**Objective:** To assess whether impaired energy metabolism in skeletal muscle is a hallmark feature of patients with dominant optic atrophy due to several different mutations in the **OPA1** gene.

**Design:** We used phosphorus 31 magnetic resonance spectroscopy to assess calf muscle oxidative metabolism in subjects with molecularly defined dominant optic atrophy carrying different mutations in the **OPA1** gene. In a subset of patients, we also evaluated serum lactate levels after exercise and muscle biopsy results for histology and mitochondrial DNA analysis.

**Setting:** University neuromuscular and neurogenetics and magnetic resonance imaging units.

**Patients:** Eighteen patients with dominant optic atrophy were enrolled from 8 unrelated families, 7 of which carried an **OPA1** mutation predicted to induce haploinsufficiency and 1 with a missense mutation in exon 27. Fifteen patients had documented optic atrophy.

**Main Outcome Measures:** Presence of skeletal muscle mitochondrial oxidative phosphorylation dysfunction as assessed by phosphorus 31 magnetic resonance spectroscopy, serum lactate levels, and histological and mitochondrial DNA analysis.

**Results:** Phosphorus 31 magnetic resonance spectroscopy showed reduced phosphorylation potential in the calf muscle at rest in patients with an **OPA1** mutation (−24% from normal mean; \(P = 0.003\)) as well as a reduced maximum rate of mitochondrial adenosine triphosphate synthesis (−36%; \(P < 0.001\); ranging from −28% to −49% in association with different mutations). In 4 of 10 patients (40%), the serum lactate level after exercise was elevated. Only 2 of 5 muscle biopsies, from the 2 patients with a missense mutation, showed slight myopathic changes. Low levels of mitochondrial DNA multiple deletions were found in all muscle biopsies.

**Conclusions:** Defective oxidative phosphorylation in skeletal muscle is a subclinical feature of patients with **OPA1**-related dominant optic atrophy, indicating a systemic expression of the **OPA1** defect, similar to that previously reported for Leber hereditary optic neuropathy due to complex I dysfunction. This defect of oxidative phosphorylation does not appear to depend on the low amounts of mitochondrial DNA multiple deletions detected in muscle biopsies.


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**Dominant Optic Atrophy (DOA),** first described by Kjer,\(^1\) is characterized by an insidious loss of central vision and color discrimination, in most cases with onset in the first decade of life, that variably progresses over the years.\(^2-3\) The pathological findings in DOA are limited to a selective degeneration of retinal ganglion cells.\(^4\) Most DOA cases are associated with mutations in the mitochondrial protein **OPA1**, a dynamin-related guanine triphosphatase located in the inner mitochondrial membrane and essential for mitochondrial fusion.\(^5-6\)

Most mutations affecting the **OPA1** gene (GenBank NC_000003.11) in patients with DOA are predicted to induce haploinsufficiency, being frameshift, stop codon, splice errors, or deletions/insertions, all leading to a variably truncated form of **OPA1**.\(^7\) Others are missense mutations, altering highly conserved amino acid positions. A subset of these missense mutations, mostly hitting the guanine triphosphatase domain, has recently been associated with a syndromic form of “DOA plus” characterized by optic atrophy, sensorineural deafness, ataxia, axonal sensorimotor polyneuropathy, chronic progressive external opthalm-
mitochondria. Besides its role in mitochondrial fusion, the OPA1 protein is involved in shaping mitochondrial cristae, and thus regulating cytochrome c availability to initiate apoptosis. In fact, suppressing OPA1 expression by RNA interference led to profound alteration of cristae morphology, loss of membrane potential, cytochrome c release, and apoptotic death of cells.

We first documented the impairment of oxidative phosphorylation (OXPHOS) in skeletal muscle from patients with DOA carrying the common c.2708delTTAG microdeletion studied by phosphorus 31 magnetic resonance spectroscopy (31P-MRS). Recently, defective adenosine triphosphate (ATP) synthesis, mainly driven by complex I substrates, was also documented in fibroblasts of patients carrying different haploinsufficiency OPA1 mutations. Loss of mitochondrial membrane potential and coupling defects have been shown in cells carrying OPA1 mutations associated with DOA or DOA-plus syndromes. However, some contradictory results have been reported by other studies failing to show defective OXPHOS in patients with DOA.

