.

In the past two decades, additional laminopathies have been described. Investigators have also provided better descriptions of the genetics, clinical phenotypes, and pathology. The development of cellular and animal models has led to a better understanding of nuclear envelope protein functions and how their dysfunction may relate to tissue-specific pathology. However, deciphering mechanisms of how these disorders affect specific tissues, especially when the mutant genes and encoded proteins are widely expressed, has remained elusive. This review covers up-to-date aspects of the molecular pathology of the laminopathies, summarizing what we know and pointing out gaps in our understanding of this group of diseases.

THE NUCLEAR ENVELOPE

The nuclear envelope separates the nucleoplasm from the cytoplasm in eukaryotic cells. It consists of the nuclear membranes, nuclear pore complexes (NPCs), and nuclear lamina (Figure 1). The nuclear membranes are separated into three morphologically distinct domains: inner, outer, and pore. The outer nuclear membrane is contiguous with the endoplasmic reticulum and similarly contains ribosomes on its outer surface. It is separated from the inner nuclear membrane by the perinuclear space, a continuation of the endoplasmic reticulum lumen. The nuclear lamina, a meshwork on intermediate filament proteins called lamins, which form noncanonical 3.5-nm-diameter filaments, lines the nucleoplasmic side of the inner nuclear membrane (12). The pore membranes connect the inner and outer nuclear membranes where NPCs are located. The pore complexes are megadalton structures that mediate active and passive transport of substances between the nucleus and the cytoplasm (13).

A unique collection of transmembrane proteins concentrate in the inner nuclear membrane, along with a few in the pore and outer nuclear membrane of interphase cells (Figure 2). An initial subtractive proteomics analysis study of extracts of rodent livers identified approximately 80 integral inner nuclear membrane proteins (14). After synthesis on membrane-bound ribosomes, transmembrane proteins most likely concentrate in the inner nuclear membrane as a result of retention by binding to lamins or chromatin after lateral diffusion through the interconnected endoplasmic reticulum and nuclear membranes (15). The pore membrane contains a small number of transmembrane nucleoporins that anchor the pore complexes (13). The outer nuclear membrane generally shares transmembrane proteins with the endoplasmic reticulum but contains uniquely localized KASH domain proteins, termed nesprins in mammals. The KASH domains of nesprins interact within the perinuclear space with the luminal domains of integral inner nuclear membrane SUN proteins, forming the linker of nucleoskeleton and cytoskeleton (LINC) complex (16, 17). SUN proteins bind to lamins. The cytoplasmic domains of different nesprins interact directly or indirectly with actin, microtubule, and intermediate filaments. These connections provide a nucleocytoskeletal network mediating proper positioning of the nucleus within the cell and the transduction of force from the cytoplasm to the nucleus (18).

Most nuclear envelope proteins appear to be expressed ubiquitously in most different cell types. For example, lamin A/C is present in most terminally differentiated somatic cells (19). However, there are differences in the nuclear envelope proteome of different cells and tissues (20). This topic has been relatively poorly studied but is likely important in understanding the generation of different cellular mechanics, cell cycle regulation, signaling, gene expression, and genome organization that may underlie the tissue-specific nature of most laminopathies.

LAMINOPATHIES

Mutations in *LMNA* Cause Four Major Types of Pathology

LMNA on chromosome 1q21.2-q21.3 encodes the A-type lamins lamin A, which is posttranslationally processed from a precursor protein, prelamin A, and lamin C (21, 22). Prelamin A and lamin C are identical for the first 566 amino acids. As a result of alternative splicing of RNA in the region encoded by exon 10, lamin C has six unique carboxyl-terminal amino acids and prelamin A 98.

Prelamin A contains a cysteine-aliphatic-aliphatic-any amino acid (CAAX) motif at its carboxyl terminus that triggers a series of processing reactions to generate lamin A (23). First, protein farnesyltransferase catalyzes the addition of a farnesyl moiety to the cysteine. Second, either Ras converting CAAX endopeptidase 1 or zinc metallopeptidase, STE24 homolog (ZMPSTE24) catalyzes the endoproteolytic cleavage of the -AAX. Third, isoprenylcysteine carboxyl methyltransferase catalyzes methylation of the farnesylcysteine. Finally, ZMPSTE24 recognizes the farnesylated protein and catalyzes an endoproteolytic cleavage leading to the removal of the last 15 amino acids, including the farnesylcysteine α-methyl ester.

Mutations in *LMNA* cause four major types of pathology involving (*a*) multiple systems with features of accelerated aging (progeroid disorders), (*b*) striated muscle, (*c*) adipose tissue, and (*d*) peripheral nerve (Table 1). Within each major pathology type, there are specific disorders that were described on the basis of clinical phenotypes before the genetics were elucidated, with overlap between them. However, while the major pathology types may share some features, they are clearly distinct.

Progeroid Disorders

The multisystem diseases with features of accelerated aging can be divided into processing-deficient and processing-proficient progeroid laminopathies (24). In the first group, mutations in *LMNA* lead to defective prelamin A processing and accumulation of farnesylated variants. Similarly, mutations in *ZMPSTE24* can lead to defective prelamin A processing, prelamin A accumulation, and progeroid syndromes. In the processing-proficient disorders, *LMNA* mutations generate amino acid substitutions in lamin A/C, but prelamin A is normally processed.

The most common albeit still ultrarare progeroid disorder caused by defective prelamin A processing is HGPS. Children with HGPS have, among other symptoms, growth impairment, sclerotic skin, micrognathia, decreased subcutaneous fat, alopecia, prominent

cutaneous vasculature, fingertip tufting, and decreased bone density; they generally die in their teens from complications of occlusive cardiovascular or cerebrovascular disease (25). A dominant de novo c.1824C>T (Gly608Gly) mutation activates a cryptic splice leading to an in-frame deletion of 150 base pairs in pre-mRNA encoding prelamin A (10, 11). As a result, an internally truncated prelamin A variant, called progerin, accumulates. Progerin lacks 50 amino acids, including the second ZMPSTE24 recognition site, and hence retains a farnesylated, carboxymethylated cysteine at its carboxyl terminus (Figure 3).

Other *LMNA* mutations can also lead to accumulation of progerin and cause phenotypes more or less severe than HGPS roughly in proportion to the amount of progerin expressed (24). An *LMNA* mutation leading to expression of a farnesylated prelamin A variant with an internal deletion of only 35 amino acids causes a progeroid disorder less severe than HGPS (24). One study also reported a patient with a de novo *LMNA* c.1940C>T transversion that resulted in a Leu to Arg amino acid substitution at residue 647, abolishing the ZMPSTE24 cleavage site; she accumulated full-length prelamin A with a single amino acid change and suffers from a relatively mild progeroid disorder (26).

Progeroid disorders also arise from loss-of-function mutations in *ZMPSTE24*. Severity of disease correlates with residual activity of the prelamin A processing protease (27). Total loss of function causes the neonatal lethal progeroid disorder restrictive dermopathy. Homozygous or compound heterozygous partial loss-of-function mutations cause mandibuloacral dysplasia type B or clinically similar progeroid disorders. In these patients, full-length farnesylated prelamin A accumulates to varying extents. The most prominent clinical features in these patients are hypoplasia of the mandible and clavicles, acro-osteolysis, and lipodystrophy. The patient with an *LMNA* point mutation that abolished the ZMPSTE24 recognition site had very similar clinical features (26).

Considerable evidence indicates that farnesylated prelamin A and its farnesylated variants are responsible for pathology in HGPS and the other processing-deficient progeroid laminopathies. Cultured cells from patients with these disorders and genetically modified mouse models have abnormal nuclear morphology with blebbing of the nuclear envelope (28-34). Treatment of these cultured cells, as well as transfected cells expressing progerin, with protein farnesyltransferase inhibitors or a statin plus an aminobisphosphonate that reduce protein prenylation restores normal nuclear shape (31-36). More significantly, Fong et al. (37) originally showed that treatment of *Zmpste24* null mice with a protein farnesyltransferase inhibitor reversed profound progeroid phenotypes and prolonged survival. Since then, several other studies have confirmed the beneficial effects of blocking protein farnesylation in mouse models of HGPS and in mice with ZMPSTE24 deficiency (38-40). Human clinical trials have also shown beneficial effects of the farnesyltransferase inhibitor lonafarnib in children with HGPS (41, 42). In 2020, the United States Food and Drug Administration approved lonafarnib for the treatment of HGPS and other processing-deficient progeroid laminopathies (42).

While the accumulation of prelamin A or variants, not loss of lamin A function, is clearly responsible for the molecular pathology in processing-deficient progeroid laminopathies, the downstream mechanistic defects these farnesylated proteins induce are less well understood.

Fibroblasts from patients with HGPS have decreased viability and increased apoptosis under repetitive mechanical strain, suggesting that accumulation of progerin may lead to the death of certain cells exposed to stress (43). Unprocessed prelamin A and progerin also perturb DNA damage repair responses, resulting in genomic instability (44). Progerin induces DNA replication fork stalling and nuclease-mediated fork degradation, causing replication stress and genomic instability, which are accompanied by upregulation of the cGAS/STING pathway and activation of an interferon-like innate immune response (45). Progerin and farnesylated prelamin A may also bind to and directly modulate the functions of proteins involved in DNA repair or other nuclear processes. For example, in induced pluripotent stem cells from patients with HGPS, progerin binds to DNA-dependent protein kinase catalytic subunit, which is known to be involved in DNA repair and various aging-related cellular events (46). Despite intensive investigation, exactly how and to what extent these or other pathogenic mechanisms may contribute to cellular dysfunction in processing-deficient progeroid laminopathies remain to be firmly established.

Point mutations in *LMNA* that do not cause farnesylated prelamin A or variant accumulation can also cause progeroid disorders. Mandibuloacral dysplasia type A is caused by a homozygous arginine-to-histidine amino acid substitution at residue 527 (8). These patients have similar symptoms to those with *ZMPSTE24* partial loss-of-function mutations. Dominant *LMNA* mutations have also been described in patients diagnosed with atypical Werner syndrome (47). Several other homozygous, heterozygous, and compound heterozygous *LMNA* mutations leading to amino acid substitutions have further been linked to progeroid disorders (24). The dominant amino acid substitutions tend to cluster in structured regions of lamin A/C, including the rod domains conserved among intermediate filament proteins and an immunoglobulin-like fold domain in the tail domain. The heterozygous amino acid substitutions mostly cluster in a portion of the immunoglobulin-like fold domain and disrupt the interaction of lamin A/C with barrier-to-autointegration factor (48). A homozygous point mutation in the gene encoding barrier-to-autointegration factor also causes a progeroid disorder, and the resulting amino acid substitution disrupts binding to lamin A/C (49). Barrier-to-autointegration factor was originally discovered as a host protein that prevents a DNA copy of a retroviral genome from integrating into itself. It was subsequently found to be involved in processes that protect genome integrity such as nuclear envelope reformation at the end of mitosis, repair of ruptured envelopes, and the DNA damage response (50). Disruption of barrier-to-autointegration factor binding to lamin A may alter its normal function. Hence, as in processing-deficient laminopathies, genomic instability may be a downstream cellular defect in processing-proficient laminopathies.

