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Emery-Dreifuss muscular dystrophy

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Emery-Dreifuss muscular dystrophy (EDMD) is characterised by early contractures, slowly progressive muscle wasting and weakness with a distinctive humero-peroneal distribution and cardiac conduction defects leading to dilated cardiomyopathy. The genes known to be responsible for EDMD encode proteins associated with the nuclear envelope: the emerin and the lamins A and C.
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Clinical definition

Emery-Dreifuss muscular dystrophy (EDMD) is a relatively benign form of dystrophy, with onset in early childhood and thereafter relatively slow progression that is characterised by the triad:[1]

(1) Early contractures, often before there is any significant weakness, of elbows, Achilles tendons, and post-cervical muscles (with subsequent limitation of neck flexion, but later forward flexion of the entire spine becomes limited).
(2) Slowly progressive muscle wasting and weakness with a distinctive humero-peroneal distribution (i.e. proximal in the upper limbs and distal in the lower limbs) early in the course of the disease. However weakness later extends to the proximal limb girdle musculature. Weakness is rarely profound.
(3) Cardiac conduction defects (ranging from sinus bradycardia, prolongation of the PR interval on electrocardiography to complete heart block). A generalised cardiomyopathy may also supervene. Thus, affected individuals may die suddenly from heart block, or develop progressive cardiac failure. The latter may occur subsequent to the insertion of a pacemaker to correct an arrhythmia.

Cardiac involvement is the most serious and important aspect of the disease. It usually becomes evident as muscle weakness progresses, but may exceptionally occur before there is any significant weakness. In almost all those affected by the disorder there is some evidence of cardiac involvement by age 30 years.

Two main modes of inheritance exist: X-linked and autosomal dominant. Rare autosomal recessive inheritance has also been described. Most X-linked EDMD patients become symptomatic in early childhood (<15 years) with mild weakness, followed by contractures. The disease is usually progressing and has a moderately benign course; loss of ambulation is exceptional. The disease course of the AD-EDMD is generally slow, but we can observe milder phenotype characterised by late onset and a mild degree of weakness and contractures or more severe phenotype with early presentation and a rapidly progressive course in few cases.[2] It seems to be somewhat more severe than X-linked EDMD. A marked inter- and intra-familial variability in the clinical expression exists in patients with AD-EDMD.[2]

Diagnosis

Diagnosis is based just on clinical observation because there is no characteristic distinction in muscle biopsies. Immunohistochemistry of muscle biopsy tissue, leucocytes, fibroblasts or exfoliative buccal cells for emerin (X-linked EDMD), can confirm the diagnosis.[3]

Disease frequency

The disease frequency is estimated at 1/100 000 for the X-linked form but is unknown for the autosomal dominant inheritance. Only a few rare autosomal recessive cases have

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been described.[4] There is a big proportion of sporadic cases with AD-EDMD.[2]

Gene

X-linked EDMD form

The gene responsible for the X-linked form was identified in 1994. It is located on chromosome Xq28. The *STA* gene is 2100 bp in length, consists in six exons and encodes 762 bp mRNA. Its 34 kD protein product of 254 amino acids has been designated 'emerin'.[5] Rat and mouse emerin sequences show >70% identity with human sequence, but there are no shared sequences in the drosophila melanogaster or C. *elegans* databases, except for the LEM domain which is also present in mammalian LAP2 and MAN1 proteins.[6]

Autosomal dominant EDMD form

The gene responsible for the autosomal dominant form was identified in 1999.[7] It is *LMNA* and located on chromosome 1q11-q23. This gene spans approximately 24 kb and is composed of 12 exons. Alternative splicing within exon 10 gives rise to two different mRNAs: a 1992 pb mRNA that codes for pre-lamin A and a 1716 bp mRNA that codes for lamin C. Consequently, two proteins are generated, lamin A (664 aa, 74 kDa) and lamin C (572 aa, 64 kDa).[8] Only the pre-lamin A, can be modified by isoprenylation. This protein cannot properly assemble into the nuclear lamina if it is not farnesylated and proteolytically processed to lamin A. In the mouse *Lmna* gene two separate promoters are identified, there is a somatic cell-acting promoter (for lamins A and C) and a testis-specific promoter (for lamin C2), which resides in the first intron. The presence of this alternative exon 1C2 that lead to lamin C2, has not been examined in humans so far, otherwise the genomic structure of murin and human *LMNA* genes is very similar. In both species the positions of intron insertion are exactly conserved, and the length of introns are also very similar.[9]

