Neurological, Cardiological, and Oculomotor Progression in 104 Patients With Friedreich Ataxia During Long-term Follow-up

Pascale Ribai, MD; Françoise Pousset, MD; Marie-Laure Tanguy, MD; Sophie Rivaud-Pechoux, PhD; Isabelle Le Ber, MD; Francesca Gasparini, MD; Perrine Charles, MD, PhD; Anne-Sophie Béraud, MD; Michele Schmitt, PhD; Michel Koenig, PhD; Alain Mallet, MD; Alexis Brice, MD; Alexandra Dürr, MD, PhD

**Background:** Friedreich ataxia (FA) is the most frequent autosomal recessive cerebellar ataxia. Although the phenotype is well known, disease progression has not been evaluated in a prospective manner.

**Objective:** To perform a long-term prospective follow-up of neurological, cardiological, and oculomotor function in patients with FA (FA patients).

**Design:** In this open-labeled prospective survey, we examined 104 FA patients every 6 months during a median period of 5 years (range, 6 months to 7 years), with a systematic standardized protocol. Data are reported as mean±SD.

**Setting:** Neurological examinations were performed at the Federation of Neurology and the Department of Genetics of the Salpêtrière Hospital, Paris, France. Cardiological follow-up was performed at the Department of Cardiology; oculomotor examinations were performed at the Institut National de la Santé et de la Recherche Médicale Unit 679, at the same hospital.

**Patients:** We studied 104 FA patients with a confirmed molecular diagnosis. None were receiving antioxidant therapy at baseline; 88 accepted treatment with the coenzyme Q10 analogue idebenone (5 mg/kg per day). Sixteen preferred not to be treated.

**Interventions:** Neurological status was evaluated with the International Cooperative Ataxia Rating Scale (ICARS) and a quantitative writing test. Cardiological evaluations included echocardiography, electrocardiography, and Holter monitoring. Oculomotor function was evaluated by electro-oculography to determine the frequency of square wave jerks.

**Results:** The total ICARS score worsened during follow-up, whether or not the patients were treated with idebenone (1.93±0.25 and 4.43±1.56 points per year, respectively). The total ICARS score increased faster in patients with onset before age 15 years compared with the others (2.6±0.4 [n=51] vs 1.1±0.3 [n=37]; P=.05). The posture subscore increased faster in patients able to stand at baseline, who also had shorter disease durations than patients unable to stand (1.25±0.12 vs 0.47±0.22 point per year; P<.001). Neurological progression was underestimated, however, by the ICARS scores, which reached a plateau in patients with long disease durations. Oculomotor function slightly deteriorated (0.09±0.02 Hz per year; P<.001). Left ventricular mass index decreased (−4.1±1.5 g/m² per year; P=.008), as did ejection fraction (−1.32%±0.29% per year; P<.001).

**Conclusions:** The neurological condition of FA patients deteriorated slowly over time, even with idebenone treatment. Although cardiac hypertrophy decreased under treatment, cardiac function did not improve. The ICARS scale is not appropriate to evaluate the progression of FA in patients with long disease durations. Additional quantitative measures may improve the reliability of this scale.

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Friedreich ataxia (FA) is the most frequently inherited ataxia in white patients, with a prevalence of approximately 1:50 000.1,2 Typical FA is an autosomal recessive disease, characterized by onset before 25 years of age; the presence of progressive limb and gait ataxia, dysarthria, and absent reflexes in the lower limbs owing to sensory axonal neuropathy; a Babinski sign; and altered vibration sense.3 These criteria are very specific because molecular diagnosis confirms the disease in 93% to 96% of such patients.4,5 However, they are not sensitive enough; up to 25% of patients who carry an FA mutation do not fulfill all of the criteria.6 Nonneurological signs are present in FA, including cardiac involvement; left ventricular hypertrophy is observed in two thirds of the patients.6,7 Cardiac involvement is not usually symptomatic, however. Ocular abnormalities such as nystagmus, optic atrophy, or fixation instability are observed in 25% of patients.8 Hypoacusis develops in 20% of patients during the disease course.8