The aim of this study was to investigate the effect of a wide range of OPA1 mutations on muscle OXPHOS, expanding previous 31P-MRS examinations of patients carrying the c.2708delTTAG microdeletion. We recruited a total of 18 patients with DOA carrying different haploinsufficiency or missense OPA1 mutations, 5 of whom also had available skeletal muscle biopsy for histological and mtDNA investigations.

METHODS

SUBJECTS

Using 31P-MRS, we studied 18 patients (10 men, 8 women; mean [SD] age, 46 [16] years; age range, 20-76 years) from 8 unrelated families carrying a defined OPA1 pathogenic mutation (eFigure [http://www.archneurol.com] and Table 1) and 14 sex- and age-matched healthy volunteers (8 men, 6 women; mean [SD] age, 45 [17] years; age range, 21-75 years). This series of patients also includes the 6 previously described by Lodi et al (families 1 and 2, cases 1-6). All patients gave written consent to their inclusion in this study, which was approved by the local ethical committee.

Fifteen subjects were clinically affected with DOA as documented by a comprehensive ophthalmologic examination including best-corrected visual acuity measurement, slitlamp microscopy, intraocular pressure measurement, indirect opthalmoscopy, optic nerve head photography, and visual field testing by Humphrey Field Analyzer (Zeiss-Humphrey Systems, Dublin, California). These patients showed a variably pale optic disc with reductions of visual acuity and central vision defect, with relative sparing of peripheral vision (Table 1). Three cases were classified as subclinical given that none of them had a visual deficit, even though a slight temporal pallor was recognized at examination of fundus oculi in 2 cases. None of the 18 subjects carrying the OPA1 mutations were limited in daily activities because of their poor vision; in particular, none of them had to lead a sedentary lifestyle. Furthermore, neither patients nor healthy control subjects followed any specific physical training regimen.

Extraocular abnormalities were observed at neurological examination, including hypacusia (2 patients), brisk deep tendon reflexes (6 patients), and mild ataxia (2 patients). Adjunctive features included migraine (2 subjects), febrile seizures (2 subjects), and muscle cramps (2 subjects). The only 2 patients carrying a missense mutation, 1 previously described by Amati-Bonneau et al (proband in family 2), were brothers and had some further extraocular features including ptosis (Table 1) and white matter hyperintense lesions on T2-weighted magnetic resonance images (Table 1).

Five cases underwent muscle biopsy, and in 10 of 18 patients we also evaluated serum lactate levels after standardized muscle exercise as previously reported. Venous blood samples were collected prior to exercise (2 samples taken 5 minutes apart), immediately after completion of exercise, and 15 minutes after completion of exercise. The muscle exercise was carried out for 15 minutes on a cycloergometer standardized by the heart rate.

MUSCLE BIOPSIES

Quadriiceps or tibialis anterior muscle biopsies were performed by open surgery under local anesthesia. Muscle specimens were frozen in cooled isopentane and stored in liquid nitrogen for histological and histoenzymatic analysis including Gomori modified trichrome staining, cytochrome-c oxidase activity, succinate dehydrogenase activity, and double cytochrome-c oxidase/succinate dehydrogenase staining according to standard protocols.

GENETIC STUDIES

The OPA1 gene was amplified by polymerase chain reaction (PCR) with specific primers designed to amplify all exons and flanking intronic regions and sequenced as previously described. Total RNA was isolated from whole blood using the PAXgene Blood RNA system (Qiagen, Hilden, Germany). Single-stranded complementary DNA was synthesized with the SuperScript First-Strand Synthesis System (Invitrogen, Carlsbad, California), and overlapping fragments of the OPA1 complementary DNA were amplified by PCR prior to direct DNA sequencing as described previously. Long-range PCR on mtDNA was performed to screen for presence of mtDNA deletions as previously detailed. The PCR was performed using Takara Ex Taq DNA polymerase (Takara Shuzo Corp, Kyoto, Japan). The PCR products were separated by a 0.8% agarose gel.

