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"Laminopathies:" a wide spectrum of human diseases

Howard J. Worman[a,*] and **Gisèle Bonne**[b,c,d]

[a] Department of Medicine and Department of Anatomy and Cell Biology, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA

[b] Institut National de la Santé et de la Recherche Médicale, U582, Institut de Myologie, Paris F-75013, France

[c] Université Pierre et Marie Curie-Paris 6, Faculté de médecine, Paris F-75013, France

[d] AP-HP, Groupe Hospitalier Pitié-Salpêtrière, U.F. Myogénétique et Cardiogénétique, service de Biochimie B, Paris F-75013, France

Abstract

Mutations in genes encoding the intermediate filament nuclear lamins and associated proteins cause a wide spectrum of diseases sometimes called "laminopathies." Diseases caused by mutations in *LMNA* encoding A-type lamins include autosomal dominant Emery-Dreifuss muscular dystrophy and related myopathies, Dunnigan-type familial partial lipodystrophy, Charcot-Marie-Tooth disease type 2B1 and developmental and accelerated aging disorders. Duplication in *LMNB1* encoding lamin B1 causes autosomal dominant leukodystrophy and mutations in *LMNB2* encoding lamin B2 are associated with acquired partial lipodystrophy. Disorders caused by mutations in genes encoding lamin-associated integral inner nuclear membrane proteins include X-linked Emery-Dreifuss muscular dystrophy, sclerosing bone dysplasias, HEM/Greenberg skeletal dysplasia and Pelger-Huet anomaly. While mutations and clinical phenotypes of "laminopathies" have been carefully described, data explaining pathogenic mechanisms are only emerging. Future investigations will likely identify new "laminopathies" and a combination of basic and clinical research will lead to a better understanding of pathophysiology and the development of therapies.

Keywords

lamin; nuclear envelope; intermediate filaments; muscular dystrophy; lipodystrophy; progeria

Introduction

Nuclear lamins are intermediate filament proteins primarily located at the inner aspect of the inner nuclear membrane [1–4]. Lamins interact with a variety of proteins in the nucleus, including several integral proteins of the inner nuclear membrane [5,6]. Lamins found in several different species were originally grouped into two types based on their isoelectric points determined by two-dimensional gel electrophoresis: A-type lamins, with near-neutral isoelectric points and B-type lamins, with acidic isoelectric points [7,8]. It is now known that

[*]Corresponding author. Department of Medicine, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, P&S 10-509, New York, NY 10032, USA; Phone: 212-305-8156; Fax: 212-305-6443; hjw14@columbia.edu.

in humans, one gene, *LMNA*, encodes A-type lamins, and two genes, *LMNB1* and *LMNB2*, encode B-type lamins.

LMNA is localized to chromosome 1q21.2 [9]. It encodes two major somatic cell variants that arise by alternative RNA splicing, prelamin A and lamin C [10]. Prelamin A and lamin C are identical for their first 566 amino acids; lamin C has 6 unique carboxyl-terminal amino acids and prelamin A 98 unique carboxyl-terminal amino acids. Prelamin A, which contains a CAAX motif at its carboxyl-terminus, is farnesylated and carboxymethylated and undergoes endoproteolyic processing catalyzed by ZMPSTE24 to yield lamin A, which lacks the last 18 amino acids, including the farnesylated and carboxymethylated cysteine, of prelamin A [11, 12]. Lamin A and lamin C are expressed in most somatic cells but absent from or expressed in significantly reduced quantities in early embryos, some hematopoietic cells, certain neurons, undifferentiated epithelial and mesenchymal cells and several types of cancer [13–17]. *LMNA* also encodes a germ cell-specific protein, lamin C2, which arises from alternative splicing of RNA encoded by an alternative first exon [18].

LMNB1 is localized to chromosome 5q23.3-q31.1 and encodes lamin B1 [9,19]. *LMNB2*, localized to chromosome 19p13.3, encodes lamin B2 and a germ cell isoform lamin B3 [20–22]. The B-type lamins have CAAX motifs at their carboxyl-termini and are fanesylated and carboxymethylated [11,12]. At least one of the B-type lamins appears to be expressed in all human cells [13–17,20]. This may be because of their requirement for spindle assembly in mitosis [23].

Approximately 80 proteins appear to be localized to the inner nuclear membrane in interphase mammalian cells [24]. Several of these proteins interact with lamins, likely playing a role in attaching the lamina to the inner nuclear membrane [5,6]. Integral membrane proteins reach the inner nuclear membrane after synthesis on the rough endoplasmic reticulum by lateral diffusion in the interconnected membranes of the endoplasmic reticulum, outer nuclear membrane, pore membranes and inner nuclear membrane [25–27]. Energy appears to be necessary for active restructuring of the nuclear pore complexes [28]. In some instances as shown in yeast, karyopherins may mediate transport of integral proteins to the inner nuclear membrane [29]. During mitosis, when the nuclear lamina depolymerizes, the integral proteins of the inner nuclear membrane are disbursed in the endoplasmic reticulum and then recruited to the decondensing chromatin when the daughter nuclei reform [27,30].