In 1996, the gene responsible for FA was identified on chromosome 9q13.9 Homozygous GAA expansions are found in
sulfur–dependent enzymes, such as complexes I to III of the iron-sequestering protein ferritin. Up-regulation of enzymes involved in the defense against oxidative stress, such as superoxide dismutase, is also impaired. The frataxin deficiency also results in intramitochondrial iron accumulation, which has been observed in the heart, liver, dentate nucleus, and fibroblasts from patients. In a cardiac mouse model completely lacking frataxin, intramitochondrial iron accumulation occurred after inactivation of the iron-sulfur–dependent enzymes and the development of cardiac pathology. This suggests that iron accumulation is a biomarker of disease progression rather than the cause of the heart pathology. In fibroblasts from patients with FA (hereafter referred to as FA patients), the decrease in iron-sulfur complexes limits their interaction with the iron regulatory protein (IRP1), decreasing the expression of the iron-sequestering protein ferritin. Up-regulation of enzymes involved in the defense against oxidative stress, such as superoxide dismutase, is also impaired.

Given the potential role of oxidative stress in the pathogenesis of the disease, several therapeutic trials have been performed with antioxidants. Most authors used idebenone, a coenzyme Q$_{10}$ short-chain analogue that crosses cellular membranes and acts as a free radical scavenger. Although idebenone has been shown to increase complexes I through IV and aconitase activity and to decrease excretion of 8-hydroxy-2'-deoxyguanosine, neurological symptoms did not improve in patients, but a 10% to 40% reduction of cardiac hypertrophy was observed. These trials involved small numbers of patients (n = 3 to n = 38) and short-term follow-up, not exceeding 1 year.

We report the results of a long-term prospective follow-up of a large cohort of FA patients in whom neurological, cardiological, and oculomotor signs were regularly and systematically evaluated for as long as 7 years.

**METHODS**

We followed up 113 FA patients prospectively from 1998 to 2005 at the referral centers of the Federation of Neurology and the Department of Genetics, Cytogenetics, and Embryology of the Salpêtrière Hospital, Paris, France, for neurogenetic diseases. All of the patients had at least 1 GAA expansion; 3 had point mutations on the other allele. Each patient was examined every 6 months. None of the patients had received antioxidant treatment when first examined. Patients who accepted treatment with idebenone (n = 88) received a dose of 5 mg/kg per day. Sixteen patients preferred not to be treated. Nine patients were lost to follow-up.

**NEUROLOGICAL EVALUATION**

During the first visit, a full neurological examination assessed gait spasticity, tendon reflexes, muscle weakness and wasting, scoliosis, hypoacusis, sphincter disturbances, swallowing difficulties, and visual complaints. We used the International Cooperative Ataxia Rating Scale (ICARS) and a quantitative writing test to evaluate cerebellar ataxia. The ICARS includes the following 4 subscores: posture (maximum score, 34), kinetic functions (maximum score, 52), speech (maximum score, 8), and oculomotor dysfunction (maximum score, 6), for a possible total of 100 points. The scores increase with severity. The interrater reliability of this scale has been shown to be acceptable. The quantitative test evaluated the time needed (in seconds) to write the sentence “Maitre corbeau sur un arbre perché.” On each consecutive visit, the patients underwent reevaluation with the ICARS and the quantitative test and were asked for a subjective estimation of worsening or improvement.

**CARDIOLOGICAL EVALUATION**

At baseline, 70 patients had cardiological evaluations, including a clinical examination, standard 12-lead electrocardiography (ECG), echocardiography, and a Holter ECG recording. Echocardiographic variables were recorded with an ultrasound device (Acuson-Sequoia 256; Siemens Technologies, Mountain View, Calif). Patients underwent an M-mode, 2-dimensional Doppler echocardiographic examination, performed according to the standards of the American Society of Echocardiography. Atrial fibrillation (AF) was defined as an atrial rate exceeding 1 year. Diagnostic criteria for the apical 4-chamber view.

