Clinical and genetic heterogeneity in laminopathies

Anne T. Bertrand*†, Khadija Chikhaoui*†, Rabah Ben Yaou*† and Gisèle Bonne*†‡[1]

*Inserm, U974, Paris, France, †Université Pierre et Marie Curie Paris 6, UM 76, CNRS, UMR 7215, Institut de Myologie, Paris, France, and ‡AP-HP, Groupe Hospitalier Pitié-Salpêtrière, U.F. Cardiogénétique et Myogénétique, Service de Biochimie Métabolique, 47 boulevard de l'Hôpital, 75651 Paris Cedex 13, France

Abstract

Mutations in the *LMNA* gene encoding lamins A/C are responsible for more than ten different disorders called laminopathies which affect various tissues in an isolated (striated muscle, adipose tissue or peripheral nerve) or systemic (premature aging syndromes) fashion. Overlapping phenotypes are also observed. Associated with this wide clinical variability, there is also a large genetic heterogeneity, with 408 different mutations being reported to date. Whereas a few hotspot mutations emerge for some types of laminopathies, relationships between genotypes and phenotypes remain poor for laminopathies affecting the striated muscles. In addition, there is important intrafamilial variability, explained only in a few cases by digenism, thus suggesting an additional contribution from modifier genes. In this regard, a chromosomal region linked to the variability in the age at onset of myopathic symptoms in striated muscle laminopathies has recently been identified. This locus is currently under investigation to identify modifier variants responsible for this variability.

Introduction

A-type and B-type lamins are the major constituents of the nuclear lamina, a meshwork of proteins underlying the inner nuclear membrane [1]. The *LMNA* gene is localized to chromosome 1q21.2–q21.3 and is composed of 12 exons that encode four A-type lamins (A, AΔ10, C and C2) by alternative splicing. Lamin A and lamin C are the two main isoforms. They are identical for their first 566 amino acids, but are distinct at their C-terminal domains (Figure 1). Lamin C has six unique C-terminal amino acids. Lamin A is synthesized as a precursor, prelamin A, which has 98 unique C-terminal amino acids. Prelamin A is farnesylated on the cysteine residue of a C-terminal CaaX (where a is an aliphatic residue) box and then is endoproteolytically processed by the ZMPSTE24 (zinc metalloprotease Ste24 homologue) protease to yield mature lamin A, which lacks the last 18 amino acids [2]. Lamin A and C (henceforth referred to as lamin A/C) are expressed in all post-mitotic cells. They dimerize and further assemble to form head-to-tail polymers which finally associate laterally and eventually form lamin filaments that, together with lamin B, constitute the nuclear lamina [3]. Lamin A/C is also found in the nucleoplasm in a still unknown conformation and may have multiple functions by association with chromatin, nuclear histones and various transcription factors [1].

Recent interest in *LMNA* has centred on the finding that mutations in this gene give rise to more than ten distinct genetic diseases, commonly named laminopathies. The first *LMNA* mutation associated with a genetic disorder was identified in autosomal dominant EDMD (Emery–Dreifuss muscular dystrophy) [4]. Since then, mutations in *LMNA* have been associated to other disorders affecting tissues in a specific manner (striated muscle, adipose tissue or peripheral nerve) or in systemic fashion (premature aging syndromes) [1,5]. This wide clinical heterogeneity is associated with a large genetic variability, with so far 408 different *LMNA* mutations reported (http://www.umd.be/LMNA/).

