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ORIGINAL ARTICLE

Overlapping syndromes in laminopathies: a meta-analysis of the reported literature

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Mutations on the *LMNA* gene are responsible for an heterogeneous group of diseases. Overlapping syndromes related to *LMNA* gene alterations have been extensively reported. Study scope is to perform a systematic analysis of the overlapping syndromes so far described and to try to correlate the clinical features to the associated genetic alterations. We evaluated all the dominant overlapping syndromes reported by means of a PubMed search and by the analysis of the main databases containing the pathogenic *LMNA* gene variations and the associated diseases.

Metabolic alterations in association to skeletal and/or cardiac alterations proved to be the most frequent overlap syndrome. Overlapping syndromes are mostly associated to inframe mutations in exons 1, 2, 8 and 9. These data further improve the understanding of the pathogenesis of laminopathies.

Key words: Lamin A/C, laminopathies, LMNA overlapping syndromes

Introduction

The *LMNA* gene, placed on chromosome 1q21-22, spans 12 exons and codes via alternative splicing for the A type lamins (1). A type lamins, which belong to the type V intermediate filaments and include lamins A, C, (the major isoforms), C2 and A 10 (the minor isoforms) (2), are characterized by an N-terminal head domain, a central α-helical rod domain, and a COOH-terminal ''tail domain'' (3). The rod domain is constituted by 4 regions with a typical α-helical organization (1A, 1B, 2A, 2B), that are interconnected by 3 intervening regions with the role of *linkers* (L1, L12, and L2). The portion of A type lamins with an α-helical organization presents the repeated sequence a-b-c-d-e-f-g with *a* and *d* being predominantly apolar and *e* and *g* polar residues; the heptad repeat sequence facilitates the interaction between lamins monomers and the formation of dimers via non covalent interactions among apolar residues located on the rod domain of different lamins (4). A type lamins dimers are also predicted to interact in a "head to tail" fashion, via non covalent interactions between regions of lamins with a different charge (4); the regions of lamin molecules predicted to allow the head to tail interaction, include two positively charged segments (the first from 1 to 28 residue, the second from residue 386 to residue 402) and two or three negatively charged segments (essentially, the N terminal and C terminal parts of the ROD domain) (4). The *LMNA* gene exon 1 yields the head domain and the first tract of the rod domain; exons 2-6 encode for what remains of the rod domain; exons 7-9 code for the portion of COOH-tail domain shared by both A and C lamins, including the region of nuclear localization signal (NLS) and the portions of lamins binding directly to DNA; the exon 10 contains the splicing site alternatively activated/silenced for the production of A and C lamins; also, exon 10 codes for the remaining portion of the COOH terminal head domain of lamins C whilst part of exon 10 and the whole exons 11 and 12 yield for the lamins A terminus portion (5).

