Extreme Variability of Phenotype in Patients With an Identical Missense Mutation in the Lamin A/C Gene

From Congenital Onset With Severe Phenotype to Milder Classic Emery-Dreifuss Variant

Eugenio Mercuri, MD; Maja Poppe, MD; Ros Quinlivan, MD; Sonia Messina, MD; Maria Kinali, MD; Laurence Demay; John Bourke, MD; Pascale Richard, MD; Caroline Sewry, PhD; Mike Pike, MD; Gisele Bonne, PhD; Francesco Muntoni, MD; Kate Bushby, MD

Background: Mutations of the LMNA gene, encoding the nuclear envelope proteins lamins A and C, have been associated with 7 distinct pathologic conditions.

Objective: To report 5 cases with the same missense mutation in exon 6 of the LMNA gene, resulting in an E358K substitution in the central rod domain.

Design: Case report.

Setting: Three muscle centers in England.

Patients: Five patients with missense mutations of the LMNA gene.

Results: All 5 individuals had muscle involvement, but the onset, severity, distribution of muscle weakness, and presence of associated features were highly variable. Three patients had humeroperoneal distribution of weakness and typical features of Emery-Dreifuss muscular dystrophy. Two other patients showed additional novel features. One had congenital onset and predominant axial weakness, with poor neck control and inability to sit independently at the age of 21 months. Another patient presented in childhood with an unusual pattern of muscle weakness, short stature, and midface hypoplasia with striking fat accumulation around the face and neck, in contrast to wasting of adipose tissue and muscle in the limbs. She developed both respiratory failure and cardiac arrhythmias in her late 20s.

Conclusion: Our cases expand the clinical spectrum associated with mutations in the LMNA gene and further illustrate the overlapping phenotypes of the laminopathies.

Arch Neurol. 2004;61:690-694

THE LMNA GENE ENCODES the nuclear envelope proteins lamins A and C and is located on chromosome 1q11-q23. Mutations in the LMNA gene are associated with 7 distinct pathologic conditions. These include autosomal dominant (AD) and autosomal recessive forms of Emery-Dreifuss muscular dystrophy (EDMD), limb-girdle muscular dystrophy type 1B, a form of dilated cardiomyopathy with conduction system disease, the Dunnigan type of familial partial lipodystrophy, a form of autosomal recessive axonal neuropathy (Charcot-Marie-Tooth disease), mandibuloacral dysplasia, and, recently, Hutchinson-Gilford progeria syndrome.

The way in which these mutations produce different clinical phenotypes remains unclear, and while an association between specific LMNA mutations and definite phenotypes has been suggested in a number of instances, such as specific mutations leading to lipodystrophy, this issue has not been fully resolved. A few studies have reported the coexistence of 2 diseases in the same patient, such as limb-girdle muscular dystrophy 1B and lipodystrophy. Other studies have described the same mutation producing different phenotypes with muscle weakness, such as limb-girdle muscular dystrophy type 1B and AD-EDMD, in the same family.

We report 5 cases in which the identical missense mutation within the LMNA gene produced phenotypes characterized by muscle involvement of variable severity and additional distinctive features, which expand the spectrum of clinical phenotypes reported in the literature.

METHODS

Five patients with the same missense LMNA mutation were identified among the clinic patients of the Dubowitz Neuromuscular Centre, Hammersmith Hospital Imperial College, London, England; Institute of Human Genetics and Department of Cardiology, University of Newcastle Upon Tyne, Newcastle, England; and Robert...
A white girl was the second child of nonconsanguineous parents. Her mother had had 2 stillbirths, which were attributed to toxemia in pregnancy. There was no family history of any neuromuscular disorder. The mother had died suddenly at the age of 45 years. Postmortem examination did not show any cardiac patterns, so the underlying cause of death was assumed to be a rhythm disturbance.

The patient had been born at 36 weeks’ gestation (2.68 kg) after delivery was induced because of toxemia. She was noted to be hypotonic and had feeding difficulties for a few weeks after birth, but motor development was within the normal range (sitting unsupported at 6–7 months, walking independently at 15 months), although she was never able to run. At the age of 7 years she was referred because of generalized hypotonia and a waddling gait. On examination she exhibited severe wasting and weakness, more marked in biceps and triceps in the upper limb and in quadriceps in the lower limb. There were also minimal contractures of the finger flexors and at the right elbow, as well as limited dorsiflexion of both feet. No significant decrease in muscle strength was noted until the age of 16 years, when the patient had difficulty in rising from a sitting to a standing position. The weakness progressed rapidly after that time, and she became wheelchair-bound in her mid-20s.

