A new mutation of the lamin A/C gene leading to autosomal dominant axonal neuropathy, muscular dystrophy, cardiac disease, and leuconychia

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The LMNA gene encodes two nuclear envelope proteins, lamins A and C, derived from alternative splicing. First identified in autosomal dominant Emery-Dreifuss muscular dystrophy (AD-EDMD),1 mutations in this gene are implicated in up to seven diseases including autosomal recessive Emery-Dreifuss muscular dystrophy (AR-EDMD),2 limb-girdle muscular dystrophy type 1B (LGMD1B),3 dilated cardiomyopathy with conduction defects (DCM-CD),4,5 autosomal dominant partial lipodystrophy of Dunnigan type,6 autosomal recessive axonal Charcot-Marie-Tooth disease (AR-CMT2),7 mandibuloacral dysplasia,8 and Hutchinson-Gilford progeria syndrome.9

In addition, some patients appear to have a combination of these different phenotypes10 11 or a clinical variant including skin abnormalities.12 To extend the clinical spectrum of laminopathies, we report a previously undescribed dominant missense mutation, E33D, identified in LMNA and clinically characterised by the combination of axonal neuropathy with myopathic features, cardiac disease including dilated cardiomyopathy, conduction disturbances and arrhythmia, and leuconychia. The LMNA gene is therefore the first gene implicated in both autosomal dominant and recessive forms of CMT2.

CASE REPORT

The pedigree of a white family originating from the south west of France is shown in fig 1. The index case (II-5) and his affected daughter (III-13) were neurologically and cardiologically assessed by one of our team; only partial information was available for other affected members through questioning of patient III-13. The clinical features of all the affected members are shown in table 1. The results of nerve electrophysiological examination of patients II-5 and III-13 are shown in table 2. A muscle CT scan performed for patient II-5 showed wasting and marked fatty infiltration predominating in paraspinal, vasti, hamstring, and gastrocnemius muscles (fig 2). Fig 3 shows the fingernails of patients II-5 and III-13, exhibiting leuconychia.

Clinical and electrical data are consistent with the diagnosis of autosomal dominant axonal neuropathy (AD-CMT2) associated with muscular dystrophy, cardiac disease, and leuconychia in patients II-5 and III-13. Owing to the lack of data this association was not always fully documented for other family members, but a CMT2 phenotype could not be formally excluded in these patients. The variable association of axonal neuropathy, muscular dystrophy, cardiac abnormalities, and leuconychia observed in this family was intriguing. Cardiac disease and/or muscular dystrophy and/or leuconychia are not considered as classical features associated with CMT2. As LMNA gene mutations can result in up to seven diseases affecting specifically nerve, muscle, and/or heart, we subsequently performed DHPLC analysis of the coding region of this gene.14 DNA samples for genetic analysis were obtained from peripheral blood lymphocytes from two patients (II-5 and III-13) and from one healthy family member (II-14), after their informed consent. DHPLC screening identified a variant of the LMNA exon 1 in the DNA samples of patients II-5 and III-13. Further sequencing of the LMNA exon 1 identified a heterozygous 99G→T transition that corresponds to a missense mutation of codon 33, E33D, at the protein level in the DNA of the two patients. This mutation, affecting E33, an amino acid highly conserved through various species and types of lamins (fig 4), was not found in the healthy family member, III-14, nor in 200 healthy unrelated control subjects.

DISCUSSION

Successive identification of LMNA mutations in seven different entities has dramatically extended the phenotypic spectrum of laminopathies.15 16 Cases displaying a combined phenotype of these entities have also been described.17 18 The

Key points

- Mutations of the lamin A/C gene (LMNA) are responsible for up to seven diseases involving muscle, heart, nerve, fat, bone, and skin tissues.
- Until now, only one mutation had been reported, in an autosomal recessive form of axonal Charcot-Marie-Tooth disease.
- We describe two members of a large family who share clinical features including axonal neuropathy, muscular dystrophy, cardiac disease, and leuconychia. Some of these features were reported in other family members.
- A new LMNA heterozygous missense mutation, E33D, was identified in the two patients.
- To our knowledge, this is the first LMNA mutation to be found in an autosomal dominant form of CMT2, and implies that LMNA is responsible for both autosomal dominant and recessive forms of axonal Charcot-Marie-Tooth disease.

Abbreviations: AD-CMT2, autosomal dominant Charcot-Marie-Tooth disease; AR-CMT2, autosomal recessive Charcot-Marie-Tooth disease; AD-EDMD, autosomal dominant Emery-Dreifuss muscular dystrophy; AR-EDMD, autosomal recessive Emery-Dreifuss muscular dystrophy; DCM-CD, dilated cardiomyopathy with conduction defects; LGMD1B, limb girdle muscular dystrophy type 1B
new E33D LMNA mutation reported here leads to an original dominantly inherited clinical variant combining axonal neuropathy, muscular dystrophy, cardiac disease, and leuconychia.