To date, three main pathophysiological hypotheses, which are not mutually exclusive, have been proposed to explain the phenotypical variability linked to *LMNA* mutations (reviewed in [1,5]). (i) The structural hypothesis is based on ideas surrounding the role of lamins and associated proteins such as the LINC (linker of nucleoskeleton and cytoskeleton) complex proteins nesprins and SUN proteins, at the nuclear periphery, in maintaining the mechanical integrity of cells by linking the nucleoskeleton to the cytoskeleton [6]. A 'weakened' lamina would lead to overall loss of the cell's ability to withstand stress-induced damage, which may be of critical significance in contracting tissues such as skeletal and cardiac muscles [7]. (ii) The gene expression hypothesis is based on the role of A-type lamins in transcription and cell signalling via their interactions with chromatin and multiple transcription factors such as Rb (retinoblastoma) or SREBP-1 (sterol-regulatory-element-binding protein 1) [1]. It proposes that mutations lead to modified or disrupted interactions within the lamin A/C multiprotein complex signalling platform, leading to downstream epigenetic chromatin modifications and/or alteration of various signalling pathways [8]. (iii) The cell

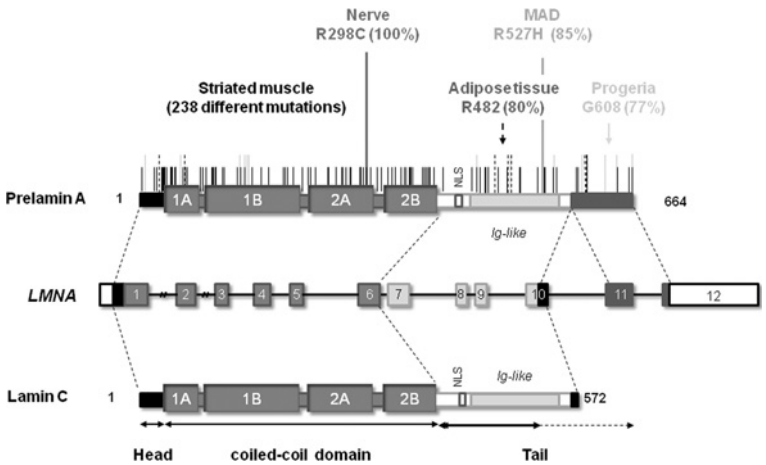
Key words: lamin A/C, laminopathy, *LMNA*, mutation database.

Abbreviations used: EDMD, Emery–Dreifuss muscular dystrophy; HGPS, Hutchinson–Gilford progeria syndrome; LGMD1B, limb-girdle muscular dystrophy type 1B; MAD, mandibuloacral dysplasia; RD, restrictive dermopathy; SML, striated muscle laminopathy.

[1]**To whom correspondence should be addressed (email g.bonne@institut-myologie.org).**

Figure 1 | Distribution of *LMNA* mutations in prelamin A and lamin C

Schematic representation of *LMNA* gene and the two main isoforms: prelamin A and lamin C. The 238 *LMNA* mutations associated with SMLs are depicted by black lines and are located along the molecules. *LMNA* mutations leading specifically to adipose tissue defects are depicted by dotted lines and are essentially located in the N- and C-terminal domains, with a hotspot in the Ig-like domain at Arg^{482} (80% of the patients). Mutations associated with premature aging syndromes (HGPS, RD, fatal fetal akinesia, Werner syndrome and MAD) are depicted in light grey. They are also essentially located in the N- and C-terminal domains, with a hotspot at position 608 (77% of HGPS patients) and at position 527 (85% of MAD patients). The position of the unique *LMNA* mutation, p.R298C, leading to axonal neuropathy, is also indicated.



toxicity hypothesis suggests that the accumulation of mutated lamins results in highly toxic effects detrimental to cell survival [2]. These hypotheses may differently apply in the different types of laminopathies.