Striated Muscle Disease

The first identified pathogenic mutations in *LMNA* segregated in affected family members with autosomal dominant Emery-Dreifuss muscular dystrophy (4). The clinical diagnosis of Emery-Dreifuss muscular dystrophy is based on distinctive features of early joint contractures, humeroperoneal wasting, and weakness and cardiomyopathy with early conduction defects (51). Subsequent studies showed that *LMNA* mutations cause dilated cardiomyopathy with other muscle groups affected, such as limb-girdle muscular dystrophy, or even minimal to no skeletal muscle pathology (52-56). In most of these disorders, the

age of onset is usually in later childhood or early adulthood, but *LMNA* mutations also sometimes cause congenital muscular dystrophy that presents in the first year of life with the eventual development of cardiomyopathy (57).

Dominant *LMNA* mutations that cause striated muscle disease lead to single amino acid substitutions, small deletions, RNA splicing defects, or haploinsufficiency. Extremely rare heterozygous mutations have been described (55, 58). Striated muscle disease-causing *LMNA* mutations likely lead to loss of some aspect of lamin A/C function, as demonstrated in *Lmna* null mice (59). Fibroblasts from these mice, as well as from patients with *LMNA* mutations and striated muscle disease, have altered nuclear morphology (59, 60). Mouse fibroblasts lacking lamin A/C have increased nuclear deformation, defective mechanotransduction, and impaired viability under mechanical strain (61). These fibroblasts as well as transfected cells expressing lamin A variants that cause muscle disease also have defective movement of the nucleus when polarizing for migration (62). Cryoelectron tomography analysis of mouse fibroblasts homozygous for an *Lmna* point mutation that causes striated muscle disease shows apparently unaltered organization of the lamin filaments but increased nuclear surface area, reduced heterochromatin, and increased lamin B1 and B2 expression (63).

Loss of lamin A/C leads to mislocalization of the integral inner nuclear membrane protein emerin to the bulk endoplasmic reticulum (59). Expression of some muscle disease–associated point mutant lamin A variants also leads to a partial mislocalization of emerin (64, 65). Emerin and lamin A/C directly interact (66). Mutations in the gene encoding emerin cause phenotypically near-identical disease to the striated muscle disease caused by *LMNA* mutations (1). Both lamin A/C and emerin interact with lamina-associated polypeptide (LAP) 1, another transmembrane protein of the inner nuclear membrane (67). Mutations in the gene encoding LAP1 also cause muscular dystrophy and cardiomyopathy in humans, and deletion of the protein from mouse skeletal and cardiac muscle, respectively, causes these phenotypes (67-69). These findings suggest that a complex of lamin A/C, emerin, and LAP1 has a critical role in striated muscle maintenance.

Adipose Tissue Disease

In 1974, Dunnigan and colleagues (70) described a dominantly inherited form of partial lipodystrophy with loss of subcutaneous fat from the limbs and trunk at around the onset of puberty. About 25 years later, three groups reported mutations in *LMNA* in individuals with so-called Dunnigan-type familial partial lipodystrophy (5-7). Subsequent to the peripheral fat loss, patients develop insulin resistance, diabetes mellitus, hypertriglyceridemia, and associated complications such as hepatic steatosis and steatohepatitis (5-7, 71, 72). *LMNA* mutations can also cause atypical lipodystrophic syndromes different from the Dunnigan-type (73).

About 90% of the mutations causing Dunnigan-type patient lipodystrophy are located in *LMNA* exon 8. These mutations create amino acid substitutions that lead to a diminution of the conserved positively charged character of a solvent-exposed surface in the lamin A/C immunoglobulin-like fold domain (74, 75). In contrast, amino acid substitutions in the same region that cause striated muscle disease disrupt the overall structure of

the immunoglobulin-like fold domain (Figure 4). This suggests that *LMNA* mutations causing partial lipodystrophy destroy a positively charged interaction site for a lamin A/C binding partner important in adipocyte function. This portion of lamin A/C binds to the transcription factor sterol response element binding protein 1, and some data suggest that its transcriptional activity is altered by a lipodystrophy-causing lamin A variant (76, 77). Overexpression of lamin A in preadipocytes inhibits lipid accumulation, triglyceride synthesis, and expression of adipogenic markers, whereas embryonic fibroblasts lacking lamin A/C accumulate more intracellular lipid (78).

Peripheral Neuropathy

An *LMNA* mutation generating an arginine-to-cysteine amino acid substitution at position 298 in the rod domain of lamin A/C causes autosomal recessive peripheral neuropathy (9). Individuals with this Charcot-Marie-Tooth disease type 2B1 suffer from an axonal neuropathy with variability in the age of onset and the course of the disease (79). Sciatic nerves of *Lmna* null mice have a reduction of axon density, axonal enlargement, and nonmyelinated axons similar to phenotypes of human peripheral axonal neuropathies (9). However, mice homozygous for the corresponding human point mutation affecting residue 298 do not develop a detectable peripheral neuropathy phenotype (80).

Mutations in Genes Encoding B-Type Lamins

B-type lamins are encoded by two independent genes in humans, *LMNB1* and *LMNB2*. Lamin B1 and lamin B2 are expressed in nearly every cell type from early stages of development. Deficiency in lamin B1 or lamin B2 in mice leads to defects in neuronal migration and layering within the cerebral cortex and cerebellum, indicating the crucial roles of these lamins in the developing brain (81, 82). Consistent with these phenotypes in knockout mice, de novo mutations in *LMNB1* have been identified in seven individuals with primary microcephaly (83). Another study reported that mutations in *LMNB1* and *LMNB2* cause syndromic microcephaly (84). Padiath et al. (85) reported that duplications of *LMNB1* cause autosomal dominant leukodystrophy, an adult-onset demyelinating disorder. Overexpression of lamin B1 in BAC transgenic mice results in aberrant myelin formation, axonal degeneration, demyelination, and cognitive and motor defects (86). B-type lamins, although widely expressed, appear to have special functions in the central nervous system.

LAMINOPATHIES INVOLVING ENVELOPE PROTEINS OTHER THAN LAMINS OR ZMPSTE24

Mutations in genes encoding nuclear envelope proteins other than lamins or the prelamin A processing enzyme ZMPSTE24 also cause rare inherited diseases (Table 2). Several of these mimic the cardiac and skeletal muscle diseases caused by *LMNA* mutations. Others affect bone or multiple organ systems.

Emerin

As discussed above, mutations in *EMD* encoding emerin, which interacts with lamin A/C and LAP1, cause X-linked Emery-Dreifuss muscular dystrophy (1). Virtually all these

mutations cause a loss of emerin expression (2, 3, 87, 88). The clinical symptoms of X-linked Emery-Dreifuss muscular dystrophy are almost identical to those of the autosomal form caused by *LMNA* mutations. As with *LMNA* mutations that cause striated muscle disease, dilated cardiomyopathy with skeletal muscle involvement different than classical Emery-Dreifuss can occur with loss of emerin (89, 90). Deletion of emerin, deletion of lamin A/C, and cardiomyopathy-causing *LMNA* mutations lead to some of the same cell signaling defects, such as ERK1/2 activation (91-93).

Two independent laboratories generated emerin knockout mouse lines. Unlike human patients, these emerin-deficient mice display minimal to no muscular dystrophy or cardiomyopathy phenotypes (94, 95). However, there is a significant excess of LAP1 relative to emerin in mouse skeletal muscle compared with that of human. In mice, loss of LAP1 from skeletal muscle causes pathology, and combined deletion of emerin significantly exacerbates it (67). This suggests that LAP1, which binds to emerin, may compensate for its depletion from mouse striated muscle.

MAN1

MAN1 was originally identified by autoantibodies from a patient with a collagen vascular disease as a nuclear envelope protein that cofractionated with nuclear lamins (96, 97). It has two transmembrane segments with nucleoplasmic amino- and carboxyl-terminal domains. The amino-terminal region contains a LAP2-emerin-MAN1 (LEM) domain, a globular module for approximately 40 amino acids common to several inner nuclear membrane proteins. A genome-wide linkage analysis identified heterozygous loss-of-function mutations in *LEMD3* encoding MAN1 in families with osteopoikilosis, nonsporadic melorheostosis, and Buschke-Ollendorff syndrome, disorders of excessive bone growth sometimes with skin abnormalities (98). Experiments in cultured cells and knockout mice clearly showed that MAN1 antagonizes bone morphogenic protein and transforming growth factor-β signaling by binding to Smad2 and Smad3 (98-102). Subsequent research determined the structural basis of MAN1 binding to Smad2, Smad3, and their inactivating phosphatase PPM1A (103). Hence, MAN1 provides an inner nuclear membrane-localized scaffold for inhibiting Smad2/Smad3-mediated signaling. This inhibitory mechanism is apparently most prominent in bone and to some extent skin cells, given the phenotypes of patients with loss-of-function mutations.

LBR

LBR is a polytopic integral protein of the inner nuclear membrane that interacts with B-type lamins and heterochromatin proteins (104-106). It is also homologous to sterol reductases of the endoplasmic reticulum (107). Hoffmann et al. (108) identified that heterozygous mutations in the *LBR* gene cause the benign Pelger-Huet anomaly, characterized by hypolobulation and altered chromatin structure of neutrophil nuclei. Subsequently, Waterham et al. (109) identified a homozygous *LBR* truncation mutation in patients with Greenberg dysplasia, a perinatal lethal syndrome that affects bone and other organ systems. A later study of three fetuses with Greenberg dysplasia identified mutations in *LBR* that resulted in the loss of sterol reductase activity (110). Tsai et al. (111) reported that disease-causing *LBR* mutations perturb LBR's ability to engage

in cholesterol synthesis, with some mutations possibly leading to defective binding of a cofactor necessary for enzymatic activity and others causing degradation. Ichthyosis mice carry a spontaneous mutation in *Lbr* and have multiple abnormalities, including alopecia, syndactyly, hydrocephalus, and neutrophil nuclear morphology similar to human Pelger-Huet anomaly (112). Mice with an *Lbr* gene trap mutation are phenotypically similar to ichthyosis mice (113).

LUMA

LUMA is an integral protein of the inner nuclear membrane that contains four transmembrane segments and is expressed in all or most cell types (114). A positional cloning study of 15 families with arrhythmogenic right ventricular dysplasia identified heterozygosity for a serine-to-leucine missense mutation at codon 358 in *TMEM43* encoding LUMA (115). Germline *Tmem43* null mice and knock-in mice with the pathogenic serine-to-leucine amino acid substitution in LUMA have normal cardiac function (116). However, transgenic mice overexpressing a human pathogenic LUMA variant in cardiomyocytes die at young ages and recapitulate aspects of the human disease, including cardiomyocyte death and severe fibrofatty replacement (117).