SKELETAL MUSCLE 31P-MRS

Investigations by 31P-MRS were performed on the right calf muscle as described. Spectra were acquired with a repetition time of 5 seconds, at rest (128-scan spectrum), during an aerobic incremental exercise (12-scan spectra), and the following recovery (32 two-scan spectra). The
Table 1. Demographic, Ophthalmologic, Neurological, and Genetic Data From 18 Patients With OPA1-Related Dominant Optic Atrophy

<table>
<thead>
<tr>
<th>Family No./ Patient No./ Sex/Age, y</th>
<th>VA, OD/OS</th>
<th>Visual Field OU</th>
<th>Optic Disc OU</th>
<th>Neurological Examination</th>
<th>Adjunctive Features</th>
<th>LA, mg/dL</th>
<th>Muscle Biopsy</th>
<th>OPA1 Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1(II-1)/F/71</td>
<td>0.05/0.05</td>
<td>Large central scotoma</td>
<td>Diffuse optic atrophy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1/3(II-7)/F/32</td>
<td>0.05/0.05</td>
<td>Large central scotoma</td>
<td>Diffuse optic atrophy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1/2(III-1)/M/41</td>
<td>0.32/0.5</td>
<td>Small central scotoma</td>
<td>Temporal optic palsy</td>
<td>Brisk deep tendon reflexes</td>
<td>Hepatitis B and C</td>
<td>10.7</td>
<td>35.3</td>
<td>NA</td>
</tr>
<tr>
<td>1/4(IV-1)/F/21</td>
<td>0.1/0.1</td>
<td>Small central scotoma</td>
<td>Temporal optic palsy</td>
<td>Brisk deep tendon reflexes</td>
<td>NA</td>
<td>10.6</td>
<td>11.4</td>
<td>9.0</td>
</tr>
<tr>
<td>2/5(II-2)/M/61</td>
<td>0.02/0.02</td>
<td>Small central scotoma</td>
<td>Temporal optic palsy</td>
<td>Brisk deep tendon reflexes</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2/6(III-1)/M/35</td>
<td>0.05/0.05</td>
<td>Incongruous bitemporal hemianopsia</td>
<td>Temporal optic palsy</td>
<td>Brisk deep tendon reflexes</td>
<td>NA</td>
<td>10.6</td>
<td>17.8</td>
<td>14.0</td>
</tr>
<tr>
<td>3/7(II-2)/M/37</td>
<td>1.0/1.0</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>NA</td>
<td>10.6</td>
<td>17.8</td>
<td>14.0</td>
</tr>
<tr>
<td>4/8(II-5)/F/76</td>
<td>0.25/0.25</td>
<td>Small central scotoma</td>
<td>Temporal optic palsy</td>
<td>Brisk deep tendon reflexes</td>
<td>NA</td>
<td>10.6</td>
<td>17.8</td>
<td>14.0</td>
</tr>
<tr>
<td>4/9(II-5)/M/43</td>
<td>0.1/0.1</td>
<td>Large central scotoma</td>
<td>Diffuse optic atrophy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>4/10(III-0)/M/39</td>
<td>0.05/0.05</td>
<td>Large central scotoma</td>
<td>Diffuse optic atrophy</td>
<td>Convergent strabismus OS</td>
<td>Cerbellar atrophy and vermian hypoplasia on MRI</td>
<td>6.6</td>
<td>13.5</td>
<td>7.0</td>
</tr>
<tr>
<td>5/11(II-1)/M/84</td>
<td>0.02/0.05</td>
<td>Large central scotoma</td>
<td>Diffuse optic atrophy</td>
<td>Right deafness, brisk deep tendon reflexes, Romberg sign, mild ataxic gait</td>
<td>Autoimmune hypothyroidism, polygenic ovary syndrome, febrile seizure</td>
<td>11.7</td>
<td>15.7</td>
<td>14.0</td>
</tr>
<tr>
<td>5/12(III-1)/F/34</td>
<td>0.4/0.4</td>
<td>Large central scotoma</td>
<td>Diffuse optic atrophy</td>
<td>Right deafness, brisk deep tendon reflexes, Romberg sign, mild ataxic gait</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>6/3(II-2)/F/40</td>
<td>0.63/0.32</td>
<td>Small central scotoma</td>
<td>Temporal optic palsy</td>
<td>Upper-limb postural tremor</td>
<td>Muscle cramps</td>
<td>15.7</td>
<td>23.0</td>
<td>20.0</td>
</tr>
<tr>
<td>6/4(II-1)/M/20</td>
<td>0.16/0.16</td>
<td>Small central scotoma</td>
<td>Temporal optic palsy</td>
<td>Brisk deep tendon reflexes</td>
<td>Muscle cramps, febrile seizure</td>
<td>9.8</td>
<td>17.8</td>
<td>14.0</td>
</tr>
<tr>
<td>7/15(II-1)/M/43</td>
<td>1.0/1.0</td>
<td>Normal</td>
<td>Mild temporal palsy</td>
<td>Normal</td>
<td>NA</td>
<td>10.4</td>
<td>29.8</td>
<td>17.0</td>
</tr>
<tr>
<td>7/16(II-5)/F/35</td>
<td>1.0/1.0</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>NA</td>
<td>10.4</td>
<td>29.8</td>
<td>17.0</td>
</tr>
<tr>
<td>8/17(II-1)/M/54</td>
<td>0.1/0.05</td>
<td>Small central scotoma</td>
<td>Diffuse optic disc palsy, myopic crescent</td>
<td>Right eyelid ptosis, upper upper limbs and brisk lower-limb deep tendon reflexes</td>
<td>White matter cerebral hyperintensities on T2-weighted MRI</td>
<td>7.6</td>
<td>11.9</td>
<td>8.0</td>
</tr>
<tr>
<td>8/18(II-3)/M/61</td>
<td>0.2/0.63</td>
<td>Small central scotoma</td>
<td>Temporal optic palsy</td>
<td>Weak deep tendon reflexes</td>
<td>White matter cerebral hyperintensities on T2-weighted MRI</td>
<td>9.6</td>
<td>37.8</td>
<td>21.0</td>
</tr>
</tbody>
</table>

