Chapter 2

Laminopathies

Tomás McKenna, Jean-Ha Baek and Maria Eriksson

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/53793

1. Introduction

1.1. The nuclear envelope

The nucleus is the defining characteristic organelle of the eukaryotes, and contains the nuclear genome. It is segregated from the cellular cytoplasm by the bilayer nuclear envelope (Figure 1), which consists of concentric inner and outer nuclear membranes, between which lies the perinuclear space. The outer nuclear membrane is contiguous with the rough endoplasmic reticulum, like which it is studded with protein producing ribosomes, and the perinuclear space is contiguous with the lumen of the endoplasmic reticulum. Transport across the nuclear envelope is accommodated by nuclear pore complexes (NPCs). The NPCs are the site where the inner and outer nuclear membranes are connected, as their shared lipid bilayers are united at that point. These NPCs are large, complex and heterogeneous protein structures, made up of multiple copies of approximately 30 different proteins, called nucleoporins [1]. NPCs span the inner and outer nuclear membranes, and allow the regulated relocation of molecules between the nucleoplasm and cytoplasm. While smaller molecules, such as small metabolites or proteins under 40 kDa, are passively transported through the NPCs, larger molecules such as mRNAs, tRNAs, ribosomes and signalling molecules can be actively transported from the nucleus, while signalling molecules, proteins, lipids and carbohydrates are actively transported both into and out of the nucleus [2,3].

The inner nuclear membrane is embedded by various inner nuclear membrane proteins, such as LAP1, LAP2 and MAN1, which are involved in cell cycle control, linking the nucleus to the cytoskeleton and chromatin organisation [4,5]. Underlying and connected by various nuclear envelope proteins to the inner nuclear membrane are the nuclear lamina, a thin (30-100nm) and densely woven fibrillar mesh of intermediate filaments, composed of evolutionarily conserved lamins A, B1, B2 and C, and lamin associated proteins. These proteins are closely associated with the NPCs (Figure 1). This assembly of outer nuclear membrane,

inner nuclear membrane, NPCs, and the lamina can be thought of as complex interface, coupling the nuclear genome to the rest of the cell, allowing for a sophisticated means of regulated traffic between inner and outer nuclear space, while compartmentalising DNA replication, RNA transcription and mRNA editing from translation at the ribosomes [3].

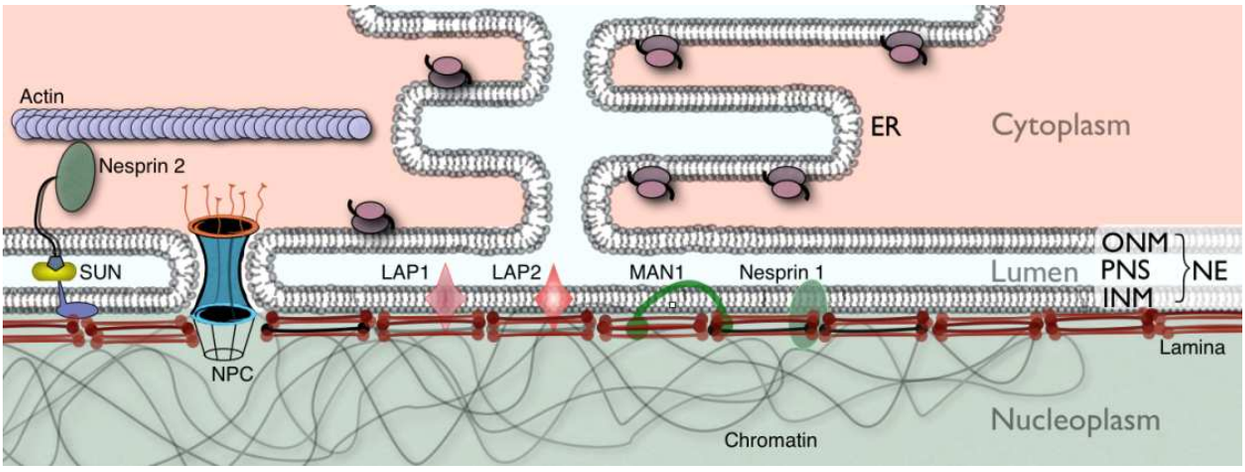

Figure 1. Structure of the nuclear envelope and associated proteins. The nuclear A-type and B-type lamins underlay the nucleoplasmic side of the inner nuclear membrane, and provide stability to the nucleus, an organisational binding platform for chromatin, and facilitate localisation and binding of nuclear pore complexes as well as a large family of nuclear envelope proteins. ONM, outer nuclear membrane; PNS, perinuclear space; INM, Inner nuclear membrane; NE, Nuclear envelope; NPC, Nuclear pore complex; ER, Endoplasmic reticulum, The structures on the ER represent ribosomes.

The nuclear lamins are type V intermediate filaments (IFs), and are closely related to the cytoplasmic intermediate filaments (types I-IV, which include the keratins), differing by the presence of a nuclear localisation signal (NLS) located in the initial section of the tail domain [6]. Physically, these lamins have the characteristic tripartite assemblage of intermediate filaments; a short globular N-terminal head domain and a long C-terminal tail domain containing an immunoglobin-like domain, separated by a conserved central alpha-helical rod domain (Figure 4). Coiled-coil homodimers of A- and B-type lamins are formed by interaction between adjacent heptad hydrophobic repeats on the central rod domain, and charged residues along the centre of this dimer promote further assembly between dimers, leading to assembly of filamentous fibrils, whereas the N and C terminal endings facilitate head-to-tail polymerisation [6-8]. The nuclear lamina has been shown to have a major role in nuclear structure, heterochromatin organisation and gene regulation [8-11].

1.2. The lamins

The *LMNA* gene (Online inheritance in man: 150330) is located on chromosome 1q21.2-q21.3 and is composed of 12 exons. Exon 1 codes the N-terminal head domain, exons 1-6 code the central rod domain, and exons 7-9 code the C-terminal tail domains. Exon 7 also contains the 6 amino acid NLS, necessary for importation of the protein into the nucleus by nuclear transport through NPCs [6,12,13]. Exons 11 and 12 specifically code lamin A, and the CaaX

motif of prelamin A (the immature form of lamin A) is located in exon 12. The CaaX motif is a series of four amino acids at the C-terminus of a protein, consisting of a cysteine, two of any aliphatic amino acid, and a terminal amino acid. It is important for the post-translational processing including farnesylation. The motif is identified by the prenyltransferases, farnesyltransferase, or geranylgeranyltransferase-I, and is modified and removed during maturation of lamin A [14]. Lamin C does not contain a CaaX motif, and terminates in an alternative six amino-acid C-terminal end (VSGSRR) (Figure 4).

LMNA produces the major lamin A and C proteins (Figure 4), and the minor AΔ10 and C2 proteins by alternative splicing within exon 10, and they are differentially expressed in a developmentally and tissue specific way [13,15]. Lamin AΔ10 is identical to lamin A, except exon 10 is absent [16], and lamin C2 (which is expressed exclusively in germ cells) is identical to lamin C, except an alternative exon, 1C2, located in intron 1 of *LMNA*, codes for the N-terminal head domain [17,18]. A TATA-like promotor sequence (TATTA) for RNA polymerase attachment, and a CAT-box for RNA transcription factor attachment, lie 236 and 297 base pairs upstream of the ATG initiation codon [6,13].

A-type lamins are expressed only in differentiated cells, suggesting that they have a role in stabilising differential gene expression [15,16,19,20]. The main products in somatic cells are lamins A and C, with C2 and AΔ10 being less common isoforms, lamin C2 being specific to the testes [6,13,16,21]. The first 566 amino acids of lamins A and C are identical. However, at the C-terminals lamin A has 98 unique amino acids, and as with lamin B1 and B2, ends in a CaaX box motif, whilst lamin C has 6 unique terminal amino acids.

The second family of lamins, the B-type lamins, consist of lamin B1 encoded by the *LMNB1* gene, and lamin B2 and B3, encoded by the *LMNB2* gene. At least one of these B-type lamins are expressed in all cell types [13,22-25]. Lamin B3 is a minor variant, arising from differential splicing and alternative polyadenylation of *LMNB2* and is expressed in male germ cells [24]. B-type lamins have a CAAX motif and are constitutively farnesylated, whereas lamin A loses its farnesyl group once targeted to the lamina [26].

The maturation process for lamin A, lamin B1 and B2 is detailed below, with these post-translational modifications taking place in the nucleus [27].

- Prenylation: A farnesyl or geranylgeranyl isoprenoid group is covalently attached to the cysteine of the CaaX motif of prelamin A, lamin B1 and B2 by farnesyltransferase or geranylgeranyltransferase-I, respectively.
- Cleavage: The terminal -aaX amino acids are removed by RCE1 and FACE1 for prelamin A, and by RCE1 alone for lamin B1 and B2.
- Methylation: The now exposed C-terminal farnesylcysteine undergoes a methylation step, performed by a carboxymethyltransferase, isoprenylcysteine carboxyl methyltransferase (ICMT) [28]. This is the final post-translational step for B-type lamins, therefore they retain the farnesylcysteine α-methyl ester at the C-terminus.
- Second cleavage (for prelamin A only): FACE1 cleaves the carboxy-terminal 15 amino acids, including the farnesylcysteine methyl ester group, at the NM [29]. This final modifi-

cation step completes the post-translational modification of prelamin A to mature lamin A. This maturation is thought to aid localisation of lamin A to the nuclear rim [30,31].

2. Laminopathies

Diseases caused by mutations in the *LMNA* gene are collectively known as primary laminopathies [32], whereas mutations in genes coding for B-type lamins (*LMNB1* and *LMNB2*), prelamin A processing proteins (such as *ZMPSTE24*), or lamin-binding proteins (such as *EMD*, *TMPO*, *LBR* and *LEMD3*) are known as secondary laminopathies [33,34]. At present, 458 different mutations from 2,206 individuals have been identified in the *LMNA* gene (www.umd.be/LMNA/). These mutations can be *de novo* or heritable, with a gain- or loss-of-function effect, and with severity ranging from minor arrhythmia arising in adolescence to a neonatally lethal tight skin condition [35]. Unlike with the *LMNA* gene, there are only a few mutations found affecting B-type lamins [36]. This is most likely due to the wide-ranging and non-redundant functions of lamin B1 in early growth and development [29].

Laminopathies are caused by a heterogeneous set of pleiotropic mutations affecting universally expressed genes. However, their effects can be tissue specific to a degree, allowing for categorisation into five groups (Table 1). Striated muscles are affected in muscular dystrophies, peripheral nerves are affected in neuropathies, adipose tissue in lipodystophies, several tissues affected with premature development of multiple markers of senescence in segmental progeriod diseases, and finally diseases displaying symptoms from more than one category are known as overlapping syndromes.

2.1. Muscular dystrophies

Within this following section, selected muscular dystrophies will be detailed, while Table 2 shows a complete listing of known muscular dystrophy laminopathies, at the time of writing.

2.1.1. Emery-dreifuss muscular dystrophy

Emery-Dreifuss muscular dystrophy (EDMD), first described in 1955 [37], is the most prevalent laminopathy, affecting 1 in 100,000 births. It is also a prototypical laminopathy, occurring both as a primary and secondary laminopathy. The most commonly occurring form is autosomal dominant (AD-EDMD). It also occurs as an autosomal recessive (AR-EDMD) or X-linked (XL-EDMD) form [38,39]. Mutations in the emerin gene are responsible for XL-EDMD [40-43], while mutations in the *LMNA* gene have been found to cause AD-EDMD, AR-EDMD and sporadic EDMD [44-47]. It most commonly occurs with nonsense mutations, although there has also been a report of at least one case with a premature stop codon in exon 1 of *LMNA* resulting in loss-of-function and haploinsufficiency as the genetic mechanism (Figure 4). The similarities in the clinical features of EDMD irrespective of whether the causative mutation is affecting emerin or lamin A/C indicates a close functional relationship between these proteins. Emerin mediates linkage between membranes and the cytoskeleton, and is closely linked to lamins [40].

http://dx.doi.org/10.5772/53793

Laminopathy	Acronym	OMIM	Locus	Gene
Muscular dystrophy				
Cardiomyopathy, dilated, 1A	CMD1A	115200	1q22	*LMNA*
Emery-Dreifuss muscular dystrophy 1, X-linked	EDMD1	310300	Xq28	*EMD*
Emery-Dreifuss muscular dystrophy 2, AD	EDMD2	181350	1q22	*LMNA*
Emery-Dreifuss muscular dystrophy 3, AR	EDMD2	181350	1q22	*LMNA*
Emery-Dreifuss muscular dystrophy 4, AD	EDMD4	612998	6q25.1-q25.2	*SYNE1*
Emery-Dreifuss muscular dystrophy 5, AD	EDMD5	612999	14q23.2	*SYNE2*
Emery-Dreifuss muscular dystrophy 6, X-linked	EDMD6	300696	Xq26.3	*FHL1*
Heart-hand syndrome, Slovenian type	HHS-S	610140	1q22	*LMNA*
Malouf syndrome	MLF	212112	1q22	*LMNA*
Muscular dystrophy, congenital	MDC	613205	1q22	*LMNA*
Muscular dystrophy, limb-girdle, type 1B	LGMD1B	159001	1q22	*LMNA*
Lipodystrophy				
Acquired partial lipodystrophy	APLD	608709	19p13.3	*LMNB2*
Lipodystrophy, familial partial, 2	FPLD2	151660	1q22	*LMNA*
Mandibuloacral dysplasia with type A lipodystrophy	MADA	248370	1q22	*LMNA*
Mandibuloacral dysplasia with type B lipodystrophy	MADB	608612	1p34.2	*ZMPSTE24*
Neuropathies				
Adult-onset autosomal dominant leukodystrophy	ADLD	169500	5q23.2	*LMNB1*
Charcot-Marie-Tooth disease, type 2B1	CMT2B1	605588	1q22	*LMNA*
Segmental progeroid diseases				
Hutchinson-Gilford progeria syndrome	HGPS	176670	1q22	*LMNA*
Restrictive dermopathy	RD	275210	1p34.2/1q22	*ZMPSTE24/LMNA*
Atypical Werner syndrome	AWRN	277700	8p12	*RECQL2*
Overlapping syndromes				
Hydrops-Ectopic calcification-moth-eaten skeletal dysplasia	HEM	215140	1q42.12	*LBR*
Pelger-Huet anomaly	PHA	169400	1q42.12	*LBR*
Reynolds syndrome	RS	613471	1q42.12	*LBR*
Buschke-Ollendorff syndrome	BOS	166700	12q14.3	*LEMD3*
Melorheostosis with osteopoikilosis	MEL	155950	12q14.3	*LEMD3*

Table 1. A summary of primary and secondary laminopathies, grouped into five categories. LMNA, Lamin A/C; EMD, Emerin; SYNE1, Nesprin-1; SYNE2, Nesprin-2; FHL1, four and a half LIM domains; LMNB1, lamin B1; LMNB2, lamin B2; ZMPSTE24, zinc metallopeptidase (STE24 homolog); RECQL2, Werner syndrome, RecQ helicase-like; LBR, lamin B receptor; LEMD3, LEM domain-containing protein 3.