So far, only one homozygous LMNA missense mutation, R298C, was reported to be associated with an autosomal form of axonal neuropathy (AR-CMT2) in four families. Histological features, highly similar to the CMT2 phenotype observed in humans, has also been reported in transgenic LMNA null mice. Our index case and his affected daughter suffered from a clinically and electrically evident axonal neuropathy, with a less severe course than previously observed, suggesting that the axonal neuropathy related to LMNA mutation could also be dominantly inherited.

In addition to the CMT2 features, our two patients displayed proximal muscle involvement in the lower limbs.

**Table 1** Clinical features of the affected family members

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Onset</th>
<th>Age at last exam</th>
<th>Muscle weakness and wasting</th>
<th>Sensory abnormalities</th>
<th>Nerve conduction study</th>
<th>Needle electromyography</th>
<th>Muscle biopsy</th>
<th>Heart</th>
<th>Leu</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-1</td>
<td>F</td>
<td>Teens</td>
<td>58</td>
<td>Pelvic, quadriceps</td>
<td>N</td>
<td>-</td>
<td>Mixed pattern</td>
<td>-</td>
<td>-</td>
<td>Y</td>
</tr>
<tr>
<td>I-2</td>
<td>F</td>
<td>Teens</td>
<td>55</td>
<td>Pelvic and distal, pes canos</td>
<td>N</td>
<td>Y (generalised)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Y</td>
</tr>
<tr>
<td>II-4</td>
<td>F</td>
<td>Juvenile</td>
<td>50</td>
<td>Pelvic, quadriceps</td>
<td>N</td>
<td>-</td>
<td>x 3</td>
<td>Myopathic pattern</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>II-5</td>
<td>M</td>
<td>Teens</td>
<td>55</td>
<td>Pelvic and distal, pes canos</td>
<td>N</td>
<td>Y (generalised)</td>
<td>x 1.8</td>
<td>Sensory motor neuropathy</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>II-5</td>
<td>M</td>
<td>Teens</td>
<td>55</td>
<td>Pelvic and distal, pes canos</td>
<td>N</td>
<td>N (distal)</td>
<td>x 1.8</td>
<td>Neurogenic pattern</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>III-13</td>
<td>F</td>
<td>Teens</td>
<td>26</td>
<td>Pelvic and distal, pes canos</td>
<td>N</td>
<td>Y (distal)</td>
<td>x 6.7</td>
<td>Sensory motor neuropathy</td>
<td>ND</td>
<td>1st degree AVB</td>
</tr>
</tbody>
</table>

ND, not done; CPK, Creatine phosphokinase expressed in number time of upper normal value; --: no data available; UL, upper limbs; LL, lower limbs; Y, presence of abnormality; N, absence of abnormality; AF, atrial fibrillation; AVB, atrioventricular block; Leu, leuconychia

**Table 2** Electrophysiological study of patients II-5 and III-13

<table>
<thead>
<tr>
<th>MNCV (m/s)</th>
<th>DL (ms)</th>
<th>CMAP (mV)</th>
<th>F-wave latency (ms)</th>
<th>Sensory nerves</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-5</td>
<td>III-13</td>
<td>II-5</td>
<td>III-13</td>
<td>II-5</td>
</tr>
<tr>
<td>II-5</td>
<td>III-13</td>
<td>II-5</td>
<td>III-13</td>
<td>II-5</td>
</tr>
<tr>
<td>Peroneal</td>
<td>35.1</td>
<td>49.54</td>
<td>6.6.5</td>
<td>34.1</td>
</tr>
<tr>
<td>Ulnar</td>
<td>45</td>
<td>ND</td>
<td>3.8</td>
<td>50.3</td>
</tr>
<tr>
<td>Posterior</td>
<td>32.7</td>
<td>ND/7.7</td>
<td>6.1/5.4</td>
<td>3.9</td>
</tr>
<tr>
<td>Median</td>
<td>42.6</td>
<td>54.3</td>
<td>4.6</td>
<td>37.1/37.8</td>
</tr>
<tr>
<td>Sural</td>
<td>32.8</td>
<td></td>
<td></td>
<td>31/30</td>
</tr>
<tr>
<td>Radial</td>
<td>32.8</td>
<td></td>
<td></td>
<td>35/35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SNVC (m/s)</th>
<th>DL (ms)</th>
<th>SNAP (µV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-5</td>
<td>III-13</td>
<td>II-5</td>
</tr>
<tr>
<td>II-5</td>
<td>III-13</td>
<td>II-5</td>
</tr>
<tr>
<td>Peroneal</td>
<td>ND</td>
<td>29</td>
</tr>
<tr>
<td>Ulnar</td>
<td>ND</td>
<td>3.8</td>
</tr>
<tr>
<td>Posterior</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Median</td>
<td>ND</td>
<td>2.9</td>
</tr>
<tr>
<td>Sural</td>
<td>ND</td>
<td>3.7</td>
</tr>
<tr>
<td>Radial</td>
<td>ND</td>
<td>3.7</td>
</tr>
</tbody>
</table>

MNCV, motor nerve conduction velocities; SNVC, sensory nerve conduction velocities; CMAP, compound action motor potential; SNAP, sensory nerve action potential; DL, distal latency; L, left; R, right; ND, not done; UR, unrecordable.