Abbreviations: AE, immediately after effort; AR, after 15 minutes of recovery; LA, lactate; MRI, magnetic resonance imaging; NA, not available; VA, visual acuity. SI conversion factor: To convert LA to millimoles per liter, multiply by 0.111.

Muscle was exercised by plantar flexion at 0.66 Hz against a pedal using a pneumatic ergometer. The force resistance of the pedal was 10% of lean body mass. After the acquisition of 2 spectra, corresponding to the first 2 minutes of exercise, the resistance was increased by 3% of lean body mass for each subsequent 1-minute spectral acquisition. As soon as the last 12-scan exercise spectrum was collected, the exercise was stopped and data were collected for 5 minutes 20 seconds.
All patients included in this study carried a pathogenic mutation in the OPA1 gene. In 16 patients from 7 unrelated families, the OPA1 mutation was predicted to lead to haploinsufficiency, whereas a further family (family 8, cases 17 and 18) carried a missense mutation. The c.2708-2711delTTAG common microdeletion was present in 6 subjects (families 1 and 2), the c.1516+1G>C splicing error was present in 1 subject (family 3), the c.948+3A>T splicing error was present in 3 subjects (family 4), the c.2819-2A>C splicing error was present in 2 subjects (family 5), the c.1346_1347insC frameshift mutation was present in 2 subjects (family 6), and the c.2815delC frameshift mutation was present in 2 subjects (family 7). The last 2 subjects from family 8 carried the missense mutation c.2792T>A (Val910Asp). All pedigrees are shown in the eFigure.