Laminopathies: a highly heterogeneous continuum of diseases

Laminopathies of the striated muscle

The first *LMNA* mutation was identified in autosomal dominant form of EDMD [4]. EDMD is characterized by early onset of Achilles tendon, elbow and spine contractures associated with slowly progressive muscular wasting and weakness of humeroperoneal muscles and, by adult age, the development of arrhythmias, conduction system defects and cardiomyopathy linked with a high frequency of cardiac sudden death which can be prevented in part by the implantation of cardiac defibrillator [9,10]. Shortly afterwards, *LMNA* mutations were reported in LGMD1B (limb-girdle muscular dystrophy type 1B), which shares the same cardiac disease characteristics as EDMD [11], but differs from EDMD by the topography of the muscle weakness and wasting, predominantly affecting the pelvic and scapular girdle muscle in LGMD1B and the severity and age at onset of contractures, being either absent or mild with late onset in LGMD1B [12]. The third main clinical entity in this group is DCM-CD (dilated cardiomyopathy associated with conduction system disease) without any skeletal muscle involvement [13], this cardiac disease being similar to the cardiac involvement seen both in EDMD and LGMD1B. Interestingly, these three clinical entities can coexist within a same family, linked to the same *LMNA* mutation [14,15]. More recently, *LMNA* mutations were reported in congenital forms of muscular dystrophy (L-CMD) [16], which is characterized by onset before 2 years of age of major muscle atrophy and weakness affecting mainly axial muscles responsible for absent or limited motor achievements, together with important multiple joint contractures sparing elbows, and severe respiratory insufficiency.

Laminopathies of the peripheral nerve

An *LMNA* mutation was identified in an autosomal recessive form of Charcot–Marie–Tooth axonal neuropathy (CMT2B1) in families originating from North-West Africa [17]. CMT2B1 is characterized by distal muscle wasting and weakness associated with absence of osteotendinous reflexes in link with axonal degeneration [18,19].

Laminopathies of the adipose tissue

The main entity of adipose tissue laminopathies is the FPLD (familial partial lipodystrophy of Dunnigan type), characterized by onset after puberty of abnormal distribution of subcutaneous fat, loss of subcutaneous fat at the extremities of the limbs and accumulation of fat in the neck and face, associated with a metabolic syndrome with insulin-resistance, acanthosis nigricans, hypertriglyceridaemia, glucose intolerance and Type 2 diabetes [20–22]. Cases of type A insulin-resistance syndrome without lipodystrophy have been also associated with *LMNA* mutations [23].

Premature aging syndromes

The first premature aging syndrome that has been linked to *LMNA* mutations is the MAD (mandibuloacral dysplasia) [24], an autosomal recessive disorder characterized by postnatal growth retardation, craniofacial anomalies, skeletal malformations and mottled cutaneous pigmentation associated with partial lipodystrophy and insulin resistance. Shortly after, *de novo* heterozygous *LMNA* mutations were reported in HGPS (Hutchinson–Gilford progeria syndrome) [25,26]. This extremely rare and sporadic multisystem disorder is characterized by features of segmental premature aging sparing the brain, with affected subjects dying at a mean age of 13 years from cardiovascular disease. Other progeroid syndromes of variable severity were also linked with *LMNA* mutations, such as atypical Werner syndrome, LIRLLC (lipoatrophy, insulin-resistant diabetes, disseminated leukomelanodermic papules, liver steatosis and cardiomyopathy) or other atypical progeroid syndromes (for a complete review, see [27]). Among these, the most severe reported laminopathies are RD (restrictive dermopathy) [28] and a case of severe form of fetal akinesia [29]. RD is a neonatal and lethal syndrome with severe intrauterine growth retardation, generalized arthrogryposis and tense skin, and clavicle osteolysis. Only three cases of RD are linked either to *de novo* heterozygous *LMNA* mutation, leading, as in HGPS, to in-frame partial or total deletion of exon 11, which lead to in-frame deletion of prelamin A that lacks its proteolytic cleavage site, stays abnormally farnesylated and accumulates in cells [27], or to a homozygous missense *LMNA* mutation [30]. In contrast, fatal fetal akinesia associates with multiple contractures, generalized muscular dystrophy with quasi absence of intercostal muscles, and is due to an homozygous nonsense *LMNA* mutation leading to the absence of A-type lamins, meaning that the total knockout of lamin A/C in human is lethal [29,31].

