Mutations on the \textit{LMNA} gene are responsible for an heterogeneous group of diseases. Overlapping syndromes related to \textit{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 \textit{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.

\textbf{Key words:} Lamin A/C, laminopathies, LMNA overlapping syndromes

\section*{Introduction}

The \textit{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 $\alpha$-helical rod domain, and a COOH-terminal “tail domain” (3). The rod domain is constituted by 4 regions with a typical $\alpha$-helical organization (1A, 1B, 2A, 2B), that are interconnected by 3 intervening regions with the role of \textit{linkers} (L1, L12, and L2). The portion of A type lamins with an $\alpha$-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 \textit{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).
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, nucleo- plasmic 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

| Overlapping syndrome | LMNA Exon | Gene mutation | Protein mutation | Mutation type | Position in protein | Aminoacid substitution | COILS probability | Heptad position | Skeletal muscle phenotype |
|---------------------|-----------|---------------|------------------|--------------|---------------------|------------------------|------------------|--------------------------|--------------------------|
| 1                   | c. 3-12 del | Deletion      | 2                | 0            | Yes                 |                        |                  |                          |                          |
| 1                   | c.11C>G    | P4R Missense  | 4                | P=apolare    | R=polare           | 0                      |                  |                          |                          |
| 2                   | c.29C>T    | T10I Missense | 10               | T=polare     | I=apolare         | 0                      |                  |                          |                          |
| 3                   | c.82C>T    | R28W Missense | 28               | R=polare     | W=apolare         | 0,997                  | a                | Yes                      |                          |
| 3                   | c.82C>T    | R28W Missense | 28               | R=polare     | W=apolare         | 0,997                  | a                |                          |                          |
| 4                   | c.99G>T    | E33D Missense | 33               | E=polare     | D=polare          | 1                      | f                | Yes                      |                          |
| 4                   | 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 ([http://www.umd.be/LMNA/](http://www.umd.be/LMNA/)) and Leiden muscular Dystrophy database ([http://www.dmd.nl/](http://www.dmd.nl/)). 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 (peripheral or central) | Nervous system | Metabolism | Ageing mechanisms | Bone/skeletal | Skin | Other | Mutation position |
|------------------------------------------|---------------|------------|------------------|---------------|------|-------|------------------|
| Neuropathy                               | Metabolic disturbances | Progeroid 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 | | Leukonichia | Head |
| Yes | Axonal neuropathy | | Leukonichia | Head |
| Yes | Neuropathy | | Leukonichia | 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=apolare             | 1                 | b              |                          |
| 5                    | 1         | c.176T>G     | L59R            | Missense      | 59                  | L=apolare             | 1                 | d              |                          |
| 6                    | 1         | c.176T>G, de novo | L59R            | Missense      | 59                  | L=apolare             | 1                 | d              |                          |
| 7                    | 1         | c.176T>G     | L59R            | Missense      | 59                  | L=apolare             | 1                 | d              |                          |
| 3                    | 1         | c.178C>G     | R60G            | Missense      | 60                  | R=polare              |                   | e              |                          |
| 13                   | 1         | c.178C>G     | R60G            | Missense      | 60                  | R=polare              |                   | e              |                          |
| 3                    | 1         | c.184C>G     | R62G            | Missense      | 62                  | R=polare              | 0.998             | g              |                          |
| 3                    | 1         | c.184C>G     | R62G            | Missense      | 62                  | R=polare              | 0.998             | g              |                          |
| 3                    | 1         | c.274C>T     | L92F            | Missense      | 92                  | L=apolare             |                   | a              | Yes                      |
| 1                    | 1         | c.331G>A     | E111K           | Missense      | 111                 | E=apolare             |                   | f              |                          |
| 3                    | 2         | c.398G>T     | R133L           | Missense      | 133                 | R=polare              |                   | g              |                          |