The clinical and laboratory findings of the subjects included in this study are summarized in Table 1. Serum lactate levels after standardized muscle exercise were abnormally elevated in 4 of the 10 available subjects. Muscle biopsies of 5 patients did not show clear-cut hallmarks of mitochondrial myopathy, such as cytochrome-c oxidase-negative or ragged red fibers, and were considered within the limits of normal muscle morphology. However, both patients from family 8, carrying the missense mutation, had nonspecific signs of myopathy (Table 1 and Figure 1).

Molecular evaluation of mtDNA by long-range PCR showed a low abundance of mtDNA deletions in 4 of 5 muscle biopsies, compatible with their age-related accumulation (age range, 35-58). However, using specific PCR primers for the common deletion as well as for the 7.7- and 8.1-kilobase deletions, we were able to detect variable amounts of these deletions (data not shown) in all biopsies, including the younger subject (aged 35 years) who failed to show multiple mtDNA deletions with long-range PCR.

**Figure 2.** Phosphorus 31 magnetic resonance spectroscopy skeletal muscle results, showing phosphorylation potential at rest (PP) (A) and maximum rate of mitochondrial adenosine triphosphate production (V_max) (B) in healthy control subjects and patients with OPA1-related dominant optic atrophy (DOA). Data are presented as box plots. Each box extends from the lower to the upper quartile of the data and is divided by a line indicating the median. The limits of the whiskers are the minimum and maximum values.
Study by $^{31}$P-MRS showed reduced phosphorylation potential in the calf muscle of the patients with OPA1 mutations who were at rest, indicating reduced energy reserve (Table 1). However, only 4 patients with OPA1 mutations showed resting phosphorylation potential below the normal range (Figure 2 and Figure 3). Compared with healthy control subjects, patients with OPA1 mutations reached the same degree of phosphocreatine consumption and pH at the end of the exercise but with shorter exercise duration (Table 2), indicating reduced oxidative capacity. All postexercise measures of mitochondrial ATP synthesis rate (time constant of postexercise phosphocreatine resynthesis reported as a function of the minimum cytosolic pH reached during recovery normalized to pH 7.00, $V$, and $V_{\text{max}}$) were abnormal in the patients with OPA1 mutations (Table 2 and Figure 2). In particular, skeletal muscle $V_{\text{max}}$ was reduced by 36% in the group of patients with OPA1 mutations compared with healthy control subjects, with only 2 patients having values within the normal range (Figure 2 and Figure 3).

Variable reductions in resting phosphorylation potential (Figure 3) and $V_{\text{max}}$ (Figure 3) were present in skeletal muscle in association with each pathogenic OPA1 mutation. The reduction from the normal mean of the phosphorylation potential at rest ranged from 4% in the two c. $2729\text{T}>\text{A}$ (Val910Asp) carriers to 45% in the c.1516 +1G>C carrier. More importantly, the reduction of $V_{\text{max}}$ for mitochondrial ATP production ranged from 28% in patients carrying the c.1346_1347insC mutation to 49% in c.948 +3A>T carriers. The only 2 patients carrying the c.2729T>A (Val910Asp) missense mutation showed a reduction in skeletal muscle $V_{\text{max}}$ that was no more severe than that found in association with the other OPA1 mutations leading to haploinsufficiency (Figure 3).

### COMMENT

In this study, we showed that different OPA1 mutations are associated with a clear deficit of skeletal muscle OXPHOS as assessed in vivo using $^{31}$P-MRS. This finding extends our initial observation of patients with DOA carrying the c.2708-2711delTAG 4-base deletion in exon 27, $^{1,4}$ included also in this study, demonstrating that mutations in the OPA1 gene result in a reduced rate of mitochondrial ATP synthesis in skeletal muscle. Although none of the 5 patients who underwent muscle biopsy displayed the hallmarks of mitochondrial myopathy, 4 of 10 patients tested for serum lactate levels after exercise showed abnormally high lactate levels. Despite the fact that the methods used for muscle mtDNA analysis were not quantitative, the multiple deletions detected did not seem sufficient to justify the OXPHOS deficiency demonstrated by $^{31}$P-MRS. Furthermore, quantitative evaluation of mtDNA copy number in these muscle biopsies did not reveal significant variations compared with control subjects (Luisa Iommarini, PhD, unpublished data, December 2009). Investigation by $^{31}$P-MRS revealed defective oxidative metabolism not only during and after