LAP1

LAP1, encoded by *TOR1AIP1*, was originally identified in rat liver extracts as an integral membrane protein of the inner nuclear membrane associated with the nuclear lamina (118). Further investigation showed that it binds to lamin A/C and lamin B1 (119). There are at least two isoforms expressed from *TOR1AIP1* in humans (120). LAP1 has a nucleoplasmic amino-terminal domain, a single transmembrane segment, and a carboxyl-terminal domain in the perinuclear space (121). Within the perinuclear space, LAP1 interacts with and is necessary to activate the AAA+ ATPase torsinA (122-124). In addition to binding to nuclear lamins, LAP1 interacts with emerin in the nucleoplasm (67). In mice, it is essential for postnatal skeletal muscle development and maintenance and proper cardiac function (67, 68, 125). Recessive mutations in *TOR1AIP1* that disrupt the LAP1B isoform cause cardiomyopathy and muscular dystrophy (69). *TOR1AIP1* mutations leading to a combined loss of both LAP1 isoforms causes multisystem disease with severe progressive neurological impairment, bilateral cataracts, growth retardation, and early lethality (126).

NET25

NET25 (also called LEM2) was identified by a subtractive proteomic study and is encoded by the *LEMD2* gene (14). NET25 is structurally related to MAN1 and contains two transmembrane segments and a LEM domain in its amino-terminal region (127). It recruits ESCRT to repair ruptured interphase nuclei and to promote nuclear envelope reformation in mitosis (128, 129). NET25 is also required for proper myogenesis (130). Two collaborating research groups have identified a de novo missense *LEMD2* mutation in two individuals with progeroid facial phenotypes and neurological anomalies (131).

SUN Proteins

SUN proteins are integral inner nuclear membrane protein components of the LINC complex. Sequence variants in *SUN1* and *SUN2* have been reported in patients with muscular dystrophy and cardiomyopathy; however, segregation with disease in the affected families has not been demonstrated (132).

Nesprins

Nesprins are integral proteins localized to the outer nuclear membrane (there are also some small inner nuclear membrane–localized isoforms) that along with SUN proteins form the core LINC complex. *SYNE1* encodes nesprin-1, which has several isoforms that interact with actin and microtubules. Deletion mutations in *SYNE1* cause a recessively inherited cerebellar ataxia (133). A homozygous splice site mutation in *SYNE1* causes recessive arthrogryposis multiplex congenita, a disorder characterized by congenital joint contractures and reduced fetal movements (134).

Studies from genetically modified mice implicate nesprin-1 and nesprin-2 function in cardiac and striated muscle function (135-137). Mutations in *SYNE1* and *SYNE2* encoding these human proteins have been associated with cardiomyopathy and muscular dystrophy; however, segregation within affected family members has not been demonstrated for *SYNE1* (138-140). Horn et al. (141) identified a homozygous truncating mutation in *SYNE4* encoding nesprin-4, an outer nuclear membrane LINC complex protein expressed in the hair cells of the inner ear. They further showed that *Syne4* null mice, as well as mice lacking SUN1, have progressive hearing loss. In these mice, cochlear outer hair cells are formed but degenerate as hearing matures, while the inner hair cells remain intact. This result suggests that nucleocytoplasmic connections mediated by the LINC complex are essential for the viability of the outer hair cells.

TorsinA

A dominantly inherited in-frame *TOR1A* mutation leading to a single glutamic acid deletion in torsinA causes DYT1 dystonia (142). Wild-type torsinA is mainly localized throughout the endoplasmic reticulum, but the dystonia-causing variant is preferentially localized in the perinuclear space (143). TorsinA is an AAA+ ATPase that is inactive unless it binds to LAP1 in the perinuclear space or to LULL1 in the bulk endoplasmic reticulum (122, 123). Although the dystonia-causing glutamic acid deletion is not located in the active site of torsinA, its deletion compromises binding to LAP1/LULL1, leading to significantly diminished ATP hydrolysis activity (122, 144).

Transgenic mice overexpressing the dystonia-causing torsinA variant in neurons exhibit abnormal involuntary movement defects and have perinuclear inclusion bodies that contain ubiquitin, lamin A, and torsinA (145). Germline deletion of *Tor1a* in mice causes perinatal lethality associated with abnormal nuclear membrane morphology of neurons (146). Various conditional deletions of *Tor1a* in subsets of neurons cause dystonic movements in mice, along with selective neurodegeneration; these results demonstrate a cell-autonomous function of torsinA in neurons (147, 148). Lack of torsinA function appears to lead to neuronal defects during development, as deleting it in mouse embryos causes dystonia

but deleting it from adult mice leads to no abnormalities. Conversely, restoring torsinA in juvenile DYT1 mice rescues motor defects, but there is no benefit from torsinA repletion in adult mice (149). Depletion of torsinA or its activator LAP1 from hepatocytes surprisingly causes reduced hepatic very-low-density lipoprotein secretion and steatosis (150). However, no genome-wide association studies so far have linked genes encoding these proteins to lipid metabolism defects or fatty liver disease in humans.

Nuclear Pore Complex Proteins

NPCs are macromolecular structures composed of multiple copies of approximately 30 distinct proteins, most of which are called nucleoporins (151). NPCs mediate the passive and active transport between the nucleus and the cytoplasm, but growing evidence indicates that the NPCs have transport-independent roles including cell differentiation, cell cycle progression, gene expression, and epigenetic regulation (152). Many of these roles appear to be cell type specific, and pore complex composition may vary between cells, as mutations in genes encoding constituent proteins cause diseases involving specific organs (Table 3). A detailed discussion of these disorders is beyond the scope of this review on laminopathies; however, they have been reviewed elsewhere (153, 154).

IN SEARCH OF PATHOGENIC MECHANISMS

As we have already discussed, the molecular and cellular consequences of disease-causing mutations in several genes encoding nuclear envelope proteins are understood. For example, in HGPS, there is an accumulation of a farnesylated prelamin A that is likely responsible for abnormal cellular function. Pathogenic lamin A/C variants in Dunnigan-type partial lipodystrophy have an alteration in the surface charge of part of the proteins. However, the mechanisms of how alterations in the nuclear envelope proteins, most of which are expressed in multiple cell types, lead to pathology affecting specific tissues or organ systems remain for the most part enigmatic. In only a few cases, such as mutations in *SYNE4* causing hearing loss, can cell type–specific expression of the gene explain the organ pathology (141).

The field has to a large extent focused on two general hypotheses to attempt to explain the tissue-selective nature of most laminopathies. One hypothesis is that the nuclear envelope regulates cell-specific transcription and that alterations in its structure lead to pathogenic changes in gene expression. The second hypothesis is that defects in the nuclear envelope make cells susceptible to damage by mechanical stress; this premise has often been invoked to explain the fact that striated muscle is often affected in laminopathies. This so-called mechanical stress hypothesis has gained traction as research into the role of the LINC complex in cellular force transduction has expanded. Some investigators have combined these two hypotheses, suggesting that increased sensitivity of cells with nuclear envelope defects to mechanical stress leads to increased activation of stress-responsive signaling pathways.

The most clear-cut example of altered gene expression as a pathogenic mechanism resulting from mutations in a gene encoding a nuclear envelope protein is the case of MAN1. As discussed above, MAN1 functions as an inner nuclear membrane scaffold to

deactivate Smad2 and Smad3. Loss of this inhibitory protein leads to increased transforming growth factor-β signaling (98-103). Transforming growth factor-β is a potent stimulant of bone formation (155). Osteopoikilosis, Buschke-Ollendorff syndrome, and nonsporadic melorheostosis caused by mutations in *LEMD3* encoding MAN1 are characterized by increased bone density, a phenotype consistent with enhanced expression and repression of genes regulated by transforming growth factor-β. However, it is not entirely clear why MAN1 plays a significant role in inhibiting transforming growth factor-β signaling only in bone and in some cases skin, as other tissues are not affected by mutations leading to its partial loss of function.

For nearly four decades, investigators have hypothesized that the nuclear envelope functions in the maintenance and the alterations of the three-dimensional structure of the genome during development, differentiation, and the cell cycle (156). There are numerous reports of altered chromatin organization and gene expression driven by disease-causing alterations in nuclear lamins and other nuclear envelope proteins. However, there are no robust examples of how alterations in the nuclear envelope in a laminopathy lead to chromatin structural changes that directly influence the expression of any single gene or group of genes involved in pathogenesis. Nonetheless, the hypothesis that disease-associated defects in the nuclear envelope alter chromatin in a way that directly leads to pathogenic gene expression changes remains prevalent in the field.

Since early reports that cells lacking lamin A/C have altered mechanical properties (61), many studies have focused on the hypothesis that stress-induced cellular damage or altered responses to mechanical strain underlie pathology in laminopathies. One study has demonstrated that in HGPS, progerin expression combined with mechanical stress promotes arterial smooth muscle cell death that is reduced by disruption of the LINC complex (157). Similarly, skeletal muscle cells with disease-causing alterations in lamin A/C have reduced nuclear stability and nuclear envelope damage, both of which are reduced by disruption of the LINC complex (158). Migrating fibroblasts, neurons, and myonuclei with alterations in lamins also have increased nuclear envelope rupture, DNA damage, and cell death (158-160). Increased susceptibility of cardiomyocytes to continuous mechanical strain may also explain the increased activation of stress-induced signaling pathways such as ERK1/2 and AKT/mTOR in hearts of mice with cardiomyopathy-causing *Lmna* mutations (91, 161). Abnormal activation of these pathways has detrimental effects on heart structure and function, whereas blocking these pathways has beneficial effects (161, 162).

Space limitations for this review prohibit us from citing all of the publications on testing the mechanical stress and gene expression hypotheses. Despite all of the research addressing these two hypotheses, neither one in and of itself is entirely satisfying. Alterations in both cell stress responses and gene expression may occur simultaneously to cause pathology. Other hypotheses must be proposed and tested as well. Mutations in different laminopathy-associated genes, or even different mutations in the same gene such as *LMNA*, clearly have different consequences in different cell types. Hence, no single hypothesis will likely explain all of the diverse laminopathies.

A major limitation of much of the research to date has been that data obtained in cell culture models, often fibroblasts from affected patients or transfected cells, cannot always be readily applicable to what is observed in affected tissues and organs. Nonetheless, studies in model cell systems are essential, as it is difficult to assess the effects of mechanical stress or certain other insults on intact organs. Measured gene expression alterations in animal or patient tissues also may not reflect the direct effect of a laminopathy-causing gene mutation but rather may indicate secondary consequences, such as inflammation or fibrosis. Therefore, future research more closely combining cell culture and in vivo approaches will help move the field forward. Furthermore, physicians who care for patients with laminopathies and pathologists who can appreciate the underlying tissue and organ dysfunction must interact more with basic scientists to assure that phenomena observed in cultured cells and even small animal models are relevant to what occurs in affected humans. To accomplish this interaction, disciplinary barriers will need to be broken down, and collaborations in which recognition and grant funding are shared will need to increase. Broader interdisciplinary research may be the only approach to elucidate the mechanisms underlying the broad range of diseases caused by mutations in genes encoding proteins of a fascinating structure common to virtually all eukaryotic cells.