Up until the 1990's, studies of the nuclear lamins and nuclear envelope were primarily in the domain of basic cell biologists. However, in 1994, Bione et al. [31] identified the gene responsible for X-linked Emery-Dreifuss muscular dystrophy and called the encoded integral membrane protein emerin. Soon afterwards, emerin was localized to the nuclear envelope [32,33]. Then, in 1999, Bonne et al. [34] reported that mutations in *LMNA* encoding A-type lamins cause autosomal dominant Emery-Dreifuss muscular dystrophy, a disease with the same phenotype as the X-linked inherited form. Since then, several different human diseases have been linked to mutations in *LMNA* and others to mutations in the genes encoding B-type lamins, lamin-associated proteins and other proteins of the nuclear envelope (Figures 1). As a result, the nuclear lamina is now positioned on the interface between cell biology and medicine. This review will summarize the wide range of diseases now sometimes referred to as "laminopathies."

Diseases caused by mutations in *LMNA* encoding A-type lamins

Over the past 10 years, there has been a rapid pace in the discovery of diseases caused by mutations in genes encoding nuclear lamins and associated nuclear envelope proteins (Figure 2). Mutations in *LMNA* encoding A-type lamins cause a wide spectrum of human diseases and more than 10 different clinical syndromes have been attributed to *LMNA* mutations (Table 1).

However, careful analysis reveals that there is considerable similarity between some of these clinically distinct diseases. Broadly, mutations in *LMNA* can be considered to cause four different groups of disorders with overlap between them: 1) diseases of striated muscle, 2) lipodystrophy syndromes, 3) a peripheral neuropathy and 4) accelerated aging disorders.

Mutations in *LMNA* were first shown to cause autosomal dominant Emery-Dreifuss muscular dystrophy [34]. *LMNA* mutations also cause rare cases of Emery-Dreifuss muscular dystrophy demonstrating autosomal recessive inheritance [35]. Emery-Dreifuss muscular dystrophy has distinctive clinical features of early contractures, humero-peroneal weakness and dilated cardiomyopathy with conduction defects [36]. Subsequently, mutations in *LMNA* were shown to cause dilated cardiomyopathy 1A [37] and limb-girdle muscular dystrophy 1B [38], both with autosomal dominant inheritance. Both of these conditions have dilated cardiomyopathy with conduction abnormalities similar to those in Emery-Dreifuss muscular dystrophy but with either minimal to no skeletal muscle involvement or skeletal muscle affected in a different pattern. Subsequent molecular genetic and phenotypic analyses of additional subjects showed that the same *LMNA* mutation can cause what is clinically diagnosed as Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy 1B and dilated cardiomyopathy 1A, even within the same family [39,40]. Hence, one group of mutations in *LMNA* cause disorders of striated muscle with predominant cardiomyopathy, which based on clinical features and inheritance pattern are classified as four different diseases.

Approximately one year after the first report that mutations in *LMNA* cause Emery-Dreifuss muscular dystrophy, three groups reported that mutations in *LMNA* also cause Dunnigan-type familial partial lipodystrophy [41–43]. Individuals with this autosomal dominant disorder have a normal fat distribution in early childhood but subcutaneous adipose tissue gradually disappears from the upper and lower extremities at the onset of puberty with adipose accumulation on the face and neck. Virtually all affected individuals have insulin resistance and many develop diabetes mellitus. A heterozygous *LMNA* mutation has also been reported in a subject with a lipodystrophy syndrome characterized by generalized lipoatrophy, diabetes mellitus, hepatic steatosis, hypertrophic cardiomyopathy and cutaneous leukomelanodermic papules [44]. More recently, a heterozygous missense mutation in *LMNA* has been reported in a subject with a type A insulin resistance syndrome characterized by glucose tolerance, insulin resistance and acanthosis nigricans in the absence of clinical lipodystrophy [45]. While the vast majority of subjects with muscular dystrophies and cardiomyopathy caused by *LMNA* mutations do not have lipodystrophy, a few case reports suggest that there may be overlap between striated muscle disease and lipodystrophy in rare subjects [46,47].

Mandibuloacral dysplasia is an autosomal recessive disorder, characterized by postnatal growth retardation, craniofacial anomalies, skeletal malformations and mottled cutaneous pigmentation frequently associated with partial lipodystrophy and insulin resistance. Novelli et al. [48] first described a homozygous missense *LMNA* mutation (R527H) that was shared by all affected subjects with mandibuloacral dysplasia in five consanguineous Italian families. The same mutation was subsequently described in affected individuals in other kindreds [49]. In one reported subject with mandibuloacral dysplasia associated with progeroid appearance and more generalized lipodystrophy, compound heterozygous mutations in *ZMPSTE24* encoding the protease that processes prelamin A to lamin A have been described [50].