Autosomal recessive EDMD form

The implication of *LMNA* as the gene also responsible of the autosomal recessive form of the disease was described in 2000.[4]

Genetic heterogeneity

There is no other gene yet identified for which mutations are responsible of EDMD. However, it is important to note that mutations in *LMNA* gene were identified for three other autosomal dominant pathologies. Two of them are as EDMD, diseases of the striated muscles: the limb girdle muscular dystrophy type 1B (LGMD1B) and the dilated cardiomyopathy with conduction defects (DCM-CD).[10–12] The third pathology is the Dunnigan type familial partial lipodystrophy (FPLD) affecting the adipose tissue.[13] Two families have been described in which a *LMNA* mutation led to different phenotypes, EDMD, LGMD1B and DCM-CD.[12,14] So far, no overlap between the three striated muscle disorders and FLPD have been described.

Function of the proteins

Emerin protein

Emerin is an inner nuclear membrane protein anchored to the inner nuclear membrane in skeletal, cardiac and smooth muscle, via a carboxy-terminal tail with remaining of the molecule projecting within the nucleoplasm. This protein presents several serine protein kinase sites.[15] Emerin appears to be important in the organisation of the nuclear membrane during cell division. Fairley *et al*[16] suggest that the primary roles of the emerin-nuclear protein complex is to stabilise the nuclear membrane against the mechanical stresses that are generated in muscle cells during contraction. Direct interaction between emerin and lamin A has been demonstrated by biomolecular interaction analysis on a BIAcore sensor and by immunoprecipitation analysis.[17,18]

Lamin A/C proteins

Lamins are components of the nuclear envelope and are located in the lamina, a multimeric structure associated with the nucleoplasmic surface of the inner nuclear membrane. Lamins A and C are members of the type V intermediate filament superfamily and are composed of different structural domains, an amino-terminal head, an α-helical rod domain made of heptade repeats, and a globular carboxy-terminal tail. Lamins form dimers through their rod domain and interact with the chromatin and integral proteins of the inner nuclear membrane (lamin B receptor, Lamin Associated Proteins (LAPs), emerin, Narf) through binding sites located in their rod domain and their carboxyl-terminal globular tail. There is compelling evidence that lamins play a role in DNA replication, chromatin organisation, spatial arrangement of nuclear pore complexes, nuclear growth, mechanical stabilisation of the nucleus and anchorage of the nuclear envelope proteins.[8]

Animal model

X-linked EDMD form

To date, there is no *X-linked EDMD* model reported.

Autosomal EDMD forms

Recently, Sullivan *et al*[19] reported the derivation of mice in which the lamins A/C have been eliminated by gene targeting (by deletion of a region extended from exon 8 to the middle of exon 11), to produce either homozygous or heterozygous offspring. Both mice develop to term with no overt abnormalities. However, the post-natal growth of the homozygous mice is severely retarded, is characterised by appearance of muscular dystrophy. They exhibited premature mortality. This phenotype $-/-$ is associated with