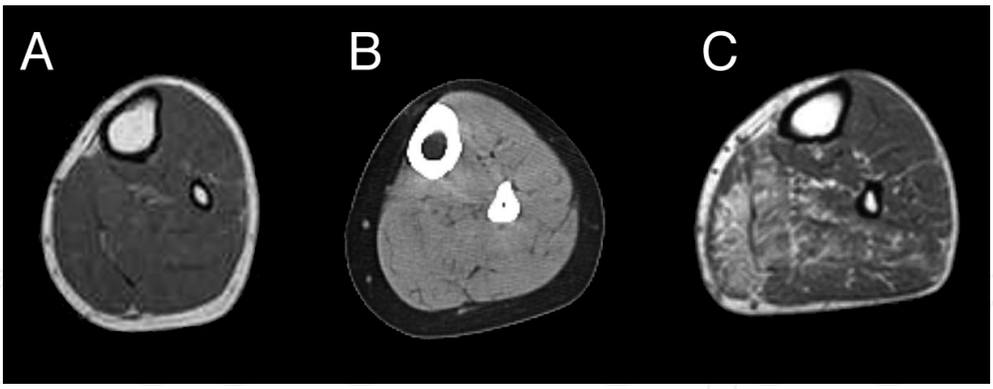

Figure 2. Lower limb imaging of skeletal muscles from patients with laminopathies. Leg muscles from an unaffected control individual (A), a 44 years old female with LGMD1B, LMNA c.673C>T, p.R225X (B), and a 50 years old male with EDMD2, LMNA c.799T>C, p.Y267H (C). While the LGMD1B muscle shows a mild involvement of the medial head of gastrocnemius and moderate involvement of soleus (B) there is a moderate to severe involvement of the same muscles in the EDMD2 patient (C). Photo courtesy of Dr. Nicola Carboni and Dr. Marco Mura, University of Cagliari, Sardinia, Italy.

EDMD is characterised by an onset in the teenage years of a slow, progressive wasting of skeletal muscle tissue in the shoulder girdle and distal leg muscles. This atrophy leads to muscle weakness around the humerus and fibula (a pattern described as scapulo-humeroperoneal), early contractures of the *pes cavus* (resulting in high arched feet), proximal muscles of the lower leg and upper arm, and the elbow and Achilles tendons. Muscle cell damage is indicated by elevated serum creatine kinase levels. Muscle pathology shows variations in muscle fibre sizes and type-1 fibre atrophy. Cardiac muscle is also affected, with problems arising in early adulthood. Atrial rhythm disturbances, atrioventricular conduction defects, arrhythmias and dilated cardiomyopathy with atrial ventricular block lead to severe ventricular dysrhythmias and death [38,48].

2.1.2. Limb-girdle muscular dystrophy, type 1B

Limb-girdle muscular dystrophy, type 1B (LGMD1B) is a slowly progressive variant caused by an autosomal dominant mutation of the *LMNA* gene, and is characterised by a limb-girdle pattern of muscular atrophy [49,50].

Patients display a classic limb-girdle pattern of muscle atrophy, with a proximal lower limb muscular weakness starting by age 20. By the 30s and 40s upper limb muscles also gradual weakened [49]. As in EDMD, serum creatine kinase levels were normal or elevated. The late occurrence or absence of spinal, elbow and Achilles contractures distinguishes LGMD1B from EDMD. Cardiac conduction abnormalities with dilated cardiomyopathy also occur. One neonatally lethal case of LGMD1B was found to be caused by a homozygous *LMNA* Y259X mutation [51].

2.1.3. Dilated cardiomyopathy with conduction defect 1

Dilated cardiomyopathy with conduction defect 1 (CMD1A) is a highly heterogeneous disease, both genetically and phenotypically, with 16 genes currently found to be causatively

mutated in cases of CMD1A [52]. Five heterozygotic missense mutations in the *LMNA* gene were identified in 5 of 11 families with autosomal dominant CMD [53].

Dilated cardiomyopathy is a serious cardiac condition, in which the heart becomes weakened and enlarged, with downstream effects on the lungs, liver and other organs. Conduction problems and dilated cardiomyopathy arise, leading to frequent heart failure and sudden death events. Affected family members have little or no associated skeletal myopathy.

2.1.4. Malouf syndrome

Malouf syndrome (MLF) is an extremely rare disorder with only a handful of cases described in the literature. The disease has been found to be caused by one of two mutations in exon 1 of the *LMNA* gene. These mutations, A57P and L59R (Figure 4), have been designated as causing AWS or atypical HGPS, however genital anomalies and missing progeroid features suggest instead a distinct laminopathy [54,55].

In males primary testicular failure, and in females premature ovarian failure, is a characteristic feature of the disease. Mild to moderate dilated cardiomyopathy also occurs. Micrognathia and sloping shoulders can give an atypical progeroid phenotype, however in patients suffering from MLF there is no severe growth failure, alopecia, or atherosclerosis [54].

2.1.5. Heart-hand syndrome, Slovenian type

The heterogeneous family of genetic diseases characterised by both congenital cardiac disease with limb deformities are known as Heart–hand syndromes (HHS). The Heart-hand syndrome, Slovenian type (HHS-S) disorder has been shown to be caused by a mutation (IVS9-12T-G) in intron 9 of the *LMNA* gene. It is an exceedingly rare disorder affecting several generations of a single family in Slovenia [56].

The characteristic changes to the hands and feet include short distal, and proximal phalanges, as well as webbing or fusion of the fingers or toes. Dilated cardiomyopathy, with an adult-onset progressive conduction disorder is also present, with sudden death due to ventricular tachyarrhythmia [56,57].

2.2. Lipodystrophies

Within this section, selected lipodystrophies were detailed, while Table 2 shows a complete listing of known lipodystrophy laminopathies, at the time of writing.

2.2.1. Familial partial lipodystrophy type 2

Familial partial lipodystrophy type 2 (FPLD2; Dunnigan variety of familial partial lipodystrophy) is an autosomal dominant lipodystophy, caused by a heterozygotic mutation in the *LMNA* gene [58-60]. Mutations are clustered in exons 8 and 11, in the globular C-terminal domain region of type-A lamins, the most common of which is a substitution of arginine at position 482 with a neutral amino acid [61].

FPLD2 shows the characteristic lypodystrophy reduction or loss of subcutaneous adipose tissue in certain regions, starting in childhood, puberty or early adulthood. Patients gradually lose fat from the upper and lower limbs, buttocks and trunk. However intramuscular and bone-marrow fat are preserved. Adipose tissue may increase around the face, neck, back and intra-abdominally [62]. Insulin resistance can occur with consequent complications of diabetes, dyslipidaemia, hypertension and hepatic steatosis. Clinical features may also include abnormalities of the menstrual cycle, hirsutism, and acanthosis nigricans.

2.2.2. Mandibuloacral dysplasia, type A and B

Mandibuloacral dysplasia (MAD) is an autosomal recessive disease, with strongly heterogeneous clinical features. It is categorised into type A (MADA), which is caused by mutations in the *LMNA* gene and type B (MADB), which is caused by mutations in the *ZMPSTE24* gene [63-65].

Patients with MADA exhibit an acral loss of adipose tissue and a normal or increased fatty layer in the face, neck and trunk, whereas MADB is marked by a severe progressive glomerulopathy, and generalised lipodystrophy affecting the extremeties, but also the face. Growth retardation, osteolysis of the digits, pigmentary changes, mandibular hypoplasia and skeletal anomalies occur in both variants. Patients may also display some symptoms of progeria, and metabolic disorders such as insulin-resistant diabetes [63,66].

2.3. Neuropathies

2.3.1. Adult-onset autosomal dominant leukodystrophy

Adult-onset autosomal dominant leukodystrophy (ADLD) is an adult-onset neuropathy, caused by a heterozygous tandem genomic duplication resulting in a duplication of the lamin B1 gene, and a corresponding over-expression of lamin B1 [67,68].

ADLD is slowly progressive, with symptoms becoming apparent in the 40s and 50s, and are markedly similar to progressive multiple sclerosis. These symptoms include symmetric demyelination of the brain and spinal cord, autonomic abnormalities, as well as pyramidal and cerebellar dysfunction. Pathological examination reveals that ADLD differs from progressive multiple sclerosis with a lack of astrogliosis and a preservation of oligodendroglia in the presence of subtotal demyelination [67].

2.3.2. Charcot-Marie-Tooth disorder

Charcot-Marie-Tooth disorder (CMT) disorder was described simultaneously by Charcot, Marie and Tooth in 1886. Today the disease is considered a spectrum of phenotypically and genetically heterogeneous inherited neuropathies, with over 40 genes known to be associated with the disorder (www.molgen.ua.ac.be/CMTMutations). The autosomal recessive variant, CMT2B1 (AR-CMT2A or CMT4C1) (OMIM: 605588), is known to be caused by a mutation in *LMNA* [69,70]. All CMT disorders affect approximately 1 in 2,500 people, making them the most common group of inherited neuropathies [71,72]. Individuals with nor-

mal or slightly reduced sensory nerve conduction velocities (greater than 38 m/s) are categorised as type 2 (CMT2), and are diagnosed as axonal neuropathies [73]. The disease-causing mutation for CMT2B1 was identified as a homozygous *LMNA* c.829C>T mutation in exon 5 of the *LMNA* gene, causing an R298C amino acid substitution [69,70].

Sufferers of CMT2B1 display an early onset muscle wasting in the distal lower limbs (peroneal muscular atrophy syndrome), high arched feet (*pes cavus*), with a curled, claw-like appearance of the toes, as well as walking difficulties stemming from reduced tendon reflexes [74,75].

2.4. Segmental progeroid diseases

2.4.1. Hutchinson-Gilford progeria syndrome

Hutchinson-Gilford progeria syndrome (HGPS) is an extremely rare, fatal genetic disorder that displays a marked phenotype of premature senility (see chapter on Hutchinson-Gilford progeria syndrome). At least 90% of all HGPS cases are caused by a *de novo* mutation, where a single base nucleotide in exon 11 of the *LMNA* gene is substituted (c.1824C>T, p.G608G). This mutation results in an increased activation of a cryptic splice site in exon 11, which in turn increases the production and subsequent accumulation of a truncated, partially processed prelamin A protein that remains farnesylated, called progerin [76].

Individuals with HGPS are born normally but they present failure to thrive and scleroderma-tous skin with loss of subcutaneous fat usually before one year of age. The early symptoms of HGPS also include short stature, and low body weight, which is followed by the occurrence of a tight skin over the abdomen and thighs beginning at the age one or two. Alopecia, scleroderma and the loss of subcutaneous fat also occur at early stages of the disease, succeeded by thin epidermis, fibrosis in the dermis and a loss of skin appendages. Patients often show micrognathia, prominent eyes and veins along with a small beaked nose. Atherosclerosis and calcification of the thoracic aorta is recurrent and death occurs in the early teenage years, most commonly due to cardiovascular complications [76-80].

2.4.2. Restrictive dermopathy

Restrictive dermopathy (RD) is a rare lethal autosomal recessive disease most often caused by loss of function mutations of the *ZMPSTE24* gene, and one case has been described with a dominant mutation in intron 11 of the *LMNA* gene (Figure 4). Similar to HGPS, progerin accumulation occurs, however at a greater level, and this accumulation has been proposed to correspond to the severity of the clinical symptoms [81].

Intrauterine growth retardation is an early sign of RD, along with decreased foetal movement. Thin, translucent, tight skin, as well as joint contractures, respiratory insufficiency, a small pinched nose, micrognathia and mouth in a characteristic fixed ‘o’ shape are the signs of the disease at birth. Usually respiratory failure due to the tight skin leads to a neonatal death within a few weeks of birth [81,82].

2.4.3. Atypical Werner syndrome

First described in 1904 by Otto Werner, Werner syndrome (WS) is caused by mutations in the *WRN* gene, encoding a nuclear helicase [83]. However approximately 20% of patients diagnosed with WS do not carry mutations in the *WRN* gene, and are classed as suffering from atypical Werner syndrome (AWS). A minority of these have been found to carry heterozygous mutations in the *LMNA* gene, typically at the N-terminal region [84].

WRN is known as 'progeria of the adult' and symptoms, such as pubertal growth failure, begin to emerge in the early teenage years. Then in the late teenage years or early 20s, skin atrophy and ulcers, cataracts, type 2 diabetes mellitus, osteoporosis, atherosclerosis, hair greying and alopecia follow. Lipoatrophy and a mild axonal sensorimotor polyneuropathy can also occur. There is also an increased risk of malignancies, reduced fertility and gonadal atrophy. Severe coronary, and peripheral artery disease is also present, and the most common causes of death are myocardial infarction and cancer by a median age of 54 [85,86].

2.5. Overlapping syndromes

2.5.1. Hydrops-Ectopic calcification-moth-eaten skeletal dysplasia

Hydrops-Ectopic calcification-moth-eaten (HEM) skeletal dysplasia is an extremely rare, autosomal recessive lethal chondrodystrophy, which was first described by Greenberg in 1988, in an examination of two sibling foetuses. A 7-bp, homozygous 1599–1605 TCTTCTArCTAGAAG substitution in exon 13 of the lamin B receptor gene (*LBR*), gave rise to a premature stop codon, resulting in a truncated protein and loss of *LBR* activity [87,88].