A homozygous *LMNA* missense mutation has been reported to cause autosomal recessive Charcot-Marie-Tooth type 2B1, a peripheral neuropathy [51]. Combined peripheral neuropathy and muscular dystrophy have also been reported in subjects some dominantly inherited *LMNA* mutations, including a mutation leading to haploinsufficiency of A-type lamins [52–54]. However, peripheral neuropathy has not been reported in most subjects with Emery-Dreifuss muscular dystrophy [31,34–36].

Arguably the most dramatic disease phenotype caused by mutation in *LMNA* is Hutchinson-Gilford progeria syndrome [55,56]. This is a rare, sporadic, multi-system disorder characterized by features of premature aging, with most affected subjects dying in the second decade from cardiovascular disease [57]. The *LMNA* mutations that cause Hutchinson-Gilford progeria syndrome, by far the most common being G608G, create an abnormal splice donor site in exon 11 leading to an mRNA that encodes a protein with 50 amino acids deleted from its carboxyl-terminal domain [55,56]. This leads to abnormal processing of prelamin A because the ZMPSTE24 endoprotease responsible for cleavage "upstream" of the farnesylated cysteine of prelamin A is lacking from the truncated protein. This truncated prelamin A retains at its carboxyl-terminus the farnesylated and carboxymethylated cysteine residue [11,12]. Lamin C, which is encoded by exons 1 through 10 of *LMNA* [10], is unaffected. Restrictive dermopathy, a neonatal, lethal syndrome with severe intrauterine growth retardation, congenital contractures and tense skin, is also caused by heterozygous splicing mutations in *LMNA* resulting in complete or partial loss of exon 11 as well as by mutations in the gene encoding ZMPSTE24 protease [58]. *LMNA* missense mutations have also been reported in subjects with variable feature of accelerated aging and a diagnosis of atypical Werner syndrome [59]. However, atypical Werner syndrome may not be a specific diagnosis but rather subjects with *LMNA* mutations that cause overlapping phenotypes or a multi-system phenotype with progeroid features, such as mandibuloacral dysplasia [60].

How do different mutations in *LMNA* cause several different diseases?

One of the key questions facing scientists who study diseases caused by *LMNA* mutations is: how do different mutations in this single gene encoding proteins expressed in most differentiated somatic cells cause different, often system-specific, disease phenotypes (Figure 3)? Despite intensive investigation over the past several years, there are no definitive answers. However, relatively recent research has provided some clues.

Figure 4 summarizes some of the proposed pathological mechanisms as to how mutations in *LMNA* and the processing of prelamin A may cause disease. In Hutchinson-Gilford progeria syndrome and some cases of restrictive dermopathy, *LMNA* mutations lead to expression of truncated forms of prelamin A that remain farnesylated in cells because of deletion of the ZMPSTE24 protease site. Similarly, unprocessed, farnesylated prelamin A is expressed in related conditions resulting from mutations in the gene encoding ZMPSTE24. *Zmpste24* null mice develop multiple abnormalities and progeroid features [61,62]. When *Zmpste24* null mice are crossed to *Lmna* +/− mice, reducing the prelamin A content by half the offspring are apparently normal, suggesting that farnesylated prelamin A is toxic and that reducing its level provides protection from disease [63]. "Knockdown" of ZMPSTE24 using RNA interference in cultured cells leads to dramatic changes in nuclear morphology and premature cell death and this is prevented by "knockdown" of prelamin A 24 hours earlier [64]. In fibroblasts from human subjects with Hutchinson-Gilford progeria syndrome, introduction of wild type lamin A does not rescue cellular morphological abnormalities; however, correction of the aberrant splicing event using a modified oligonucleotide has been reported to reverse abnormalities in nuclear morphology and induce proper expression of misregulated genes [65]. Additional data suggest that the farnesyl group of unprocessed lamin A and truncated prelamin A is responsible for "toxicity." Treatment of cells from mice with *Zmpste24* deficiency, mice with a targeted Hutchinson-Gilford progeria syndrome mutation, human subjects with Hutchinson-Gilford progeria syndrome and cultured cells overexpressing the truncated prelamin A in this disorder with farnesyltransferase inhibitors reverses the nuclear morphological abnormalities normally present [66–70]. Furthermore, treatment with farnesyltransferase inhibitors improves the whole animal abnormal phenotypes of mice with *Zmpste24* deficiency and mice with a targeted Hutchinson-Gilford progeria syndrome mutation [71,72]. These results suggests that farnesylated prelamin A that accumulates with *ZMPSTE24* mutations in some cases of

restrictive dermopathy and farnesylated truncated prelamin A resulting from *LMNA* mutations in Hutchinson-Gilford progeria syndrome are involved in the pathogenesis of these disorders.

It is still not known how the abnormal farnesylated polypeptides resulting from *LMNA* and *ZMPSTE24* mutations contribute to an accelerated aging phenotype. Some data suggest that these proteins perturb DNA damage response and repair, resulting in genomic instability [73]. However, blocking protein farnesylation does not appear to reverse these DNA damage responses [74]. Other studies suggest that farnesylated prelamin A activates p53, which may somehow be linked to accelerated aging [75]. The truncated prelamin A in Hutchinson-Gilford progeria syndrome also alters the mechanism of A-type and B-type lamin polymerization into the lamina and cells expressing this polypeptide have abnormal nuclear mechanics and an abnormal response to heat stress [76–78].

