Phenotypic spectrum of mutations in cardiolaminopathies

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Abstract

Phenotypic plasticity of mutations in *LMNA*, which encodes Lamin A/C, is unsurpassed by any other gene. Mutations in *LMNA* are responsible for least a dozen distinct phenotype sthat affect various mesenchymal organs and are collectively referred to as laminopathies or less frequently envelopathies. Cardiolaminopathies are a subset of laminopathies wherein involvement of the heart is the most prominent feature. The typical phenotype of cardiolaminopathies encompasses dilated cardiomyopathy (DCM) and conduction defects. *LMNA* is probably the most common causal gene for human DCM, being responsible up to 8% of all familial DCM. Several hundred mutations in the *LMNA* gene have already been described. The p.R644C mutation is the most commonly reported mutation in cardiolaminopathies. The phenotype in cardiolaminopathies is notable for a rapid progression of cardiac failure, conduction defects and arrhythmias, often necessitating implantation of a pacemaker and/or a defibrillator. The molecular pathogenesis of cardiolaminopathies is poorly understood. Studies in animal models and cultured cells suggest involvement of the Mitogen-Activated Protein Kinase (MAPK) and transforming growth factor –β1 pathways. Comprehensive molecular genetics studies complemented with mechanistic studies are needed to delineate the mechanistic underpinnings of cardiolaminopathies, prerequisite for the ultimate cure of these potentially deadly disorders.

Lamin A (LMNA) is an intermediate filament protein and a member of nuclear lamina. It is encoded by *LMNA*, which is comprised of 12 exons and spans approximately 25 Kbp on 1q22 locus [NC_000001.10 (156084461. 156109878)](Figure 1). *LMNA* codes for lamin A as well as lamin C through an alternative splicing site in exon 10, which is imposed by a C>T transition.[1] Accordingly, lamin A and C are identical in the first 566 amino acids (aa). Lamin C is encoded in the presence of the T allele at the alternative splicing site, which leads to introduction of six unique amino acids after amino acid 566 and premature termination (Figure 1). Consequently, lamin C is a 572 amino acid-long protein (65 KDa), as opposed to lamin A, which is comprised of 646 aa (74 KDa). In addition to lamin A and C isoforms, *LMNA* also codes for two minor isoforms, which are referred to as lamin AΔ10, as it skips the entire exon 10 through alternative splicing; and lamin C2, which utilizes an alternative downstream initiation (ATG) site in intron 1. While lamins are diffusely expressed in various tissues, lamin C2 is a germ cell-specificisoform.

LMNA has a short globular head, a 360 aa conserved α-helical and a tail domains (Figure 2). The tail domain contains a nuclear localization signal and an immunoglobulin-like domain. *LMNA* is expressed as prelamin, which is a 664 aa protein that terminates in a CAAX (C: Cysteine; A: Any aliphatic residue; and X: any uncharged amino acid) box. Prelamin undergoes maturation to lamin A through a multi-step process (Figure 2). First, the cysteine residue at CAAX undergoes farnesylation by farnesyl transferase, which is followed by removal of the last three residues (AAX) by an endopeptidase. The terminal cysteine amino acid then undergoes methylation by a carboxyl methyl transferase. The latter sets the protein for proteolytic cleavage of its last 15 amino acids by a zinc metallopeptidase ZMPSTE24 (STE24 homolog, S. cerevisiae) at the putative recognition sequence (RSY↓LLG). This proteolytic cleavage also removes the attached farnesyl group from the last cysteine. Therefore, mature *LMNA* is shorter than prelamin by 18 amino acids, which are cleaved from prelamin during maturation. The mature lamin A self-assemble into higher order structures in nuclear lamina, wherein it regulates various nuclear functions.[2,3]

Biological functions of *LMNA*

As an intermediate filament protein, *LMNA* has a 360-residue α-helical rod domain, which is essential for the assembly of the nuclear lamina proteins. Lamin molecules form coiled-coil dimers by wounding around each other at the α-helical rod domain. Lamin dimers are then registered in a head-to-tail fashion to form higher order filaments that serve as the framework for the assembly of numerous lamin-associated proteins, including emerin, lamin-associated protein 2 α (LAP2α), MAN1 and Nesprin 1, to name a few. Collectively, these proteins form the inner layering of the nuclear envelope, which not only provide structural support to nuclear membrane but also regulate a diverse array of biological processes, including chromatin organization and remodeling, histone methylations, gene expression, DNA replication, cell cycle progression and apoptosis[4-6] (Table 1).