In utero radiological examination revealed ectopic calcifications, a 'moth eaten' appearance of the shortened tubular bones. Extramedullary erythropoiesis was also found in both foetuses [89].

2.5.2. Pelger-Huet anomaly

Pelger-Huet anomaly (PHA) is a benign, autosomal dominant blood disorder, with characteristic misshapen, hypolobulated nuclei and abnormally course chromatin in blood granulocytes, caused by a mutation in the *LBR* gene [89,90]. As PHA was found in relatives to two HEM cases, it is thought that these disorders may be related [91].

Heterozygous patients are clinically normal, while homozygosity has been associated with skeletal dysplasia and early lethality in animal models, although at least one case of non-lethal homozygotic PHA has been found in humans [92].

2.5.3. Reynolds syndrome

Reynolds syndrome (RP) is caused by a heterozygous mutation in the *LBR* gene, and was first described in 1971 by Reynolds *et al*. [93].

RP displays a highly heterogeneous set of clinical features similar to the elements of CREST syndrome (CREST is an acronym that stands for calcinosis, Raynaud's phenomenon, esoph-

ageal dysmotility, sclerodactyly, and telangiectasia). These symptoms include scleroderma, liver disease, telangiectasia, eosophageal varicies and Raynaud's phenomenon [94].

2.5.4. Osteopoikilosis/Buschke-Ollendorff syndrome

Osteopoikilosis/Buschke-Ollendorff syndrome (BOS) is a highly penetrant, benign, rare, autosomal dominant bone disorder. It is caused by a mutation in the *LEMD3* gene, which encodes the MAN1 protein, an integral protein of the inner nuclear membrane. BOS gives rise to osteopoikilosis with subcutaneous nevi or nodules [95], and is known as osteopoikilosis if no skin phenotype is present [96]. It displays an extremely variable set of clinical features even within the same family [97].

The osteopoikilosis is revealed by radiographs as numerous and widespread grain- to pea-sized areas of increased bone density, most often in the cancellous bone regions of the epiphyses and metaphyses, although they are found in almost all bones in the body, with the exception of the cranium where they are rarely found. The skin phenotype is manifested as firm lesions, which histologically are revealed to be either elastic-type (juvenile elastoma) or collagen-type (dermatofibrosis lenticularis disseminata) nevi. Joint stiffness may also be present [98].

2.5.5. Melorheostosis with osteopoikilosis

Melorheostosis with osteopoikilosis (MEL) has been thought to be caused by a mutation in the *LEMD3* gene [96]. It is sometimes a features of BOS, however not universally, and evidence for *LEMD3* mutations causing isolated sporadic melorheostosis has not yet been found [97].

MEL is characterised by the flowing hyperostosis of the tubular bone cortices, and sometimes accompanied by abnormalities in surrounding soft-tissue, such as muscle atrophy, joint-contractures, epidermal lesions or hemangiomas [96].

3. Linking genotype and phenotype of laminopathies

A marked change in heterochromatin is one of the most apparent features noted when examining cells affected by laminopathies, from loci of diminished or clumped heterochromatin to total loss of peripheral heterochromatin [99-103]. This alteration of normal heterochromatin, coupled with the known interactions between lamins and gene regulatory proteins, defines a major constituent for the molecular mechanism behind laminopathies [104]. Lamins have been shown to interact with proteins of the inner nuclear membrane (emerin, myne-1, nesprin, LAP1 and LAP2, LBR and MAN1), and chromatin-associated proteins (H2a, H2B, H3-H4, Ha95, HP1 and BAF) [105-109]. These associations allow for gene silencing by means of heterochromatin reorganisation, which could be a causative factor for phenotypic changes [107]. Recruiting genes selectively to the inner nuclear membrane has also been shown to result in their transcriptional repression [10]. The tissue specific gene

regulatory role of lamins is thought to underlie the tissue-specific symptoms observed in laminopathies [34,110]. Tissue specific regulation of lamin A expression may also be an explanatory factor for tissue-specific symptoms. Low-level of prelamin A expression in the brain has been shown to be due to a brain-specific microRNA, miRNA-9 [111], and miR-9 overexpression has been shown to alleviate nuclear blebbing in non-neural cells [112].

A mouse model with the *LMNA* H222P mutation for EDMD, displaying muscular dystrophy and cardiomyopathy, was investigated in order to see how gene regulation and metabolic pathways are affected. This investigation revealed that the extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) branches of the Mitogen-Activated Protein Kinase (MAPK) pathway were activated before any histological changes were visible in the animals. This result was then *in vitro* confirmed by expressing the mutant lamin A *in vitro* [113]. This MAPK signalling change is known to be associated with cardiomyopathy [114-116]. Similar results have been demonstrated in an *EMD*-knockout mouse model for X-linked EDMD, in which MAPK pathway was activated [117].

The possibility of complex interactions between these different causative mechanisms, the complex multirole functionality of lamins, along with widely varying environmental and genetic co-factors affecting this spectrum of processes, would afford a possible explanation for the heterogeneity of disease effects amongst the sufferers of laminopathies [48,118,119]. This variance of disease is one of the most fascinating aspects of laminopathies, the disparity between how a very large family of mutations affecting many genes give rise to diseases with such interrelated clinical features, and on the other hand how even amongst members of a single family carrying the same mutation, disease manifestations are diverse and variable. In AD-EDMD, heterozygous mutations in the *LMNA* gene can give rise to diverse effects, varying from typical EDMD to no disease phenotype, while members of the same family displaying the same mutation can be disease free, or suffer from contractures and muscular atrophy [120].

The diversity of disease phenotypes in consanguineous patients with identical mutations, such as disease onset, severity and progress, indicates that laminopathies are strongly influenced by disease modifiers such as genetic or environmental factors. For example, female sufferers of FPLD2 exhibit a more pronounced phenotype than male [121], family members with BOS can have both or just one of the bone and skin manifestations of that disease. Different missense mutations at the same locus can also give rise to different laminopathies. For example, in the *LMNA* gene, R527H and R527C result in MAD [122,123], while R527P causes EMDM (Figure 4) [46]. The same missense mutation at the same locus can also give rise to different laminopathies. For example, S573L in exon 11 of the *LMNA* in one family gave rise to CDM1A, and in another FPLD2. Of five patients with the same E358K mutation in the *LMNA* gene, three were diagnosed with autosomal dominant EDMD, one with early-onset LGMD1B, and the last patient with congenital muscular dystrophy (Figure 4] [124]. Although the R644C mutation in exon 11 of *LMNA* is associated with CDM1A, three cases with this mutation, and one with an R644H mutation were found to have very high variance in their disease phenotypes, with features ranging from reduced foetal movement and a severe congenital muscular dystrophy-like phenotype, to mild skeletal muscle aberrations and

http://dx.doi.org/10.5772/53793

severe and fatal hypertrophic cardiomyopathy [125, 126]. Even amongst members of the same family with the same single nucleotide deletion at position 959, in exon 6 of *LMNA*, one was classified as having DCM, one with EDMD and two with LGMD (Figure 4) [118]. This variation in phenotypes is a recurrent theme in the history of laminopathies, with multiple examples in the literature, which reinforces the importance of disease modifiers.

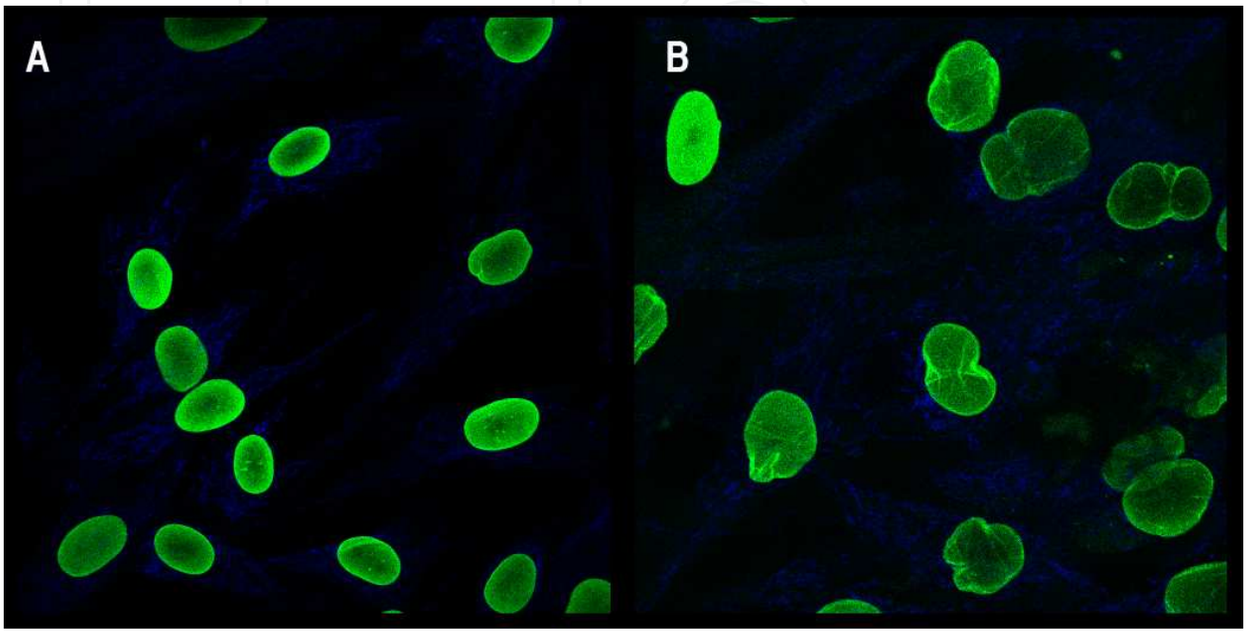

Figure 3. Nuclei showing characteristic blebbing and herniation as a result of a mutation in the LMNA gene. (A) is from sample AG06298 (unaffected HGPS parent) and (B) is from sample AG06917 (HGPS), and has the c.1824C>T, G608G mutation in the LMNA gene. Approximately 50% of the AG06917 cells display blebs. Both are primary fibroblasts hybridised with an antibody for lamin A/C (green) and mitochondria (blue). Photo courtesy of Dr. Peter Berglund.

The *LMNA* missense mutations causing FPLD have been shown to result in nuclei with abnormal shapes, herniated NE and increased fragility, and other laminopathies (including HGPS, Figure 3) have also been found to cause severe changes in nuclear morphology [76,127]. A-type lamin knockout cells display misshapen nuclei with herniations of the NE, slight clustering of NPCs, with mislocalised emerin and B-type lamins. Whereas cells expressing progerin display nuclear blebbing, thickening and honeycombing of the lamina, intranuclear lamina foci, loss of heterochromatin and NPC clustering [2,113,117,128-132]. In PHA however, normally lobulated mature neutrophils exhibit hypolobulation and fail to correctly function [90,133].

An altered nuclear integrity, leading to a weakness in cell structure and a susceptibility to mechanical stress as a constituent of the causative mechanism for laminopathies is supported by the specificity of some laminopathies, such as HGPS or EDMD, to tissues affected by high levels of mechanical stress (the skin, muscles and aortic arch), as well as the similarity of muscular dystrophies caused by mutations in genes responsible for karyoskeleton, cytoskeleton and myotubule proteins to laminopathic muscular dystrophies. The unique expression pattern of lamins in muscle cells might also illuminate a causative system for

laminopathies. As no lamin B1 is expressed in muscle cells at all, when *LMNA* protein products are expressed at reduced levels, or functionally impaired, lamin B2 alone must fulfil the lamina requirements of the cell, undergirding the inner nuclear membrane, localising and supporting key proteins of the inner nuclear membrane and organising and regulating the heterochromatin [134].

Various hypotheses have been put forward to account for the muscle cell specificity of EDMD [135]. Muscle cells contain very low or undetectable amounts of lamin B1, whereas in most other cell types lamin B1 is a major lamin, leaving muscle cells more sensitive to loss of function of either emerin or lamin A/C [42,136]. Emerin may also interact with transcription factors or directly with DNA to cause specific gene regulation in muscle cells [137]. Finally, muscle cells also undergo mechanical stress, and emerin, as part of a nucleo-cytoskeletal system may have a protective role against mechanical stress [138].

Lamin A mutations have also been shown to cause premature exhaustion of somatic stem cell populations, as well as stem cell dysfunction. As adult somatic stem cell population is depleted, tissues undergoing a high rate of turnover, such as the skin, would be affected first [139,140].