ACKNOWLEDGMENTS

This work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under award number R01AR048997. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

LITERATURE CITED

1. Bione S, Maestrini E, Rivella S, Mancini M, Regis S, et al. 1994. Identification of a novel X-linked gene responsible for Emery-Dreifuss muscular dystrophy. Nat. Genet 8:323–27 [PubMed: 7894480]
2. Nagano A, Koga R, Ogawa M, Kurano Y, Kawada J, et al. 1996. Emerin deficiency at the nuclear membrane in patients with Emery-Dreifuss muscular dystrophy. Nat. Genet 12:254–59 [PubMed: 8589715]
3. Manilal S, Nguyen TM, Sewry CA, Morris GE. 1996. The Emery-Dreifuss muscular dystrophy protein, emerin, is a nuclear membrane protein. Hum. Mol. Genet 5:801–8 [PubMed: 8776595]
4. Bonne G, Di Barletta MR, Varnous S, Becane HM, Hammouda EH, et al. 1999. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. Nat. Genet 21:285–88 [PubMed: 10080180]
5. Cao H, Hegele RA. 2000. Nuclear lamin A/C R482Q mutation in Canadian kindreds with Dunnigan-type familial partial lipodystrophy. Hum. Mol. Genet 9:109–12 [PubMed: 10587585]
6. Shackleton S, Lloyd DJ, Jackson SN, Evans R, Niermeijer MF, et al. 2000. LMNA, encoding lamin A/C, is mutated in partial lipodystrophy. Nat. Genet 24:153–56 [PubMed: 10655060]
7. Speckman RA, Garg A, Du F, Bennett L, Veile R, et al. 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 66:1192–98 [PubMed: 10739751]
8. Novelli G, Muchir A, Sangiuolo F, Helbling-Leclerc A, D'Apice MR, et al. 2002. Mandibuloacral dysplasia is caused by a mutation in LMNA-encoding lamin A/C. Am. J. Hum. Genet 71:426–31 [PubMed: 12075506]
9. De Sandre-Giovannoli A, Chaouch M, Kozlov S, Vallat J-M, Tazir M, 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 70:726–36 [PubMed: 11799477]

10. De Sandre-Giovannoli A, Bernard R, Cau P, Navarro C, Amiel J, et al. 2003. Lamin A truncation in Hutchinson-Gilford progeria. Science 300:2055 [PubMed: 12702809]
11. Eriksson M, Brown WT, Gordon LB, Glynn MW, Singer J, et al. 2003. Recurrent de novo point mutations in lamin A cause Hutchinson–Gilford progeria syndrome. Nature 423:293–98 [PubMed: 12714972]
12. Turgay Y, Eibauer M, Goldman AE, Shimi T, Khayat M, et al. 2017. The molecular architecture of lamins in somatic cells. Nature 543:261–64 [PubMed: 28241138]
13. Knockenhauer KE, Schwartz TU. 2016. The nuclear pore complex as a flexible and dynamic gate. Cell 164:1162–71 [PubMed: 26967283]
14. Schirmer EC, Florens L, Guan T, Yates JR, Gerace L. 2003. Nuclear membrane proteins with potential disease links found by subtractive proteomics. Science 301:1380–82 [PubMed: 12958361]
15. Soullam B, Worman HJ. 1995. Signals and structural features involved in integral membrane protein targeting to the inner nuclear membrane. J. Cell Biol 130:15–27 [PubMed: 7790369]
16. Crisp M, Liu Q, Roux K, Rattner J, Shanahan C, et al. 2006. Coupling of the nucleus and cytoplasm: role of the LINC complex. J. Cell Biol 172:41–53 [PubMed: 16380439]
17. Sosa BA, Rothballer A, Kutay U, Schwartz TU. 2012. LINC complexes form by binding of three KASH peptides to domain interfaces of trimeric SUN proteins. Cell 149:1035–47 [PubMed: 22632968]
18. Gundersen GG, Worman HJ. 2013. Nuclear positioning. Cell 152:1376–89 [PubMed: 23498944]
19. Rober R-A, Weber K, Osborn M. 1989. Differential timing of nuclear lamin A/C expression in the various organs of the mouse embryo and the young animal: a developmental study. Development 105:365–78 [PubMed: 2680424]
20. Korfali N, Wilkie GS, Swanson SK, Srsen V, de Las Heras J, et al. 2012. The nuclear envelope proteome differs notably between tissues. Nucleus 3:552–64 [PubMed: 22990521]
21. Lin F, Worman HJ. 1993. Structural organization of the human gene encoding nuclear lamin A and nuclear lamin C. J. Biol. Chem 268:16321–26 [PubMed: 8344919]
22. 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 32:474–78 [PubMed: 8838815]
23. 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 46:2531–58 [PubMed: 16207929]
24. Marcelot A, Worman HJ, Zinn-Justin S. 2021. Protein structural and mechanistic basis of progeroid laminopathies. FEBS J. 288:2757–72 [PubMed: 32799420]
25. Merideth MA, Gordon LB, Clauss S, Sachdev V, Smith AC, et al. 2008. Phenotype and course of Hutchinson–Gilford progeria syndrome. N. Engl. J. Med 358:592–604 [PubMed: 18256394]
26. Wang Y, Lichter-Konecki U, Anyane-Yeboa K, Shaw JE, Lu JT, et al. 2016. A mutation abolishing the ZMPSTE24 cleavage site in prelamin A causes a progeroid disorder. J. Cell Sci 129:1975–80 [PubMed: 27034136]
27. Barrowman J, Wiley PA, Hudon-Miller SE, Hrycyna CA, Michaelis S. 2012. Human ZMPSTE24 disease mutations: Residual proteolytic activity correlates with disease severity. Hum. Mol. Genet 21:4084–93 [PubMed: 22718200]
28. Moulson CL, Go G, Gardner JM, van der Wal AC, Smitt JHS, et al. 2005. Homozygous and compound heterozygous mutations in *ZMPSTE24* cause the laminopathy restrictive dermopathy. J. Investig. Dermatol 125:913–19 [PubMed: 16297189]
29. Navarro CL, Cadinanos J, Sandre-Giovannoli AD, Bernard R, Courrier S, et al. 2005. Loss of ZMPSTE24 (FACE-1) causes autosomal recessive restrictive dermopathy and accumulation of Lamin A precursors. Hum. Mol. Genet 14:1503–13 [PubMed: 15843403]
30. Goldman RD, Shumaker DK, Erdos MR, Eriksson M, Goldman AE, et al. 2004. Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson–Gilford progeria syndrome. PNAS 101:8963–68 [PubMed: 15184648]

31. Yang SH, Bergo MO, Toth JI, Qiao X, Hu Y, et al. 2005. Blocking protein farnesyltransferase improves nuclear blebbing in mouse fibroblasts with a targeted Hutchinson–Gilford progeria syndrome mutation. PNAS 102:10291–96 [PubMed: 16014412]
32. Toth JI, Yang SH, Qiao X, Beigneux AP, Gelb MH, et al. 2005. Blocking protein farnesyltransferase improves nuclear shape in fibroblasts from humans with progeroid syndromes. PNAS 102:12873–78 [PubMed: 16129834]
33. Capell BC, Erdos MR, Madigan JP, Fiordalisi JJ, Varga R, et al. 2005. Inhibiting farnesylation of progerin prevents the characteristic nuclear blebbing of Hutchinson-Gilford progeria syndrome. PNAS 102:12879–84 [PubMed: 16129833]
34. 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 14:2959–69 [PubMed: 16126733]
35. Mallampalli MP, 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. PNAS 102:14416–21 [PubMed: 16186497]
36. Wang Y, Östlund C, Worman H. 2010. Blocking protein farnesylation improves nuclear shape abnormalities in keratinocytes of mice expressing the prelamin A variant in Hutchinson-Gilford progeria syndrome. Nucleus 1:432–39 [PubMed: 21326826]
37. Fong LG, Frost D, Meta M, Qiao X, Yang SH, et al. 2006. A protein farnesyltransferase inhibitor ameliorates disease in a mouse model of progeria. Science 311:1621–23 [PubMed: 16484451]
38. Yang SH, Meta M, Qiao X, Frost D, Bauch J, et al. 2006. A farnesyltransferase inhibitor improves disease phenotypes in mice with a Hutchinson-Gilford progeria syndrome mutation. J. Clin. Investig 116:2115–21 [PubMed: 16862216]
39. Capell BC, Olive M, Erdos MR, Cao K, Faddah DA, et al. 2008. A farnesyltransferase inhibitor prevents both the onset and late progression of cardiovascular disease in a progeria mouse model. PNAS 105:15902–7 [PubMed: 18838683]
40. Varela I, Pereira S, Ugalde AP, Navarro CL, Suárez MF, et al. 2008. Combined treatment with statins and aminobisphosphonates extends longevity in a mouse model of human premature aging. Nat. Med 14:767–72 [PubMed: 18587406]
41. Gordon LB, Kleinman ME, Miller DT, Neuberg DS, Giobbie-Hurder A, et al. 2012. Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson–Gilford progeria syndrome. PNAS 109:16666–71 [PubMed: 23012407]
42. Mullard A 2021. The FDA approves a first farnesyltransferase inhibitor. Nat. Rev. Drug Discov 20:8
43. 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 7:383–93 [PubMed: 18331619]
44. Liu B, Wang J, Chan KM, Tjia WM, Deng W, et al. 2005. Genomic instability in laminopathy-based premature aging. Nat. Med 11:780–85 [PubMed: 15980864]
45. Kreienkamp R, Graziano S, Coll-Bonfill N, Bedia-Diaz G, Cybulla E, et al. 2018. A cell-intrinsic interferon-like response links replication stress to cellular aging caused by progerin. Cell Rep. 22:2006–15 [PubMed: 29466729]
46. Liu GH, Barkho BZ, Ruiz S, Diep D, Qu J, et al. 2011. Recapitulation of premature ageing with iPSCs from Hutchinson-Gilford progeria syndrome. Nature 472:221–25 [PubMed: 21346760]
47. Chen L, Lee L, Kudlow BA, Dos Santos HG, Sletvold O, et al. 2003. LMNA mutations in atypical Werner's syndrome. Lancet 362:440–45 [PubMed: 12927431]
48. Samson C, Petitalot A, Celli F, Herrada I, Ropars V, et al. 2018. Structural analysis of the ternary complex between lamin A/C, BAF and emerin identifies an interface disrupted in autosomal recessive progeroid diseases. Nucleic Acids Res. 46:10460–73 [PubMed: 30137533]
49. Puente XS, Quesada V, Osorio FG, Cabanillas R, Cadiñanos J, et al. 2011. Exome sequencing and functional analysis identifies BANF1 mutation as the cause of a hereditary progeroid syndrome. Am. J. Hum. Genet 88:650–56 [PubMed: 21549337]
50. Sears RM, Roux KJ. 2020. Diverse cellular functions of barrier-to-autointegration factor and its roles in disease. J. Cell Sci 133:jcs246546 [PubMed: 32817163]