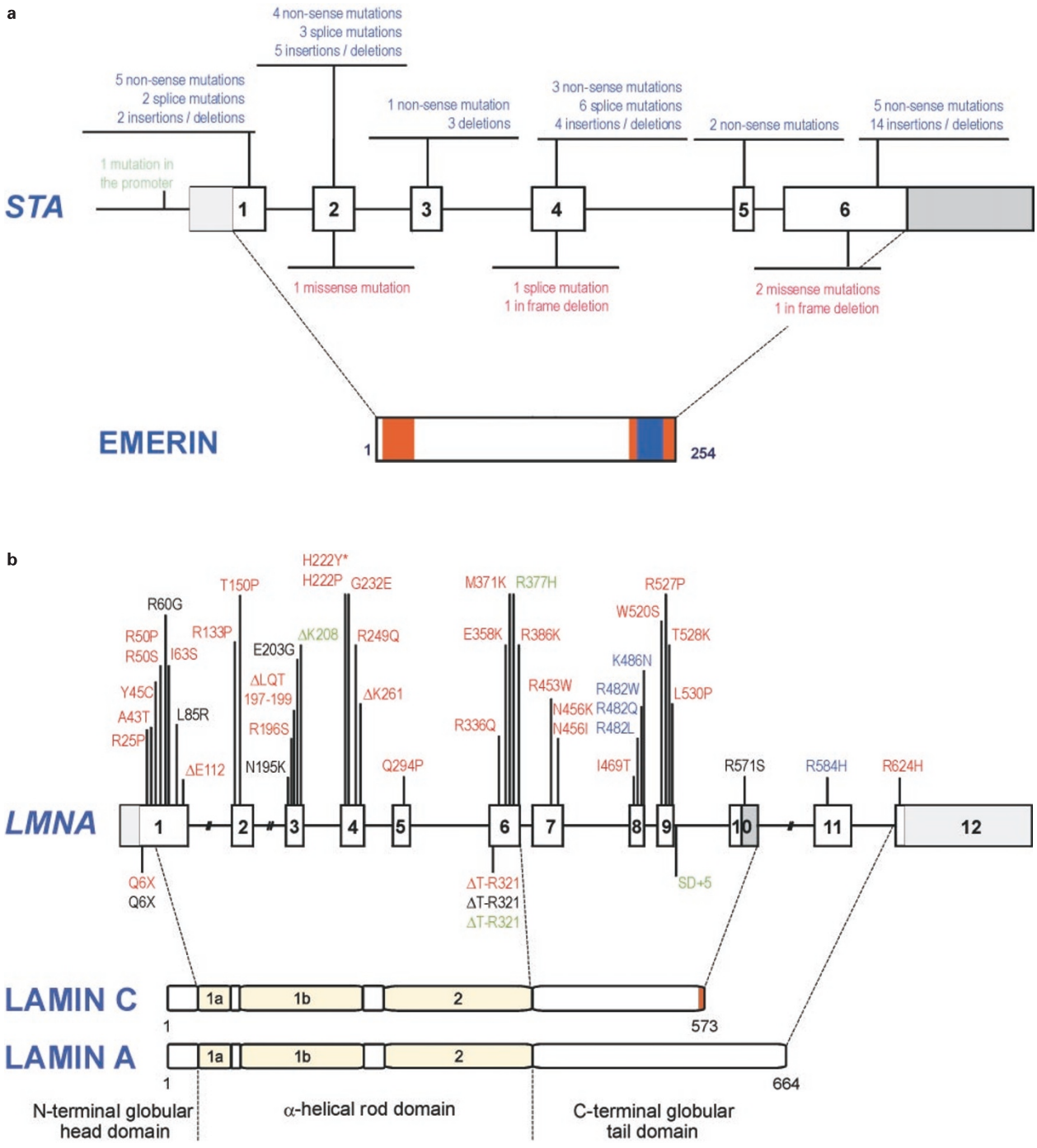

Figure 1 (**a**) *STA* mutations identified in XL-EDMD and their consequences on the protein structure of emerin. Mutations identified in XL-EDMD are presented.[20] Above the gene are mutations leading to truncated emerin: insertions/deletions, splice site mutations and nonsense point mutation suppressing ATG or introducing a stop codon (in blue). Below the gene are mutations leading to mutated emerin: in frame deletions, missense point mutations and splice donor site mutations (in red). Blue box on emerin structure corresponds to the transmembrane domain; orange boxes correspond to part of emerin that are homologous to LAP2 domains.[5] (**b**) *LMNA* mutations identified in AD-EDMD and other pathologies (LGMD1B, DCM-CD, FPLD) and their position on the protein structure of lamins A and C. Mutations identified in AD-EDMD are presented in red. The AR-EDMD mutation is depicted by an asterisk. LGMD1B mutations are in green. Black mutations correspond to DCM-CD mutations. The FPLD mutations are presented in blue. Above the gene are mutations leading to mutated lamins. Below the gene are mutations leading to truncated lamins.

ultrastructural perturbations to the nuclear envelope and with the mislocalisation of emerin in skeletal muscle. Mice heterozygous for the *lmna* mutation are overtly normal at 6–10 months with minimal evidence of dystrophy.