![Figure 3](image-url)
effort but also at rest. Reduced phosphorylation potential at rest is a common finding not only in patients with mitochondrial myopathies but also in those with OXPHOS deficits without myopathy, for example, patients with Leber hereditary optic neuropathy (LHON) who have mutations affecting complex I subunits where histopathological evidence of mitochondrial myopathy is generally absent or mild. The relationship between resting and exercise deficit of muscle oxidative metabolism is unclear. However, it should be pointed out that, despite the significant reduction in phosphorylation potential at rest in patients with OPA1 mutations and DOA as a group, 14 of 18 patients (78%) showed phosphorylation potential values within the normal range (Figure 2 and Figure 3) while postexercise $V_{max}$ was below the normal range in all but 2 patients (Figure 2 and Figure 3).

The relatively small number of patients studied for each OPA1 mutation did not allow for a tight correlation of genotype with OXPHOS impairment. However, $^{31}$P-MRS showed that $V_{max}$ for mitochondrial ATP production was clearly reduced in association with each of the OPA1 mutations investigated and that both missense and haploinsufficiency mutations were associated with impaired muscle OXPHOS. It is debated whether all mutations in the OPA1 gene may impair OXPHOS or whether only certain mutations are able to affect it and ultimately whether the OXPHOS defect is relevant to the pathogenesis of optic neuropathy.

In this study, we also tested the hypothesis that the OPA1 mutations inducing haploinsufficiency may induce abnormal accumulation of mtDNA deletions similar to some missense mutations, which were previously associated with a DOA-plus phenotype. Our results do not support the hypothesis in this series of patients. The traces of mtDNA deletions found in our patients are possibly compatible with the aging process.

There may be several pathogenic mechanisms of OXPHOS deficit secondary to OPA1 mutations in the absence of pathogenic amounts of mtDNA multiple deletions. The main function of OPA1 is to regulate mitochondrial fusion. Defective fusion, as variably seen with OPA1 mutations, leads to a loss of tubular-reticular organization of the mitochondrial network in cells, an abnormal shape of mitochondrial cristae, and a net increase of fragmented mitochondria. In 9 of the 18 patients described here, carrying OPA1 mutations inducing haploinsufficiency (5 patients with c.2708-2711delTTAG, 1 patient with c.1516+1G>C, 2 patients with c.2819-2A>C, and 1 patient with c.1346_1347insC), Zanna et al documented defective ATP synthesis driven by complex I substrates in fibroblasts.

The remodeling of the cristae morphology due to defective fusion is a possible mechanism, which could account for the OXPHOS defect. In particular, the supercomplex organization of the respiratory chain may be affected, leading to decreased ATP synthesis even though the single complexes can still carry out their specific activities in the presence of appropriate substrates. The complex I-driven defect of ATP synthesis is possibly more directly related to the early involvement of the optic nerve, which cannot be associated with mtDNA instability as recently highlighted by studies of a DOA animal model with mutant OPA1 where the search for mtDNA deletions in the retinal ganglion cells was negative. It remains the formal, still untested possibility that other mtDNA defects (point mutations) may accumulate besides multiple deletions, and an appropriate investigation to resolve this point is needed.

The 2 brothers from family 8, 1 of whom was included in our previous study on patients with DOA plus (proband in family 2 from the study by Amati-Bonneau et al), stood out from the group in various respects. They were the only patients showing some nonspecific signs of myopathy at muscle biopsy, and both showed white matter abnormalities on brain magnetic resonance imaging. This family was found to carry a missense mutation (Val910Asp) that did not affect the guanine triphosphatase domain as in all of the other patients with DOA-plus phenotype described by Amati-Bonneau et al. Thus, this family was probably improperly aggregated to the other DOA-plus cases but showed rather a more severe phenotype than canonical nonsyndromic DOA, likely belonging to the wider range of intermediate phenotypes that has been recently described in the largest series of patients with DOA plus so far. It must be noted that in the case series of patients described here who visited us with only visual loss, adjunctive extraocular features were observed at neurological examination or by cerebral magnetic resonance imaging as in the case of patient 10 from family 4. Thus, this study confirms a wide variability in clinical expression of OPA1 mutations, including those leading to haploinsufficiency, possibly qualifying many patients as having DOA plus.