Note the reduced or abolished CMAP and reduced SNAP with normal or slightly reduced MNCV proportional to the reduction of CMAP.
This latter observation can be explained by a probable primary involvement of muscular tissues associated to the nerve degeneration. It is supported in our family by the increased level of serum CPK present in the index case (II-5) and his daughter (III-13), brother, and sister (II-1 and II-4), the dystrophic pattern observed on muscle biopsy of the index case and his sister (II-4), and the muscle CT scan aspect of index case, which shows a predominant fatty infiltration of paraspinal, vasti, hamstring, and gastrocnemius muscles while other muscles in lower limbs were mildly affected. This specific pattern of infiltration is similar to those observed in AD-EDMD,16 and in two cases of laminopathies with a combined phenotype.11 This family confirms that muscular and nerve degeneration may occur concomitantly in laminopathies.

Cardiac abnormalities were obvious in our family whereas cardiac investigations remained normal in the families reported by De Sandre et al.7 Several authors have described such CMT families with cardiac abnormalities including cardiomyopathy, conduction abnormalities, and rhythm disturbances.17–22 Some groups consider this association to be the coincidental occurrence of a relatively common disorder, heart disease, and a less common entity, CMT.20 22 In contrast, others suggest that involvements of heart and nerve have a common primary origin.17–19 21 In a recent review,23 24 the authors do not consider cardiac disease to be a feature found in CMT2. The cardiac abnormalities reported in the present family are similar to the typical features observed in patients with laminopathies affecting the striated muscle—that is, EDMD, LGMD1B, and DCM-CD, characterised by dilated cardiomyopathy, conduction system disease and rhythm disturbances.2 3 11 12 14 Therefore, our family is the first report of a family carrying a LMNA mutation, in which cardiac disease co-segregates with CMT2 features.

Finally, the co-segregation of leuconychia in several affected members of this family is also unexpected, as it has never been reported in patients carrying the LMNA mutation or CMT2 phenotype. Our observation argues for including this feature in the clinical spectrum of laminopathies. It could be included in the group of skin and phaners premature ageing features observed in mandibuloacral dysplasia and Hutchinson-Gilford progeria syndrome.

**Figure 2** Muscle CT scan of patient II-5. Cross section of the scapular girdle (A), pelvic girdle (B), arms (C), thighs (D), forearms and paraspinal muscles (E), and legs (F). Note the selective atrophy and marked fatty infiltration predominating in paraspinal (*), vasti, hamstring (+) and gastrocnemius ($) muscles.

**Figure 3** Leuconychia features. Fingernails of index case (A) with complete leuconychia and of his daughter (B) with partial leuconychia starting at the periphery of the fingernails (arrows).
From the pathophysiological point of view, lamins A and C are intermediate filaments that localise at the nucleoplasmic surface of the inner nuclear membrane as a meshwork structure, and have multiple interactions with proteins and chromatin.\textsuperscript{19} It has been speculated that the primary defect may have downstream effects on chromatin structure or gene expression, explaining in part the tissue specificity observed in laminopathies.\textsuperscript{25} Despite the growing number of mutations identified in LMNA, no clear phenotype-genotype relation has been established. Several mutations affecting amino acids close to E33 have been reported. S22L, R25P, R28W, \(\Delta K32\), A43T, Y45C, R50P, and R50S lead to EDMD of variable severity, DCM-CD or combination of partial lipodystrophy with cardiomyopathy, but no CMT2 features have been observed.\textsuperscript{12 14 26–28} Interestingly, a mutation (98A\textsuperscript{\textendash}G) affecting the same codon and leading to E33G was identified in two patients who had typical EDMD phenotype without any CMT2 features (unpublished data). This illustrates the difficulties in establishing any phenotype-genotype relation. However, the involvement of peripheral nervous system observed in our family probably suggests that E33, like \(\Delta K32\), is functionally important for the nerve tissue. These observations highlight the crucial role of LMNA in the maintenance of peripheral nervous system integrity.

In conclusion, the present cases are the first report of AD-CMT2 due to LMNA mutation. We propose that LMNA should be included in the spectrum of genes responsible for AD-CMT2 particularly when associated with proximal muscle involvement, cardiac abnormalities, or leuconychia. Thus, LMNA represents the first gene implicated in both recessive and dominant forms of CMT2.

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