Virtually all *LMNA* mutations causing Dunnigan-type familial partial lipodystrophy lead to amino acid substitutions on the surface of an immunoglobulin-like fold in the tails of lamin A and lamin C, altering the surface charge but not overall fold structure [79,80] (see Figure 3). As the lipodystrophy-causing amino acid substitutions change the charge of a very precise domain of the proteins, they may lead to alteration of an adipocyte-specific function of A-type lamins. One study suggests that these amino acid changes may alter the binding of A-type lamins to the adipogenic differentiation factor, sterol responsive element binding protein 1 [81].

The majority of *LMNA* mutations in subjects with striated muscle diseases are missense and lead to amino acid substitutions almost anywhere in lamins A and C and not in a specific domain of the proteins [34,39,82,83; see also UMD-*LMNA* mutation database at http://www.UMD.be:2000]. The mutations that cause amino acid substitutions in the immunoglobulin-like fold of lamins A and C lead to overall disruption of fold structure in contrast to the less dramatic alterations occurring with mutations causing Dunnigan-type familial partial lipodystrophy [79,80]. Nonsense or other truncating mutations leading to haploinsufficiency of A-type lamins, which comprise approximately 15% of all *LMNA* mutations, have only been reported in subjects with striated muscle disease (see UMD-*LMNA* mutation database at http://www.UMD.be:2000). Thus, striated muscle appears to be sensitive to both the expression of A-type lamins with certain amino acid changes as well as to reduced expression of A-type lamins. Similarly, both *Lmna* “knockout” mice and “knock-in” mice with *Lmna* mutations corresponding to those that cause striated muscle abnormalities in humans develop skeletal muscle and cardiac disease [84–87]. *Lmna* “knockout” mice to do not have lipodystrophy [88].

LMNA missense mutations that cause striated muscle diseases appear to encode polypeptides that disrupt the structure of the nuclear lamina and nuclear envelope in a “dominant” manner. Expression of several such mutant lamin polypeptides in transfected cells produces visible alterations in the lamina and envelope [89,90]. Fibroblasts from human subjects with *LMNA* mutations that cause muscle disorders have similar abnormalities in nuclear structure [91]. Cardiac-selective transgenic overexpression of human lamin A with an amino acid substitution encoded by a *LMNA* mutation causing Emery-Dreifuss muscular dystrophy leads to profound nuclear shape abnormalities and severe heart damage while overexpression of wild type human lamin A has minimal effects [92]. However, various nuclear structural abnormalities have been reported in cells expressing A-type lamins causing other “laminopathies” and are not specific for striated muscle diseases [55,56,58,59,[65],[66–70],[74],[76–78],91,93–96].

The observed morphological abnormalities in cells expressing A-type lamin variants causing striated muscle diseases, along with similar abnormalities in cells lacking A-type lamins [84], has led to the hypothesis that either expression of lamin polypeptides with certain amino acid

changes or partial loss of A-type lamins make the lamina “weaker.” As maintenance of the structural integrity of the cell nucleus was one of the first proposed functions of the nuclear lamina, a “weakened” lamina may lead to overall loss of a cell’s ability to withstand stress-induced damage, which may be of critical significance in contracting skeletal and cardiac muscle. Further support for this as a possible pathogenic mechanism comes from the observations that fibroblasts from *Lmna* null mice have defects in nuclear mechanics and mechanotransduction [97,98].

Some studies suggest that A-type lamins with amino acid substitutions causing striated muscle disease and lipodystrophy inhibit differentiation of precursor cells into myocytes and adipocytes. Expression of a mutant lamin A that causes Emery-Dreifuss muscular dystrophy inhibits *in vitro* differentiation of C2C12 myoblasts [99,100]. Overexpression of both wild type lamin A and a mutant lamin A that causes Dunnigan-type familial partial lipodystrophy inhibits differentiation of 3T3-L1 preadipocytes into adipocytes, suggesting that lamin A may negatively regulate adipocyte differentiation and that amino acid changes on the surface of the immunoglobulin-like fold of A-type lamins somehow lead to a “gain” of this function [101]. Another study has shown that accumulation of unprocessed prelamin A blocks adipocyte differentiation [102]. It remains to be determined how these *in vitro* observations relate to the maintenance of normally differentiated tissues in whole animals.

Diseases caused by genes encoding B-type lamins

Abnormalities in genes encoding B-type lamins have been linked to two very different disorders (Table 2). Adult-onset autosomal dominant leukodystrophy is a slowly progressive disorder characterized by symmetrical widespread myelin loss in the central nervous system with a phenotype is similar chronic progressive multiple sclerosis [103]. In 2000, Coffeen et al. [104] reported that the responsible genetic locus was localized to chromosome 5q31. In 2006, the same group reported that duplication of *LMNB1* was the cause of adult-onset autosomal dominant leukodystrophy and that overexpression of lamin B1 was detected in brains of affected individuals [105]. A very different disease, Barraquer-Simons syndrome, is a mostly sporadic acquired form of progressive lipodystrophy [106]. In 2006, based on the fact the *LMNA* mutations cause a type of lipodystrophy, Hegele et al. [107] sequenced *LMNB2* and found several nucleotide variants with a higher frequency in individuals with acquired Barraquer-Simons syndrome than in the control population.