51. Emery AE. 2000. Emery–Dreifuss muscular dystrophy—a 40 year retrospective. Neuromuscul. Disord 10:228–32 [PubMed: 10838246]
52. Fatkin D, MacRae C, Sasaki T, Wolff MR, Porcu M, 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 341:1715–24 [PubMed: 10580070]
53. Muchir A, Bonne G, van der Kooi AJ, van Meegen M, Baas F, et al. 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 9:1453–59 [PubMed: 10814726]
54. Bonne G, Mercuri E, Muchir A, Urtizberea A, Becane HM, 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 48:170–80 [PubMed: 10939567]
55. Raffaele Di Barletta M, Ricci E, Galluzzi G, Tonali P, Mora M, et al. 2000. Different mutations in the LMNA gene cause autosomal dominant and autosomal recessive Emery-Dreifuss muscular dystrophy. Am. J. Hum. Genet 66:1407–12 [PubMed: 10739764]
56. Brodsky GL, Muntoni F, Miocic S, Sinagra G, Sewry C, et al. 2000. Lamin A/C gene mutation associated with dilated cardiomyopathy with variable skeletal muscle involvement. Circulation 101:473–76 [PubMed: 10662742]
57. Quijano-Roy S, Mbieleu B, Bönnemann CG, Jeannet PY, Colomer J, et al. 2008. De novo LMNA mutations cause a new form of congenital muscular dystrophy. Ann. Neurol 64:177–86 [PubMed: 18551513]
58. Jimenez-Escrig A, Gobernado I, Garcia-Villanueva M, Sanchez-Herranz A. 2012. Autosomal recessive Emery–Dreifuss muscular dystrophy caused by a novel mutation (R225Q) in the lamin A/C gene identified by exome sequencing. Muscle Nerve 45:605–10 [PubMed: 22431096]
59. Sullivan T, Escalante-Alcalde D, Bhatt H, Anver M, Bhat N, et al. 1999. Loss of A-type lamin expression compromises nuclear envelope integrity leading to muscular dystrophy. J. Cell Biol 147:913–20 [PubMed: 10579712]
60. Muchir A, Medioni J, Laluc M, Massart C, Arimura T, 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 30:444–50 [PubMed: 15372542]
61. Lammerding J, Schulze PC, Takahashi T, Kozlov S, Sullivan T, et al. 2004. Lamin A/C deficiency causes defective nuclear mechanics and mechanotransduction. J. Clin. Investig 113:370–78 [PubMed: 14755334]
62. Folker ES, Östlund C, Luxton GG, Worman HJ, Gundersen GG. 2011.Lamin A variants that cause striated muscle disease are defective in anchoring transmembrane actin-associated nuclear lines for nuclear movement. PNAS 108:131–36 [PubMed: 21173262]
63. Kronenberg-Tenga R, Tatli M, Eibauer M, Wu W, Shin J-Y, et al. 2021. A lamin A/C variant causing striated muscle disease provides insights into filament organization. J. Cell Sci 134:jcs256156 [PubMed: 33536248]
64. 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 114:4435–45 [PubMed: 11792809]
65. 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 114:4447–57 [PubMed: 11792810]
66. Clements L, Manilal S, Love DR, Morris GE. 2000. Direct interaction between emerin and lamin A. Biochem. Biophys. Res. Commun 267:709–14 [PubMed: 10673356]
67. Shin JY, Mendez-Lopez I, Wang Y, Hays AP, Tanji K, et al. 2013. Lamina-associated polypeptide-1 interacts with the muscular dystrophy protein emerin and is essential for skeletal muscle maintenance. Dev. Cell 26:591–603 [PubMed: 24055652]
68. Shin JY, Le Dour C, Sera F, Iwata S, Homma S, et al. 2014. Depletion of lamina-associated polypeptide 1 from cardiomyocytes causes cardiac dysfunction in mice. Nucleus 5:260–68 [PubMed: 24859316]

69. Kayman-Kurekci G, Talim B, Korkusuz P, Sayar N, Sarioglu T, et al. 2014. Mutation in *TOR1AIP1* encoding LAP1B in a form of muscular dystrophy: a novel gene related to nuclear envelopathies. Neuromuscul. Disord 24:624–33 [PubMed: 24856141]
70. Dunnigan M, Cochrane M, Kelly A, Scott J. 1974. Familial lipoatrophic diabetes with dominant transmission: a new syndrome. Quart. J. Med 43:33–48 [PubMed: 4362786]
71. Vigouroux C, Magre J, Vantyghem M-C, Bourut C, Lascols O, 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 lipoatrophy. Diabetes 49:1958–62 [PubMed: 11078466]
72. Lüdtke A, Genschel J, Brabant G, Bauditz J, Taupitz M, et al. 2005. Hepatic steatosis in Dunnigan-type familial partial lipodystrophy. Am. J. Gastroenterol 100:2218–24 [PubMed: 16181372]
73. Decaudain A, Vantyghem MC, Guerci B, Hecart AC, Auclair M, et al. 2007. New metabolic phenotypes in laminopathies: LMNA mutations in patients with severe metabolic syndrome. J. Clin. Endocrinol. Metab 92:4835–44 [PubMed: 17711925]
74. Dhe-Paganon S, Werner ED, Chi Y-I, Shoelson SE. 2002. Structure of the globular tail of nuclear lamin. J. Biol. Chem 277:17381–84 [PubMed: 11901143]
75. Krimm I, Östlund C, Gilquin B, Couprie J, Hossenlopp P, et al. 2002. The Ig-like structure of the C-terminal domain of lamin A/C, mutated in muscular dystrophies, cardiomyopathy, and partial lipodystrophy. Structure 10:811–23 [PubMed: 12057196]
76. Lloyd DJ, Trembath RC, Shackleton S. 2002.A novel interaction between lamin A and SREBP1: implications for partial lipodystrophy and other laminopathies. Hum. Mol. Genet 11:769–77 [PubMed: 11929849]
77. Vadrot N, Duband-Goulet I, Cabet E, Attanda W, Barateau A, et al. 2015. The p.R482W substitution in A-type lamins deregulates SREBP1 activity in Dunnigan-type familial partial lipodystrophy. Hum. Mol. Genet 24:2096–109 [PubMed: 25524705]
78. Boguslavsky RL, Stewart CL, Worman HJ. 2006. Nuclear lamin A inhibits adipocyte differentiation: implications for Dunnigan-type familial partial lipodystrophy. Hum. Mol. Genet 15:653–63 [PubMed: 16415042]
79. Tazir M, Azzedine H, Assami S, Sindou P, Nouioua S, et al. 2004. Phenotypic variability in autosomal recessive axonal Charcot–Marie–Tooth disease due to the R298C mutation in lamin A/C. Brain 127:154–63 [PubMed: 14607793]
80. Poitelon Y, Kozlov S, Devaux J, Vallat J-M, Jamon M, et al. 2012. Behavioral and molecular exploration of the AR-CMT2A mouse model Lmna R298C/R298C. Neuromol. Med 14:40–52
81. Coffinier C, Chang SY, Nobumori C, Tu Y, Farber EA, et al. 2010. Abnormal development of the cerebral cortex and cerebellum in the setting of lamin B2 deficiency. PNAS 107:5076–81 [PubMed: 20145110]
82. Coffinier C, Jung H-J, Nobumori C, Chang S, Tu Y, et al. 2011. Deficiencies in lamin B1 and lamin B2 cause neurodevelopmental defects and distinct nuclear shape abnormalities in neurons. Mol. Biol. Cell 22:4683–93 [PubMed: 21976703]
83. Cristofoli F, Moss T, Moore HW, Devriendt K, Flanagan-Steet H, et al. 2020. De novo variants in *LMNB1* cause pronounced syndromic microcephaly and disruption of nuclear envelope integrity. Am. J. Hum. Genet 107:753–62 [PubMed: 32910914]
84. Parry DA, Martin C-A, Greene P, Marsh JA, Blyth M, et al. 2021. Heterozygous lamin B1 and lamin B2 variants cause primary microcephaly and define a novel laminopathy. Genet. Med 23:408–14 [PubMed: 33033404]
85. Padiath QS, Saigoh K, Schiffmann R, Asahara H, Yamada T, et al. 2006. Lamin B1 duplications cause autosomal dominant leukodystrophy. Nat. Genet 38:1114–23 [PubMed: 16951681]
86. Heng MY, Lin S-T, Verret L, Huang Y, Kamiya S, et al. 2013. Lamin B1 mediates cell-autonomous neuropathology in a leukodystrophy mouse model. J. Clin. Investig 123:2719–29 [PubMed: 23676464]
87. Manilal S, Recan D, Sewry CA, Hoeltzenbein M, Llense S, et al. 1998. Mutations in Emery-Dreifuss muscular dystrophy and their effects on emerin protein expression. Hum. Mol. Genet 7:855–64 [PubMed: 9536090]

88. Yates JR, Bagshaw J, Aksmanovic VM, Coomber E, McMahon R, et al. 1999. Genotype-phenotype analysis in X-linked Emery–Dreifuss muscular dystrophy and identification of a missense mutation associated with a milder phenotype. Neuromuscul. Disord 9:159–65 [PubMed: 10382909]

89. Muntoni F, Lichtarowicz-Krynska EJ, Sewry CA, Manilal S, Recan D, et al. 1998. Early presentation of X-linked Emery–Dreifuss muscular dystrophy resembling limb-girdle muscular dystrophy. Neuromuscul. Disord 8:72–76 [PubMed: 9608559]

90. Astejada M, Goto K, Nagano A, Ura S, Noguchi S, et al. 2007. Emerinopathy and laminopathy clinical, pathological and molecular features of muscular dystrophy with nuclear envelopathy in Japan. Acta Myol. 26:159–64 [PubMed: 18646565]

91. Muchir A, Pavlidis P, Decostre V, Herron AJ, Arimura T, et al. 2007. Activation of MAPK pathways links LMNA mutations to cardiomyopathy in Emery-Dreifuss muscular dystrophy. J. Clin. Investig 117:1282–93 [PubMed: 17446932]

92. Muchir A, Wu W, Worman HJ. 2009. Reduced expression of A-type lamins and emerin activates extracellular signal-regulated kinase in cultured cells. Biochim. Biophys. Acta Mol. Basis Dis 1792:75–81

93. Muchir A, Pavlidis P, Bonne G, Hayashi YK, Worman HJ. 2007. 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 16:1884–95 [PubMed: 17567779]

94. Melcon G, Kozlov S, Cutler DA, Sullivan T, Hernandez L, et al. 2006. Loss of emerin at the nuclear envelope disrupts the Rb1/E2F and MyoD pathways during muscle regeneration. Hum. Mol. Genet 15:637–51 [PubMed: 16403804]