Laminopathies: a wide genetic complexity

In addition to this large clinical pleiotropy, there is also a wide genetic variability, with 408 different *LMNA* mutations identified, of which approximately 100 are unpublished (A.T. Bertrand, K. Chikhaoui, R. Ben Yaou and G. Bonne). The published ones are available within the UMD-*LMNA* mutation database available at http://www.umd.be/LMNA/, gathering all of the genetic details and associated clinical phenotypes of each individual carrying an *LMNA* mutation.

So far, 301 different mutations have been reported, identified in 1559 subjects from 721 families (Figure 1). Among these, a large majority (almost 80%) corresponds to mutations leading to SMLs (striated muscle laminopathies) (Table 1). Among the remainder, 11% of the mutations lead to overlapping phenotypes, 9.3% to premature aging syndromes and 8.3% to laminopathies affecting the adipose tissue. Those affecting the peripheral nerves, with axonal neuropathy, remain extremely rare and represent only 0.3% of the *LMNA* mutations. All types of mutation are found: missense, nonsense, in-frame and out-of-frame insertions/deletions, as well as splice site mutations. Rare large exonic deletions have been also observed. However, missense mutations turned out to be the most frequent type of mutations, as they represent 72% of all *LMNA* mutations (Table 1). Mutations leading to premature stop codon, i.e. nonsense and out-of-frame insertions/deletions, represent 14% of the *LMNA* mutations, whereas splice site mutations and in-frame deletions/insertions represent 7.3 and 6.6% of the *LMNA* mutations respectively.

Striated muscle laminopathies

The 238 different *LMNA* mutations leading to an SML were identified in 795 patients, which represent more than 50% of all laminopathy cases. Missense mutations and small in-frame insertion/deletions represent 75.2% of these mutations; 16.8% are mutations leading to premature stop codon (nonsense and out-of-frame insertion/deletions); and 8% are splice site mutations (Table 1). Interestingly, nonsense and out-of-frame insertion/deletions are almost exclusively found in SML. Mutations are evenly distributed all along the gene, without any hotspot site, making the elucidation of any relationship between phenotype and genotype quite difficult. The only relationship that has emerged so far has been reported by Benedetti et al. [32], who showed that patients with early skeletal muscle involvement carry essentially missense mutations, whereas patients presenting with a later onset of their muscle symptoms carried frameshift mutations, presumably leading to truncated proteins.

However, the same mutation within a single family can give rise to variable phenotypes [14,15,33–38], suggesting that, besides *LMNA* mutation, additional players are involved to account for this variability. Among these players, digenism has been reported in a few cases that may explain in part this variability. Indeed, mutations in two different genes, *LMNA* and *EMD* (encoding emerin) or *DES* (encoding desmin), were reported to be associated with phenotypes of variable severity [39,40]. However, it does not explain all of the variability observed in SML. In this regard, we recently re-analysed the large French family that allowed us to find the first *LMNA* mutation [4] looking for a modifier locus. The clinical re-evaluation of this family pointed out that the age of the patients at the onset of their musculoskeletal symptoms (when they had some) were highly variable, ranging from early childhood to late adulthood. By plotting this parameter as a quantitative trait against data obtained from a whole genome scan of microsatellite markers, we identified a locus on chromosome 2 that may contain modifier variants that could explain this variability of age at onset of myopathic symptoms [41]. Unfortunately, we did not yet identify such a variant in the locus, although it contained two potential interesting candidates: the desmin and the myosin light chain genes (*DES* and *MYL1*).

Peripheral nerve laminopathies

So far, only one mutation with a founder effect has been reported in the *LMNA* gene leading to CMT2B1. A missense substitution of arginine for cysteine at position 298 has

Table 1 | Distribution of the different types of *LMNA* mutations according to their associated clinical phenotypes

Numbers of all published *LMNA* mutations are given for the different laminopathies and for the various types of mutation. Corresponding percentages are given in parentheses.