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These proteins take part in the constitution of the nuclear lamina, a complex network of proteins located underneath the inner nuclear membrane (1). Lamins interact with several partners including nuclear envelope constituents, nucleoplasmic actin, chromatin, DNA, regulators of genes expression and molecules implicated in signal transduction (6). Such a plethora of interactions explains why A type lamins play a central role in the physiologic processes of cell life, including formation and homeostasis of the nucleus (7), apoptosis (8), repair (9), replication and transcription of DNA (10), regulation of chromosomal positioning (10). They are also involved in other important processes including metabolic, biochemical and signal transduction pathways (11, 12). Mutations on the Lamin A/C gene cause several defined clinical conditions, commonly termed as *laminopathies*, consisting in a heterogeneous group of diseases which include: the autosomal dominant and recessive forms of Emery Dreifuss muscular dystrophy (EDMD2 and EDMD3); the limb girdle muscular dystrophy 1B (LGMD1B); the congenital muscular dystrophy-L (CMD-L); the dilated cardiomyopathy with conduction defects (DCM1A); the heart hand syndrome of Slovenian type (HHS); a recessive form of sensory-motor peripheral neuropathy (CMT2B); the familial partial lipodystrophy of the Dunnigan type (FPLD2); the Hutchinson-Gilford progeria syndrome (HGPS); the atypical form of Werner syndrome (WS); the restrictive dermopathy (RD) and the mandibuloacral dysplasia (MADA) (13). Several clinical complex entities, obtained by the concomitant presence in the same subject of different diseases related to *LMNA* gene mutations, have also been reported (14-60). Diseases characterized by the compromise of skeletal muscles and/or the heart are associated to mutations spread throughout the gene (14), while diseases primarily affecting the peripheral nerves, the metabolism, the bones or causing alterations of the ageing mechanisms tend to be associated to particular mutations and to cluster to peculiar regions of the gene (62-65). A full correlation between genetic alterations and clinical manifestations has not been established; however, genetic studies demonstrated the presence of a non random association between clinical manifestations and Lamin A/C gene alterations (66), and the presence of a clustering among neuromuscular phenotypes (46); in particular, phenotypes characterized by skeletal and cardiac compromise tend to be associated to *LMNA* gene alterations placed upstream of the NLS, while clinical entities affecting the metabolism, the bones or causing premature ageing syndromes tend to be caused by alterations located downstream of the NLS (66). It has also been reported that frameshift and nonsense mutations are frequently associated to late onset cardiac and skeletal phenotypes; the possible pathogenic mechanism invoked is haploinsufficiency due to non-sense mediated mRNA decay or a rapid degradation of the aberrant transcript (46). On the other hand, early onset phenotypes affecting the skeletal muscles are mostly associated to alterations of the *LMNA* gene maintaining the reading frame; in this case, the pathogenic mechanism hypothesized is the poison peptide effect caused by the altered properties of mutated lamins (46). In the present paper, the authors showed the results of a meta-analysis study aimed at evaluating the pathogenic bases and the clinical manifestations of the

Table 1. Characteristics of complex phenotypes caused by dominant *LMNA* gene mutations and of the related genetic alterations.

Overlapping syndrome	LMNA Exon	Gene mutation	Protein mutation	Mutation type	Position in protein	Aminoacid substitution	COILS probability	Heptad position	Skeletal muscle phenotype
4	1	c. 3-12 del		Deletion	2		0		Yes
1	1	c.11C>G	P4R	Missense	4	P=apolare R=polare	0		
2	1	c.29C>T	T10I	Missense	10	T=polare I=apolare	0		
2	1	c.29C>T	T10I	Missense	10	T=polare I=apolare	0		
3	1	c.82C>T	R28W	Missense	28	R=polare W=apolare	0,997	a	Yes
3	1	c.82C>T	R28W	Missense	28	R=polare W=apolare	0,997	a	
3	1	c.82C>T	R28W	Missense	28	R=polare W=apolare	0,997	a	
4	1	c.99G>T	E33D	Missense	33	E=polare D=polare	1	f	Yes
4	1	c.99G>T	E33D	Missense	33	E=polare D=polare	1	f	Yes
4	1	c.99G>T	E33D	Missense	33	E=polare D=polare	1	f	Yes

overlapping syndromes related to Lamin A/C gene and identifying a possible relationship between the complex phenotypes producing the overlapping syndromes and the mutations of *LMNA* gene.

Materials and methods

We searched, by indicating in PubMed as keywords LMNA and Lamin A/C, for all papers reporting the overlapping syndromes related to *LMNA* gene mutations. We also looked at the UMD-LMNA mutations databases (14) [http://www. umd.be/LMNA/ (Universal Mutation Database The UMD-LMNA mutations database)] and Leiden muscular Dystrophy database (15) [http://www.dmd.nl/ (Leiden Muscular Dystrophy pages©)] in order to identify all the dominant *LMNA* gene mutations associated to overlapping syndromes and the papers cited in the references. We prepared a database containing the mutations identified and the complex phenotypes associated to the mutations, specifying the tissues and organs compromised; we also indicated any alterations of metabolisms or signs of premature ageing. Then, we considered the type of mutation, its position on the gene and on the protein, the effect on the aminoacidic sequence and the possible pathogenic role (haploinsufficiency, poison peptide effect) exerted by the mutations. We also calculated the frequency of the mutations per exon, associated to the overlapping syndromes. Finally, COILS software was applied to predict the coiled-coil forming and the heptad position for each aminoacidic substitution evaluated. Coils software gives a score from 0 to 1 (0: no possibility of coiled coil; 1: highest probability of coiled coil), according to the probability for the aminoacid to belong to the coiled-coil region (67).