On examination, the patient was 30 years old and of normal intelligence. She was of short stature (1.47 m in height) and had a marked midface hypoplasia with a broad nasal bridge and some mild weakness of eye closure. There was a striking discrepancy between her rather broad, short “buffalo neck,” with increased subcutaneous adipose tissue and fat accumulation also in the facial region, and the extremely thin trunk and extremities (Figure 1). The deltoid and shoulder muscles were relatively well preserved compared with biceps and triceps. There were contractures in the elbows, finger flexors, spine, and Achilles tendons. Muscle power was most markedly reduced in the biceps, triceps, and quadriceps. The patient showed moderate weakness of neck flex-
was early onset in the second year of life and a rapidly progressive course with loss of independent ambulation at 5 years. This child also showed progressively reduced respiratory function, and at age 6 years he had forced vital capacity less than 40%. The other 2 patients had onset at school age and a slowly progressive course (Table).

Muscle magnetic resonance imaging was performed in cases 3, 4, and 5 (Figure 2) and showed selective involvement of the quadriceps muscles in the thigh in cases 4 and 5 and selective involvement of quadriceps and adductor magnus in case 3. At calf level they all showed more diffuse involvement of the gastrocnemius and soleus muscles, with the medial head of the gastrocnemius relatively spared compared with the lateral one.

The cases described in this article show that the phenotype of patients with laminopathies can be far more severe than has been reported so far and expand the spectrum of clinical phenotype associated with a single LMNA mutation reported in the literature.

All patients described herein carried the same mutation but different phenotypes, and 2 of the 5 cases had peculiar features that have not been previously described in patients with laminopathy. All the cases were de novo mutations, confirming previous observations that de novo mutations are extremely common in patients with dominant mutations in the LMNA gene.

Patient 1 had laminopathy associated with congenital onset, with clear signs of muscle involvement such as severe weakness and hypotonia in the first months of life. In patients with AD-EDMD, onset is typically at school age with contractures. An earlier onset, associated with a more severe phenotype, has been reported, but even in those cases the onset was after these children had acquired independent ambulation. In our patient, independent sitting posture was never achieved.

Patient 2 had a limb-girdle distribution of weakness and also showed a pattern of abnormal fat accumulation around the face and neck, together with marked lack of subcutaneous fat in the limbs in a manner reminiscent of familial partial lipodystrophy. It has up to now been believed that there was a correlation between the genotype and the phenotype in LMNA gene mutations regarding familial partial lipodystrophy. It has up to now been believed that there was a correlation between the genotype and the phenotype in LMNA gene mutations regarding familial partial lipodystrophy, in which 90% mutations were localized in exon 8 of the LMNA gene. Recently, the association of lipodystrophy in patients with other characteristic presentations of EDMD, limb-girdle muscular dystrophy type 1B, or dilated cardiomyopathy with conduction system disease has been highlighted in patients who demonstrated overlapping phenotypes, ie, laminopathies affecting striated muscles and adipose tissue. These patients carried mutations in exons 1 and 9, and so far there is no report of signs of lipodystrophy associated with mutations in exon 6. Patient 2 also showed unique features of short stature and dysmorphisms, indicating skeletal involvement. The phenotype in this case is not the same as mandibuloacral dysplasia, but it does suggest that skeletal involvement may be a broader part of the phenotype than previously thought. So far, only one LMNA mutation, homozygous R527P, was reported in patients with autosomal dominant mutations in the LMNA gene.

The cases described in this article show that the phenotype of patients with laminopathies can be far more severe than has been reported so far and expand the spectrum of clinical phenotype associated with a single LMNA mutation reported in the literature.

All patients described herein carried the same mutation but different phenotypes, and 2 of the 5 cases had peculiar features that have not been previously described in patients with laminopathy. All the cases were de novo mutations, confirming previous observations that de novo mutations are extremely common in patients with dominant mutations in the LMNA gene.

Patient 1 had laminopathy associated with congenital onset, with clear signs of muscle involvement such as severe weakness and hypotonia in the first months of life. In patients with AD-EDMD, onset is typically at school age with contractures. An earlier onset, associated with a more severe phenotype, has been reported, but even in those cases the onset was after these children had acquired independent ambulation. In our patient, independent sitting posture was never achieved.

Patient 2 had a limb-girdle distribution of weakness and also showed a pattern of abnormal fat accumulation around the face and neck, together with marked lack of subcutaneous fat in the limbs in a manner reminiscent of familial partial lipodystrophy. It has up to now been believed that there was a correlation between the genotype and the phenotype in LMNA gene mutations regarding familial partial lipodystrophy, in which 90% mutations were localized in exon 8 of the LMNA gene. Recently, the association of lipodystrophy in patients with other characteristic presentations of EDMD, limb-girdle muscular dystrophy type 1B, or dilated cardiomyopathy with conduction system disease has been highlighted in patients who demonstrated overlapping phenotypes, ie, laminopathies affecting striated muscles and adipose tissue. These patients carried mutations in exons 1 and 9, and so far there is no report of signs of lipodystrophy associated with mutations in exon 6. Patient 2 also showed unique features of short stature and dysmorphisms, indicating skeletal involvement. The phenotype in this case is not the same as mandibuloacral dysplasia, but it does suggest that skeletal involvement may be a broader part of the phenotype than previously thought. So far, only one LMNA mutation, homozygous R527P, was reported in patients with autosomal dominant mutations in the LMNA gene.