The role of LMNA in maintaining integrity of the nuclear membrane is best illustrated in lamin deficient cells, which exhibit membrane deformities and blebbing.[22] Nuclear membrane blebbing is considered a feature of envelopathies and is commonly observed in premature aging syndromes caused by LMNA mutations.[7] LMNA directly or indirectly through lamin-associated proteins interacts with chromatin and regulates gene expression.[5,8-10] LMNA is also involved in the regulation of cell cycle progression through its interactions with retinoblastoma protein (pRB), a tumor suppressor transcription factor.[23] In its active (hypophosphorylated) pRB binds to E2F transcription factors and maintains the cells in the quiescent state (G0).Upon hyperphosphorylation by CDK4/6, pRB becomes inactive and looses its suppressive effect on E2Fs. Hence, cells exist the G0 phase and enter the cell cycle. Likewise, LAP2α, which is an interacting partner of LMNA, binds to and regulates E2Fs-mediated cell cycle progression.[24] Therefore, not only LMNA but also LAP2α interact with the pRB/E2F complex and modulate cell cycle progression. In addition, various signaling pathways including Mitogen-Activated Protein Kinase (MAPK) and canonical Wnt signaling pathways are altered in models of laminopathies.[16-19] Table 1 provides a partial list of various biological functions that have been attributed to LMNA.

Phenotypic consequences of LMNA mutations

LMNA is responsible for a diverse array of phenotypes, which are collectively referred to as laminopathies[25,26] (Table 2). Hutchinson-Gilford Progeria Syndrome (HGPS), Emery-Dreifuss muscular dystrophy, Dannigan partial lipodystrophy, peripheral neuropathy, dilated cardiomyopathy (DCM) and cardiac conduction defects are among the commonly recognized laminopathies.[2,25,26] Laminopathies typi-

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Key words: cardiolaminopathies, Lamin A/C, dilated cardiomyopathy.

Received for publication: 6 April 2011.
Accepted for publication: 25 June 2011.

Cardiogenetics 2011; 1:e6
doi:10.4081/cardiogenetics.2011.e6

cally involve tissues of mesenchymal origin, namely muscles, subcutaneous fat and nerves. Often there is considerable phenotypic overlap with one component being the predominant features but others showing variable degrees of involvement. Over 400 mutations, each infrequent and rare, in association with various laminopathies have been reported in the *LMNA* gene (*http://www.umd.be/LMNA*).

Among the most notable systemic laminopathies is HGPS, a rare premature aging syndrome,characterized by bone, muscle and subcutaneous fat abnormalities, alopecia and premature atherosclerosis (Table 2). The majority of HGPS cases is cased by a synonymous GGC>GGT change (p.G608G) in exon 11.[27] The mutation leads to deletion of 50 residues from amino acids 607 to 656 because of alternative splicing as well as retention of the CAAX motif, which undergoes farnesylation. The mutant prelamin A – commonly referred to as progerin or lamin A Δ50 – is incapable of undergoing proteolytic cleavageby ZMPSTE24. Hence, farnesylated progerin accumulates in the nucleus and affects integrity of the nuclear lamina and induces characteristic nuclear blebs, which is considered an indicator of cell senescence.[27,37]

Cardiac involvement in *LMNA* mutations is referred to as cardiolaminopathies, because of the involvement of multiple cardiac tissues.[38] The phenotype is typically characterized by a progressive DCM, supraventricular arrhythmias and conduction system disease.[38-40] Conduction defect often is progressive and may involve the entire conduction system from the sinus node to the Purkinje fibers. It typically leads to advanced heart block as well as chronotropic deficiency, requiring implantation of a pacemaker. Prognosis of patients with cardiolaminopathies is relatively poor and the risk of sudden cardiac death is relatively high.[41] Accordingly, patients with cardiolaminopathies are considered candidates for implantation of a pacemaker/defibrillator upon diagnosis. *LMNA* is among the most common causative genes in familial DCM, accounting for up to 8% of all familial DCM.[42] A diverse array of mutations in cardiolaminopathies has been described, each with a relatively low frequency. A notable mutation is the p.R644C mutation, which is the most frequently reported mutations in cardiolaminopathies.[38,43-46] This mutation also has been linked to limb girdle muscular dystrophy, lipodystrophy, insulin resistance, and atypical progeria.[47]