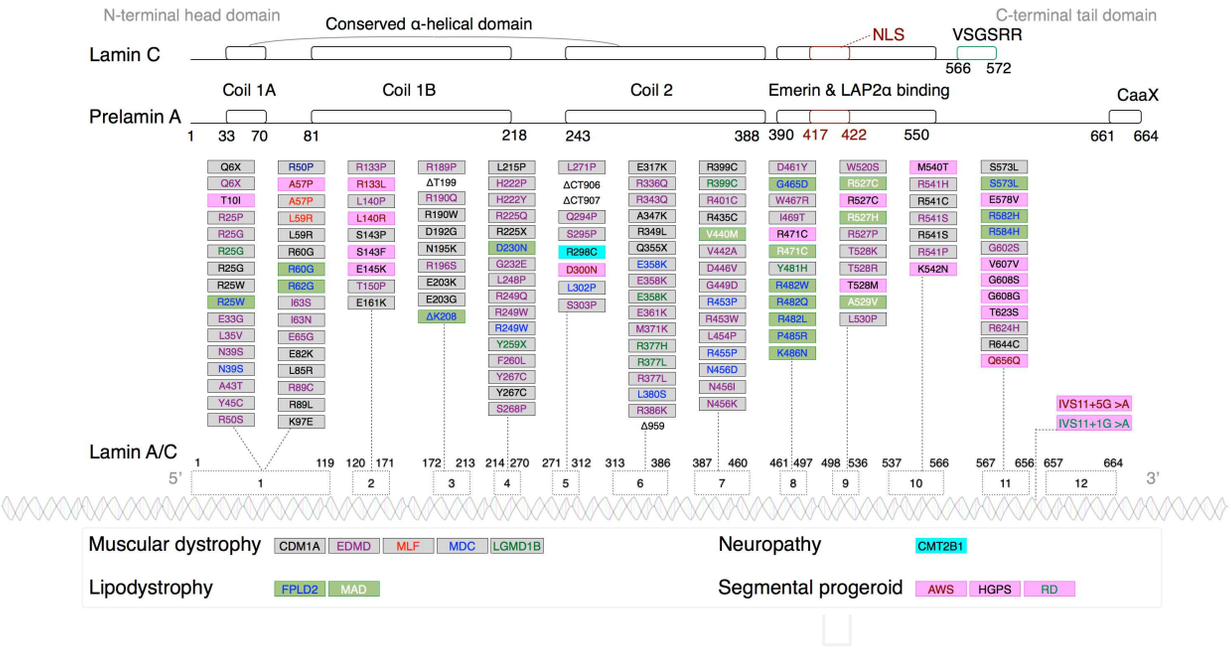

Figure 4. Distribution of laminopathy-causing mutations causing mutations in the LMNA gene. Exons 1-9 and a section of exon 10 encode Lamin C, Lamin A is a result of alternative splicing, adding exon 11 and 12, but removing the lamin C specific part of exon 10 (lamin C specific amino acids marked in green). The conserved α-helical segments of the central rod domain marked with coil 1a, coil 1b, and coil 2. Numbers refer to residues in the primary sequence. Lipodystrophy causing mutations are clustered at exon 8, which codes for an Ig-like domain. The majority (80%) of lipodystrophy cases are caused by a mutation at p.482. Similarly most (>90%) HGPS patients carry the de novo c. 1824C>T, G608G mutation, and most (85%) MAD patients carry a homozygous mutation at p.527 [76,141]. The size of introns are not to scale. CDM1A, dilated cardiomyopathy, type 1A; EDMD, Emery–Dreifuss muscular dystrophy; MLF, Malouf Syndrome; MDC, Muscular dystrophy, congenital; LGMD1B, limb girdle muscular dystrophy, type 1B; FPLD, Dunnigan familial partial lipodystrophy; MAD, mandibuloacral dysplasia; CMT2B1, Charcot–Marie–Tooth disorder, type 2B1; AWS, atypical Werner syndrome; HGPS, Hutchinson–Gilford progeria syndrome;

http://dx.doi.org/10.5772/53793

A consistent relationship between mutation location on the *LMNA* gene and its subsequent effect is difficult to pin down, as shown in figure 4, mutations causing muscular dystrophies are spread all along the gene. However the majority of mutations causing lipodystrophies are located at codon R482, which is conserved across human, mouse, rat and chicken lamin A/C genes [7]. Additionally, the vast majority of segmental progeriod cases are caused by mutations at G608, which affect splicing [34]. The position of the mutation on the *LMNA* gene relative to the NLS seems to play a significant role in the type of laminopathy induced. When laminopathies were segregated on the basis of which organs they showed clinical pathology in, it was found that there was a strong correlation between the position of the mutation relative to the NLS, and the group the resultant laminopathy was sorted into. For example laminopathies with mutations upstream (N-terminally) of the NLS were more likely to display cardiomyopathy and muscle atrophy, while laminopathies with mutations downstream of the NLS (C-Terminally) were more likely to have progeriod symptoms [32]. The tissue-specificity of the mutations may then be correlated with whether the mutation affects the conserved structurally important rod-domain that lies upstream of the NLS, or if it affects the region downstream of the NLS which has been shown to associate with chromatin and/or transcription factors (Figure 4) [142].

It was suspected that a duplication of the *LMNB1* gene was the cause behind ADLD as *LMNB1* was the only gene in the duplicated region expressed in the brain, as well as detection of increased levels of lamin B1 in the brains of affected individuals. The role of *LMNB1* was confirmed by over-expressing lamin B1 in *Drosophila melanogaster*, and in HEK293 cells, which showed a strong phenotype, and nuclear folding and blebbing respectively [67,68].

Finally, a link between levels of progerin produced in laminopathies that exhibit an accumulation of the mutant lamin A/C precursor, and both the severity and age of onset of the phenotype has been shown. RD is considered to be similar but more severe than HGPS, with a correspondingly higher rate of prelamin A accumulation [143,144]. Two cases of a Werner syndrome-like form of progeria displayed a progeria-like aspect with middle age onset coronary artery disease, with a level of progerin that was one quarter of that seen in HGPS cells [85]. Further proof of the toxicity of accumulated progerin is shown by the decrease of progerin levels in cell cultures by treatment with rapamycin, with a resultant rescue of the phenotype [145]. As allele dependant differences in expression of the *LMNA* gene have been observed, with one allele accounting for 70% and the other accounting for 30% of the expressed lamin A and C transcripts, one explanation for phenotype variation might depend on which allele the disease-causing mutation is located [146].

These details paint a complex picture of a heterogeneous family of mutations resulting in varying and overlapping phenotypes, with a diversity in severity and age of onset resulting from tissue specific gene regulation, site of mutation and various genetic and possibly environmental co-factors.

4. Mouse models

Mouse models have yielded invaluable knowledge about the functions of the *LMNA* gene and about the molecular effects of mutations that cause laminopathies. Possibilities for treatment have also been explored with mouse models for these diseases. Various methods have been used to produce strains of mice with similar phenotype to those shown in human laminopathies. Most of the available relevant models have been summarized in the table below (Table 2).

Mice that were thought to completely lack A-type lamin expression were created in order to study a model with no expressed lamin A/C. These *Lmna*-null mice are phenotypically normal at birth, but develop a condition similar to EDMD. By two to three weeks of age they display a growth retardation and arrest. Skeletal abnormalities including kyphosis occur, and a loss of white adipose tissue was noted. Cardiac myopathies also develop, and death occurred within eight weeks. An analysis of mouse embryonic fibroblasts (MEFs) showed misshapen, herniated nuclei. Mice heterozygous for *Lmna* were phenotypically normal [101]. The phenotype for *Lmna* knockout mice showed neuropathic features, decreased axon density paired with increased axon diameter and non-myelinated axons, features that are markedly similar to human axonopathies [70,101]. The only known case of an *LMNA*-null human, with homozygous nonsense mutations in *LMNA*, resulted in a perinatal lethality, exhibiting small size, retrognathia, severe limb and phalangeal contractures, fractures in the femur and arm, muscular dystrophy. Death was due to respiratory failure [51]. Apart from these differences in disease severity, changes in the proliferation of *LMNA*-null fibroblasts were also markedly dissimilar for human as compared to mouse. Patient fibroblasts showed a reduced proliferation [160], while MEFs showed an increased proliferative potential compared to wild-type MEFs [161]. Recently these mice have been found to express a C-terminally truncated *Lmna* gene product, missing residues 461–657 of wild-type lamin A, which are normally encoded by exons 8–11. This expression, both on a transcriptional and protein level, perhaps explains the difference in fibroblast proliferative potential between human *LMNA*-null fibroblasts and MEFs from this mouse model, as well as raising questions about the many studies that have been performed on these mice [162].

Mice with the *Zmpste24* gene knocked out were created independently by two groups [151,163]. While loss of the *ZMPSTE24* gene due to homozygous or compound heterozygous mutations in humans results in the neonatally lethal disease, RD, these mouse models did not display an equivalent phenotype. The *Zmpste24*$^{-/-}$ mice lack the ability to convert farnesylated prelamin A to mature lamin A, and so accumulate prelamin A at the nuclear rim, resulting in aberrant nuclear morphology. Normal at birth, they develop a HGPS-like condition, showing growth retardation, alopecia, kyphosis, weight loss and incisor defects. Spontaneous bone fractures also occur as the animals age and death occurs prematurely, at 20-30 weeks [150,151]. That the accumulation of prelamin A was the direct cause of the disease state was demonstrated when *Zmpste24*$^{-/-}$ mice with only one allele for the *Lmna* gene were compared to *Zmpste24*$^{-/-}$ mice with two copies of *Lmna*. The *Zmpste24*$^{-/-}$*Lmna*$^{+/-}$ mice had significantly reduced levels of prelamin A compared to *Zmpste24*$^{-/-}$*Lmna*$^{+/+}$ mice. All disease phenotype was missing, and the ratio of misshapen nuclei to normal was also reduced [103].

Mouse model	Description	Pathology	Reference
Lmna $^{-/-}$	These *Lmna* null mice were designed to produce no lamin A or C. Recently however they have been found to produce a truncated lamin A protein.	Postnatal lethality, with cardiomyopathy and muscular dystrophy	[101,147]
Lmna $^{GT-/-}$	These mice have a total loss of lamin A/C.	Growth retardation, developmental heart defects, skeletal muscle hypotrophy, decreased subcutaneous adipose tissue. Death occurs at 2 to 3 weeks *post partum*, without dilated cardiomyopathy or an obvious progeroid phenotype.	[148]
Lmna $^{LCO/LCO}$	These lamin C only mice carry a mutant Lmna allele that yields lamin C exclusively, without lamin A.	No disease phenotypes and a normal lifespan.	[132]
Lmna $^{LAO/LAO}$	Mature lamin A only mouse, bypassing prelamin A synthesis and processing.	No detectable pathology, fibroblasts show misshapen nuclei.	[149]
Zmpste24 $^{-/-}$	These mice are null for the endoprotease responsible for the final cleavage step in prelamin A maturation, leading to an accumulation of farnesylated pre-lamin A.	Mice have rib fractures, osteoporosis, muscle weakness and die at 6–7 months.	[150] [99]
		Postnatal growth retardation, shortened lifespan, loss of fat layer and muscular dystrophy.	[151]
Lmna $^{N195K/N195K}$	These mice have a missense CDM1A-associated lamin A mutation, N195K.	Postnatal death associated with cardiomyopathy. MEFs showed nuclear abnormalities.	[152]
Lmna $^{H222P/H222P}$	These mice have a missense EDMD-associated lamin A mutation, H222P.	These mice show a stiff walking posture and cardiac dysfunction. Death occurs by 9 months of age. MEFs showed nuclear abnormalities.	[153]
Lmna $^{HG/HG}$	These mice carry an *Lmna*-knock in allele that produces progerin. Mice accumulate farnesyl–prelamin A.	Heterozygous mice, *Lmna* $^{HG/-}$, express large amounts of progerin and develop many disease phenotypes of progeria. MEFs display nuclear blebbing.	[154]
Lmna$^{L530P/L530P}$	These mice have a L530P mutation in the lamin A gene that is associated with EDMD in humans.	Homozygous mice display defects consistent with HGPS, and die within 4-5 weeks of birth.	[155]
Lmna ^{M371K}	cDNA with mis-sense mutation expressed with a heart specific promoter.	Cardiomyopathy and early postnatal lethality	[156]
Lmna ^{G609G}	The wild-type mouse *lmna* gene is replaced with a copy containing the c. 1827C>T;p.G609G mutation. This is the equivalent of the HGPS c.1824C>T;p.G608G mutation in the human *LMNA* gene.	Growth retardation, weight loss, cardiovascular problems and shortened lifespan.	[157]
Lmnb1 $^{-/-}$	These mice have an insertional mutation in *Lmnb1*, resulting in a mutant lamin B1 protein missing several functional domains.	Mice survive embryonic development, however die at birth with lung and bone defects.	[29]
Emd $^{-/-}$	These mice do not express emerin.	Mice overtly normal but with slightly retarded muscle regeneration.	[158,159]

Table 2. Selected mouse models relevant for studying laminopathies.

A mouse model for EDMD was created by knocking out the *Emd* gene. These animals had no abnormal clinical features outside of a slightly retarded muscle regeneration, and altered motor coordination when tested on a rotarod [158,159]. The human AD-EDMD mutations in the *LMNA* gene, H222P (with a histidine substituting for a proline at residue 222) and N195K (with a lysine substituting for asparagine at residue 195), have also been used to create mouse models for AD-EDMD. Again, mice heterozygous for the mutations are indistinguishable from wild-type animals. Mice with two copies of the mutation however, showed a muscular dystrophy and cardiomyopathy phenotype [152,153].

Knock-in mouse models such as the $Lmna^{G609G}$ mouse model closely mimic the human disease HGPS. A copy of the wild-type mouse *lmna* gene was replaced with a copy containing the c.1827C>T;p.G609G mutation, the equivalent of the HGPS c.1824C>T;p.G608G mutation in the human *LMNA* gene. This gave a phenotype of growth retardation, weight loss, cardiovascular problems and curtailed lifespan, correlating neatly with the clinical features found in the human disease. However, the disease symptoms were most marked and similar in the homozygous state, whereas in humans an autosomal dominant state with only a single mutated allele confers the disease state [157].

A mouse model where only lamin-C is produced ($Lmna^{LCO}$), without producing any prelamin A or mature lamin A. These $Lmna^{LCO/LCO}$ animals were entirely healthy, with only a minimal alteration to normal nuclear shape [132]. More recently a mouse model where only mature lamin A is expressed was made. These $Lmna^{LAO/LAO}$ mice synthesis mature lamin A without any prelamin A synthesis or processing steps. They display no disease phenotype, but do have an increased level of nuclear blebbing compared to wild-type, demonstrating that bypassing prelamin A processing and directly synthesising mature lamin A has little effect on the transportation of lamin A to the nuclear envelope [149].

In order to study early post-natal development effects caused by loss of lamin A/C, an $Lmna^{GT-/-}$ model was created. This model simultaneously inactivates and reports the expression of *Lmna*. Loss of lamin A/C resulted in growth retardation, developmental defects of the heart, skeletal muscle hypotrophy, loss of subcutaneous adipose tissue and impaired *ex vivo* adipogenic differentiation. Premature death occurred at two to three week *post partum* [148].

A mouse model was created using a heart-selective promoter (α-myosin heavy chain promoter) to control the expression of human normal lamin A, and lamin A containing the EDMD causing mutation M371K. Mice expressing the wild-type human lamin A were born at slightly less than expected rates, and had a normal lifespan. However, mice expressing mutant M371K lamin A exhibited a much higher risk of prenatal death, and were born at only a fraction (0.07) of the expected frequency. Those animals that were born died within 2-7 weeks, and displayed pulmonary and cardia edema. Cardiac cells from these mice showed abnormal, convoluted nuclear envelopes with clumped chromatin and intranuclear foci of lamins [156].