Mutations

STA gene

To date, around 100 mutations in the *STA* gene have been reported. They are approximately composed of 39.5% of small deletions, 31% of non-sense mutations, 15.5% of mutations in splice sites, 4% of large deletion of a part or the totality of the gene, 8.5% of missense mutations and 1.5% of mutation in the promoter (data base: www.path.cam.ac.uk/emd/mutation.html) (Figure 1a).[20] Almost all mutations (86%) result in a complete absence of emerin on both Western blotting and immunocytochemistry. Since emerin mRNA levels are usually normal, absence of emerin suggests that truncated emerin mutants which lack the C-terminal transmembrane sequence are unstable under normal conditions. This enables rapid diagnosis of most X-linked cases by immunocytochemistry on skin biopsies or buccal smears or by Western blotting of white blood cells.[3] Rare cases with reduced amount of the protein (due to a missense mutation) may have a milder phenotype.[21] Ultrastructure analysis was performed on patient tissue: nuclear changes were observed in nuclei of skeletal muscle and cultured fibroblasts. Different degree of abnormalities in the nuclei, ranging from marked condensation of the chromatin to complete damage of the nuclear component, were observed in 10–18% of the cells. The extrusion of nuclear chromatin into sarcoplasm as a consequence of the nuclear membrane disintegration was observed in numerous nuclei.[22,23]

LMNA gene

To date, 32 different mutations in *LMNA* gene are published to be responsible of AD-EDMD: 1 non-sense, 27 missense, 2 deletions of a codon, 1 deletion of 3 codons and 1 deletion of one nucleotide leading a frameshift (Figure 1b).[2,4,24,25] They are distributed along the gene between exons 1 and 9 in the region common to lamins A and C excepted for one missense mutation which is located in exon 11 specific for lamin A.[25] The mutation R453W was found in 16% of AD-EDMD patients. One mutation, H222Y, was identified at homozygous state in a patient from a consanguineous family. The unaffected parents carried the mutation at heterozygous state, demonstrating that *LMNA* mutations are responsible for the AR-EDMD.[4] Mutations in *LMNA* gene are found in 100% of familial cases and in 35% of sporadic cases. The clinical picture is often compatible with other muscular dystrophies such as congenital muscular dystrophy or Bethlem muscular dystrophy. This could explain the low efficiency of *LMNA* mutation detection in the sporadic cases.

For the three striated muscles disorders (EDMD, LGMD1B and DCM-CD), there is no clear correlation between the phenotype and type or localisation of the mutation in the gene and a wide intra- and inter-familial clinical variability is observed (Figure 1b). For example, the Q6stop mutation identified in a big French family gives rise to phenotypes ranging from an isolated cardiac involvement, ie DCM-CD, to severe muscular and cardiac involvements.[2,14] Another mutation, R366Q, was identified in a family in which only two out of the four members carrying the mutation, were affected.[4] Finally, one severely affected patient possessed two mutations, one specific to lamin A that may modify the phenotype of this patient.[25] Further studies are needed to identify the factors modifying striated muscle phenotypes among patients harbouring mutations within lamin A/C. In contrast, *LMNA* mutations described in FPLD affect for the majority of them (90%) the same codon of exon 8, R482.[26]

Immunocytochemical analysis of lamin A/C and emerin on skeletal muscle biopsies of AD-EDMD patients carrying *LMNA* mutation showed no detectable differences from control muscles, indicating that the mutations do not significantly alter the structure of the nuclear envelope.[27] At ultrastructure level, nuclear changes were observed with alterations in the chromatin distribution. However, it is not in a large extent and only a small proportion of muscle nuclei exhibit abnormalities.[27,28] Additional cases are needed before drawing any conclusion.

Treatment

There is no specific treatment. Development of specific therapeutic approaches may require a faithful animal model.

Great care should be given to proper diagnosis and follow-up of patients with EDMD. All patients should have a detailed cardiac investigation and regular follow-up by cardiologist since sudden death can be seen in these patients and early detection of arrhythmias can be lifesaving by pacemaker or defibrillator implantation. Also their relatives should be screened from the cardiologic point of view even if they show no subjective neuromuscular or cardiac symptoms. Apart from the patients with a typical presentation of weakness, contractures, and rhythm, especially in familial cases with a history of sudden death LMNA mutation should be searched for.

Accession numbers

(XL-EDMD, MIM no. 310300, *STA* gene coding for emerin); (AD-EDMD, MIM no. 181350, *LMNA* gene coding for lamin A/C).

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