95. Ozawa R, Hayashi YK, Ogawa M, Kurokawa R, Matsumoto H, et al. 2006. Emerin-lacking mice show minimal motor and cardiac dysfunctions with nuclear-associated vacuoles. Am. J. Pathol 168:907–17 [PubMed: 16507906]

96. Lin F, Blake DL, Callebaut I, Skerjanc IS, Holmer L, et al. 2000. MAN1, an inner nuclear membrane protein that shares the LEM domain with lamina-associated polypeptide 2 and emerin. J. Biol. Chem 275:4840–47 [PubMed: 10671519]

97. Paulin-Levasseur M, Blake DL, Julien M, Rouleau L. 1996. The MAN antigens are non-lamin constituents of the nuclear lamina in vertebrate cells. Chromosoma 104:367–79 [PubMed: 8575249]

98. Hellemans J, Preobrazhenska O, Willaert A, Debeer P, Verdonk PC, et al. 2004. Loss-of-function mutations in *LEMD3* result in osteopoikilosis, Buschke-Ollendorff syndrome and melorheostosis. Nat. Genet 36:1213–18 [PubMed: 15489854]

99. 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 14:437–45 [PubMed: 15601644]

100. Pan D, Estévez-Salmerón LD, Stroschein SL, Zhu X, He J, et al. 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 280:15992–6001 [PubMed: 15647271]

101. Ishimura A, Ng JK, Taira M, Young SG, Osada S-I. 2006. Man1, an inner nuclear membrane protein, regulates vascular remodeling by modulating transforming growth factor β signaling. Development 133:3919–28 [PubMed: 16943282]

102. Cohen TV, Kosti O, Stewart CL. 2007. The nuclear envelope protein MAN1 regulates TGFβ signaling and vasculogenesis in the embryonic yolk sac. Development 134:1385–95 [PubMed: 17329363]

103. Bourgeois B, Gilquin B, Tellier-Lebègue C, Östlund C, Wu W, et al. 2013. Inhibition of TGF-β signaling at the nuclear envelope: characterization of interactions between MAN1, Smad2 and Smad3, and PPM1A. Sci. Signal 6:ra49 [PubMed: 23779087]

104. Worman HJ, Yuan J, Blobel G, Georgatos SD. 1988. A lamin B receptor in the nuclear envelope. PNAS 85:8531–34 [PubMed: 2847165]

105. 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 111:1535–42 [PubMed: 2170422]
106. 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 271:14653–56 [PubMed: 8663349]
107. Holmer L, Pezhman A, Worman HJ. 1998. The human lamin B receptor/sterol reductase multigene family. Genomics 54:469–76 [PubMed: 9878250]
108. Hoffmann K, Dreger CK, Olins AL, Olins DE, Shultz LD, et al. 2002. Mutations in the gene encoding the lamin B receptor produce an altered nuclear morphology in granulocytes (Pelger–Huet anomaly). Nat. Genet 31:410–14 [PubMed: 12118250]
109. Waterham HR, Koster J, Mooyer P, van Noort G, Kelley RI, et al. 2003. Autosomal recessive HEM/Greenberg skeletal dysplasia is caused by 3β-hydroxysterol Δ^{14}-reductase deficiency due to mutations in the lamin B receptor gene. Am. J. Med. Genet 72:1013–17
110. Clayton P, Fischer B, Mann A, Mansour S, Rossier E, et al. 2010. Mutations causing Greenberg dysplasia but not Pelger anomaly uncouple enzymatic from structural functions of a nuclear membrane protein. Nucleus 1:354–66 [PubMed: 21327084]
111. Tsai P-L, Zhao C, Turner E, Schlieker C. 2016. The Lamin B receptor is essential for cholesterol synthesis and perturbed by disease-causing mutations. eLife 5:e16011 [PubMed: 27336722]
112. Shultz LD, Lyons BL, Burzenski LM, Gott B, Samuels R, et al. 2003. Mutations at the mouse ichthyosis locus are within the lamin B receptor gene: a single gene model for human Pelger–Huet anomaly. Hum. Mol. Genet 12:61–69 [PubMed: 12490533]
113. Cohen TV, Klarmann KD, Sakchaisri K, Cooper JP, Kuhns D, et al. 2008. The lamin B receptor under transcriptional control of C/EBPε is required for morphological but not functional maturation of neutrophils. Hum. Mol. Genet 17:2921–33 [PubMed: 18621876]
114. Bengtsson L, Otto H. 2008. LUMA interacts with emerin and influences its distribution at the inner nuclear membrane. J. Cell Sci 121:536–48 [PubMed: 18230648]
115. Merner ND, Hodgkinson KA, Haywood AF, Connors S, French VM, et al. 2008. Arrhythmogenic right ventricular cardiomyopathy type 5 is a fully penetrant, lethal arrhythmic disorder caused by a missense mutation in the *TMEM43* gene. Am. J. Hum. Genet 82:809–21 [PubMed: 18313022]
116. Stroud MJ, Fang X, Zhang J, Guimarães-Camboa N, Veevers J, et al. 2018. Luma is not essential for murine cardiac development and function. Cardiovasc. Res 114:378–88 [PubMed: 29040414]
117. Padrón-Barthe L, Villalba-Orero M, Gómez-Salinero JM, Domínguez F, Román M, et al. 2019. Severe cardiac dysfunction and death caused by arrhythmogenic right ventricular cardiomyopathy type 5 are improved by inhibition of glycogen synthase kinase-3β. Circulation 140:1188–204 [PubMed: 31567019]
118. Senior A, Gerace L. 1988. Integral membrane proteins specific to the inner nuclear membrane and associated with the nuclear lamina. J. Cell Biol 107:2029–36 [PubMed: 3058715]
119. Foisner R, Gerace L. 1993. Integral membrane proteins of the nuclear envelope interact with lamins and chromosomes, and binding is modulated by mitotic phosphorylation. Cell 73:1267–79 [PubMed: 8324822]
120. Santos M, Domingues SC, Costa P, Muller T, Galozzi S, et al. 2014. Identification of a novel human LAP1 isoform that is regulated by protein phosphorylation. PLOS ONE 9:e113732 [PubMed: 25461922]
121. Martin L, Crimaudo C, Gerace L. 1995. cDNA cloning and characterization of lamina-associated polypeptide 1C(LAP1C), an integral protein of the inner nuclear membrane. J. Biol. Chem 270:8822–28 [PubMed: 7721789]
122. Zhao C, Brown RS, Chase AR, Eisele MR, Schlieker C. 2013. Regulation of torsin ATPases by LAP1 and LULL1. PNAS 110:E1545–54 [PubMed: 23569223]
123. Sosa BA, Demircioglu FE, Chen JZ, Ingram J, Ploegh HL, et al. 2014. How lamina-associated polypeptide 1 (LAP1) activates Torsin. eLife 3:e03239 [PubMed: 25149450]
124. 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 168:855–62 [PubMed: 15767459]

125. Shin J-Y, Méndez-López I, Hong M, Wang Y, Tanji K, et al. 2017. Lamina-associated polypeptide 1 is dispensable for embryonic myogenesis but required for postnatal skeletal muscle growth. Hum. Mol. Genet 26:65–78 [PubMed: 27798115]

126. Fichtman B, Zagairy F, Biran N, Barsheshet Y, Chervinsky E, et al. 2019. Combined loss of LAP1B and LAP1C results in an early onset multisystemic nuclear envelopathy. Nat. Commun 10:605 [PubMed: 30723199]

127. Brachner A, Reipert S, Foisner R, Gotzmann J. 2005. LEM2 is a novel MAN1-related inner nuclear membrane protein associated with A-type lamins. J. Cell Sci 118:5797–810 [PubMed: 16339967]

128. Halfmann CT, Sears RM, Katiyar A, Busselman BW, Aman LK, et al. 2019. Repair of nuclear ruptures requires barrier-to-autointegration factor. J. Cell Biol 218:2136–49 [PubMed: 31147383]

129. von Appen A, LaJoie D, Johnson IE, Trnka MJ, Pick SM, et al. 2020. LEM2 phase separation promotes ESCRT-mediated nuclear envelope reformation. Nature 582:115–18 [PubMed: 32494070]

130. Huber MD, Guan T, Gerace L. 2009. Overlapping functions of nuclear envelope proteins NET25 (Lem2) and emerin in regulation of ERK signaling in myoblast differentiation. Mol. Cell. Biol 29:5718–28 [PubMed: 19720741]

131. Marbach F, Rustad CF, Riess A, Đukić D, Hsieh T-C, et al. 2019. The discovery of a LEMD2-associated nuclear envelopathy with early progeroid appearance suggests advanced applications for AI-driven facial phenotyping. Am. J. Hum. Genet 104:749–57 [PubMed: 30905398]

132. Meinke P, Mattioli E, Haque F, Antoku S, Columbaro M, et al. 2014. Muscular dystrophy-associated SUN1 and SUN2 variants disrupt nuclear-cytoskeletal connections and myonuclear organization. PLOS Genet 10:e1004605 [PubMed: 25210889]

133. Gros-Louis F, Dupré N, Dion P, Fox MA, Laurent S, et al. 2007. Mutations in *SYNE1* lead to a newly discovered form of autosomal recessive cerebellar ataxia. Nat. Genet 39:80–85 [PubMed: 17159980]

134. Attali R, Warwar N, Israel A, Gurt I, McNally E, et al. 2009. Mutation of *SYNE-1*, encoding an essential component of the nuclear lamina, is responsible for autosomal recessive arthrogryposis. Hum. Mol. Genet 18:3462–69 [PubMed: 19542096]

135. Banerjee I, Zhang J, Moore-Morris T, Pfeiffer E, Buchholz KS, et al. 2014. Targeted ablation of nesprin 1 and nesprin 2 from murine myocardium results in cardiomyopathy, altered nuclear morphology and inhibition of the biomechanical gene response. PLOS Genet. 10:e1004114 [PubMed: 24586179]

136. Puckelwartz MJ, Kessler E, Zhang Y, Hodzic D, Randles KN, et al. 2009. Disruption of nesprin-1 produces an Emery Dreifuss muscular dystrophy-like phenotype in mice. Hum. Mol. Genet 18:607–20 [PubMed: 19008300]

137. Zhang J, Felder A, Liu Y, Guo LT, Lange S, et al. 2010. Nesprin 1 is critical for nuclear positioning and anchorage. Hum. Mol. Genet 19:329–41 [PubMed: 19864491]

138. Zhang Q, Bethmann C, Worth NF, Davies JD, Wasner C, et al. 2007. Nesprin-1 and -2 are involved in the pathogenesis of Emery Dreifuss muscular dystrophy and are critical for nuclear envelope integrity. Hum. Mol. Genet 16:2816–33 [PubMed: 17761684]

139. Puckelwartz MJ, Kessler EJ, Kim G, Dewitt MM, Zhang Y, et al. 2010. Nesprin-1 mutations in human and murine cardiomyopathy. J. Mol. Cell. Cardiol 48:600–8 [PubMed: 19944109]