There are little data as to how mutations in genes encoding B-type lamins cause disease. Homozygous mice with *Lmnb1* deleted survive embryonic development but die at birth with defects in lung and bone [108]. Embryonic fibroblasts from these mice have severe abnormalities in nuclear structure but normal mechanical properties [108,109]. Overexpression of lamin B1 in *Drosophila* eye leads to a degenerative phenotype and overexpression in cultured cells induced morphological abnormalities similar to those in cell with abnormal A-type lamins [105].

Diseases caused by genes encoding lamin-associated integral proteins of the inner nuclear membrane

Abnormalities in genes encoding lamin-associated integral proteins of the inner nuclear membrane have been linked todisorders primarily affecting nuclear structure, striated muscle or bone (Table 3). As noted above, X-linked Emery-Dreifuss muscular dystrophy is due to mutation in the *EMD* gene encoding emerin, an integral protein of the inner nuclear membrane [31–33]. The clinical features of X-linked and autosomal dominant Emery-Dreifuss muscular dystrophy are very similar, with the only reported difference being no significant increase in cardiac sudden death in individuals with the X-linked disorder (82,110). In contrast,

implantation of a cardiac defibrillator has been recommended for individuals with cardiomyopathy and *LMNA* mutations [111].

As with *LMNA* mutations, it is not understood how *EMD* mutations cause striated muscle disease. However, emerin interacts with A-type lamins [84,112–115], providing a rationale as to why certain mutations in *LMNA* encoding A-type lamins and mutations in *EMD* encoding emerin cause disorders with very similar phenotypes. The vast majority of *EMD* mutations causing Emery-Dreifuss muscular dystrophy lead to the absence of emerin from cells [32,33; see also UMD-*EMD* mutation database at http://www.umd.be:2010]. Similarly, many *LMNA* mutations causing striated muscle disease or loss of A-type lamins from cells leads to a redistribution of emerin from the nuclear envelope to the bulk endoplasmic reticulum [84,89, 90]. Emerin that has “escaped” from the nuclear envelope in cells lacking A-type lamins may be degraded by proteasomes [116]. Hence, both *EMD* mutations and *LMNA* mutations that cause Emery-Dreifuss muscular dystrophy may lead to some loss of an emerin at the inner nuclear membrane. Emerin may also regulate the activities of several other proteins involved in muscle cell differentiation and function [117]. In rare human subjects with mutations in both *LMNA* and *EMD*, the presentation severity of Emery-Dreifuss muscular dystrophy is increased, provide genetic evidence for the interaction between emerin and A-type lamins [118].

Deletion of *Emd* from mice does not lead to significant pathology [119,120]. However, fragility of myocyte nuclei and impaired expression of mechanosensitive genes in embryonic fibroblasts in response to strain have been reported in these emerin-deficient mice [120,121]. Furthermore, regenerating muscle from *Emd* null mice have cell cycle abnormalities and delayed myogenic differentiation, which are associated with perturbations to transcriptional pathways regulated by the retinoblastoma protein and MyoD [119]. Analysis of transcriptomes from muscles of human subjects with X-linked and autosomal dominant Emery-Dreifuss muscular dystrophy similarly shows disruption of retinoblastoma protein and MyoD pathways in muscle regeneration [122].

LBR is an integral inner nuclear membrane with a basic, amino-terminal domain that faces the nucleoplasm and a hydrophobic domain with multiple transmembrane segments [123,124]. LBR binds to B-type lamins, DNA and chromatin proteins [124–126]. Its hydrophobic domain is highly homologous to sterol reductases [127]. Heterozygous mutations in *LBR* cause Pelger-Huet anomaly [128]. Homozygous mutations lead to HEM/Greenberg skeletal dysplasia, which is associated with 3 beta-hydroxysterol delta 14-reductase deficiency [129]. Whereas Pelger-Huet anomaly is a benign disorder characterized by abnormal nuclear shape and chromatin organization in blood granulocytes, HEM/Greenberg skeletal dysplasia is generally lethal *in utero* and characterized by chondrodystrophy, fetal hydrops, short limbs and abnormal chondro-osseous calcification. Loss of function of one *LBR* allele therefore leads to subtle abnormalities of a highly structured nucleus whereas mutation in both alleles leads to a severe phenotype, which may result both from loss of the protein’s role in maintaining nuclear structure as well as its sterol reductase activity. Mutations in *Lbr* are responsible for the ichthyosis mouse, which have misshapen granulocyte nuclei similar to humans with Pelger-Huet anomaly and develop other abnormalities including alopecia, variable expression of syndactyly and hydrocephalus [130].