Mouse models of laminopathies are limited by the gross physiological differences between rodent (mouse models being the most relevant models used to investigate laminopathies)

http://dx.doi.org/10.5772/53793

and human. However, despite the limitations of mouse models, the advantages are legion; being able to study very rare diseases at any stage of disease, with limitless sampling, temporal and physically controlled expression of mutant protein, and with the possibilities for testing different type of treatment.

5. Treatment

Current treatments for laminopathies are largely symptomatic, controlling the secondary effects of the disease. Corrective surgery is used to treat the EDMD contractures, coronary artery bypass surgery for HGPS, pacemaker installation or heart transplantation for DCMI or LGMD1B patients [164]. FPLD2 patients with diabetes mellitus and hypertension are treated with antidiabetic drugs, angiotensin converting enzyme inhibitors, calcium channel blockers and beta blockers [52,165,166]. The administration of a recombinant methionyl human leptin has been tried with some success in patients suffering from FPLD, giving rise to improved fasting glucose concentrations, insulin sensitivity, and triglyceride levels [167,168]. The impairment of pre-adipocyte differentiation, an impairment which is brought about by the negative effects of prelamin A accumulation on the rate of DNA-bound SREBP1, may also be treated with troglitazone, a PPAR-gamma ligand which promotes the adipogenic program [169].

Curative treatment for laminopathies that are autosomal-recessive involving loss-of-function of a protein, such as EDMD-AR, would require the expression of a healthy wild-type allele in the affected tissue. However, autosomal dominant laminopathies require a more complex treatment, in which the production, modification and/or the effect of the mutant protein also need to be eliminated. For example, in a phase II clinical trial with HGPS patients, lonafarnib, a farnesyl transferase inhibitor (FTI) is being given as treatment (see chapter on Hutchinson-Gilford progeria syndrome) [170]. FTI is normally used as an anti-tumour treatment, but it also reduces the amount of progerin produced by inhibiting the farnesylation of prelamin A. Previous experiments with FTIs in cell cultures showed marked improvements, with a reduction of misshapen nuclei [171]. With mouse models for HGPS an improvement in disease phenotype was noted, although no total reversal was apparent [172-176]. This may be due to the fact that although FTI treatment inhibits the farnesylation of prelamin-A by farnesyl transferase, a secondary modification pathway, a geranylgeranylation by geranylgeranyltransferase, allows prelamin A to be processed into progerin despite the FTI treatment [177]. However, a combination of statins (a potent HMG-CoA reductase inhibitor, used to inhibit the production of cholesterol in the liver) and bisphosphonates (a class of drugs used to treat osteoporosis), was used to inhibit the synthesis of farnesyl pyrophosphate, a co-substrate of farnesyltransferase and a precursor of a substrate for geranylgeranyltransferase I. This combination inhibits prenylation, and when used to treat laminopathies, resulted in an increased longevity, reduced oxidative stress, cellular senescence and improved phenotype in mice [61,154,172,178,179]. A triple drug trial was initiated in 2009 to examine the efficacy of treatment involving an FTI, a statin and a bisphosphonate, however the results of this trial have not yet been made public.

Long-term treatment with FTIs is not without risks. All CaaX box/motif proteins would have their farnesylation processing inhibited, which would mean an inhibition of lamin-B maturation. Non-farnesylated lamins might also accumulate in the cell, with unexpected effects. In a mice model where non-farnesylated prelamin-A was solely expressed, with the CaaX motif/box mutated to SAAX, a cardiomyopathy was observed to occur [180]. In HIV treatment, acquired lipodystrophy is a possible side-effect of the use of HIV protease inhibitors, which cause pre-lamin A accumulation [181]. This pre-lamin accumulation was also observed in fibroblasts from FPLD2 patients, further hinting at the toxicity of pre-lamin A accumulation [61].

Rapamycin, an immunosuppressant antibiotic drug, has also been examined as a possible treatment in laminopathies. Rapamycin treatment in HGPS cell cultures resulted in reduced nuclear blebbing and decreased rates of senescence, as well as a marked reduction of progerin and prelamin A levels, a restoration of wildtype LAP2α, BAF and trimethylated H3K9 organisation, and a rescue of the normal chromatin phenotype. These effects come about by means of autophagic degradation of prelamin A, triggered by inactivation of the inhibitory mammalian target of rapamycin (mTOR) dependent pathway [145,182]. In an *Lmna*$^{-/-}$ mouse model treatment with rapamycin was shown to improve cardiac and skeletal muscle function, as well as improving the survival rate [183]. In the *Lmna*$^{H222P/H222P}$ mouse model, rapamycin treatment was shown to improve cardiac function [184]. This mouse model has also been treated with other inhibitors of MAPK/ERK kinase (MEK) (the mitogen-activated protein kinase (MAPK kinase) that activates extracellular signal-regulated protein kinase (ERK)), in order to see if administration would alleviate or prevent the cardiomyopathy. The MEK-inhibitor treated animals were indistinguishable from wild-type animals, while untreated control animals displayed reduced ejection fraction, indicating a dilated cardiomyopathy. Interestingly, abnormal elongation of heart cell nuclei was noted in untreated control animals, but was not observed in the treatment group [113,185]. As with FTIs, the long-term treatment of patients with rapamycin would entail the acceptance of know side-effects, such as lung toxicity, insulin resistance, cataracts and testicular degeneration [186-189].

Pre-lamin A antisense oligonucleotides were used to reduce pre-lamin A levels, with a resultant decrease in misshapen nuclei. The most common HGPS point mutation causes an increased usage of a cryptic splice site in exon 11, CAG#GTGGGC, which is also used at near-undetectable levels in wild-type cells. Antisense morpholino oligonucleotides directed to this site resulted in an improvement of HGPS fibroblast disease phenotype [190]. RNA interference has also been used to successfully improve proliferation and nuclear morphology, as well as reducing senescence in fibroblasts expressing mutant lamin A [191]. In another experiment exon 11 splice donor site antisense oligonucleotides were also used to promote the alternative splice pathway, leading to an increased in progerin production in fibroblast cells, and short hairpin RNA (shRNA) were then used to diminish this production in fibroblasts, leading to an improvement of phenotype [192]. Morpholinos have also been used to target the cryptic splicing event in mouse. The use of antisense morpholinos to the exon 10 lamin A splice donor site and the c.1827C>T;p.G609G mutation of the *LMNA* transcript was shown to reduce progerin levels, partially restore a wild-type phenotype and extend lifespan of a mouse model for HGPS [157].

In light of the recent Glybera Gene therapy [193], future gene therapies for the treatment of the cardiomyopathy prevalent in muscular dystrophies may also be an area of interest [194-196].

6. Conclusion

During the last decade the number of diseases found to be caused by mutations in lamin or lamin associated genes has increased significantly. These phenotypically diverse diseases have been categorised both phenotypically and genetically, and today research is focused on both deciphering the pathogenic mechanisms behind their pathophysiological processes, as well as understanding how such diverse pathologies can arise from this related family of mutations. During that time the appreciated role for lamins has changed from being regarded merely as a structural scaffold for the nucleus, to a key element in DNA replication and transcription, chromatin organisation, cell replication and differentiation. Future research is sure to continue at an ever-increasing pace, especially as the development and integration of next generation sequencing technologies and technologies that allows for global analysis of the genome and epigenome into both research and clinical settings. For researchers this level of genomic interrogation brings about unprecedented access to new information about our genome, which will be valuable for the creation of maps of genetic and possibly epigenetic variation that influence disease.

The laminopathies described in this review are without a doubt, exceedingly rare. However by researching these rare conditions, it is hoped that we can shed light on their all too common clinical symptoms, such as cardiac disease, metabolic disorders such as insulin resistance, and even ageing itself.

Acknowledgements

Our work is supported by a VINNMER fellow grant from VINNOVA, and an Innovator grant from The Progeria Research Foundation. We thank the patients, and Dr. Nicola Carboni and Dr Marco Mura for contributing photos of patients. Primary fibroblast cultures were obtained from the Aging Repository of the Coriell Cell Repository.

Author details

Tomás McKenna*, Jean-Ha Baek and Maria Eriksson

*Address all correspondence to: tomas.mckenna@ki.se

Department of Biosciences and Nutrition, Center for Biosciences, Karolinska Institutet, Huddinge, Sweden

References

[1] Cronshaw JM, Krutchinsky AN, Zhang W, Chait BT, Matunis MJ. Proteomic analysis of the mammalian nuclear pore complex. Journal of Cell Biology. 2002Sep.2;158(5): 915–27.

[2] Shimi T, Butin-Israeli V, Goldman RD. The functions of the nuclear envelope in mediating the molecular crosstalk between the nucleus and the cytoplasm. Current Opinion in Cell Biology. 2012Feb.;24(1):71–8.

[3] Fried H, Kutay U. Nucleocytoplasmic transport: taking an inventory. Cell. Mol. Life Sci. 2003Aug.;60(8):1659–88.

[4] Zastrow MS, Vlcek S, Wilson KL. Proteins that bind A-type lamins: integrating isolated clues.

[5] Lin F. MAN1, an integral protein of the inner nuclear membrane, binds Smad2 and Smad3 and antagonizes transforming growth factor- signaling. Human Molecular Genetics. 2004Dec.8;14(3):437–45.

[6] Fisher D, Chaudhary N. cDNA sequencing of nuclear lamins A and C reveals primary and secondary structural homology to intermediate filament proteins. Proceedings of the …. 1986Jan.1.

[7] Stuurman N, Heins S, Aebi U. Nuclear Lamins: Their Structure, Assembly, and Interactions* 1. Journal of structural biology. 1998Aug.18;:1–25.

[8] Dechat T, Pfleghaar K, Sengupta K, Shimi T, Shumaker DK, Solimando L, et al. Nuclear lamins: major factors in the structural organization and function of the nucleus and chromatin. Genes & development. 2008Apr.1;22(7):832–53.

[9] Moir R, Spann T. The structure and function of nuclear lamins: implications for disease. Cellular and Molecular Life Sciences. 2001Jan.1.

[10] Reddy KL, Zullo JM, Bertolino E, Singh H. Transcriptional repression mediated by repositioning of genes to the nuclear lamina. Nature. 2008Mar.13;452(7184):243–7.

[11] Gruenbaum Y, Margalit A, Goldman RD, Shumaker DK, Wilson KL. The nuclear lamina comes of age. Nat Rev Mol Cell Biol. 2005Jan.;6(1):21–31.

[12] Rout MP. The Nuclear Pore Complex as a Transport Machine. Journal of Biological Chemistry. 2001Apr.5;276(20):16593–6.

[13] Lin F, Worman HJ. Structural organization of the human gene encoding nuclear lamin A and nuclear lamin C. J Biol Chem. 1993Aug.5;268(22):16321–6.

[14] Barrowman J, Hamblet C, George CM, Michaelis S. Analysis of prelamin A biogenesis reveals the nucleus to be a CaaX processing compartment. Mol. Biol. Cell. 2008Dec.;19(12):5398–408.

[15] Röber RA, Weber K, Osborn M. Differential timing of nuclear lamin A/C expression in the various organs of the mouse embryo and the young animal: a developmental study. Development. 1989Feb.;105(2):365–78.

[16] Zorenc AHG. An Alternative Splicing Product of the Lamin A/C Gene Lacks Exon 10. Journal of Biological Chemistry. 1996Apr.19;271(16):9249–53.

[17] Jahn D, Schramm S, Benavente R, Alsheimer M. Dynamic properties of meiosis-specific lamin C2 and its impact on nuclear envelope integrity. Nucleus. 2010May;1(3): 273–83.

[18] Alsheimer M, Benavente R. Change of karyoskeleton during mammalian spermatogenesis: expression pattern of nuclear lamin C2 and its regulation. Experimental Cell Research. 1996Nov.1;228(2):181–8.

[19] Stick R, Hausen P. Changes in the nuclear lamina composition during early development of Xenopus laevis. Cell. 1985May;41(1):191–200.

[20] Lehner CF, Stick R, Eppenberger HM, Nigg EA. Differential expression of nuclear lamin proteins during chicken development. Journal of Cell Biology. 1987Jul.;105(1): 577–87.

[21] Furukawa K, Inagaki H, Hotta Y. Identification and cloning of an mRNA coding for a germ cell-specific A-type lamin in mice. Experimental Cell Research. 1994Jun.;212(2): 426–30.

[22] Lin F, Worman HJ. Structural organization of the human gene (LMNB1) encoding nuclear lamin B1. Genomics. 1995May20;27(2):230–6.

[23] Biamonti G, Giacca M, Perini G, Contreas G, Zentilin L, Weighardt F, et al. The gene for a novel human lamin maps at a highly transcribed locus of chromosome 19 which replicates at the onset of S-phase. Mol. Cell. Biol. 1992Aug.;12(8):3499–506.

[24] Furukawa K, Hotta Y. cDNA cloning of a germ cell specific lamin B3 from mouse spermatocytes and analysis of its function by ectopic expression in somatic cells. The EMBO journal. 1993Jan.;12(1):97–106.

[25] Pollard KM, Chan EK, Grant BJ, Sullivan KF, Tan EM, Glass CA. In vitro posttranslational modification of lamin B cloned from a human T-cell line. Mol. Cell. Biol. 1990May;10(5):2164–75.

[26] Kitten GT, Nigg EA. The CaaX motif is required for isoprenylation, carboxyl methylation, and nuclear membrane association of lamin B2. Journal of Cell Biology. 1991Apr.;113(1):13–23.

[27] Lutz RJ, Trujillo MA, Denham KS, Wenger L, Sinensky M. Nucleoplasmic localization of prelamin A: implications for prenylation-dependent lamin A assembly into the nuclear lamina. Proceedings of the National Academy of Sciences of the United States of America. 1992Apr.1;89(7):3000–4.

[28] Holtz D, Tanaka RA, Hartwig J, McKeon F. The CaaX motif of lamin A functions in conjunction with the nuclear localization signal to target assembly to the nuclear envelope. Cell. 1989Dec.22;59(6):969–77.