**OCULOMOTOR EVALUATION**

Eye movements were recorded by electro-oculography in 37 patients at least once before and several times after study inclusion. Patients were asked to look at a central point for 30 seconds. Fixation instability was evaluated by the frequency of square wave jerks (SWJ), which are ocular saccades with amplitudes of 2° to 15° and mean durations of 100 to 300 milliseconds.

**BIOLOGICAL MEASUREMENTS**

At baseline and once a year thereafter, each patient had a blood test to evaluate concentrations of dietary glucose, liver enzymes (aspartate aminotransferase and alanine aminotransferase), glycosylated hemoglobin, iron, and ferritin.
The overall clinical picture of the 104 patients was that of typical FA at first examination (Table 1). However, 10 (10%) of the 104 patients had retained tendon reflexes, and plantar responses were flexor in 10 (10%) of 96. Because of the long disease duration (mean, 16±8 years), hypoacusis was present in 11 (22%) of 51 patients, decreased visual acuity in 13 (27%) of 48, and swallowing difficulties in 34 (64%) of 53. Echocardiograms showed abnormal findings in 69% (48/70) and lower limb contracture was present in 11 (11%) of 104 patients. Contractile function was normal, with a mean frequency of 0.6±0.5 (range, 0-2.4) Hz. Neurological and oculomotor variables of patients who subsequently underwent idebenone treatment did not differ from those of untreated patients.

### Neurological and Oculomotor Evaluations

Atypical chest pain or exercise dyspnea was present in 17 (26%) of 66 patients. Only 2 (3%) had palpitations. Four had previous atrial fibrillation but had sinusoidal rhythms when first examined. Premature supraventricular beats were observed in 13 (21%) of 62 of the patients by Holter monitoring. Cardiac hypertrophy was detected in 59 (88%) of 67 patients by ECG and in 48 (69%) of 70 by echocardiography. According to the monograms of Henry et al., 44 (63%) of 70 of the patients had hypertrophic septal wall thickness and 39 (56%) of 70 had hypertrophic posterior wall thickness. Left ventricular outflow obstruction was not observed in our patients. Contractile function was normal, with a mean ejection fraction of 71%±9%.

### Cardiological Evaluation

There was a significant correlation between the smallest GAA expansion length and age at disease onset (r=0.77; P<.001). There was a significant correlation between the severity of neurological involvement (total ICARS score) and the severity of cardiac hypertrophy (left ventricular mass index) (r=0.48; P=.01).

### DISEASE PROGRESSION DURING FOLLOW-UP

#### Neurological Progression

The neurological condition of all patients worsened during follow-up. The total ICARS score increased from 53±23 at baseline to 59±21 at the end of the study. All ICARS subscores also increased, except the oculomotor subscore. The total ICARS score increased at a signifi-
cantly greater rate in patients with disease onset before age 15 years compared with the others (2.6±0.4 [n=51] vs 1.1±0.3 [n=37]; P = .05). There was no correlation between the increase in the total ICARS score and the length of the small GAA expansion or retained tendon reflexes. However, there was a significant relationship between the length of the GAA expansion and the time from disease onset to wheelchair use. During follow-up, 18 additional treated and untreated patients became wheelchair-bound (79 of 104 vs 61 of 104). Multivariate analysis showed that patients with GAA expansions of more than 2 kb needed a wheelchair significantly earlier than did the others, with a relative risk of 2.86 (95% confidence interval, 1.76-4.63). The time to write the sentence increased in all patients, from 38±16 seconds at baseline to 48±20 seconds at the end of the study (Table 2).

For the 16 untreated patients, the mean total ICARS score worsened by 4.43±1.56 points per year (P<.001), as did all ICARS subscores. These findings reflect the natural history of FA for a mean disease duration of 11±8 years. For the 88 treated patients, the mean total ICARS score increased by 1.93±0.25 points per year (P<.001). Most treated patients were wheelchair bound at baseline (53/88). However, 64 of 88 were still able to stand up with or without help (ICARS standing capacities subscore, >5).