Mutation	SMLs	Laminopathies of adipose tissue	Laminopathies of peripheral nerve	Progeroid syndromes	Overlapping phenotypes*	Total
Total	238 (79.1%)	26 (8.6%)	1 (0.3%)	28 (9.3%)	35 (8) (10.9%)	301 (100%)
Missense	161 (67.6%)	24 (92.3%)	1 (100%)	25 (89.3%)	30 (6) (90.9%)	217 (72.1%)
Nonsense	14 (5.9%)	0	0	0	1 (0) (3.0%)	14 (4.7%)
In-frame deletion/insertion	18 (7.6%)	1 (3.8%)	0	0	2 (1) (6.1%)	20 (6.6%)
Out-of-frame deletion/insertion	26 (10.9%)	0	0	1 (3.6%)	2 (1) (6.1%)	28 (9.3%)
Splice site	19 (8.0%)	1 (3.8%)	0	2 (7.1%)	0 (0)	22 (7.3%)

*Mutations leading to overlapping phenotypes can also lead to phenotypes without overlaps. The corresponding number of these non-overlapping mutations is indicated in parentheses.

been reported in the homozygous state in 44 patients from 14 families, all originating from North-West Africa (northwest of Algeria and east of Morocco). Affected individuals were demonstrated to share a common ancestral haplotype of about 1.0 Mb and that the most recent common ancestor would have lived approximately 800–900 years ago [42].

Adipose tissue laminopathies

LMNA mutations leading to metabolic phenotypes have been reported in 267 patients, representing 17% of all laminopathies. Some 80% of the cases carry a substitution of the same amino acid, Arg^{482}, located in the Ig-like domain (Table 1 and Figure 1). This residue can be mutated to tryptophan, glutamine or leucine [20–22]. Other mutations were reported in N-terminal and Ig-like domains (http://www.umd.be/LMNA; Figure 1). The reported cases of type A of insulin-resistance syndrome without lipodystrophy are associated with either a leucine to valine mutation at the position 387 common to lamin A and C or a glycine to serine mutation at position 602, affecting only lamin A [23].

Premature aging syndromes

A majority of MAD patients (85%) carry a homozygous mutation at position 527. This arginine residue can be found replaced by a histidine residue (17 cases) or a cysteine residue (one case) [24,43]. Two other mutations, involving amino acids away from Arg^{527}, were reported in MAD patients, modifying Arg^{529} to valine or threonine [44,45].

Among the 67 patients reported with HGPS, 77% of them carry the same *de novo* heterozygous mutation c.1827C>T in exon 11. This mutation activates a cryptic splicing site, leading to an in-frame deletion of 50 amino acids from the prelamin A-specific tail. The resulting deleted protein, called progerin, lacks the proteolytic cleavage site essential for the post-translational processing of prelamin A. This abnormally processed protein accumulates and exerts toxic effects on cells and tissues [2]. Few other mutations have been identified in HGPS patients. They either activate the same cryptic splicing site or modify the splicing site of exon 11, but all lead to the same results: a toxic progerin of variable size [26,28,46].

A total of 13 heterozygous *LMNA* missense mutations were reported in other progeroid syndromes essentially located either in the head or in the coil1b domain [47–49]. To date, these different mutations were not reported to lead to accumulation of a toxic immature lamin A and may act through a different pathway [50].

Concluding remarks

Over the last 12 years, a wide clinical and genetic variability has been linked to the *LMNA* gene. This heterogeneity is still expanding, not only within the laminopathies, but also towards other nuclear envelope components and/or interacting partners of A-type lamins such as the nesprins, lamin B1 or lamin-associated peptide 2α [5]. Most probably in the near future, other pathogenic and/or modifier variants will be identified in genes encoding nuclear envelope components and their interacting partners that will certainly complete and reinforce the wide complexity of the mechanistic puzzle of these disorders.

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