MAN1, encoded by the gene now called *LEMD3*, is an integral inner nuclear membrane protein with an amino-terminal nucleoplasmic domain that contained a LEM motif, two transmembrane segments and a nucleoplasmic carboxyl-terminal domain [131]. The amino-terminal domain of MAN1 interacts directly with A-type lamins and the protein barrier-to-autointegration factor [132]. The carboxyl-terminal nucleoplasmic domain binds to regulatory-Smads and inhibits signaling by transforming growth factor-beta and bone morphogenic protein [133–137]. This explains why heterozygous loss-of-function mutations cause the

sclerosing bone dysplasias osteopoikilosis, Buschke-Ollendorff syndrome, and familial melorheostosis, which are sometimes associated with hyperproliferative skin and tendon lesions [135]. *LEMD3* germline mutations are not found in most subjects with sporadic, non-familial melorheostosis; however, somatic mutations have not been excluded [138,139]. The portion of MAN1 involved in Smad-binding also exhibits a DNA-binding winged helix domain [140]. Genetically modified mice that do not express MAN1 have abnormal remodeling of the embryonic vasculature, a process mediated by transforming growth factor-beta [141]. Mice with one copy of the allele encoding MAN1 are apparently normal [141].

Concluding comments and future directions

The nuclear lamina and nuclear envelope have become focal points of investigation for scientists and clinicians interested in a wide spectrum of human diseases. In the future, it is likely that more “laminopathies” will be identified as mutations are discovered in other genes encoding lamin-associated proteins and perhaps other mutations in genes encoding lamins are shown to cause additional disorders. Taylor et al. [142] recently reported a polymorphism in the *TMPO* gene encoding LAP2-alpha in two family members with cardiomyopathy. The polymorphism affected an amino acid located in the domain of the LAP2-alpha known to interact with A-type lamins, compromising the interaction. Whether the reported polymorphism is a mutation causing dilated cardiomyopathy still requires further confirmation with the identification of additional cases. More recently, Gros-Louis [143] reported that mutations in *SYNE1* cause a rare form of autosomal recessive cerebellar ataxia. *SYNE1* is one of two mammalian genes encoding multiple isoforms of proteins that have been given several different names but are most commonly referred to as nesprins. Depending on their size, nesprins are localized to either the inner nuclear membrane, where they may interact with lamins, or to the outer nuclear membrane, where they interact with transmembrane SUN proteins in the perinuclear space, which in turn bind to lamins inside the nucleus [144].

Studies of other inherited diseases involving proteins localized to the nuclear envelope may provide insights into the pathophysiology of “laminopathies.” Mutations in a gene encoding a nuclear pore complex protein called ALADIN cause triple A syndrome, an autosomal recessive disorder characterized by adrenal insufficiency, achalasia and alacrima [145]. Notably, little attention has been given to examining nucleocytoplasmic transport in “laminopathies” but selective defects in this process could potentially be involved in pathogenesis. Mutations in the gene *DYT1* encoding torsinA cause the movement disorder DYT1 dystonia [146]. TorsinA is an ATPase normally localized to the bulk endoplasmic reticulum but the mutations cause the protein to be concentration in the perinuclear space, between the inner and outer nuclear membrane [147–149]. In the perinuclear space, torsinA interacts with the luminal portion of the transmembrane protein lamina-associated polypeptide 1, which binds to lamins on the other side of the inner nuclear membrane [150].

Future clinical and genetic studies of “laminopathies” need to consider newly described functions of lamins, such as their role connecting the nucleus to the cytoskeleton via SUNs and nesprins [144]. At the same time, scientists studying the properties of nuclear lamins and associated proteins *in vitro*, in cell culture and in animal models must consider what is learned from genetics and clinical investigations involving human subjects. Only a combination of basic and clinical research will provide novel insights into pathophysiology and the development of novel treatments.

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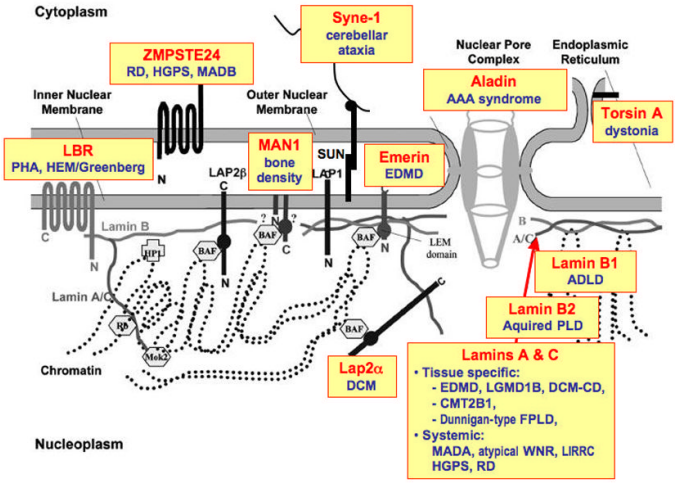

Figure 1.