| 3                    | 2         | c.398G>T     | R133L           | Missense      | 133                 | R=polare              |                   | g              |                          |
| 1                    | 2         | c.406G>C     | D136H           | Missense      | 136                 | D=apolare             |                   | c              |                          |
| 1                    | 2         | c.412G>A     | E138K           | Missense      | 138                 | E=apolare             |                   | e              |                          |
| 7                    | 2         | c.412G>A     | E138K           | Missense      | 138                 | E=apolare             |                   | e              |                          |
| 6                    | 2         | 428 C>T de novo | S143F           | Missense      | 143                 | S=apolare             | 0.999             | c              | Yes                      |
| 8                    | 2         | 428 C>T de novo | S143F           | Missense      | 143                 | S=apolare             | 0.999             | c              | Yes                      |
| 2                    | 2         | c.433G>A     | E145K           | Missense      | 145                 | E=apolare             | 0.999             | e              |                          |
| 4                    | 2         | c.471G>A     | T157T           | Synonymous    | 157                 |                       |                   | c              | Yes                      |
| 1                    | 2         | c.475G>A     | E159K           | Missense      | 159                 | E=apolare             |                   | e              |                          |
| 2                    | 2         | c.407A>G     | D163G           | Missense      | 163                 | D=apolare             |                   | b              |                          |
| 4                    | 5         | c.864-867del; fs’190 | H289fsX     | Frameshift    | 190                 | H=apolare             |                   | e              | Yes                      |
| 3                    | 3         | c.575A>T     | D192V           | Missense      | 192                 | D=apolare             |                   | c              |                          |
| 3                    | 3         | c.575A>T     | D192V           | Missense      | 192                 | D=apolare             |                   | c              |                          |
| 9                    | 5         | c.832G>A     | A278T           | Missense      | 278                 | A=apolare             | 0.63              | a              | Yes                      |
| 3                    | 6         | c.1001-1003 del GCC p.Ser334-Ser334 del | S334del   | Deletion      | 334                 |                       |                   | d              | Yes                      |
| 10                   | 6         | c.1003 C>T   | R335W           | Missense      | 335                 | R=apolare             |                   | e              | Yes                      |
| 3                    | 6         | c.1045 C>T   | R349W           | Missense      | 349                 | R=apolare             |                   | e              | Yes                      |
| Cardiac phenotype | Nervous system (peripheral or central) | Metabolism | Ageing mechanisms | Bone/skeletal | Skin | Other | Mutation position |
|-------------------|---------------------------------------|------------|-------------------|--------------|-----|-------|------------------|
| Yes               | Partial lipodystrophy                 | Atypical WS|                   | Stopping shoulders hypogonadism (ovarian failure) | c-Fos binding domain 1 |
| Yes               | Partial lipodystrophy                 | Atypical WS|                   | Stopping shoulders hypogonadism (ovarian failure) | c-Fos binding domain 1 |
| Yes               | Werner S                               | MADA       |                   | c-Fos binding domain 1 |
| Yes               | Fat accumulation on face and neck and lipoatrophy on limbs | Progerioid features | MADA | c-Fos binding domain 1 |
| Yes               | Axonal peripheral neuropathy           | Fat accumulation on face and neck and lipoatrophy on limbs | Progerioid features | MADA | c-Fos binding domain 1 |
| Yes               | FPLD2                                 | Progerioid features | Bones abnormalities | Yes | c-Fos binding domain 1 |
| Yes               | Lipodystrophy + hepatic steatosis + high triglycerides | Progerioid features | Bones abnormalities | Yes | c-Fos binding domain 1 |
| Yes               | Lipodystrophy, diabetes, liver steatosis | Progerioid features | Bones abnormalities | Progeria syndrome | MADA | c-Fos binding domain 1 |
| Yes               | Progeria                              | Leukomelanodermic papules | - | - | Contractures | c-Fos binding domain 1 |
| Yes               | Progeria                              | Leukomelanodermic papules | - | - | Persisting coarse hair | c-Fos binding domain 1 |
| Yes               | Lipodystrophy, insulin resistance     | Acanthosis nigricans | - | - | Acanthosis nigricans | c-Fos binding domain 1 |
| Yes               | Myopathic and neurogenic features, at muscle biopsy | - | - | - | - | e1b 19K |