The current results have striking similarities with our previous findings in patients with LHON, for whom the OXPHOS defect is due to mtDNA mutations affecting complex I. In fact, $^{31}$P-MRS investigation of skeletal muscle from subjects carrying one of the common LHON pathogenic mutations at positions 11778/ND4, 3460/ND1, or 14484/ND6 showed, as in the patients with OPA1-related DOA, a reduced phosphorylation potential at rest and a reduced rate of skeletal muscle mitochondrial ATP production after effort. The few reports of muscle biopsy in patients with LHON have shown mild subsarcolemmal mitochondrial proliferation, as documented by the succinate dehydrogenase stain and at electron microscopy, sometimes with aberrant mitochondria carrying paracrystalline inclusions. The similarities between LHON and DOA converge to a final pathway of biochemical dysfunction involving complex I, as we and others have recently documented, and the common selective involvement of retinal ganglion cells.

In conclusion, our current results demonstrate that various different OPA1 mutations, either missense or leading to haploinsufficiency, share an OXPHOS impairment in skeletal muscle as shown by $^{31}$P-MRS and serum lactate levels. Furthermore, this may result in a more widespread clinical expression, qualifying some of these patients as having DOA plus as recently emphasized. As in patients with LHON, unknown compensatory mechanisms, absent or insufficient in retinal ganglion cells, may prevent the clinical involvement of skeletal muscle or other extraocular features in most patients with OPA1-related DOA.
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Author Affiliations: MR Spectroscopy Unit, Department of Internal Medicine, Aging, and Nephrology (Drs Lodi, Tonon, Manners, Testa, Malucelli, and Barbiroli) and Department of Neurological Sciences (Drs Valentino, La Morgia, Barboni, Carbonelli, Baruzzi, Liguori, and Carelli), University of Bologna, and Studio Oculistico d’Azzeglio (Dr Carbonelli), Bologna, and Unit of Molecular Neurogenetics, Pierfranco and Luisa Mariani Center for the Study of Children’s Mitochondrial Disorders, National Neurological Institute, Milan (Dr Zeviani), Italy; and Molekulargenetisches Labor, Universität-Augenklinik, Tubingen, Germany (Ms Schimpf and Dr Wissinger).

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Correspondence: Raffaele Lodi, MD, MR Spectroscopy Unit, Department of Internal Medicine, Aging, and Nephrology, University of Bologna, Via Massarenti 9, 40138 Bologna, Italy (raffaele.lodi@unibo.it).

Author Contributions: Study concept and design: Lodi, Valentino, Zeviani, Baruzzi, Barbiroli, and Carelli. Acquisition of data: Barboni, Carbonelli, Liguori, and Carelli. Analysis and interpretation of data: Tonon, Manners, Testa, Malucelli, La Morgia, Schimpf, Wissinger, and Carelli. Drafting of the manuscript: Lodi, Malucelli, La Morgia, Barbiroli, and Carelli. Critical revision of the manuscript for important intellectual content: Tonon, Valentino, Manners, Testa, La Morgia, Carbonelli, Schimpf, Wissinger, Zeviani, Baruzzi, Liguori, Barbiroli, and Carelli. Statistical analysis: Manners, Malucelli, and Baruzzi. Obtained funding: Carelli. Administrative, technical, and material support: Testa and Schimpf. Study supervision: Lodi, Tonon, Valentino, Carbonelli, Wissinger, Zeviani, Liguori, Barbiroli, and Carelli.

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Online-Only Material: The eFigure is available at http://www.archneurol.com.

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