[29] Vergnes L, Péterfy M, Bergo MO, Young SG, Reue K. Lamin B1 is required for mouse development and nuclear integrity. Proceedings of the National Academy of Sciences of the United States of America. 2004Jul.13;101(28):10428–33.

[30] Hennekes H, Nigg EA. The role of isoprenylation in membrane attachment of nuclear lamins. A single point mutation prevents proteolytic cleavage of the lamin A precursor and confers membrane binding properties. 1994.

[31] Worman HJ, Fong LG, Muchir A, Young SG. Laminopathies and the long strange trip from basic cell biology to therapy. J. Clin. Invest. 2009Jul.;119(7):1825–36.

[32] Hegele R. LMNA mutation position predicts organ system involvement in laminopathies. Clinical Genetics. 2005Apr.5;68(1):31–4.

[33] Landires I, Pascale JM, Motta J. The position of the mutation within the LMNA gene determines the type and extent of tissue involvement in laminopathies. Clinical Genetics. 2007Apr.25;71(6):592–3.

[34] Broers JLV, Ramaekers FCS, Bonne G, Yaou RB, Hutchison CJ. Nuclear lamins: laminopathies and their role in premature ageing. Physiological Reviews [Internet]. 2006Jul.;86(3):967–1008. Available from: http://physrev.physiology.org/cgi/content/abstract/86/3/967

[35] Zaremba-Czogalla M, Dubińska-Magiera M, Rzepecki R. Laminopathies: the molecular background of the disease and the prospects for its treatment. Cell. Mol. Biol. Lett. 2011Mar.;16(1):114–48.

[36] Hegele RA, Cao H, Liu DM, Costain GA, Charlton-Menys V, Rodger NW, et al. Sequencing of the reannotated LMNB2 gene reveals novel mutations in patients with acquired partial lipodystrophy. Am. J. Hum. Genet. 2006Aug.;79(2):383–9.

[37] Emery AE, Dreifuss FE. Unusual type of benign x-linked muscular dystrophy. J. Neurol. Neurosurg. Psychiatr. 1966Aug.;29(4):338–42.

[38] Muchir A, Worman HJ. Emery-Dreifuss muscular dystrophy. Curr Neurol Neurosci Rep. 2007Jan.;7(1):78–83.

[39] Helbling-Leclerc A, Bonne G, Schwartz K. Emery-Dreifuss muscular dystrophy. Eur J Hum Genet. 2002Mar.;10(3):157–61.

[40] Manilal S, Nguyen TM, Sewry CA, Morris GE. The Emery-Dreifuss muscular dystrophy protein, emerin, is a nuclear membrane protein. Human Molecular Genetics. 1996Jun.;5(6):801–8.

[41] Nagano A, Koga R, Ogawa M, Kurano Y, Kawada J, Okada R, et al. Emerin deficiency at the nuclear membrane in patients with Emery-Dreifuss muscular dystrophy. Nat Genet. 1996Mar.;12(3):254–9.

[42] Manilal S. Distribution of emerin and lamins in the heart and implications for Emery-Dreifuss muscular dystrophy. Human Molecular Genetics. 1999Feb.1;8(2):353–9.

[43] Meinke P, Nguyen TD, Wehnert MS. The LINC complex and human disease. Biochem. Soc. Trans. 2011Dec.;39(6):1693–7.

[44] Scharner J, Brown CA, Bower M, Iannaccone ST, Khatri IA, Escolar D, et al. Novel LMNA mutations in patients with Emery-Dreifuss muscular dystrophy and functional characterization of four LMNA mutations. Hum. Mutat. 2011Feb.;32(2):152–67.

[45] Lassuthová P, Baránková L, Kraus J, Maríková T, Seeman P. Emery-Dreifuss muscular dystrophy: a novel mutation in the LMNA gene. Pediatr. Neurol. 2009Aug.;41(2): 127–30.

[46] Bonne G, Di Barletta MR, Varnous S, Bécane HM, Hammouda EH, Merlini L, et al. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. Nat Genet. 1999Mar.;21(3):285–8.

[47] Felice KJ, Schwartz RC, Brown CA, Leicher CR, Grunnet ML. Autosomal dominant Emery-Dreifuss dystrophy due to mutations in rod domain of the lamin A/C gene. Neurology. 2000Jul.25;55(2):275–80.

[48] Canki-Klain N, Récan D, Milicić D, Llense S, Leturcq F, Deburgrave N, et al. Clinical variability and molecular diagnosis in a four-generation family with X-linked Emery-Dreifuss muscular dystrophy. Croat. Med. J. 2000Dec.;41(4):389–95.

[49] Muchir A, Bonne G, van der Kooi AJ, van Meegen M, Baas F, Bolhuis PA, et al. Identification of mutations in the gene encoding lamins A/C in autosomal dominant limb girdle muscular dystrophy with atrioventricular conduction disturbances (LGMD1B). Human Molecular Genetics. 2000May22;9(9):1453–9.

[50] Yuan W-L, Huang C-Y, Wang J-F, Xie S-L, Nie R-Q, Liu Y-M, et al. R25G mutation in exon 1 of LMNA gene is associated with dilated cardiomyopathy and limb-girdle muscular dystrophy 1B. Chin. Med. J. 2009Dec.5;122(23):2840–5.

[51] van Engelen BGM, Muchir A, Hutchison CJ, van der Kooi AJ, Bonne G, Lammens M. The lethal phenotype of a homozygous nonsense mutation in the lamin A/C gene. Neurology. 2005Jan.24;64(2):374–6.

[52] Song K, Dubé MP, Lim J, Hwang I, Lee I, Kim J-J. Lamin A/C mutations associated with familial and sporadic cases of dilated cardiomyopathy in Koreans. Exp. Mol. Med. 2007Feb.28;39(1):114–20.

[53] Fatkin D, MacRae C, Sasaki T, Wolff MR, Porcu M, Frenneaux M, et al. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. New England journal of medicine. 1999Dec. 2;341(23):1715–24.

[54] McPherson E, Turner L, Zador I, Reynolds K, Macgregor D, Giampietro PF. Ovarian failure and dilated cardiomyopathy due to a novel lamin mutation. Am. J. Med. Genet. 2009Feb.15;149A(4):567–72.

[55] Garg A, Subramanyam L, Agarwal AK, Simha V, Levine B, D'Apice MR, et al. Atypical Progeroid Syndrome due to Heterozygous Missense LMNA Mutations. Journal of Clinical Endocrinology & Metabolism. 2009Dec.3;94(12):4971–83.

[56] Renou L, Stora S, Yaou RB, Volk M, Sinkovec M, Demay L, et al. Heart-hand syndrome of Slovenian type: a new kind of laminopathy. Journal of Medical Genetics. 2008Jun.25;45(10):666–71.

[57] Sinkovec M, Petrovič D, Volk M, Peterlin B. Familial progressive sinoatrial and atrioventricular conduction disease of adult onset with sudden death, dilated cardiomyopathy, and brachydactyly. A new type of heart-hand syndrome? Clinical Genetics. 2005Jun.17;68(2):155–60.

[58] Morel CF. A LMNA Splicing Mutation in Two Sisters with Severe Dunnigan-Type Familial Partial Lipodystrophy Type 2. Journal of Clinical Endocrinology & Metabolism. 2006Apr.18;91(7):2689–95.

[59] Shackleton S, Lloyd DJ, Jackson SN, Evans R, Niermeijer MF, Singh BM, et al. LMNA, encoding lamin A/C, is mutated in partial lipodystrophy. Nat Genet. 2000Feb.;24(2):153–6.

[60] Saha B, Lessel D, Hisama FM, Leistritz DF, Friedrich K, Martin GM, et al. A Novel LMNA Mutation Causes Altered Nuclear Morphology and Symptoms of Familial Partial Lipodystrophy (Dunnigan Variety) with Progeroid Features. Mol Syndromol. 2010Sep.;1(3):127–32.

[61] Caron M, Auclair M, Donadille B, Béréziat V, Guerci B, Laville M, et al. Human lipodystrophies linked to mutations in A-type lamins and to HIV protease inhibitor therapy are both associated with prelamin A accumulation, oxidative stress and premature cellular senescence. Cell Death Differ. Nature Publishing Group; 2007Jul. 6;14(10):1759–67.

[62] GARG A, Wilson R, Barnes R, Arioglu E, Zaidi Z, Gurakan F, et al. A gene for congenital generalized lipodystrophy maps to human chromosome 9q34. Journal of Clinical Endocrinology & Metabolism. 1999Sep.;84(9):3390–4.

[63] Garavelli L, D'Apice MR, Rivieri F, Bertoli M, Wischmeijer A, Gelmini C, et al. Mandibuloacral dysplasia type A in childhood. Am. J. Med. Genet. 2009Oct.;149A(10): 2258–64.

[64] Agarwal AK, Fryns J-P, Auchus RJ, Garg A. Zinc metalloproteinase, ZMPSTE24, is mutated in mandibuloacral dysplasia. Human Molecular Genetics. 2003Aug. 15;12(16):1995–2001.

[65] Garg A, Cogulu O, Ozkinay F, Onay H, Agarwal AK. A novel homozygous Ala529Val LMNA mutation in Turkish patients with mandibuloacral dysplasia. Journal of Clinical Endocrinology & Metabolism. 2005Sep.;90(9):5259–64.

[66] Zirn B, Kress W, Grimm T, Berthold LD, Neubauer B, Kuchelmeister K, et al. Association of homozygous LMNA mutation R471C with new phenotype: mandibuloacral dysplasia, progeria, and rigid spine muscular dystrophy. Am. J. Med. Genet. 2008Apr.15;146A(8):1049–54.

[67] Padiath QS, Saigoh K, Schiffmann R, Asahara H, Yamada T, Koeppen A, et al. Lamin B1 duplications cause autosomal dominant leukodystrophy. Nat Genet. 2006Oct.; 38(10):1114–23.

[68] Schuster J, Sundblom J, Thuresson A-C, Hassin-Baer S, Klopstock T, Dichgans M, et al. Genomic duplications mediate overexpression of lamin B1 in adult-onset autosomal dominant leukodystrophy (ADLD) with autonomic symptoms. Neurogenetics. 2011Feb.;12(1):65–72.

[69] Bouhouche A, Benomar A, Birouk N, Mularoni A, Meggouh F, Tassin J, et al. A locus for an axonal form of autosomal recessive Charcot-Marie-Tooth disease maps to chromosome 1q21. 2-q21. 3. Am. J. Hum. Genet. Elsevier; 1999;65(3):722–7.

[70] de Sandre-Giovannoli A, Chaouch M, Kozlov S, Vallat J-M, Tazir M, Kassouri N, et al. 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. 2002Mar.;70(3):726–36.

[71] Skre H. Genetic and clinical aspects of Charcot-Marie-Tooth's disease. Clinical Genetics. Wiley Online Library; 1974;6(2):98–118.

[72] Krajewski KM, Lewis RA, Fuerst DR, Turansky C, Hinderer SR, Garbern J, et al. Neurological dysfunction and axonal degeneration in Charcot-Marie-Tooth disease type 1A. Brain. 2000Jul.;123 (Pt 7):1516–27.

[73] Garcia CA. A clinical review of Charcot-Marie-Tooth. Ann. N. Y. Acad. Sci. 1999Sep. 14;883:69–76.

[74] De Jonghe P, Timmerman V, Van Broeckhoven C. 2nd Workshop of the European CMT Consortium: 53rd ENMC International Workshop on Classification and Diagnostic Guidelines for Charcot-Marie-Tooth Type 2 (CMT2–HMSN II) and Distal Hereditary Motor Neuropathy (Distal HMN–Spinal CMT) 26–28 September 1997, Naarden, The Netherlands. Neuromuscular Disorders. Elsevier; 1998;8(6):426–31.

[75] Gemignani F, Marbini A. Charcot-Marie-Tooth disease (CMT): distinctive phenotypic and genotypic features in CMT type 2. J. Neurol. Sci. 2001Feb.15;184(1):1–9.

[76] Eriksson M, Brown WT, Gordon LB, Glynn MW, Singer J, Scott L, et al. Recurrent de novo point mutations in lamin A cause Hutchinson–Gilford progeria syndrome. Nature. Nature Publishing Group; 2003Apr.25;423(6937):293–8.

[77] Salamat M, Dhar PK, Neagu DL, Lyon JB. Aortic calcification in a patient with hutchinson-gilford progeria syndrome. Pediatr Cardiol. 2010Aug.;31(6):925–6.

[78] Rodríguez JI, Pérez-Alonso P, Funes R, Pérez-Rodríguez J. Lethal neonatal Hutchinson-Gilford progeria syndrome. Am. J. Med. Genet. 1999Jan.29;82(3):242–8.

[79] Gillar PJ, Kaye CI, McCourt JW. Progressive Early Dermatologic Changes in Hutchinson-Gilford Progeria Syndrome. Pediatr Dermatol. 1991Sep.;8(3):199–206.

[80] Merideth MA, Gordon LB, Clauss S, Sachdev V, Smith ACM, Perry MB, et al. Phenotype and course of Hutchinson–Gilford progeria syndrome. New England journal of medicine. Mass Medical Soc; 2008;358(6):592–604.

[81] Smigiel R, Jakubiak A, Esteves-Vieira V, Szela K, Halon A, Jurek T, et al. Novel frameshifting mutations of the ZMPSTE24 gene in two siblings affected with restrictive dermopathy and review of the mutations described in the literature. Am. J. Med. Genet. 2010Feb.;152A(2):447–52.

[82] Mok Q, Curley R, Tolmie J, Marsden R. Restrictive dermopathy: a report of three cases. Journal of Medical Genetics. 1990Jan.1.

[83] Yu CE, Oshima J, Fu YH, Wijsman EM, Hisama F, Alisch R, et al. Positional cloning of the Werner's syndrome gene. Science. 1996Apr.12;272(5259):258–62.

[84] Chen L, Lee L, Kudlow BA, Santos Dos HG, Sletvold O, Shafeghati Y, et al. LMNA mutations in atypical Werner's syndrome. The Lancet. Elsevier; 2003;362(9382):440–5.

