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

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**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.

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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...
Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, England. Clinical and investigation details were obtained from the records. Patients had been followed up for 1 to 23 years.

Analysis of LMNA was carried out by denaturing high-performance liquid chromatography sequencing techniques for the 12 exons of the gene as described by Bonne et al.\(^2\) Exon 6 was amplified by polymerase chain reaction with the use of an intronic set of primers in flanking regions (6F 5’-CAAACCCTCCACCCCCCC-3’ and 6R 5’-CAAGTTGCGGAGCCAGAG-3’). The WaveMaker software (Transgenomic, Inc, Omaha, Neb) was used to calculate specific melting curves for each polymerase chain reaction fragment and to determine the optimal temperature for heteroduplex separation. A denaturing high-performance liquid chromatography profile showing both heteroduplexes and homoduplexes (64°C), as compared with unaffected controls showing only homoduplexes, was identified in the index cases for exon 6. Sequencing of the corresponding exon 6 polymerase chain reaction products showed a heterozygous 1072G→A transition in LMNA, resulting in the replacement of glutamine 358 (GAG) by a lysine (AAG). This abnormal pattern was not found in 150 unrelated control subjects.

### RESULTS

Two of the 5 patients had the most common phenotype reported in AD-EDMD.\(^2\) Another patient also had an AD-EDMD phenotype, but with a relatively early and more severe presentation; this patient has already been described.\(^3\) The remaining 2 cases have additional atypical features and will be reported in detail.

### REPORT OF CASES

#### CASE 1

A white girl was the second child of nonconsanguineous parents with no family history of neuromuscular disorders. The girl was born at 37 weeks of gestation by emergency low-segment cesarean section. The mother reported the presence of reduced fetal movements in comparison with her first pregnancy. Perinatal and neonatal course were uneventful.

At the age of 5 months the infant lost the ability to roll over (recently acquired at that time). A month later, after a respiratory tract infection, she showed difficulties in lifting her arms and poor head control. These signs persisted, and at 10 months she was found to have elevated serum creatine kinase levels (between 1000 and 2000 U/L) and underwent electromyography, which showed a myopathic pattern; motor and sensory nerve velocities were normal. A muscle biopsy specimen (quadriceps) showed myopathic changes and a mild up-regulation of major histocompatibility complex class I antigens on some fibers, leading to a suspicion of an inflammatory myopathy. Treatment was started with corticosteroids (prednisolone acetate, 1 mg/kg per day) at the age of 12 months. This did not produce any clinical improvement, and corticosteroids were therefore slowly discontinued over 3 months. During this period, there was an increase in weakness and feeding difficulties, which required the introduction of nasogastric tube feeding. At the age of 15 months, the infant had severe feeding difficulties and a marked axial and limb weakness affecting the upper more than the lower limbs. There was some thinning of her biceps and triceps muscles and wasting of the calf muscles in the lower limbs with talipes. At 21 months the patient continued to be nasogastrically fed; although she had acquired better head control in sitting, her upper limb function remained very poor and had possibly deteriorated further. She also had a narrow chest and a predominantly diaphragmatic pattern of breathing.

A second open muscle biopsy specimen of the vastus intermedius at 16 months also showed myopathic changes with occasional basophilic fibers and a few fibers of varying size expressing fetal myosin, suggesting some ongoing muscle damage. Major histocompatibility complex class I antigens were still present on some fibers, and there was no apparent abnormality in immunolabeling of nuclei with antibodies to emerin or lamins A, A/C, B1, or B2. Electron microscopy showed only mild nonspecific changes with well-preserved myofibrils. An electrocardiogram and magnetic resonance images of the brain and spinal cord were all normal.

#### CASE 2

A 30-year-old white woman was the only child of healthy 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-
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 laminoapthy. 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.2

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;2,3 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.15,16 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 dysmorphism, 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 LMNA.

The other 3 patients all had typical humeroperoneal distribution of muscle weakness. In 1 of the 3 (case 3) there 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.

### CASES 3, 4, AND 5

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eral recessive mandibuloacral dysplasia phenotype. It is clear from this and other studies that there may be more of an overlap of these different features of laminopathies 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 prevalently diaphragmatic 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 previously been 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 I on the sarcolemma 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 prevalently diaphragmatic breathing pattern and patient 3 a forced vital capacity of 40% at age 6 years.

Clinical Details of Patients With Missense LMNA Mutation

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, y</th>
<th>Sex</th>
<th>Phenotype</th>
<th>Onset of symptoms, y</th>
<th>Course</th>
<th>Maximum functional ability</th>
<th>Severity</th>
<th>Feeding difficulties</th>
<th>Wasting</th>
<th>Weakness</th>
<th>Contractures</th>
<th>Spine</th>
<th>CK (times the normal value)</th>
<th>ECG</th>
<th>24-h Holter monitoring</th>
<th>Echocardiogram</th>
<th>FVC, %</th>
<th>Nocturnal ventilation, y</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 1/4</td>
<td>F</td>
<td>EDM</td>
<td>0.5</td>
<td>Slowly progressive</td>
<td>Sitting with support</td>
<td></td>
<td>+++</td>
<td>NG feeding</td>
<td>UL&gt;LL</td>
<td>Elbow, hip, talipes</td>
<td>Rigid</td>
<td>50</td>
<td>Normal</td>
<td>Not done</td>
<td>Normal (age 30 y)</td>
<td>Normal</td>
<td>Too young</td>
<td>OFC and weight less than third percentile</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>M</td>
<td>LGMD</td>
<td>7</td>
<td>Progressive</td>
<td>Walking independently</td>
<td></td>
<td>++</td>
<td>First few weeks of life</td>
<td>UL&gt;LL</td>
<td>Elbow, LFF, AT</td>
<td>Rigid</td>
<td>74 UL (NR, 0-160 U/L) at age 31 y</td>
<td>Recurrent atrial fibrillation, brady-tachy syndrome</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal (age 30 y)</td>
<td>38 (age 30 y)</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>M</td>
<td>EDM</td>
<td>1</td>
<td>Progressive</td>
<td>Walking independently</td>
<td></td>
<td>+++</td>
<td>No</td>
<td>UL&gt;LL</td>
<td>Elbow, hips, AT</td>
<td>Rigid</td>
<td>4</td>
<td>Normal</td>
<td>Arrhythmia</td>
<td>Ventricular dysfunction</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>M</td>
<td>EDM</td>
<td>4</td>
<td>Slowly progressive</td>
<td>Walking independently</td>
<td></td>
<td>++</td>
<td>No</td>
<td>UL&gt;LL</td>
<td>Elbow, hips, AT</td>
<td>Rigid</td>
<td>5</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>F</td>
<td>EDM</td>
<td>6</td>
<td>Stationary</td>
<td>Walking independently</td>
<td></td>
<td>+</td>
<td>No</td>
<td>Diffuse UL, LL</td>
<td>Elbow, hips, AT, HS</td>
<td>Rigid</td>
<td>4</td>
<td>RBBB</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AT, Achilles tendon; CK, creatine kinase; ECG, electrocardiogram; EDM, 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.

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REFERENCES


Figure 2. T1-weighted image of the thigh (transverse section) in patient 4. Note the selective involvement of the vastus lateralis and intermedius and the relative sparing of the medial and posterior muscles.