Results

Table 1 shows the complex phenotypes related to dominant *LMNA* gene mutations and the characteristics of the genetic alterations. Of the identified syndromes, 69 cases are associated to 46 dominant mutations, 41 of them proved to be unique missense mutations located in 41 different positions; 31 of the 41 missense mutations involve a polar aminoacid residue, which is mutated in an apolar aminoacid in about 50% of cases; the remaining 10 missense mutations involve an apolar residue and determine in half of the cases a substitution with an aminoacid with the same polarity. Among the missense mutations, we decided to include c. 1698+13 C > T, p. Arg566 +5Cys observed in exon10; we considered the mutation position as a terminal part of the gene region coding for C lamin. A higher frequency of mutations causing overlapping syndromes per exon was observed in exons 1-2, 8 and 9 (Table 2). About half of the missense mutations are located in coiled coils regions (predicted by COILS with a probability higher than 0.5), involving in about 20% of cases the positions *a* and *d* of the heptad repeat. Six missense mutations are predicted to occur within the head-to- tail interaction region as defined by Strelkov (*P4R, T101, R28W, E33D, E358K, R386T*). Figure 1 also summarizes the clinical phenotypes of the overlapping syndromes associated to the reported *LMNA A/C* gene missense mutations, related to lamin structure and its main partners.

	Cardiac phenotype	Nervous system (peripheral or central)	Metabolism	Ageing mechanisms	Bone/skeletal	Skin	Other	Mutation position
		Neuropathy				-		Head
			Metabolic disturbances	Progerioid features	Bones abnormalities	Yes		Head
		-	High triglycerides + glycemia, lipoatrophy	Progeroid features		Thinned skin	Short stature	Head
			High triglycerides + glycemia, lipoatrophy	Progeroid features		Thinned skin	Short stature	Head
	Yes		FLPD2					Head
	Yes		FPLD2			-		Head
	Yes		FPLD			-		Head
	Yes	Neuropathy				-		Head
	Yes	Axonal neuropathy					Leukonichia	Head
	Yes	Neuropathy				-	Leuconichia	Head

Overlapping syndrome	LMNA Exon	Gene mutation	Protein mutation	Mutation type	Position in protein	Aminoacid substitution	COILS probability	Heptad position	Skeletal muscle phenotype
5	1	c.169G>C	A57P	Missense	57	A=polare P=apolare	1	b	
5	1	c.176T>G	L59R	Missense	59	L=apolare R=polare	1	d	
6	1	c.176T>G, de novo	L59R	Missense	59	L=apolare R=polare	1	d	
7	1	c.176T>G	L59R	Missense	59	L=apolare R=polare	1	d	
3	1	c.178C>G	R60G	Missense	60	R=polare G=apolare	1	e	
13	1	c.178C>G	R60G	Missense	60	R=polare G=apolare	1	e	
3	1	c.178C>G	R60G	Missense	60	R=polare G=apolare	1	e	
3	1	c.184C>G	R62G	Missense	62	R=polare G=apolare	0,998	g	
3	1	c.184C>G	R62G	Missense	62	R=polare G=apolare	0,998	g	
3	1	c.274C>T	L92F	Missense	92	L=apolare F=apolare	1	a	Yes
1	1	c.331G>A	E111K	Missense	111	E=polare K=polare	1	f	
3	2	c. 398 G>T	R133L	Missense	133	R=polare L=apolare	1	g	
3	2	c.398G>T	R133L	Missense	133	R=polare L=apolare	1	g	
1	2	c.406G>C	D136H	Missense	136	D=polare K=polare	1	c	
1	2	c.412G>A	E138K	Missense	138	E=polare K=polare	1	e	
7	2	c. 412 G>A	E138K	Missense	138	E=polare K=polare	1	e	
6	2	428 C>T de novo	S143F	Missense	143	S=polare F=apolare	0,999	c	Yes
8	2	428 C>T de novo	S143F	Missense	143	S=polare F=apolare	0,999	c	Yes
2	2	c.433 G>A	E145K	Missense	145	E=polare K=polare	0,999	e	
4	2	c. 471 G>A	T157T	Synonymous	157		1	c	Yes
1	2	c.475G>A	E159K	Missense	159	E=polare K=polare	1	e	
2	2	c. 407A>G	D163G	Missense	163	D=polare G=apolare	1	b	
4	5	c.864-867del; fs*190	H289fsX	Frameshift	190	H=polare A=apolare	1	e	Yes
3	3	c. 575 A>T	D192V	Missense	192	D=polare V=apolare	1	c	
3	3	c. 575 A>T	D192V	Missense	192	D=polare V=apolare	1	c	
9	5	c.832 G>A	A278T	Missense	278	A=apolare T=polare	0,63	a	Yes
3	6	c. 1001-1003 del GCC p.Ser334-Ser334 del	S334del	Deletion	334		1	d	Yes
10	6	c. 1003 C>T	R335W	Missense	335	R=polare W=apolare	1	e	Yes
3	6	c.1045 C>T	R349W	Missense	349	R=polare W=apolare	1	e	Yes

