Leigh Syndrome Associated With Mitochondrial Complex I Deficiency Due to a Novel Mutation in the NDUFS1 Gene

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Background: Mutations in the nuclear-encoded subunits of complex I of the mitochondrial respiratory chain are a recognized cause of Leigh syndrome (LS). Recently, 6 mutations in the NDUFS1 gene were identified in 3 families.

Objective: To describe a Spanish family with LS, complex I deficiency in muscle, and a novel mutation in the NDUFS1 gene.

Design: Using molecular genetic approaches, we identified the underlying molecular defect in a patient with LS with a complex I defect.

Patient: The proband was a child who displayed the clinical features of LS.

Results: Muscle biochemistry results showed a complex I defect of the mitochondrial respiratory chain. Sequencing analysis of the mitochondrial DNA–encoded ND genes, the nuclear DNA–encoded NDUFV1, NDUFS1, NDUFS2, NDUFS4, NDUFS6, NDUFS7, NDUFS8, and NDUFAB1 genes, and the complex I assembly factor CIA30 gene revealed a novel homozygous L231V mutation (c.691C→G) in the NDUFS1 gene. The parents were heterozygous carriers of the L231V mutation.

Conclusions: Identifying nuclear mutations as a cause of respiratory chain disorders will enhance the possibility of prenatal diagnosis and help us understand how molecular defects can lead to complex I deficiency.

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Leigh syndrome (LS) (Online Mendelian Inheritance in Man 256000) is a devastating neurodegenerative disorder characterized neuropathologically by focal bilaterally symmetrical lesions, especially in the thalamus and brainstem regions, and clinically by psychomotor retardation, respiratory difficulties, nystagmus, ophthalmoparesis, optic atrophy, ataxia, and dystonia.1 In most patients, mitochondrial respiratory chain defects and pyruvate dehydrogenase complex deficiency are the underlying causes of the disease.2 Mitochondrial respiratory chain complex I (nicotinamide adenine dinucleotide:ubiquinone oxidoreductase) contains at least 46 subunits, 7 of which are encoded by mitochondrial DNA (mtDNA).2 Various mutations in a few subunits of complex I encoded by nuclear DNA (nDNA) (NDUFV1, NDUFV2, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS7, and NDUFS8)3-10 are associated with LS or Leigh-like disease (Online Mendelian Inheritance in Man 157655).2 Herein, we describe a Spanish patient with LS, complex I deficiency in muscle, and a novel mutation in the NDUFS1 gene.

METHODS

REPORT OF A CASE

The first child (a girl) of healthy nonconsanguineous parents (aged 30 years) of Spanish origin was born after a term pregnancy (birth weight, 3560 g). She was hospitalized at age 8½ months for recurrent episodes of vomiting, floppiness, and growth retardation. She presented with irritability, horizontal nystagmus, and dystonia.1 In most patients, mitochondrial respiratory chain defects and pyruvate dehydrogenase complex deficiency are the underlying causes of the disease.2 Mitochondrial respiratory chain complex I (nicotinamide adenine dinucleotide:ubiquinone oxidoreductase) contains at least 46 subunits, 7 of which are encoded by mitochondrial DNA (mtDNA).2 Various mutations in a few subunits of complex I encoded by nuclear DNA (nDNA) (NDUFV1, NDUFV2, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS7, and NDUFS8)3-10 are associated with LS or Leigh-like disease in patients with complex I deficiency. The NDUFS1 gene encodes the largest (75-kDa subunit) protein of complex I.11 Recently, 6 mutations in the NDUFS1 gene were identified in 3 families with LS or Leigh-like disease and complex I deficiency (Online Mendelian Inheritance in Man 157655).2 Herein, we describe a Spanish patient with LS, complex I deficiency in muscle, and a novel mutation in the NDUFS1 gene.
The activities of respiratory chain complexes in muscle showed a single defect of nicotinamide adenine dinucleotide:ubiquinone oxidoreductase (complex I), accounting for 25% of the mean of the control subjects (Table). Given the clinical picture and the biochemical findings, we searched for the underlying molecular alteration of this defect. Sequencing analysis of the genes listed in the “Methods” section showed a novel homozygous missense mutation (L231V) that replaces a leucine by a valine in the 231 amino acid residue of the protein as a result of a c.691C→G transversion in exon 8 of the NDUF51 gene (Figure). Additional nucleotide changes were not found. The parents were heterozygous carriers of the L231V mutation.

**Table. Activities of Mitochondrial Respiratory Chain Complexes in Muscle Homogenate**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Control Subjects, Mean (SD) (n = 100)</th>
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<tbody>
<tr>
<td>Nicotinamide adenine dinucleotide:</td>
<td></td>
</tr>
<tr>
<td>ubiquinone oxidoreductase</td>
<td>5.0</td>
</tr>
<tr>
<td>Succinate dehydrogenase</td>
<td>8.7</td>
</tr>
<tr>
<td>Decylubiquinol-cytochrome c oxidoreductase</td>
<td>50.7</td>
</tr>
<tr>
<td>Cytochrome c oxidase</td>
<td>22.8</td>
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| *Data are given as percentage of citrate synthase activity. Activities were measured as nanomoles per minute per milligram of protein.*

**Figure.** Polymerase chain reaction–restriction fragment length polymorphism results (A), sequencing (B), and sequence alignment of the NDUF51 protein from various species (C). A. Lane 1: control DNA. Lane 2: muscle DNA from the patient. Lane 3: blood DNA from the mother. Lane 4: blood DNA from the father. The L231V mutation was detected by digesting the NDUF51 exon 8 fragment with the restriction enzyme *SacI*. The 312→base pair (bp) wild-type DNA was digested by *SacI* into 2 fragments of 180 and 132 bp, whereas the 312-bp fragment remained uncut in the patient, who was homozygous for the mutation. B. Electrophoreograms showing the change in the patient (top) and the normal sequence in a control subject (bottom). Asterisk represents the nucleotide substitution. C. Evolutionary conservation of the 231 amino acid residue (arrow) of the NDUF51 protein.
healthy controls of similar ethnic background; and (5) although the amino acid substitution does not result in a polarity change, the mutation is highly conserved during evolution and is situated in a region of the protein subunit where 3 other mutations were found (Figure).³

Reliable prenatal diagnosis is a difficult task in many cases of mitochondrial respiratory chain disorders. The identification of mutations in nuclear genes in families with a clear-cut pattern of autosomal recessive inheritance makes it possible to predict diagnosis in the fetus.¹⁶,¹⁷

In addition to this family, we analyzed the nuclear-encoded mitochondrial genes described herein in a series of 13 pediatric patients with LS or Leigh-like disease with a complex I defect and found no additional patients with mutations in these genes. In other reports, frequencies of patients with these mutations ranged between 17% and 25%.²,⁵ Only 7.7% of our patients with LS or Leigh-like disease and an isolated complex I defect harbor mutations in these genes.

CONCLUSIONS

We describe a family with LS, complex I deficiency, and a novel mutation in the NDUFS1 gene. The rapidly progressive nature of the disease, absence of effective treatment, and commonly fatal course of the disease make prenatal diagnosis a valuable tool in families with this condition. Identifying nuclear mutations as a cause of mitochondrial respiratory chain disorders will enhance the possibility of prenatal diagnosis and help us understand how molecular defects can lead to complex I deficiency.

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REFERENCES