[85] Hisama FM, Lessel D, Leistritz D, Friedrich K, McBride KL, Pastore MT, et al. Coronary artery disease in a Werner syndrome-like form of progeria characterized by low levels of progerin, a splice variant of lamin A. Am. J. Med. Genet. 2011Dec.;155A(12):3002–6.

[86] Hisama FM, Kubisch C, Martin GM, Oshima J. Clinical utility gene card for: Werner syndrome. Eur J Hum Genet. Nature Publishing Group; 2012Jan.18;20(5):1–3.

[87] Wassif CA, Brownson KE, Sterner AL, Forlino A, Zerfas PM, Wilson WK, et al. HEM dysplasia and ichthyosis are likely laminopathies and not due to 3beta-hydroxysterol Delta14-reductase deficiency. Human Molecular Genetics. 2007May15;16(10):1176–87.

[88] Waterham HR, Koster J, Mooyer P, Noort G, Kelley RI, Wilcox WR, et al. 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. Hum. Genet. Elsevier; 2003;72(4):1013–7.

[89] Konstantinidou A, Karadimas C, Waterham HR, Superti-Furga A, Kaminopetros P, Grigoriadou M, et al. Pathologic, radiographic and molecular findings in three fetuses diagnosed with HEM/Greenberg skeletal dysplasia. Prenat. Diagn. 2008;28(4):309–12.

[90] Hoffmann K, Dreger CK, Olins AL, Olins DE, Shultz LD, Lucke B, et al. Mutations in the gene encoding the lamin B receptor produce an altered nuclear morphology in granulocytes (Pelger-Huët anomaly). Nat Genet. 2002Aug.;31(4):410–4.

[91] Waterham HR, Koster J, Mooyer P, Noort Gv GV, Kelley RI, Wilcox WR, et al. 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. Hum. Genet. 2003Apr.;72(4):1013–7.

[92] Oosterwijk JC. Congenital abnormalities reported in Pelger-Huet homozygosity as compared to Greenberg/HEM dysplasia: highly variable expression of allelic phenotypes. Journal of Medical Genetics. BMJ Group; 2003Dec.1;40(12):937–41.

[93] Reynolds TB, Denison EK, Frankl HD, Lieberman FL, Peters RL. Primary biliary cirrhosis with scleroderma, Raynaud's phenomenon and telangiectasia. New syndrome. Am. J. Med. 1971Mar.;50(3):302–12.

[94] Gaudy-Marqueste C, Roll P, Esteves-Vieira V, Weiller PJ, Grob JJ, Cau P, et al. LBR mutation and nuclear envelope defects in a patient affected with Reynolds syndrome. Journal of Medical Genetics. 2010Jun.3;47(6):361–70.

[95] Berlin R, Hedensiö B, Lilja B, Linder L. Osteopoikilosis—-a Clinical and Genetic Study. Acta Medica Scandinavica. Wiley Online Library; 1967;181(3):305–14.

[96] Hellemans J, Preobrazhenska O, Willaert A, Debeer P, Verdonk PCM, Costa T, et al. Loss-of-function mutations in LEMD3 result in osteopoikilosis, Buschke-Ollendorff syndrome and melorheostosis. Nat Genet. 2004Oct.17;36(11):1213–8.

[97] Zhang Y, Castori M, Ferranti G, Paradisi M, Wordsworth BP. Novel and recurrent germline LEMD3mutations causing Buschke-Ollendorff syndrome and osteopoikilosis but not isolated melorheostosis. Clinical Genetics. 2009Jun.;75(6):556–61.

[98] Schena D, Germi L, Zamperetti MR, Colato C, Girolomoni G. Buschke-Ollendorff syndrome. Int. J. Dermatol. 2008Nov.;47(11):1159–61.

[99] Liu B, Wang J, Chan KM, Tjia WM, Deng W, Guan X, et al. Genomic instability in laminopathy-based premature aging. Nat Med. 2005Jul.;11(7):780–5.

[100] Scaffidi P, Misteli T. Reversal of the cellular phenotype in the premature aging disease Hutchinson-Gilford progeria syndrome. Nat Med. 2005Apr.;11(4):440–5.

[101] Sullivan T, Escalante-Alcalde D, Bhatt H, Anver M, Bhat N, Nagashima K, et al. Loss of A-type lamin expression compromises nuclear envelope integrity leading to muscular dystrophy. Journal of Cell Biology. 1999Nov.29;147(5):913–20.

[102] Goldman A, Erdos M, Eriksson M, Collins FS. Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson–Gilford progeria syndrome. Proceedings of the National Academy of Sciences. 2004Jan.1.

[103] Fong LG, Ng JK, Meta M, Coté N, Yang SH, Stewart CL, et al. Heterozygosity for Lmna deficiency eliminates the progeria-like phenotypes in Zmpste24-deficient mice. Proceedings of the …. 2004.

[104] Arancio W. A Bioinformatics Analysis of Lamin-A Regulatory Network: A Perspective on Epigenetic Involvement in Hutchinson–Gilford Progeria Syndrome. Rejuvenation Research. 2012Apr.;15(2):123–7.

[105] Padmakumar VC, Libotte T, Lu W, Zaim H, Abraham S, Noegel AA, et al. The inner nuclear membrane protein Sun1 mediates the anchorage of Nesprin-2 to the nuclear envelope. Journal of Cell Science. 2005Aug.1;118(Pt 15):3419–30.

[106] Mislow JMK, Kim MS, Davis DB, McNally EM. Myne-1, a spectrin repeat transmembrane protein of the myocyte inner nuclear membrane, interacts with lamin A/C. Journal of Cell Science. 2002Jan.1;115(Pt 1):61–70.

[107] Maraldi NM, Lattanzi G. Linkage of lamins to fidelity of gene transcription. Crit. Rev. Eukaryot. Gene Expr. 2005;15(4):277–94.

[108] Lattanzi G, Cenni V, Marmiroli S, Capanni C, Mattioli E, Merlini L, et al. Association of emerin with nuclear and cytoplasmic actin is regulated in differentiating myoblasts. Biochem Biophys Res Commun. 2003Apr.11;303(3):764–70.

[109] Lattanzi G, Columbaro M, Mattioli E, Cenni V, Camozzi D, Wehnert M, et al. Pre-Lamin A processing is linked to heterochromatin organization. J. Cell. Biochem. 2007Dec.1;102(5):1149–59.

[110] Vlcek S, Foisner R. Lamins and lamin-associated proteins in aging and disease. Current Opinion in Cell Biology. 2007Jun.;19(3):298–304.

[111] Jung HJ, Sun T, Pleasure S, Young S, al E. Regulation of prelamin A but not lamin C by miR-9, a brain-specific microRNA. Proceedings of the …. 2012.

[112] Nissan X, Blondel S, Navarro C, Maury Y, Denis C, Girard M, et al. Unique Preservation of Neural Cells in Hutchinson- Gilford Progeria Syndrome Is Due to the Expression of the Neural-Specific miR-9 MicroRNA. Cell Reports. 2012Jul.;2(1):1–9.

[113] Muchir A, Pavlidis P, Decostre V, Herron AJ, Arimura T, Bonne G, et al. Activation of MAPK pathways links LMNA mutations to cardiomyopathy in Emery-Dreifuss muscular dystrophy. J. Clin. Invest. 2007May;117(5):1282–93.

[114] Haq S, Choukroun G, Lim H, Tymitz KM, del Monte F, Gwathmey J, et al. Differential activation of signal transduction pathways in human hearts with hypertrophy versus advanced heart failure. Circulation. 2001Feb.6;103(5):670–7.

[115] Cook S. Activation of c-Jun N-Terminal Kinases and p38-Mitogen-activated Protein Kinases in Human Heart Failure Secondary to Ischaemic Heart Disease. Journal of Molecular and Cellular Cardiology. 1999Aug.;31(8):1429–34.

[116] Nicol RL, Frey N, Pearson G, Cobb M, Richardson J, Olson EN. Activated MEK5 induces serial assembly of sarcomeres and eccentric cardiac hypertrophy. The EMBO journal. 2001Jun.1;20(11):2757–67.

[117] Muchir A, Pavlidis P, Bonne G, Hayashi YK, Worman HJ. Activation of MAPK in hearts of EMD null mice: similarities between mouse models of X-linked and autosomal dominant Emery Dreifuss muscular dystrophy. Human Molecular Genetics. 2007Aug.1;16(15):1884–95.

[118] Brodsky GL, Muntoni F, Miocic S, Sinagra G, Sewry C, Mestroni L. Lamin A/C gene mutation associated with dilated cardiomyopathy with variable skeletal muscle involvement. Circulation. 2000Feb.8;101(5):473–6.

[119] Vytopil M, Ricci E, Russo Dello A, Hanisch F, Neudecker S, Zierz S, et al. Frequent low penetrance mutations in the Lamin A/C gene, causing Emery Dreifuss muscular dystrophy. Neuromuscular Disorders. 2002Dec.;12(10):958–63.

[120] Marina Raffaele di Barletta ERGGPTMMLMARTVKHOLMCTVBIHPSBRRKSGBDT. Different Mutations in the LMNA Gene Cause Autosomal Dominant and Autosomal Recessive Emery-Dreifuss Muscular Dystrophy. Am. J. Hum. Genet. Elsevier; 2000Apr.1;66(4):1407.

[121] Genschel J, Schmidt HHJ. Mutations in the LMNA gene encoding lamin A/C. Hum. Mutat. Wiley Online Library; 2000;16(6):451–9.

[122] Novelli G, Muchir A, Sangiuolo F, Helbling-Leclerc A, D'Apice MR, Massart C, et al. Mandibuloacral dysplasia is caused by a mutation in LMNA-encoding lamin A/C. Am. J. Hum. Genet. 2002Aug.;71(2):426–31.

[123] Shen JJ, Brown CA, Lupski JR, Potocki L. Mandibuloacral dysplasia caused by homozygosity for the R527H mutation in lamin A/C. Journal of Medical Genetics. 2003Nov.;40(11):854–7.

[124] Mercuri E, Poppe M, Quinlivan R, Messina S, Kinali M, Demay L, et al. Extreme variability of phenotype in patients with an identical missense mutation in the lamin A/C gene: from congenital onset with severe phenotype to milder classic Emery-Dreifuss variant. Arch. Neurol. 2004May;61(5):690–4.

[125] Mercuri E, Brown SC, Nihoyannopoulos P, Poulton J, Kinali M, Richard P, et al. Extreme variability of skeletal and cardiac muscle involvement in patients with mutations in exon 11 of the lamin A/C gene. Muscle Nerve. 2005;31(5):602–9.

[126] Genschel J, Bochow B, Kuepferling S, Ewert R, Hetzer R, Lochs H, et al. A R644C mutation within lamin A extends the mutations causing dilated cardiomyopathy. Hum. Mutat. 2001Feb.;17(2):154.

[127] Vigouroux C, Auclair M, Dubosclard E, Pouchelet M, Capeau J, Courvalin J-C, et al. Nuclear envelope disorganization in fibroblasts from lipodystrophic patients with heterozygous R482Q/W mutations in the lamin A/C gene. Journal of Cell …. 2001.

[128] Gonzalez JM, Navarro-Puche A, Casar B, Crespo P, Andres V. Fast regulation of AP-1 activity through interaction of lamin A/C, ERK1/2, and c-Fos at the nuclear envelope. The Journal of Cell Biology. 2008Nov.10;183(4):653–66.

[129] de Sandre-Giovannoli A, Bernard R, Cau P, Navarro C, Amiel J, Boccaccio I, et al. Lamin a truncation in Hutchinson-Gilford progeria. Science. 2003Jun.27;300(5628): 2055.

[130] Muchir A, Wu W, Worman HJ. Reduced expression of A-type lamins and emerin activates extracellular signal-regulated kinase in cultured cells. Biochim. Biophys. Acta. 2009Jan.;1792(1):75–81.

[131] Emerson LJ, Holt MR, Wheeler MA, Wehnert M, Parsons M, Ellis JA. Defects in cell spreading and ERK1/2 activation in fibroblasts with lamin A/C mutations. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. Elsevier; 2009;1792(8):810–21.

[132] Fong LG. Prelamin A and lamin A appear to be dispensable in the nuclear lamina. J. Clin. Invest. 2006Mar.1;116(3):743–52.

[133] Olins AL, Olins DE. Cytoskeletal influences on nuclear shape in granulocytic HL-60 cells. BMC Cell Biol. 2004Aug.19;5:30.

[134] Dahl KN, Booth-Gauthier EA, Ladoux B. In the middle of it all: mutual mechanical regulation between the nucleus and the cytoskeleton. Journal of biomechanics. Elsevier; 2010;43(1):2–8.

[135] Morris GE. Heart to heart: from nuclearproteins to Emery-Dreifuss muscular dystrophy. Human Molecular Genetics. 1999Sep.1;8(10):1847–51.

[136] Broers J, Machiels B, Kuijpers H, Smedts F, van den Kieboom R, Raymond Y, et al. A- and B-type lamins are differentially expressed in normal human tissues. Histochemistry and cell biology. 1997;107(6):505–17.

[137] Ostlund C, Ellenberg J, Hallberg E, Lippincott-Schwartz J, Worman HJ. Intracellular trafficking of emerin, the Emery-Dreifuss muscular dystrophy protein. Journal of Cell Science. 1999Jun.;112 (Pt 11):1709–19.

[138] Maniotis AJ, Chen CS, Ingber DE. Demonstration of mechanical connections between integrins, cytoskeletal filaments, and nucleoplasm that stabilize nuclear structure. Proceedings of the National Academy of Sciences of the United States of America. 1997Feb.4;94(3):849–54.

[139] Rosengardten Y, McKenna T, Grochová D, Eriksson M. Stem cell depletion in Hutchinson-Gilford progeria syndrome. Aging Cell. 2011Sep.8.

[140] Meshorer E, Gruenbaum Y. Gone with the Wnt/Notch: stem cells in laminopathies, progeria, and aging. The Journal of Cell Biology. 2008Apr.7;181(1):9–13.

[141] Bertrand AT, Chikhaoui K, Yaou RB, Bonne G. Clinical and genetic heterogeneity in laminopathies. Biochem. Soc. Trans. 2011Nov.21;39(6):1687–92.