Cardiac phenotype	Nervous system (peripheral or central)	Metabolism	Ageing mechanisms	Bone/skeletal	Skin	Other	Mutation position
Yes		Partial lipodystrophy	Atypical WS			Slopping shoulders hypogonadism (ovarian failure)	c-Fos binding domain 1
Yes		Partial lipodystrophy	Atypical WS			Slopping shoulders hypogonadism (ovarian failure)	c-Fos binding domain 1
Yes		-	Werner S		-		c-Fos binding domain 1
			Progerioid features	MADA			c-Fos binding domain 1
Yes		Fat accumulation on face and neck and lipoatrophy on limbs			-		c-Fos binding domain 1
Yes	Axonal peripheral neuropathy	Fat accumulation on face and neck and lipoatrophy on limbs			-		c-Fos binding domain 1
Yes		FPLD2			-		c-Fos binding domain 1
Yes		FPLD2			-		c-Fos binding domain 1
Yes		FPLD2					c-Fos binding domain 1
	-	FPLD			-		coil 1b
		Metabolic disturbances	Progerioid features	Bones abnormalities	Yes		coil 1b
Yes		Lipodystrophy+ hepatic steatosis+ high triglycerides		-	Skin changes		coil 1b
Yes		Lipoatrophy, diabetes, liver steatosis			-	Leukomelanodermic papules	coil 1b
		Metabolic disturbances	Progerioid features	Bones abnormalities			coil1b
		Metabolic disturbances	Progerioid features	Bones abnormalities			coil1b
			Progeria syndrome	MADA			coil 1b
Yes		-	Progeria		-	Contractures	coil 1b
Yes		-	Progeria	Ospteolysis, ospeopenia, midface hypoplasia		Leukomelanodermic papules	coil1b
		Alterations of subcutaneous fat distribution	Atypical HGPS		-	Persisting coarse hair	coil 1b
	Neuropathy				-		coil 1b
		Metabolic disturbances	Progerioid features	Bones abnormalities			coil1b
		Lipodystrophy, insulin resistence	Progeroid facies		Achantosis nigricans		coil1b
Yes	Myopathic and neurogenic features, at muscle biopsy				-		E 1B 19K
Yes		FPLD2			-		coil 1b
Yes		FPLD			-		coil 1b
Yes					Acanthosis nigricans		E 1B 19K
		FPLD			-		Local interaction site
Yes		High triglycerides		Acro-osteolysis			Local interaction site
		Lipodystrophy			-		Local interaction site