Schematic diagram of the nuclear envelope showing localizations and interactions of various proteins. Boxes highlight diseases caused by mutations in genes encoding the proteins indicated. RD: restrictive dermopathy, HGPS: Hutchinson-Gilford progeria syndrome, PHA: Pelger-Huet anaomaly, EDMD: Emery-Dreifuss muscular dystrophy, ADLD: Adult onset autosomal dominant leukodystrophy, BSS: Barraquer-Simons syndrome, LGMD: limb-girdle muscular dystrophy; DCM: dilated cardiomyopathy; CMT: Charcot-Marie-Tooth, FPLD: familial partial lipodystrophy, MADA / MADB: mandibuloacral dysplasia, WNR: Werner syndrome. For more specific disease nomenclature, see Table 1, Table 2 and Table 3.

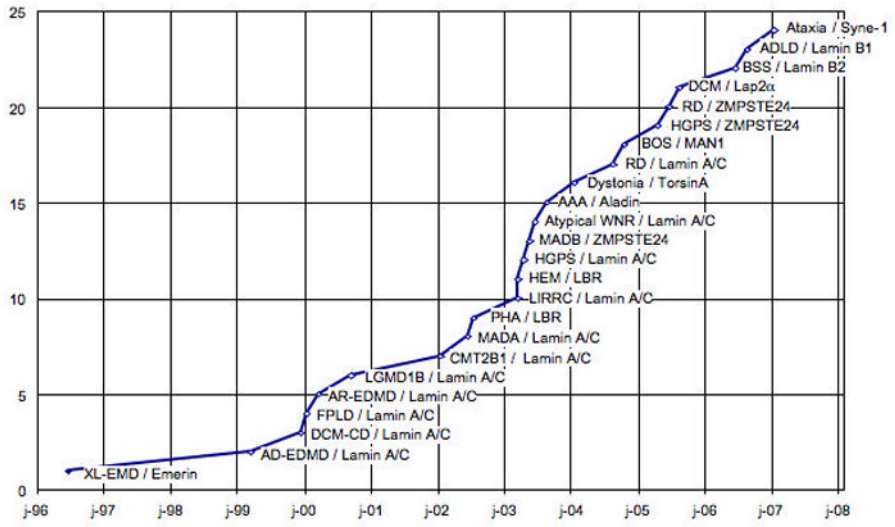

Figure 2.

Graph showing number of diseases caused by mutations in genes encoding nuclear lamins or associated proteins reported (y-axis) versus year (x-axis). Emerin, which is mutated in X-linked EDMD, was localized to the nuclear envelope in 1996. *LMNA* mutations were reported to cause autosomal dominant EDMD in 1999. In 2000, *LMNA* mutations were reported to cause autosomal recessive EDMD, cardiomyopathy dilated 1A, limb girdle muscular dystrophy type 1B and Dunnigan-type familial partial lipodystrophy. In 2002, *LMNA* mutations were reported to cause mandibulacral dysplasia and Charcot-Marie-Tooth disorder type 2B1 and mutations in *LBR* were reported to cause Pelger-Huet anomaly. In 2003, *LMNA* mutations were reported to cause Hutchinson-Gilford progeria syndrome, atypical Werner syndrome and lipoatrophy with diabetes, hepatic steatosis, hypertrophic cardiomyopathy and leukomelanodermic papules; *LBR* mutations were reported in HEM/Greenberg dysplasia; *ZMPSTE24* reported in mandibulacral dysplasia and mutation in the gene encoding Aladin reported in triple A syndrome. In 2004, mutations in torsinA that cause DYT1 dystonia were reported to lead to abnormal protein localization in the perinuclear space, *LMNA* mutations were reported to cause restrictive dermopathy and *LEMD3* mutations to cause Buschke-Ollendorff Syndrome and related sclerosing bone dysplasias. In 2005, *ZMPSTE24* mutations were reported to cause a progeria syndrome and restrictive dermopathy; Lap2α polymorphisms were reported in two siblings with dilated cardiomyopathy. In 2006, duplication of *LMNB1* was reported to cause adult- onset, autosomal dominant leukodystrophy and mutations in *LMNB2* Barraquer-Simons syndrome. In 2007, mutations in *SYNE1* were reported to cause a form of cerebellar ataxia.

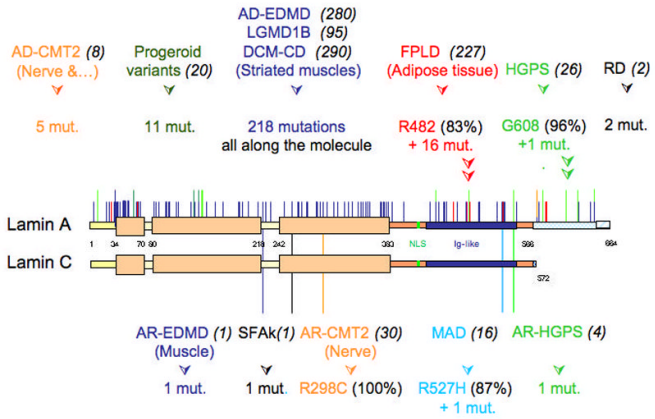

Figure 3.