Disease progression, measured by changes in the posture subscore (ranging from 0-34), was faster in patients able to stand at baseline compared with patients unable to stand (1.25±0.1 vs 0.47±0.22 points per year; P<.001). There

### Table 2. Neurological, Oculomotor, and Cardiological Data at Baseline and at the End of the Study

<table>
<thead>
<tr>
<th>Measure (Total Points Possible)</th>
<th>At Baseline</th>
<th>At the End of the Study</th>
<th>Evolutions Per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients</td>
<td>Future Treated Patients</td>
<td>Future Untreated Patients</td>
</tr>
<tr>
<td>Neurological Data</td>
<td></td>
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<tr>
<td>ICARS score</td>
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<td></td>
<td></td>
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<tr>
<td>No. of patients</td>
<td>104</td>
<td>88</td>
<td>16</td>
</tr>
<tr>
<td>Total (100)</td>
<td>53±23</td>
<td>53±22</td>
<td>53±25</td>
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<td>Posture and gait disturbance (34)</td>
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<td>24±9</td>
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<td>Kinetic functions (52)</td>
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<td>23±12</td>
<td>24±15</td>
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<tr>
<td>Dysarthria (8)</td>
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<td>3±2</td>
<td>3±2</td>
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<tr>
<td>Oculomotor disorders (6)</td>
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<td>2±2</td>
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<tr>
<td>Writing</td>
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<td></td>
<td></td>
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<tr>
<td>No. of patients</td>
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<td>3</td>
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<tr>
<td>Time, s</td>
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<td>38±15</td>
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<tr>
<td>Oculomotor Data</td>
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<tr>
<td>No. of patients</td>
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<td>3</td>
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<tr>
<td>SWJ frequency, Hz</td>
<td>0.6±0.5</td>
<td>0.5±0.4</td>
<td>Individual values, 1.2, 0.4, and 0.8</td>
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<tr>
<td>Cardiological Data</td>
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<td></td>
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</tr>
<tr>
<td>No. of patients</td>
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<td>61</td>
<td>9</td>
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<td>LVMI, g/m²</td>
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<td>SWT, mm</td>
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<td>LVDD, mm</td>
<td>42±5</td>
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<tr>
<td>FS, %</td>
<td>0.42±0.06</td>
<td>0.41±0.07</td>
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</tr>
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</table>

Abbreviations: EF, ejection fraction; FS, fractional shortening; ICARS, International Cooperative Ataxia Rating Scale; LVDD, left ventricular diastolic diameter; LVMI, left ventricular mass index; NED, not enough data; PWT, posterior wall thickness; SWJ, square wave jerks; SWT, septal wall thickness.

×Unless otherwise indicated, data are expressed as mean ± SD. All analyses were adjusted for age at onset, GAA expansion length, and disease duration. For some measures, means and SDs were not calculated for untreated patients.

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was no significant difference between the groups in terms of the evolution of the total ICARS score, kinetic functions, or dysarthria. Patients able to stand had shorter disease durations at baseline compared with patients unable to stand (13.2±6.3 vs 23.8±6.8 years; *P*<.001). These results suggest that neurological deterioration assessed by the ICARS score was faster in patients with shorter disease durations. They also show that the ICARS scores reach ceiling values after long disease durations, preventing accurate evaluation of disease progression (Figure).

The time to write the requested sentence increased in treated patients by 1.8±0.5 seconds per year (*P*<.001), without ceiling effect.

Oculomotor Progression

All patients undergoing testing had SWJ at the end of the study, compared with 35 of 37 at the beginning. The frequency of SWJ increased from 0.6±0.5 Hz at baseline to 0.9±0.6 Hz at the end of the study. This was associated with functional impairment in 2 of 34 patients, who reached a threshold of 2 Hz with amplitudes of 7°. The increase of SWJ was significant in treated patients (0.09±0.02 Hz per year; *P*=.001), but we did not have enough data in untreated patients to compare their evolutions.