Overlapping syndrome	LMNA Exon	Gene mutation	Protein mutation	Mutation type	Position in protein	Aminoacid substitution	COILS probability	Heptad position	Skeletal muscle phenotype
3	6	c. 1045 C>T	R349W	Missense	349	R=polare W=apolare	1	e	
10	6	c. 1072 G>A	E358K	Missense	358	E=polare K=polare	1	c	Yes
3	6	c.1157G >C	R386T	Missense	386	R=polare T=polare	0,638	g	
3	7	c.1262 T>C	L421P	Missense	421	L=apolare P=apolare	0		Yes
3	7	c.1262 T>C	L421P	Missense	421	L=apolare P=apolare	0		
3	7	c.1315 C>T	R439C	Missense	439	R=polare C=polare	0		Yes
3	7	c. 1315 C>T	R439C	Missense	439	R=polare C=polare	0		Yes
14	7	c. 1318 G>A	V440M	Missense	440	V=apolare M=apolare	0		Yes
3	7	c.1357 C>T	R453W	Missense	453	R=polare W=apolare	0		Yes
14	8	c. 1411 C>T	R471C	Missense	471	R=polare C=polare	0		Yes
3	8	c.1411C>G	R471G	Missense	471	R=polare G=apolare	0		Yes
11	8	c.1444 C>T	R482W	Missense	482	R=polare W=apolare	0		
3	8	c.1444 C>T	R482W	Missense	482	R=polare W=apolare	0		Yes
3	8	c.1444 C>T	R482W	Missense	482	R=polare W=apolare	0		Yes
2	8	c.1454C>G	P485R	Missense	485	P=apolare R=polare	0		
4	9	c. 1496delC fsX49	A499V	Missense	499	A=apolare V=apolare	0		Yes
3	9	c. 1516 C>G	H506D	Missense	506	H=polare D=polare	0		Yes
4	9	c. 1535 T>C	L512P	Missense	512	L=apolare P=apolare	0		Yes
12	9	c.1551G>A	Q517Q	Synonymous	517		0		
12	9	c. 1551G>A	Q517Q	Synonymous	517		0		
3	9	c.1580G>C	R527P	Missense	527	R=polare P=apolare	0		Yes
3	9	c.1580G>C	R527P	Missense	527	R=polare P=apolare	0		Yes
12	10	c. 1683 G>C	L561L	Synonymous	561		0		
13	11	c. 1711 A >T	S571C	Missense	571	S=polare C=apolare	0		Yes
1	11	c.1762T>C	C588R	Missense	588	C=polare R=polare	0		
3	11	c. 1772 G>T	C591F	Missense	591	C=polare F=apolare	0		
3	11	c.1772G>T	C591F	Missense	591	C=polare F=apolare	0		Yes
3	11	c. 1804 G>A	G602S	Missense	602	G=apolare S=polare	0		Yes
1	11	c.1930C>T	p.R644C	Missense	644	R=polare C=polare	0		

Cardiac phenotype	Nervous system (peripheral or central)	Metabolism	Ageing mechanisms	Bone/skeletal	Skin	Other	Mutation position
Yes		FPLD			-		Local interaction site
Yes		FPLD2 like phenotype		Midfacial hypoplasia; short stature		Broad nasal bridge, limited eye closure, uterine fibroids; Respiratory failure	Local interaction site
Yes		FPLD			-		Emerin binding domain
		IRS			-		NLS
Yes		Met syndrome			-		NLS
		FPLD			-		PCNA interaction site
		Met syndrome and fat distribution abnormalities			-		PCNA interaction site
				MADA			PCNA interaction site
		FPLD			-		c-Fos binding domain 2
				MADA			Actin binding domain (1)
		FPLD2			-		Actin binding domain (1)
-	Akineto-hypertonic syndrome	FPLD2			-	Multinodular goiter, primary hyperaldosteronism	Actin binding domain (1)
		Lipodystrophy			-		Actin binding domain (1)
		FPLD			-		Actin binding domain (1)
		FPLD	WS Actin binding domain		-		Actin binding domain
Yes	Neuropathy						PKC Alpha Binding site
	-	FPLD			-		PKC Alpha Binding site
	HNPP + Axonal Loss						PKC Alpha Binding site
	Neuropathy	FPLD2					PKC Alpha Binding site
	Neuropathy	PLD					PKC Alpha Binding site
Yes		FPLD2					PKC Alpha Binding site
Yes		Lipoatrophy of trunk and proximal limbs					PKC Alpha Binding site
	Neuropathy	FPLD2					PKC Alpha Binding site
	Neuropathy	PLD					Lamin A tail
		Metabolic disturbances	Progerioid features	Bones abnormalities			Lamin A tail
Yes		FPLD2, liver steatosis			-		Lamin A tail
Yes		FPLD2				Polymenorrhea	Lamin A tail
		IRS					Lamin A tail
		Metabolic disturbances	Progerioid features	Bones abnormalities			Lamin A tail