Spectrum of disease-causing *LMNA* mutations. Schematic representations of lamin A and lamin C are shown. Portions of the proteins affected by *LMNA* mutations identified causing different diseases are indicated. Dominant disorders due to heterozygous *LMNA* mutations are depicted on the top and recessive disorders due to homozygous mutations are presented below (for more details, see UMD-LMNA mutation database at http://www.umd.be). Numbers in parentheses in black next to each disease acronym indicate the numbers of reported individuals carrying that *LMNA* mutation and presenting the corresponding phenotype. Figure is updated from Broers J, Ramaekers F, Bonne G, Hutchison C. The nuclear lamins: laminopathies and their role in premature ageing. *Physiological Reviews* 2006;86:967–1008 (used with permission).

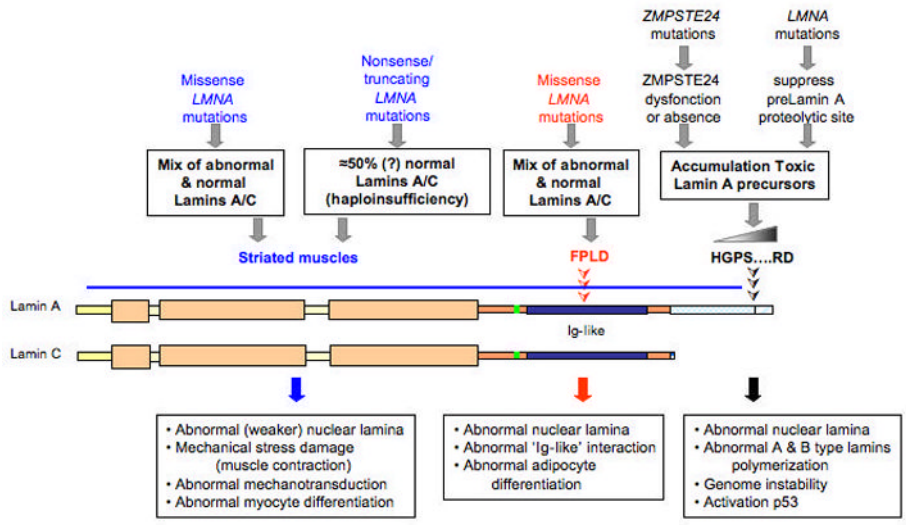

Figure 4.

Summary of potential pathogenic mechanisms resulting from mutations in *LMNA* and *ZMPSTE24*. See text for details.

Table 1

Diseases caused by mutations in *LMNA*. On-line Mendelian Inheritance in Man (OMIM ; http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM) entry numbers are given in parentheses.

Diseases of Striated Muscle
Autosomal Dominant Emery-Dreifuss Muscular Dystrophy (#181350)
Autosomal Recessive Emery-Dreifuss Muscular Dystrophy (#604929)
Autosomal Dominant Cardiomyopathy Dilated 1A (#115200)
Autosomal Dominant Limb Girdle Muscular Dystrophy Type 1B (#159001)
Peripheral Neuropathy
Autosomal Recessive Charcot-Marie-Tooth Disorder Type 2B1 (#605588)
Lipodystrophy Syndromes
Autosomal Dominant Dunnigan-type Familial Partial Lipodystrophy (#151660)
Autosomal Dominant Lipoatrophy with Diabetes, Hepatic Steatosis, Hypertrophic Cardiomyopathy and Leukomelanodermic Papules (#608056)
Autosomal Recessive Mandibuloacral Dysplasia (#248370)*
Accelerated Aging Disorders
Autosomal Dominant Atypical Werner Syndrome (#277700 for Werner syndrome)
Autosmal Dominant Hutchinson-Gilford Progeria Syndrome (#176670)
Autosomal Dominant Restrictive Dermopathy Lethal (#275210)

*Mandibuloacral dysplasia also has features of accelerated aging.

Table 2

Diseases caused by mutations in *LMNB1* and *LMNB2* encoding B-type lamins. On-line Mendelian Inheritance in Man entry numbers are given in parentheses.

LMNB1
Adult-onset, Autosomal dominant Leukodystrophy (#169500)
LMNB2
Barraquer-Simons Syndrome, Heterozygous Mutations (#608709)

Table 3

Diseases caused by mutations in genes encoding lamin-associated proteins of the inner nuclear. On-line Mendelian Inheritance in Man entry numbers are given in parentheses.

EMD
X-linked Emery-Dreifuss Muscular Dystrophy (#310300)
LBR
Pelger-Huet Anomaly, Autosomal Recessive (#169400)
Hydrops-Ectopic Calcification-Moth-Eaten Skeletal Dysplasia (HEM)/Greenberg Skeletal Dysplasia, Autosomal Dominant (#215140)
LEMD3 (MAN1)
Buschke-Ollendorff Syndrome, Autosomal Recessive (#166700)
Melorheostosis, Familial and Melorheostosis with Osteopoikilosis, Autosomal Recessive (#155950)