Cardiological Progression

Left ventricular mass index decreased in all patients (from 138±45 to 123±39 g/m²), as did posterior wall thickness (from 11±3 to 10±2 mm), but not septal wall thickness (from 12±3 to 12±3 mm). The decrease of the posterior wall thickness was greater in patients with GAA expansion length greater than 2 kb, compared with the others (−0.48 vs −0.04; *P*=.009). Ejection fraction decreased from 71%±9% to 67%±8% and fractional shortening from 0.42%±0.06% to 0.39%±0.08%. Among the 70 patients who underwent cardiological evaluation at baseline, 61 received treatment. For those patients, left ventricular mass index decreased by 4.1±1.5 g/m² per year (*P*=.008) and posterior wall thickness by 0.40±0.08 mm per year (*P*<.001). Ejection fraction slightly but significantly decreased by 1.32%±0.29% per year (*P*<.001). Changes of fractional shortening were not significant (*P*=.21). We did not have enough data in untreated patients to determine whether changes were significant or to compare cardiological evolution of treated and untreated patients.

BIOLOGICAL ANALYSES AND SUBJECTIVE EVOLUTION

Weight gain was noted in 18 (19%) of 95 patients receiving treatment and increased liver enzyme levels were detected in 7 (7%). During follow-up, a subjectively estimated improvement in dysarthria was mentioned by 29 (31%) of the 95 patients, fatigue by 16 (17%), writing by 13 (14%), and gait by 11 (12%). In contrast, 21 (22%) of the patients reported worsening of gait and 10 (11%) reported worsening of swallowing difficulties.

To our knowledge, this is the first long-term follow-up (≤7 years) of a large group of patients with FA (n=104). In other studies, smaller numbers of patients (n=3 to n=38) were followed up for a maximum of 1 year.16-23 Our study showed that the neurological and oculomotor condition of FA patients deteriorated over time. Except for the oculomotor subscore, all variables measured by the ICARS worsened, as did writing ability.
Progression was mild in treated patients, because the total ICARS score increased by only 2 points per year. However, the neurological progression of treated patients, who also had longer disease durations, was underestimated by the ICARS. First, the total ICARS score reached a plateau after long disease durations (Figure); second, untreated patients and patients still able to stand, who also had shorter disease durations at baseline, progressed more rapidly; and third, 13 of the 88 treated patients already had maximum subscore values at baseline. Their ICARS values were therefore unable to progress during follow-up, although their clinical status continued to decline. The total ICARS score increased more rapidly in patients with onset before 15 years of age, suggesting a more rapid disease progression in younger patients. Although patients with larger GAA expansion started the disease earlier, as reported previously,1,4,6,9,11,12 they did not progress faster during follow-up. This was shown by the absence of correlation between GAA expansion length and the increase of the total ICARS score.

Ocular recordings showed a slight increase in the frequency of SWJ, which was not quantifiable by bedside examination. Although their pathophysiological basis is still unknown, SWJ with amplitudes greater than 3° are rarely observed in healthy individuals33 but are usually present in patients with supranuclear palsy.34 Patients who reached a frequency of 2 Hz with a mean amplitude of 7° had difficulty reading, watching television, using a computer screen, or performing other activities that needed good ocular fixation. In accordance with other authors,35 we found that the ICARS oculomotor subscore was not sensitive enough to evaluate the progression of FA. Furthermore, unlike fixation instability, nystagmus is rarely present in FA patients.