[142] Herrmann H, Aebi U. Intermediate filaments: molecular structure, assembly mechanism, and integration into functionally distinct intracellular Scaffolds. Annu. Rev. Biochem. 2004;73:749–89.

[143] Reunert J, Wentzell R, Walter M, Jakubiczka S, Zenker M, Brune T, et al. Neonatal progeria: increased ratio of progerin to lamin A leads to progeria of the newborn. Eur J Hum Genet. 2012Mar.14.

[144] Moulson C, Fong L, Gardner J. Increased progerin expression associated with unusual LMNA mutations causes severe progeroid syndromes. Hum. Mutat. 2007Jan.1.

[145] Cenni V, Capanni C, Columbaro M, Ortolani M, D'Apice MR, Novelli G, et al. Autophagic degradation of farnesylated prelamin A as a therapeutic approach to lamin-linked progeria. Eur J Histochem. 2011;55(4):e36.

[146] Rodriguez S, Eriksson M. Low and high expressing alleles of the LMNA gene: implications for laminopathy disease development. PLoS ONE. 2011;6(9):e25472.

[147] Jahn D, Schramm S, Schnölzer M, Heilmann CJ, de Koster CG, Schütz W, et al. A truncated lamin A in the Lmna (-/-) mouse line: Implications for the understanding of laminopathies. Nucleus. 2012Sep.1;3(5).

[148] Kubben N, Voncken JW, Konings G, van Weeghel M, van den Hoogenhof MMG, Gijbels M, et al. Post-natal myogenic and adipogenic developmental: Defects and metabolic impairment upon loss of A-type lamins. Nucleus. Landes Bioscience; 2011May1;2(3):195–207.

[149] Coffinier C, Jung HJ, Li Z, Nobumori C, Yun UJ, Farber EA, et al. Direct Synthesis of Lamin A, Bypassing Prelamin A Processing, Causes Misshapen Nuclei in Fibroblasts but No Detectable Pathology in Mice. Journal of Biological Chemistry. 2010Jun. 25;285(27):20818–26.

[150] Bergo M, Gavino B, Ross J. Zmpste24 deficiency in mice causes spontaneous bone fractures, muscle weakness, and a prelamin A processing defect. Proceedings of the National Academy of Sciences. 2002Jan.1.

[151] Pendás AM, Zhou Z, Cadiñanos J, Freije JMP, Wang J, Hultenby K, et al. Defective prelamin A processing and muscular and adipocyte alterations in Zmpste24 metalloproteinase-deficient mice. Nat Genet. 2002May;31(1):94–9.

[152] Mounkes LC, Kozlov SV, Rottman JN, Stewart CL. Expression of an LMNA-N195K variant of A-type lamins results in cardiac conduction defects and death in mice. Human Molecular Genetics. 2005Aug.1;14(15):2167–80.

[153] Arimura T, Helbling-Leclerc A, Massart C, Varnous S, Niel F, Lacène E, et al. Mouse model carrying H222P-Lmna mutation develops muscular dystrophy and dilated cardiomyopathy similar to human striated muscle laminopathies. Human Molecular Genetics. 2005Jan.1;14(1):155–69.

[154] Yang SH, Bergo MO, Toth JI, Qiao X, Hu Y, Sandoval S, et al. Blocking protein farnesyltransferase improves nuclear blebbing in mouse fibroblasts with a targeted Hutch-

inson-Gilford progeria syndrome mutation. Proceedings of the National Academy of Sciences. 2005Jul.19;102(29):10291–6.

[155] Mounkes LC, Kozlov S, Hernandez L, Sullivan T, Stewart CL. A progeroid syndrome in mice is caused by defects in A-type lamins. Nature. 2003May15;423(6937):298–301.

[156] Wang Y, Herron AJ, Worman HJ. Pathology and nuclear abnormalities in hearts of transgenic mice expressing M371K lamin A encoded by an LMNA mutation causing Emery-Dreifuss muscular dystrophy. Human Molecular Genetics. 2006Aug. 15;15(16):2479–89.

[157] Osorio FG, Navarro CL, Cadinanos J, Lopez-Mejia IC, Quiros PM, Bartoli C, et al. Splicing-Directed Therapy in a New Mouse Model of Human Accelerated Aging. Science Translational Medicine. 2011Oct.26;3(106):106ra107–7.

[158] Melcon G, Kozlov S, Cutler DA, Sullivan T, Hernandez L, Zhao P, et al. Loss of emerin at the nuclear envelope disrupts the Rb1/E2F and MyoD pathways during muscle regeneration. Human Molecular …. 2006.

[159] Ozawa R, Hayashi YK, Ogawa M, Kurokawa R, Matsumoto H, Noguchi S, et al. Emerin-lacking mice show minimal motor and cardiac dysfunctions with nuclear-associated vacuoles. Am. J. Pathol. 2006Mar.;168(3):907–17.

[160] Muchir A, van Engelen BG, Lammens M, Mislow JM, McNally E, Schwartz K, et al. Nuclear envelope alterations in fibroblasts from LGMD1B patients carrying nonsense Y259X heterozygous or homozygous mutation in lamin A/C gene. Experimental Cell Research. 2003Dec.10;291(2):352–62.

[161] Van Berlo JH, Voncken JW, Kubben N, Broers JLV, Duisters R, van Leeuwen REW, et al. A-type lamins are essential for TGF-beta1 induced PP2A to dephosphorylate transcription factors. Human Molecular Genetics. 2005Oct.1;14(19):2839–49.

[162] Jahn D, Schramm S, Schnölzer M, Heilmann CJ, de Koster CG, Schütz W, et al. A truncated lamin A in the Lmna−/− mouse line: Implications for the understanding of laminopathies. Nucleus. 2012Sep.1;3(5).

[163] Leung GK, Schmidt WK, Bergo MO, Gavino B, Wong DH, Tam A, et al. Biochemical studies of Zmpste24-deficient mice. J Biol Chem. 2001Aug.3;276(31):29051–8.

[164] Ambrosi P, Mouly-Bandini A, Attarian S, Habib G. Heart transplantation in 7 patients from a single family with limb-girdle muscular dystrophy caused by lamin A/C mutation. International Journal of Cardiology. 2009Nov.;137(3):e75–6.

[165] Dyck JD, David TE, Burke B, Webb GD, Henderson MA, Fowler RS. Management of coronary artery disease in Hutchinson-Gilford syndrome. The Journal of Pediatrics. 1987Sep.;111(3):407–10.

[166] Savage DB, Tan GD, Acerini CL, Jebb SA, Agostini M, Gurnell M, et al. Human metabolic syndrome resulting from dominant-negative mutations in the nuclear receptor peroxisome proliferator-activated receptor-gamma. Diabetes. 2003Apr.;52(4):910–7.

[167] Javor ED, Cochran EK, Musso C, Young JR, Depaoli AM, Gorden P. Long-term efficacy of leptin replacement in patients with generalized lipodystrophy. Diabetes. 2005Jul.;54(7):1994–2002.

[168] Park JY, Javor ED, Cochran EK, Depaoli AM, Gorden P. Long-term efficacy of leptin replacement in patients with Dunnigan-type familial partial lipodystrophy. Metab. Clin. Exp. 2007Apr.;56(4):508–16.

[169] Maraldi NM, Capanni C, Lattanzi G, Camozzi D, Facchini A, Manzoli FA. SREBP1 interaction with prelamin A forms: A pathogenic mechanism for lipodystrophic laminopathies. Advances in Enzyme Regulation. Advances in enzyme …; 2008Jan.;48(1): 209–23.

[170] Kieran MW, Gordon L, Kleinman M. New approaches to progeria. Pediatrics. 2007Oct.;120(4):834–41.

[171] Capell B, Erdos M, Madigan J, Fiordalisi J. Inhibiting farnesylation of progerin prevents the characteristic nuclear blebbing of Hutchinson- …. Proceedings of the National Academy of Sciences. 2005Jan.1.

[172] Mallampalli MP, Huyer G, Bendale P, Gelb MH, Michaelis S. Inhibiting farnesylation reverses the nuclear morphology defect in a HeLa cell model for Hutchinson-Gilford progeria syndrome. Proceedings of the National Academy of Sciences of the United States of America. 2005Oct.4;102(40):14416–21.

[173] Toth J, Yang S, Qiao X, Beigneux A, Gelb M. Blocking protein farnesyltransferase improves nuclear shape in fibroblasts from humans with …. Proceedings of the National Academy of Sciences. 2005Jan.1.

[174] Capell BC, Olive M, Erdos MR, Cao K, Faddah DA, Tavarez UL, et al. A farnesyltransferase inhibitor prevents both the onset and late progression of cardiovascular disease in a progeria mouse model. Proceedings of the National Academy of Sciences. 2008Oct.14;105(41):15902–7.

[175] Yang S. Treatment with a farnesyltransferase inhibitor improves survival in mice with a Hutchinson–Gilford progeria syndrome mutation. Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids. 2008Jan.1;1781(1-2):36–9.

[176] Fong L, Frost D, Meta M, Qiao X, Yang S. A Protein Farnesyltransferase Inhibitor Ameliorates Disease in a Mouse Model of Progeria. Science. 2006Jan.1.

[177] Shao H Yang DAAHPSSGYLGF. Progerin elicits disease phenotypes of progeria in mice whether or not it is farnesylated. The Journal of Clinical Investigation. American Society for Clinical Investigation; 2008Oct.1;118(10):3291.

[178] Varela I, Pereira S, Ugalde AP, Navarro CL, Suárez MF, Cau P, et al. Combined treatment with statins and aminobisphosphonates extends longevity in a mouse model of human premature aging. Nat Med. 2008Jun.29;14(7):767–72.

[179] Glynn M, Glover T. Incomplete processing of mutant lamin A in Hutchinson-Gilford progeria leads to nuclear …. Human Molecular Genetics. 2005Jan.1.

[180] Davies BSJ, Barnes RH, Tu Y, Ren S, Andres DA, Spielmann HP, et al. An accumulation of non-farnesylated prelamin A causes cardiomyopathy but not progeria. Human Molecular Genetics. 2010Jun.10;19(13):2682–94.

[181] Coffinier C, Hudon SE, Farber EA, Chang SY, Hrycyna CA, Young SG, et al. HIV protease inhibitors block the zinc metalloproteinase ZMPSTE24 and lead to an accumulation of prelamin A in cells. Proceedings of the National Academy of Sciences of the United States of America. 2007Aug.14;104(33):13432–7.

[182] Cao K, Graziotto JJ, Blair CD, Mazzulli JR, Erdos MR, Krainc D, et al. Rapamycin reverses cellular phenotypes and enhances mutant protein clearance in Hutchinson-Gilford progeria syndrome cells. Science Translational Medicine. 2011Jun.29;3(89): 89ra58.

[183] Ramos FJ, Chen SC, Garelick MG, Dai D-F, Liao C-Y, Schreiber KH, et al. Rapamycin Reverses Elevated mTORC1 Signaling in Lamin A/C-Deficient Mice, Rescues Cardiac and Skeletal Muscle Function, and Extends Survival. Science Translational Medicine. 2012Jul.25;4(144):144ra103.

[184] Choi JC, Muchir A, Wu W, Iwata S. Temsirolimus activates autophagy and ameliorates cardiomyopathy caused by lamin A/C gene mutation. Science. 2012.

[185] Wu W, Muchir A, Shan J, Bonne G, Worman HJ. Mitogen-Activated Protein Kinase Inhibitors Improve Heart Function and Prevent Fibrosis in Cardiomyopathy Caused by Mutation in Lamin A/C GeneClinical Perspective. Circulation. Am Heart Assoc; 2011;123(1):53–61.

[186] Chhajed PN, Dickenmann M, Bubendorf L, Mayr M, Steiger J, Tamm M. Patterns of pulmonary complications associated with sirolimus. Respiration. 2006;73(3):367–74.

[187] Filippone EJ, Carson JM, Beckford RA, Jaffe BC, Newman E, Awsare BK, et al. Sirolimus-induced pneumonitis complicated by pentamidine-induced phospholipidosis in a renal transplant recipient: a case report. Transplant. Proc. 2011Sep.;43(7):2792–7.

[188] Pham P-TT, Pham P-CT, Danovitch GM, Ross DJ, Gritsch HA, Kendrick EA, et al. Sirolimus-Associated Pulmonary Toxicity. Transplantation. 2004Apr.27;77(8):1215.

[189] Lamming DW, Ye L, Katajisto P, Goncalves MD, Saitoh M, Stevens DM, et al. Rapamycin-induced insulin resistance is mediated by mTORC2 loss and uncoupled from longevity. Science. 2012Mar.30;335(6076):1638–43.

[190] Scaffidi P. Lamin A-Dependent Nuclear Defects in Human Aging. Science. 2006.

[191] Huang S, Chen L, Libina N, Janes J, Martin GM, Campisi J, et al. Correction of cellular phenotypes of Hutchinson-Gilford Progeria cells by RNA interference. Hum. Genet. 2005Dec.;118(3-4):444–50.

[192] Fong LG, Vickers TA, Farber EA, Choi C, Yun UJ, Hu Y, et al. Activating the synthesis of progerin, the mutant prelamin A in Hutchinson-Gilford progeria syndrome, with antisense oligonucleotides. Human Molecular Genetics. 2009Jun.10;18(13):2462–71.

[193] Flemming A. Regulatory watch: Pioneering gene therapy on brink of approval. Nat Rev Drug Discov. 2012Aug.31;11(9):664.

[194] Mazhari R, Hare JM. Mechanisms of action of mesenchymal stem cells in cardiac repair: potential influences on the cardiac stem cell niche. Nat Clin Pract Cardiovasc Med. 2007Feb.;4 Suppl 1:S21–6.

[195] Trollet C, Athanasopoulos T, Popplewell L, Malerba A, Dickson G. Gene therapy for muscular dystrophy: current progress and future prospects. Expert Opin. Biol. Ther. 2009Jul.;9(7):849–66.

[196] Merkulov S, Chen X, Chandler MP, Stelzer JE. In Vivo cMyBPC Gene Transfer Rescues Myofilament Contractile Dysfunction in cMyBPC Null Mice. Circ Heart Fail. 2012Aug.1.

IntechOpen