Table 2. Distribution and frequency of the mutations causing the complex phenotypes distributed per exon.

Exon	Unique mutations	% unique mutations	Total mutations	% total mutations	Protein exon length	Total frequency normalized by exon length
1	11	23.91	21	30.43	119	25.58
2	8	17.39	11	15.94	52	30.66
3	1	2.17	2	2.90	42	6.90
4	0	0	0	0	57	0
5	2	4.35	2	2.90	42	6.90
6	4	8.70	5	7.25	73	9.93
7	4	8.70	6	8.70	73	11.91
8	4	8.70	7	10.14	36	28.18
9	5	10.87	7	10.14	40	25.36
10	2	4.35	2	2.90	30	9.66
11	5	10.87	6	8.70	80	10.87
12	0	0	0	0	9	0
TOT	46		69			

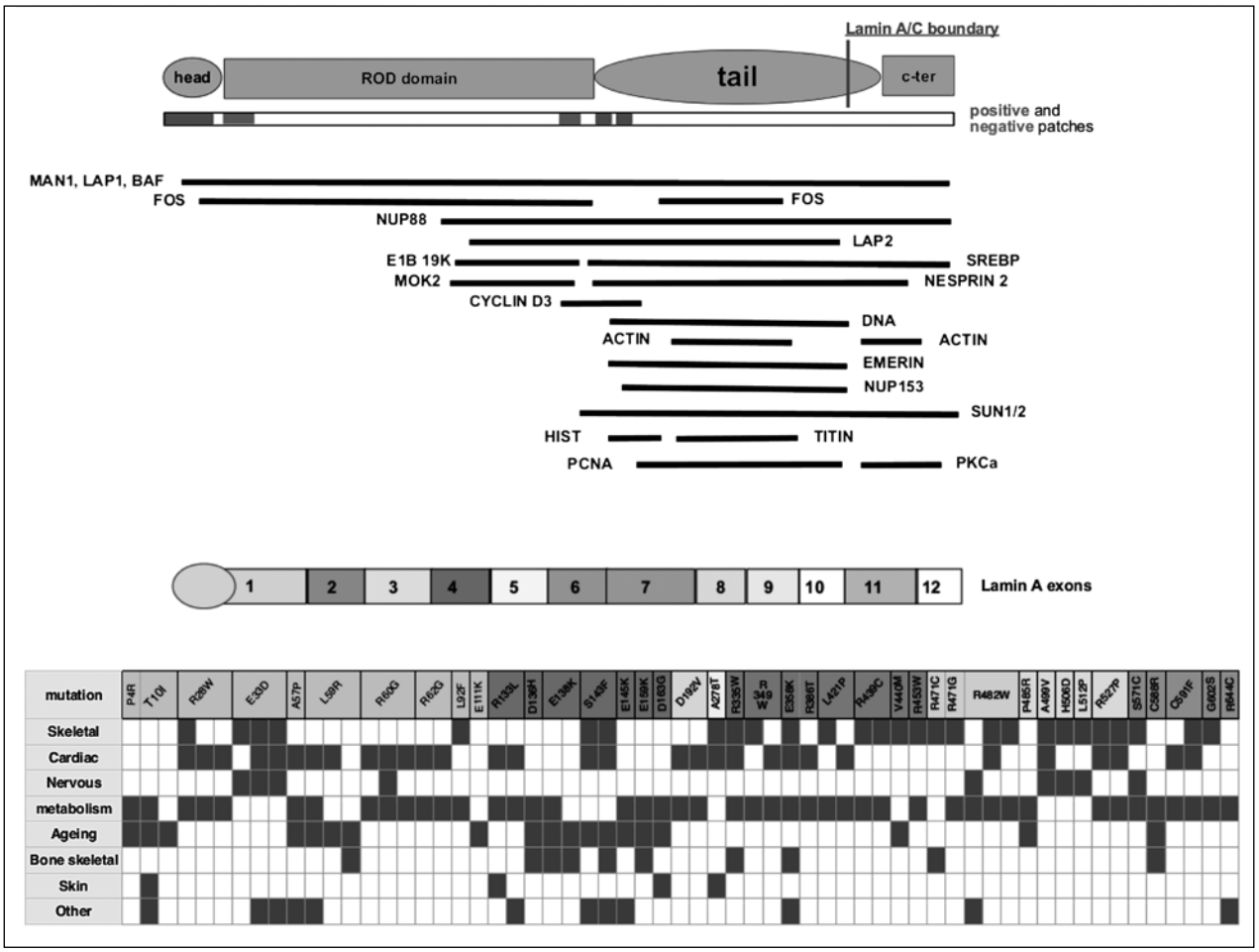

Figure 1. Causative missense mutations in the context of the lamin A/C protein organization and related overlapping syndromes.

Discussion

We report a meta-analysis describing the clinical features of all overlapping syndromes related to dominant *LMNA* gene mutations so far published and the possible relationship with the underlying genetic alterations. We identified at least 14 different overlapping syndromes due to dominant mutations on the Lamin A/C gene. As shown in tables 1 and 2, *LMNA* gene mutations may be associated to complex phenotypes obtained by the variable association of different phenotypes including metabolism disturbances, premature ageing syndromes, dermatologic changes, skeletal and cardiac compromise, nervous system alterations. The most frequent overlapping syndrome linked to *LMNA* gene alterations is the association between metabolic alterations and skeletal and/or cardiac involvement caused by inframe mutations spread throughout the gene. It is likely that the pathogenic mechanism underlying this condition is the poison peptide effect: as a matter of fact, all the mutations so far identified alter the biochemical properties of A type lamins, either perturbing their stability or modifying the possible interactions with the numerous binding partners (54).