| Yes               | FPLD2                                 | - | - | - | - | c-Fos binding domain 1 |
| Yes               | FPLD                                  | - | - | - | - | c-Fos binding domain 1 |
| Yes               | FPLD                                  | Acanthosis nigricans | - | - | Acanthosis nigricans | c-Fos binding domain 1 |
| Yes               | High triglycerides                    | Acro-osteolysis | - | - | Acro-osteolysis | Local interaction site |
| Yes               | 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               | 1                | e              |                          |
| 10                   | 6         | c. 1072 G>A   | E358K           | Missense      | 358                 | E=polare               | 1                | c              | Yes                       |
| 3                    | 6         | c.1157G >C    | R386T           | Missense      | 386                 | R=polare               | 0.638            | g              |                          |
| 3                    | 7         | c.1262 T>C    | L421P           | Missense      | 421                 | L=apolare              | 0                | Yes            |                          |
| 3                    | 7         | c.1262 T>C    | L421P           | Missense      | 421                 | L=apolare              | 0                | Yes            |                          |
| 3                    | 7         | c.1315 C>T    | R439C           | Missense      | 439                 | R=polare               | 0                | Yes            |                          |
| 3                    | 7         | c.1315 C>T    | R439C           | Missense      | 439                 | R=polare               | 0                | Yes            |                          |
| 14                   | 7         | c.1318 G>A    | V440M           | Missense      | 440                 | V=apolare              | 0                | Yes            |                          |
| 3                    | 7         | c.1357 C>T    | R453W           | Missense      | 453                 | R=polare               | 0                | Yes            |                          |
| 14                   | 8         | c.1411 C>T    | R471C           | Missense      | 471                 | R=polare               | 0                | Yes            |                          |
| 3                    | 8         | c.1411C>G     | R471G           | Missense      | 471                 | R=polare               | 0                | Yes            |                          |
| 11                   | 8         | c.1444 C>T    | R482W           | Missense      | 482                 | R=polare               | 0                | Yes            |                          |
| 3                    | 8         | c.1444 C>T    | R482W           | Missense      | 482                 | R=polare               | 0                | Yes            |                          |
| 3                    | 8         | c.1444 C>T    | R482W           | Missense      | 482                 | R=polare               | 0                | Yes            |                          |
| 2                    | 8         | c.1454C>G     | P485R           | Missense      | 485                 | P=apolare              | 0                | Yes            |                          |
| 4                    | 9         | c.1496delC fsX49 | A499V     | Missense      | 499                 | A=apolare              | 0                | Yes            |                          |
| 3                    | 9         | c.1516 C>G    | H506D           | Missense      | 506                 | H=apolare              | 0                | Yes            |                          |
| 4                    | 9         | c.1535 T>C    | L512P           | Missense      | 512                 | L=apolare              | 0                | Yes            |                          |
| 12                   | 9         | c.1551G>A     | Q517Q           | Synonymous    | 517                 | Synonymous             | 0                | Yes            |                          |
| 12                   | 9         | c.1551G>A     | Q517Q           | Synonymous    | 517                 | Synonymous             | 0                | Yes            |                          |
| 3                    | 9         | c.1580G>C     | Rs277P          | Missense      | 527                 | R=polare               | 0                | Yes            |                          |
| 3                    | 9         | c.1580G>C     | Rs277P          | Missense      | 527                 | R=polare               | 0                | Yes            |                          |
| 12                   | 10        | c.1683 G>C    | L561L           | Synonymous    | 561                 | Synonymous             | 0                | Yes            |                          |
| 13                   | 11        | c.1711 A>T    | SS71C           | Missense      | 571                 | S=apolare              | 0                | Yes            |                          |
| 1                    | 11        | c.1762T>C     | C588R           | Missense      | 588                 | C=apolare              | 0                | Yes            |                          |