140. Zhou C, Li C, Zhou B, Sun H, Koullourou V, et al. 2017. Novel nesprin-1 mutations associated with dilated cardiomyopathy cause nuclear envelope disruption and defects in myogenesis. Hum. Mol. Genet 26:2258–76 [PubMed: 28398466]

141. Horn HF, Brownstein Z, Lenz DR, Shivatzki S, Dror AA, et al. 2013. The LINC complex is essential for hearing. J. Clin. Investig 123:740–50 [PubMed: 23348741]

142. Ozelius LJ, Hewett JW, Page CE, Bressman SB, Kramer PL, et al. 1997. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. Nat. Genet 17:40–48 [PubMed: 9288096]

143. Goodchild RE, Dauer WT. 2004. Mislocalization to the nuclear envelope: an effect of the dystonia-causing torsinA mutation. PNAS 101:847–52 [PubMed: 14711988]

144. Naismith TV, Dalal S, Hanson PI. 2009. Interaction of torsinA with its major binding partners is impaired by the dystonia-associated ΔGAG deletion. J. Biol. Chem 284:27866–74 [PubMed: 19651773]

145. Shashidharan P, Sandu D, Potla U, Armata I, Walker R, et al. 2005. Transgenic mouse model of early-onset DYT1 dystonia. Hum. Mol. Genet 14:125–33 [PubMed: 15548549]

146. Goodchild RE, Kim CE, Dauer WT. 2005. Loss of the dystonia-associated protein torsinA selectively disrupts the neuronal nuclear envelope. Neuron 48:923–32 [PubMed: 16364897]

147. Liang CC, Tanabe LM, Jou S, Chi F, Dauer WT. 2014. TorsinA hypofunction causes abnormal twisting movements and sensorimotor circuit neurodegeneration. J. Clin. Investig 124:3080–92 [PubMed: 24937429]

148. Pappas SS, Darr K, Holley SM, Cepeda C, Mabrouk OS, et al. 2015. Forebrain deletion of the dystonia protein torsinA causes dystonic-like movements and loss of striatal cholinergic neurons. eLife 4:e08352 [PubMed: 26052670]

149. Li J, Levin DS, Kim AJ, Pappas SS, Dauer WT. 2021. TorsinA restoration in a mouse model identifies a critical therapeutic window for DYT1 dystonia. J. Clin. Investig 131:e139606

150. Shin JY, Hernandez-Ono A, Fedotova T, Ostlund C, Lee MJ, et al. 2019. Nuclear envelope-localized torsinA-LAP1 complex regulates hepatic VLDL secretion and steatosis. J. Clin. Investig 130:4885–900

151. Wente SR, Rout MP. 2010. The nuclear pore complex and nuclear transport. Cold Spring Harb. Perspect. Biol 2:a000562 [PubMed: 20630994]

152. Ibarra A, Hetzer MW. 2015. Nuclear pore proteins and the control of genome functions. Genes Dev. 29:337–49 [PubMed: 25691464]

153. Nofrini V, Di Giacomo D, Mecucci C. 2016. Nucleoporin genes in human diseases. Eur. J. Hum. Genet 24:1388–95 [PubMed: 27071718]

154. Jühlen R, Fahrenkrog B. 2018. Moonlighting nuclear pore proteins: tissue-specific nucleoporin function in health and disease. Histochem. Cell Biol 150:593–605 [PubMed: 30361777]

155. Baylink DJ, Finkelman RD, Mohan S. 1993. Growth factors to stimulate bone formation. J. Bone Miner. Res 8:S565–72 [PubMed: 8122528]

156. Blobel G 1985. Gene gating: a hypothesis. PNAS 82:8527–29 [PubMed: 3866238]

157. Kim PH, Luu J, Heizer P, Tu Y, Weston TA, et al. 2018. Disrupting the LINC complex in smooth muscle cells reduces aortic disease in a mouse model of Hutchinson-Gilford progeria syndrome. Sci. Transl. Med 10:eaat7163 [PubMed: 30257952]

158. Earle AJ, Kirby TJ, Fedorchak GR, Isermann P, Patel J,et al. 2020. Mutant lamins cause nuclear envelope rupture and DNA damage in skeletal muscle cells. Nat. Mater 19:464–73 [PubMed: 31844279]

159. Chen NY, Kim P, Weston TA, Edillo L, Tu Y, et al. 2018. Fibroblasts lacking nuclear lamins do not have nuclear blebs or protrusions but nevertheless have frequent nuclear membrane ruptures. PNAS 115:10100–5 [PubMed: 30224463]

160. Chen NY, Yang Y, Weston TA, Belling JN, Heizer P, et al. 2019. An absence of lamin B1 in migrating neurons causes nuclear membrane ruptures and cell death. PNAS 116:25870–79 [PubMed: 31796586]

161. Choi JC, Muchir A, Wu W, Iwata S, Homma S, et al. 2012. Temsirolimus activates autophagy and ameliorates cardiomyopathy caused by lamin A/C gene mutation. Sci. Transl. Med 4:144ra102

162. Muchir A, Reilly SA, Wu W, Iwata S, Homma S, et al. 2012. Treatment with selumetinib preserves cardiac function and improves survival in cardiomyopathy caused by mutation in the lamin A/C gene. Cardiovasc. Res 93:311–19 [PubMed: 22068161]

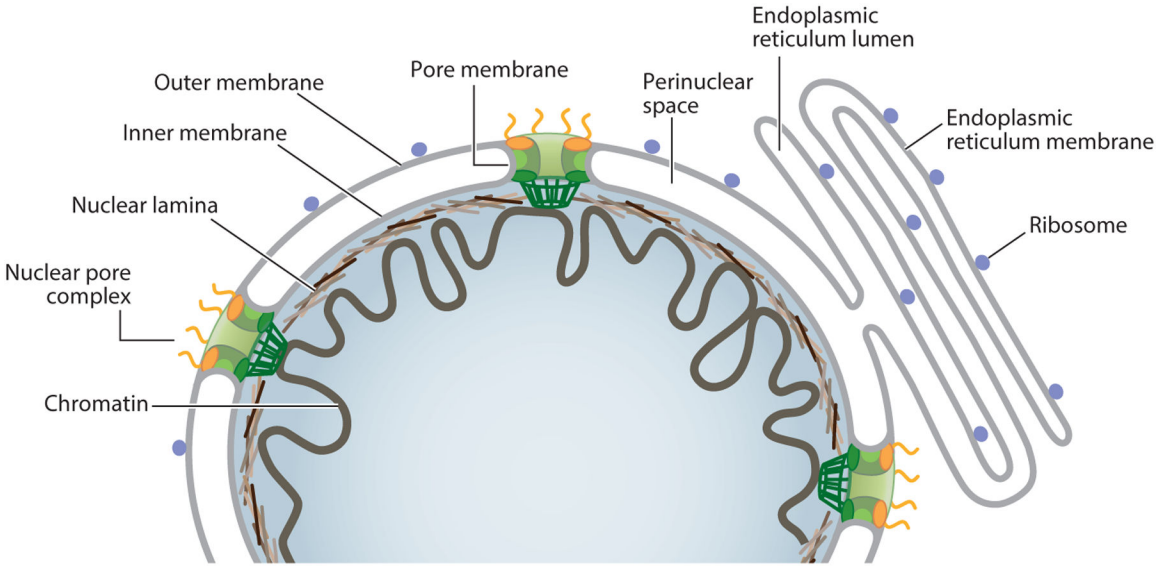

Figure 1.

Schematic diagram of the nuclear envelope showing the nuclear membranes, nuclear lamina, and a nuclear pore complex. Ribosomes are on the rough endoplasmic reticulum and continuous outer nuclear membrane. The nuclear pore complexes are associated with the pore membranes, and lamina and chromatin are associated with the inner nuclear membrane.

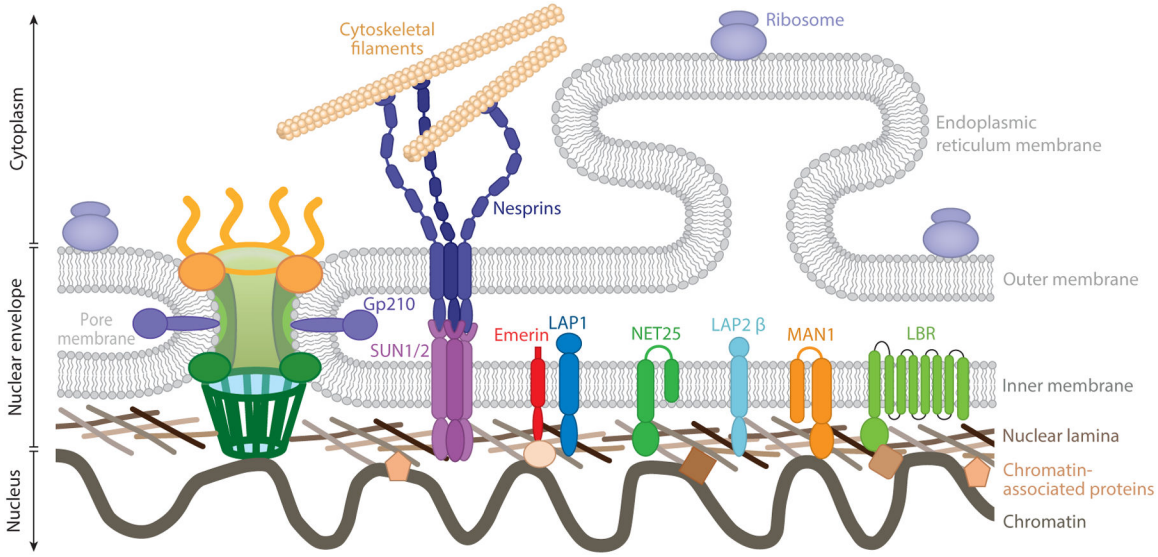

Figure 2.

Schematic diagram showing select transmembrane proteins of the inner, pore, and outer membranes of the nuclear envelope. Representative transmembrane proteins that concentrate in the inner nuclear membrane are SUN1/2, emerin, LAP1, NET25, LAP2 β, MAN1, and LBR. Gp210 is a representative integral protein of the pore membrane. Nesprins concentrate in the outer nuclear membrane by binding within the perinuclear space to the luminal domains of SUN proteins and also bind to cytoskeletal filaments.