The cases described in this article show that the phenotype of patients with laminopathies can be far more severe than has been reported so far and expand the spectrum of clinical phenotype associated with a single LMNA mutation reported in the literature.

All patients described herein carried the same mutation but different phenotypes, and 2 of the 5 cases had peculiar features that have not been previously described in patients with laminopathy. All the cases were de novo mutations, confirming previous observations that de novo mutations are extremely common in patients with dominant mutations in the LMNA gene. Patient 1 had laminopathy associated with congenital onset, with clear signs of muscle involvement such as severe weakness and hypotonia in the first months of life. In patients with AD-EDMD, onset is typically at school age with contractures. An earlier onset, associated with a more severe phenotype, has been reported, but even in those cases the onset was after these children had acquired independent ambulation. In our patient, independent sitting posture was never achieved.

Patient 2 had a limb-girdle distribution of weakness and also showed a pattern of abnormal fat accumulation around the face and neck, together with marked lack of subcutaneous fat in the limbs in a manner reminiscent of familial partial lipodystrophy. It has up to now been believed that there was a correlation between the genotype and the phenotype in LMNA gene mutations regarding familial partial lipodystrophy, in which 90% mutations were localized in exon 8 of the LMNA gene. Recently, the association of lipodystrophy in patients with other characteristic presentations of EDMD, limb-girdle muscular dystrophy type 1B, or dilated cardiomyopathy with conduction system disease has been highlighted in patients who demonstrated overlapping phenotypes, ie, laminopathies affecting striated muscles and adipose tissue. These patients carried mutations in exons 1 and 9, and so far there is no report of signs of lipodystrophy associated with mutations in exon 6. Patient 2 also showed unique features of short stature and dysmorphisms, indicating skeletal involvement. The phenotype in this case is not the same as mandibuloacral dysplasia, but it does suggest that skeletal involvement may be a broader part of the phenotype than previously thought. So far, only one LMNA mutation, homozygous R527P, was reported in patients with autosomal dominant mutations in the LMNA gene.
Our cases increase the spectrum of phenotypes associated with lamin A/C mutations. The wide spectrum of conditions caused by mutations in the LMNA gene strongly supports the hypothesis that a multiprotein complex exists at the nuclear envelope whose alterations might be responsible for the different phenotypes described. The existence of distinct functional domains in lamin A/C might be essential for the maintenance and integrity of different cell lineages. The interactions of lamin A/C may be diverse in different cell types, and specific mutations may modify some of these interactions, eventually causing tissue- or cell type–specific alterations of the nuclear envelope.

Accepted for publication November 19, 2003.

From the Dubowitz Neuromuscular Centre, Hammersmith Hospital Imperial College, London, England (Drs Mercuri, Missina, Kinali, Sewry, and Muntoni); Institute of Human Genetics and Department of Cardiology, University of Newcastle Upon Tyne, Newcastle, England (Drs Poppe, Bourke, and Bushby); Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry.

Clinicopathological Variability in Patients With LMNA Mutations

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of symptoms, y</td>
<td>11⁄4</td>
<td>31</td>
<td>6</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>Sex</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Maximum functional ability</td>
<td>Sitting with support</td>
<td>Progressively</td>
<td>Walking independently</td>
<td>Walking independently</td>
<td>Walking independently</td>
</tr>
<tr>
<td>Wasting</td>
<td>Scapuloperoneal</td>
<td>First few weeks of life</td>
<td>Scapuloperoneal</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CK (times the normal value)</td>
<td>50</td>
<td>74 U/L (NR, 0–160 U/L) at age 31 y</td>
<td>Recurrent atrial fibrillation, brady-tachy syndrome</td>
<td>Normal</td>
<td>Arrhythmia</td>
</tr>
<tr>
<td>24-h Holter monitoring</td>
<td>Normal</td>
<td>Recurrent atrial fibrillation, brady-tachy syndrome</td>
<td>Normal</td>
<td>Ventricular dysfunction</td>
<td>Normal</td>
</tr>
<tr>
<td>FVC, %</td>
<td>Too young</td>
<td>38 (age 30 y)</td>
<td>40</td>
<td>78</td>
<td>85</td>
</tr>
<tr>
<td>Other</td>
<td>OFC and weight less than third percentile</td>
<td>Short stature, midfacial hypoplasia, broad nasal bridge, limited eye closure, uterine fibroids</td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: AT, Achilles tendon; CK, creatine kinase; ECG, electrocardiogram; EDMD, Emery-Dreifuss muscular dystrophy; FVC, forced vital capacity; HS, hamstrings; LFF, long finger flexors; LGMD, limb girdle muscular dystrophy; LL, lower limbs; LMNA, gene encoding nuclear envelope proteins lamins A and C; NG, nasogastric; NR, normal range; OFC, occipitofrontal circumference; RBBB, right bundle-branch block; UL, upper limbs; +, mild; ++, moderate; +++, severe.