Pathogenesis of cardiolaminopathies

Cardiac involvement in LMNA mutations was one of the first phenotypes to be reported in humans[25,43] In spite of that the pathogenesis of cardiolaminopathies remains obscure. The existing mouse models of laminopathies typically represent progeriod syndromes, muscular dystrophies and less so cardiolaminopathies.[25,48-52] Studies in Lmna$^{-/-}$, Lmna$^{H222p/H222p}$, Zmpste$^{24-/-}$, Lmna^{HG}, Lmna^{mHG}, Lamin C only mice implicate abnormal activation of ERK1/2 and JNKs in the heart in progeroid syndromes.[16,25] Likewise, studies in COS7 cells suggest loss of sumoylation and disturbed distribution pattern of SUMO1 in the pathogenesis of the cardiac phenotype associated with LMNA mutations.[53,54] In addition, the trans-

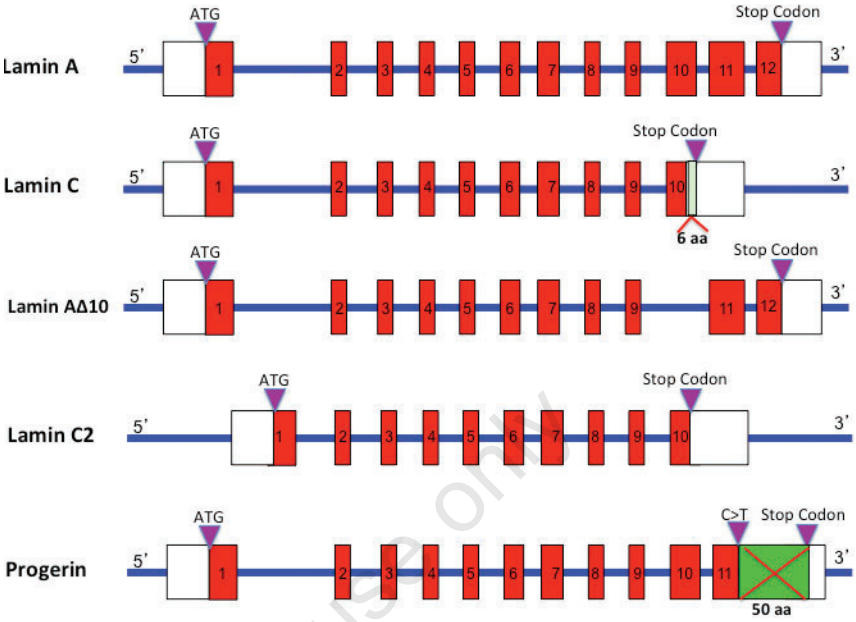

Figure 1. Alternative splicing of *LMNA:* LMNA has 12 exons. A C>T transition in exon 10 is responsible for the alternating splicing and generation of short form (Lamin C) or long form (Lamin A) isoforms. Lamin C has 6 novel amino acids at the C-terminus domain and is 572 aa long, while Lamin A is a 646 aa protein. Lamin A Δ10 isoform skips exon 10 completely, while Lamin C2 utilizes an alternative initiation codon in intron 1. Progerin, responsible for Hutchinson-Gilford Progeria Syndrome results from a synonymous change in exon 11 that leads to deletion of 50 amino acids but retention of the CAAX box at the C-terminus.

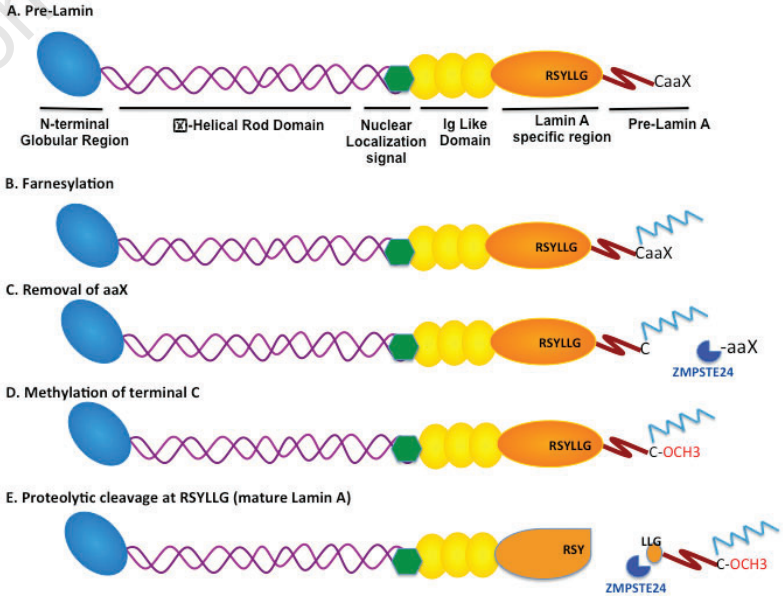

Figure 2. Steps involved in maturation of prelamin to Lamin A: Lamin is expressed as prelamin, which is comprised of 664 amino acids (Panel A). Prelamin mature into a 646 amino acid lamin A through a series of modification that include farnesylation at the C-terminus (Panel B), removal of the last three amino acids (AAX) (Panel C) followed by methylation at the last cysteine residue (Panel D) and finally cleavage of the last 15 amino acids at the RSY^LLG site by ZMPSTE24 (Panel E).