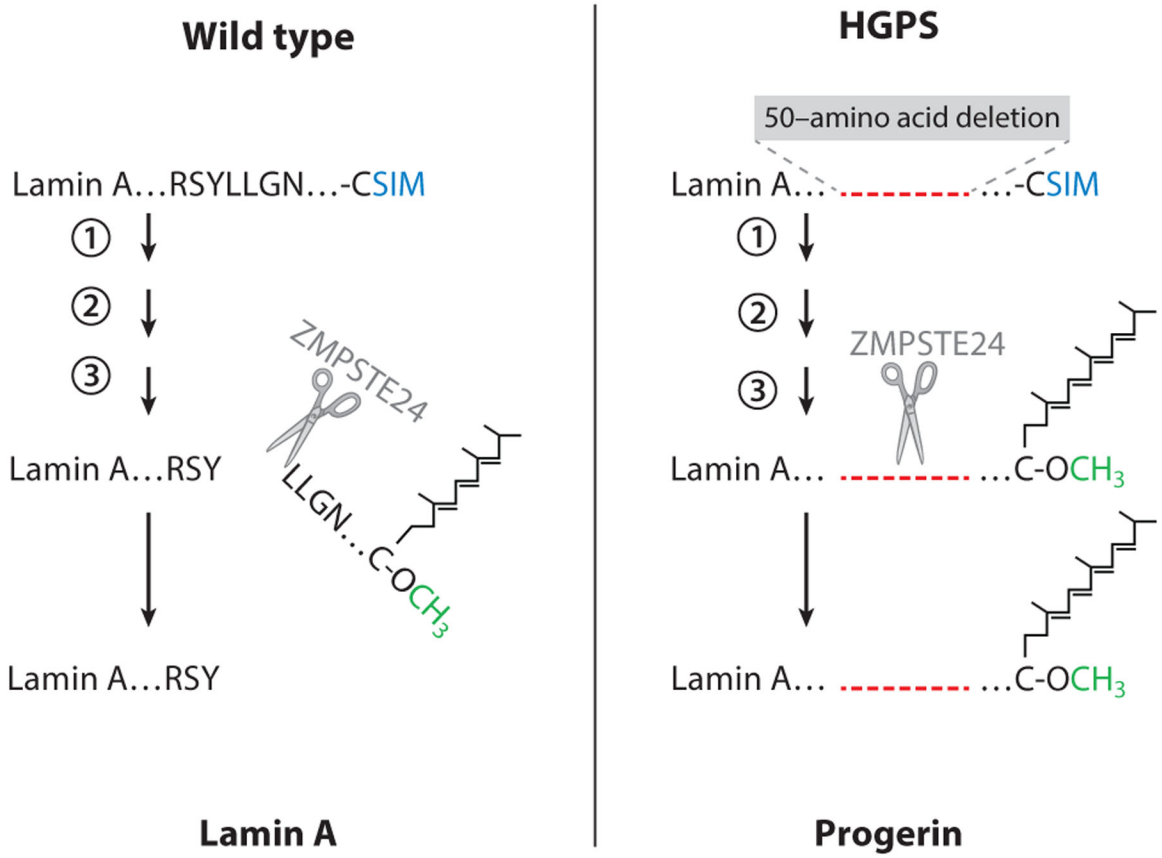

Figure 3.

Progerin is a farnesylated prelamin A variant that accumulates in Hutchinson-Gilford progeria syndrome (HGPS). The cysteine-isoleucine-serine-methionine (CISM) [cysteine-aliphatic-aliphatic-any amino acid (CAAX) motif] in prelamin A triggers three sequential reactions: (①) Protein farnesyltransferase catalyzes the addition of a farnesyl moiety to the cysteine (C), (②) CAAX endopeptidase 1 or ZMPSTE24 catalyzes the endoproteolytic cleavage of the -ISM, and (③) isoprenylcysteine carboxyl methyltransferase catalyzes methylation of the farnesylcysteine. Normally, ZMPSTE24 (wild type) then recognizes farnesylated prelamin A and catalyzes an endoproteolytic cleavage (*scissors*), leading to removal of the last 15 amino acids, including the farnesylcysteine α-methyl ester, to generate prelamin A. In HGPS, an *LMNA* mutation activates an RNA cryptic splice, leading to expression of an internally truncated prelamin A variant, called progerin, that lacks 50 amino acids (*red dashed line*). This deletion includes the second ZMPSTE24 recognition site, and hence it is cleaved and retains a farnesylated, carboxymethylated cysteine at its carboxyl terminus.

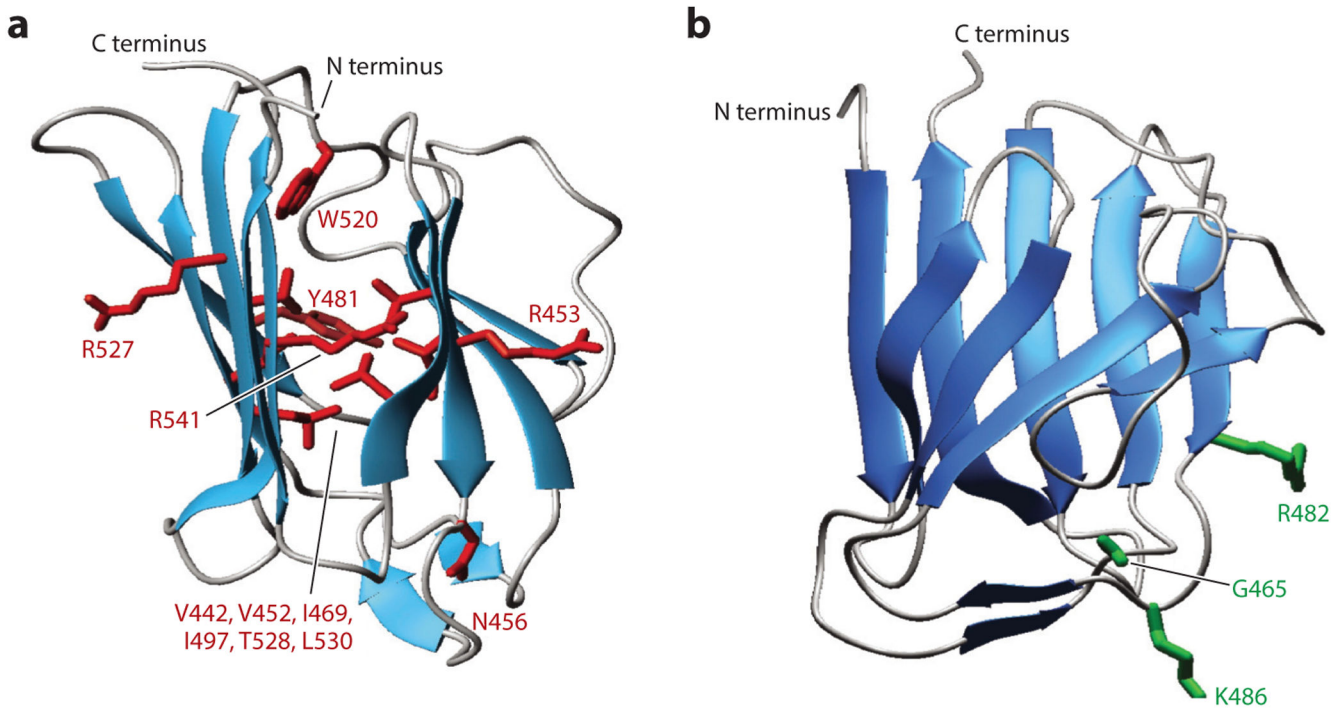

Figure 4.

Amino acid substitutions that cause Dunnigan-type familial partial lipodystrophy diminish the positivity of a surface of the lamin A/C immunoglobulin-like fold domain, while those in the same region causing striated muscle disease disrupt overall structure. (*a*) Localization of the amino acid substitutions (*red*) within the immunoglobulin-like fold domain causing striated muscle disease. (*b*) Three amino acid substitutions (*green*) causing Dunnigan-type familial partial lipodystrophy at R482, G465, and K486 that do not affect overall fold domain structure but diminish the positive charge of a solvent-exposed surface. In the disease-causing variants, glycine (neutral) at residue 465 is replaced by an aspartic acid (negative); arginine (positive) at residue 482 is replaced by a glutamine, tryptophan, or leucine (all neutral); or lysine (positive) at residue 486 is replaced by an asparagine (neutral). Figure adapted with permission from Reference 75.

Table 1

Mutations in *LMNA* cause four groups of diseases affecting different tissues

Type of pathology	Specific disorders
Progeroid disorders	
Prelamin A processing-deficient laminopathies	Hutchinson-Gilford progeria syndrome
	Other progeroid disorders
Prelamin A processing-proficient laminopathies	Mandibuloacral dysplasia type A
	Other progeroid disorders
Striated muscle disease	
Dilated cardiomyopathy with variable skeletal muscle involvement	Emery-Dreifuss muscular dystrophy
	Limb-girdle muscular dystrophy 1B
	Dilated cardiomyopathy with minimal/variable skeletal muscle involvement
	Congenital muscular dystrophy
Adipose tissue disease	
Lipodystrophy	Dunnigan-type familial partial lipodystrophy
	Atypical lipodystrophy syndromes
Peripheral neuropathy	
Charcot-Marie-Tooth disease type 2	Charcot-Marie-Tooth disease type 2B1

Table 2

Genes encoding nuclear envelope proteins other than lamins linked to human diseases

Nuclear envelope compartment	Gene	Protein	Affected tissues	Disease
Inner nuclear transmembrane	*EMD*	Emerin	Striated muscle	X-linked Emery-Dreifuss muscular dystrophy and related myopathies/cardiomyopathy
	LEMD3	MAN1	Bone Skin	Osteopoikilosis Nonsporadic melorheostosis Buschke-Ollendorff syndrome
	LBR	LBR	Neutrophils Bone Multisystem	Pelger-Huet anomaly Greenberg skeletal dysplasia
	TMEM43	LUMA	Striated muscle	Arrhythmogenic right ventricular dysplasia
	TOR1AIP1	LAP1	Striated muscle Multisystem	Cardiomyopathy/muscular dystrophy Multisystemic abnormalities with progressive neurological degeneration and early death
	LEMD2	NET25 (LEM2)	Multisystem	Progeria-like facial phenotypes with other developmental abnormalities
	SUN1/SUN2	SUN1/SUN2	Striated muscle	Muscular dystrophy/cardiomyopathy
Outer nuclear transmembrane	*SYNE1*	Nesprin-1	Central nervous system Striated muscle	Autosomal recessive spinocerebellar ataxia 8 Arthrogryposis multiplex congenita Muscular dystrophy/cardiomyopathy
	SYNE2	Nesprin-2	Striated muscle	Cardiomyopathy/muscular dystrophy
	SYNE4	Nesprin-4	Inner ear	High-frequency hearing loss
Perinuclear space	*TOR1A*	TorsinA	Central nervous system	DYT1 dystonia

Table 3

Genes encoding nuclear pore complex proteins linked to human diseases

Gene	Protein	Affected tissues	Disease
AAAS	Aladin	Autonomic nervous system	Triple-A syndrome
NUP155	Nup155	Heart	Atrial fibrillation
NUP62	Nup62	Central nervous system	Infantile bilateral striatal necrosis
GLE1	GLE1	Motor neurons	Lethal congenital contracture syndrome-1
RanBP2/NUP358	RanBP2 (Nup358)	Central nervous system	Acute necrotizing encephalopathy
NUP107	Nup107	Kidney	Galloway-Mowat syndrome
NUP107, NUP93, NUP205, NUP85, NUP133, NUP160	NUP107, NUP93, NUP205, NUP85, NUP133, NUP160	Kidney	Steroid-resistant nephrotic syndrome