It is clear from this and other studies that there may be more of an overlap of these different features of laminopathy than has previously been reported. Patient 2 also exhibited early respiratory failure and nocturnal hypoventilation requiring ventilatory support, which has also been previously reported in patients with R453W LMNA mutations. It is of interest that another 2 patients (cases 1 and 3) also had signs of respiratory impairment, with patient 1 having a previously diaphragmatically breathing pattern and patient 3 a forced vital capacity of 40% at age 6 years.

Muscle biopsy specimens showed myopathic changes in all cases, but patient 1 additionally had other peculiar features that have not been previously reported. Mild up-regulation of major histocompatibility complex I on the sarcolemma of mature fibers was seen in 2 muscle biopsy specimens, leading to the initial diagnosis of an inflammatory myopathy. Up-regulation of major histocompatibility complex class I has not previously been described in Duchenne and Becker muscular dystrophy and in cases with dysferlin deficiency. The reasons for and consequences of this up-regulation for disease are not clear and in our case might be related to the age of the patient studied or the severity of the pathological process.

Our cases increase the spectrum of phenotypes associated with this E358K LMNA mutation, which in the past has been found associated with limb-girdle muscular dystrophy type 1D in 1 patient and with AD-EDMD in 3 patients. These findings confirm previous observations that the same mutation in the LMNA gene can be associated with a large spectrum of clinical phenotypes and that overlapping features of the different conditions in which lamin A/C mutations have been described may be seen in individual patients. The way in which the mutations alter the function of the protein to produce the different clinical phenotypes remains unclear, although the wide spectrum of conditions caused by mutations in the LMNA gene strongly supports the hypothesis that a multiprotein complex exists at the nuclear envelope whose alterations might be responsible for the different phenotypes described. The existence of distinct functional domains in lamin A/C might be essential for the maintenance and integrity of different cell lineages. The interactions of lamin A/C may be diverse in different cell types, and specific mutations may modify some of these interactions, eventually causing tissue- or cell type–specific alterations of the nuclear envelope.
England (Drs Quinlivan and Sewry); Cardiogénétique et Myogénétique, Service de Biochimie B, General Hospital Pitie´Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France (Drs Demay and Richard); Department of Pediatrics, John Radcliffe Hospital, Oxford, England (Dr Pike); INSERM U582, Institut de Myologie, General Hospital Pitie´-Salpe´trie`re, Paris (Dr Bonne); Department of Child Neurology, Catholic University, Rome, Italy (Dr Mercuri); and Department of Neurosciences, Psychiatry and Anesthesiology, University of Messina, Messina, Italy (Dr Messina).

Author contributions: Study concept and design (Drs Mercuri, Bourke, Muntoni, and Bushby); acquisition of data (Drs Mercuri, Poppe, Quinlivan, Messina, Kinali, Demay, Bourke, Richard, Sewry, Pike, Bonne, and Bushby); analysis and interpretation of data (Drs Mercuri, Bourke, Sewry, Bonne, and Muntoni); drafting of the manuscript (Drs Mercuri, Poppe, Messina, Kinali, Demay, Bourke, Richard, Sewry, and Bushby); critical revision of the manuscript for important intellectual content (Drs Mercuri, Quinlivan, Pike, Bonne, Muntoni, and Bushby); statistical expertise (Drs Mercuri, Bourke, and Muntoni); obtained funding (Dr Muntoni); administrative, technical, and material support (Drs Poppe, Quinlivan, Messina, Kinali, Demay, Richard, and Sewry); study supervision (Dr Bushby).

This study was supported by grants from the European Union Fifth Framework (contract QLG1-1999-00870 from the MYO-CLUSTER/EUROMEN, Brussels, Belgium). Dr Bonne was also supported by grant RGP0057/2001-M101 from the Human Frontier Science Program, Strasbourg, France. Support from the NSCAD (National Specialist Commissioning Advisory Group) and the Muscular Dystrophy Campaign, London, England, to the Hammer smith and Newcastle muscle centers is also acknowledged.

Corresponding author: Eugenio Mercuri, MD, Department of Paediatrics, Hammersmith Hospital, Du Cane Road, London W12 OHN, England (e-mail: e.mercuri@ic.ac.uk).

REFERENCES