Most of our patients were receiving idebenone treatment, and our findings are in accordance with those previously reported, which showed a worsening of cerebellar impairment with idebenone treatment.19,21 In those short-term follow-up studies (6 weeks to 1 year), patients were younger (aged 4-54 years) and had a shorter disease duration (11-19 years) at baseline compared with our patients. Our results were also confirmed by the single reported placebo-controlled study25 of 14 younger treated patients (aged 23-30 years) with shorter disease duration (11-19 years), followed up for 1 year. Two open-label studies, however, found that the total ICARS score improved with idebenone treatment. In 1 of those studies,36 9 young patients (aged 11-19 years) were treated with idebenone, 5 mg/kg per day, for 1 year. In the other study,37 77 adult patients were treated with a combination of high doses of coenzyme Q10 and vitamin E for a maximum of 4 years. Because only 1 placebo-controlled study is reported thus far, additional long-term controlled studies are needed to further assess the disease progression of FA patients receiving idebenone treatment.

Finally, our study confirms that cardiac hypertrophy assessed by ECG (88%) or echocardiography (69%) is common in FA patients, although a few (26%) have clinical symptoms. Like others,19,21-23 we observed that idebenone treatment caused a small decrease in cardiac hypertrophy. The clinical relevance of this finding remains to be determined because we also noted a small but significant decrease in the ejection fraction under treatment, suggesting that cardiac function deteriorated slightly. However, the shortening fraction was not significantly affected. One prospective open trial reported 11% to 26% reduction of the shortening fraction in 6 of 38 patients treated with idebenone for 6 months.23 Because the ejection and shortening fractions both reflect contractile function, we make a conclusion about the evolution of contractile function in FA patients receiving idebenone treatment. Patients with severe neurological conditions at baseline also had severe cardiac hypertrophy, as shown by the significant correlation between total ICARS score and left ventricular mass index. However, we did not find any correlation between the evolutions of both systems during treatment. The increase of the total ICARS score was not influenced by the GAA expansion length, whereas the posterior wall thickness decreased more in patients with GAA expansion length greater than 2 Kb.

This study allowed us to raise the following methodological implications for future trials in FA: (1) Qualitative clinical scales such as the ICARS are not appropriate for following neurological progression after a long disease duration. (2) Quantitative measures and reliable functional scales can be used as extensions of the ICARS, especially in patients with long disease durations. (3) Studies are needed to evaluate whether earlier intervention would modify the neurological progression of FA patients.

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Author Affiliations: Departments of Genetics (Drs Ribai, Rivaud-Pechoux, Charles, Brice, and Dürr), Cardiology (Drs Pousset and Béraud), and Biostatistics (Drs Tanguy and Mallet) and Fédération de Neurologie (Drs Le Ber, Gasparini, and Brice), Assistance Publique–Hôpitaux de Paris, and Institut National de la Santé et de la Recherche Médicale (INSERM) 679 (formerly 289), Federative Institute for Neuroscience Research (Dr Ribai, Le Ber, Brice, and Dürr), Salpêtrière Hospital, and Salpêtrière Medical School, Pierre et Marie Curie University (Dr Brice), Paris, France; Department of Clinical Genetics, Hôpitaux Universitaires de Strasbourg, Strasbourg, France (Drs Schmitt and Koenig); and Institute of Genetics, Molecular and Cellular Biology, Centre National de la Recherche Scientifique/INSERM/University Louis Pasteur, Illkirch, France (Dr Koenig).

Correspondence: Alexandra Dürr, MD, PhD, Institut National de la Santé et de la Recherche Médicale U 679, Hôpital de la Salpêtrière, Bd de l'hôpital 47, 75013 Paris, France (duerr@ccr.jussieu.fr).

Author Contributions: Study concept and design: Pousset, Brice, and Dürr. Acquisition of data: Ribai, Pousset, Rivaud-Pechoux, Le Ber, Gasparini, Charles, Béraud, Schmitt, Koenig, and Dürr. Analysis and interpretation of data: Ribai, Pousset, Tanguy, Béraud, Mallet, Brice, and Dürr. Drafting of the manuscript: Ribai, Charles, and Béraud. Critical revision of the manuscript for important intellectual content: Pousset, Tanguy, Rivaud-Pechoux, Le Ber, Gasparini, Schmitt, Koenig, Mallet, Brice, and Dürr. Statistical analysis: Tanguy and Mallet. Obtained funding: Brice and Dürr.
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