Table 1. Partial list of biological functions of *LMNA*.

Function	Phenotype
Integrity of nuclear membrane	Nuclear membrane deformity and blebbing[7]
Chromatin remodeling	Lamin interacts with chromatin associated proteins such as BAF[8] Lamin binds to Histons[5] Reduced H3K9me3 and H3K27me3 and increased H3K20me3 levels[9,10]
DNA replication	Lamin associated with PCNA and Lamin-null cells replicate slower[11,12]
Transcription	Lamin regulates RNA polymerase II[13] Lamin interacts with pRb/E2Fs[14] Lamin binds to c-Fos (AP-1) and OCT-1[15]
Signaling pathways	
MAPK pathway	ERK1/2 and JNKs are activated in certain laminopathies[16]
TGF- pathway	Lamin interacts with PP2A, which targets Smads[17]
Notch signaling pathway	Notch signaling is activated in cells expressing progerin[18]
Canonical Wnt signaling	Suppressed Wnt activity in Zmpste24 null mice[19]
Cell cycle regulation	Lamin and LAP2 modulated Rb/E2Fs regulation of cell cycle progression[14]
Myogenesis	Lamin influences myogenesis through modulating interactions of Rb with MyoD[20]
Adipogenesis	Lamin interacts with SREBP1c and PPAR-γ[21]

Table 2. Partial list of phenotypes caused by *LMNA* mutations.

Phenotype	Features
Hutchinson-Gilford Progeria[27,28]	Premature aging syndrome with alopecia, joint contraction, decreased subcutenous fat, joint contraction, and growth retardation
Atypical Werner Syndrome[29]	Premature aging syndrome with slecleroderma like skin, cataract, subcutenous calcifications and arteriosclerosis
Restrictive dermopathy	A rare autosomal recessive disease characterized by tight skin
Emery-Dreifuss muscular dystrophy[30]	Autosomal dominant disease (typically) characterized by contractures of joints and tendons and muscle weakness, DCM and AV block
Dilated Cardiomyopathy[31]	DCM in conjunction with AV block and LBBB
Limb-Girdle muscular dystrophy[32]	Progressive myopathy initially involving pelvic and less frequently the shoulder girdle
Heart-Hand syndrome[33]	Congenital heart disease and limb deformity
Dunnigan-type familial partial lipodystrophy[34]	Absent or reduced subcutaneous fat, insulin resistance and diabetes
Charcot-Marie-Tooth disease[35]	Peripheral neuropathy associated with muscle weakness and atrophy involving peroneal and distal muscles of the arms
Mandibuloacral dysplasia[36]	Small jaw, other bone abnormalities typicaly in association with lipodystrophy

forming growth factor- (TGF-) β1 signaling pathway, primarily through MAN1, a lamin-associated protein, has been implicated in the pathogenesis of cardiolaminopathies.[17,52] LMNA also associates with protein phosphatase PP2A, which in response to TGF-β1 signalingcould dephosphorylates pRB and hence, suppress gene expression through E2Fs. Despite these advances, however, there is a considerable gap in our understanding of the molecular pathogenesis of cardiolaminopathies.

Concluding remarks

Laminopathies encompass at least a dozen distinct phenotypes that primarily involve the mesenchymal organs. LMNA is expressed in multiple cell types. Accordingly, cardiolaminopathies are typically characterized not only by involvement of the myocardium but also the conduction system. A notable feature of laminopathies is the presence of considerable phenotypic overlap but one phenotype typically is the predominant feature. The remarkable phenotypic plasticity of *LMNA* mutations is indicative of multiple biological functions of LMNA encompassing structure and physical support of the nuclear membrane to chromatin modification and regulation of gene expression. Presumably, laminopathies are the phenotypic consequences of perturbed complex protein-protein interactions in nuclear lamina. The loss or gain of interactions not only may involve known inter-related pathways but also biological networks that are generally not known to interact. Nevertheless, our current understanding of molecular pathogenesis of cardiolaminopathies is limited. Comprehensive genetic analyses in conjunction with complementary mechanistic studies are necessary to gain insights into the molecular pathogenesis of the cardiolaminopathies. The ultimate cure of cardiolaminopathies would necessitate a clear understanding of the responsible molecular pathways involved in the pathogenesis of the phenotype.

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