| 3                    | 11        | c.1772 G>T    | C591F           | Missense      | 591                 | C=apolare              | 0                | Yes            |                          |
| 3                    | 11        | c.1772G>T     | C591F           | Missense      | 591                 | C=apolare              | 0                | Yes            |                          |
| 3                    | 11        | c.1804 G>A    | G602S           | Missense      | 602                 | G=apolare              | 0                | Yes            |                          |
| 1                    | 11        | c.1930C>T     | p.R644C         | Missense      | 644                 | R=polare               | 0                | Yes            |                          |
### Overlapping syndromes in laminopathies: a meta-analysis of the reported literature

| Cardiac phenotype | Nervous system phenotype (peripheral or central) | Metabolism | Ageing mechanisms | Bone/skeletal | Skin | Other | Mutation position |
|-------------------|-----------------------------------------------|------------|------------------|---------------|-----|-------|------------------|
| Yes               | FPLD                                          | -          |                  | Broad nasal bridge, limited eye closure, uterine fibroids, Respiratory failure | Local interaction site |
| Yes               | FPLD2 like phenotype                          | Midfacial hypoplasia; short stature | -               | Emerin binding domain |
| Yes               | Met syndrome                                  | -          |                  | NLS           |
| Yes               | Met syndrome                                  | -          |                  | PCNA interaction site |
| Yes               | Met syndrome and fat distribution abnormalities| -          |                  | MADA          |
| Yes               | Met syndrome                                  | -          |                  | PCNA interaction site |
| Yes               | Met syndrome                                  | -          |                  | MADA          |
| Yes               | Met syndrome and fat distribution abnormalities| -          |                  | MADA          |
| Yes               | Lipodystrophy                                 | -          |                  | Actin binding domain (1) |
| Yes               | Neuropathy                                    | -          |                  | Actin binding domain (1) |
| Yes               | Neuropathy                                    | -          |                  | Actin binding domain (1) |
| -                 | Akinetohypertonic syndrome                    | -          |                  | Actin binding domain (1) |
| -                 | FPLD                                          | -          |                  | Actin binding domain (1) |
| Yes               | Neuropathy                                    | -          |                  | PKC Alpha Binding site |
| Yes               | Neuropathy                                    | -          |                  | PKC Alpha Binding site |
| Yes               | Neuropathy                                    | -          |                  | PKC Alpha Binding site |
| Yes               | Neuropathy                                    | -          |                  | PKC Alpha Binding site |
| Yes               | Neuropathy                                    | -          |                  | PKC Alpha Binding site |
| Yes               | Neuropathy                                    | -          |                  | PKC Alpha Binding site |
| Yes               | Neuropathy                                    | -          |                  | PKC Alpha Binding site |
| Yes               | Neuropathy                                    | -          |                  | PKC Alpha Binding site |
| Yes               | Neuropathy                                    | -          |                  | PKC Alpha Binding site |
| Yes               | Lipoatrophy of trunk and proximal limbs       | -          |                  | PKC Alpha Binding site |
| Yes               | Neuropathy                                    | -          |                  | PKC Alpha Binding site |
| Yes               | Neuropathy                                    | -          |                  | PKC Alpha Binding site |
| Yes               | Metabolic disturbances                        | Progeroid features | Bones abnormalities | Lamin A tail |
| Yes               | FPLD2, liver steatosis                        | -          |                  | Lamin A tail |
| Yes               | FPLD2                                         | -          |                  | Lamin A tail |
| Yes               | FPLD2                                         | -          |                  | Lamin A tail |
| Yes               | FPLD                                          | -          |                  | Lamin A tail |
| Yes               | FPLD2                                         | -          |                  | Lamin A tail |
| -                 | IRS                                           | -          |                  | Lamin A tail |
| Yes               | Metabolic disturbances                        | Progeroid 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 an 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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