The overlapping syndrome characterized by the association of skeletal and/or cardiac compromise with neuropathy and inconstant dermatologic abnormalities are caused by mutations spread throughout the gene; a possible pathogenic effect should be either a dominant negative or even a haploinsufficiency secondary to the production of un unstable mRNA or of a mutated protein, lacking the typical structure of intermediate filaments. For the third and fourth group of complex phenotypes, obtained by the variable association among muscle and/or heart disease, peripheral neuropathy, metabolism disturbances and concomitant presence of lipodystrophy, the few reports so far published do not consent any final correlation. However, the presence of either missense or silent mutations suggest that a dominant negative effect may play a major role in the pathogenesis of these two entities. For overlapping syndromes with variable association of MADA/bones alterations, metabolism abnormalities and premature ageing syndromes and other clinical entities such as dermatologic abnormalities, skeletal and/or cardiac diseases, the paucity of reports again do not consent any correlation with the mutation's position. Furthermore any direct correlation between clinical manifestations and *LMNA* gene mutations is hampered by the pleiotropic effect possibly exerted by Lamin A/C gene mutations (17-18, 36, 39, 53, 55, 69-70).

However, we can speculate that overlapping syndromes are mostly associated to inframe mutations able to alter the stability of A type lamins and the interactions with the numerous partners (54), causing a perturbation of the physiologic processes regulated by lamins on the different tissues. These data contribute to further improve the understanding of the pathogenic mechanisms of laminopathies.

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