Exonic Deletions of FXN and Early-Onset Friedreich Ataxia

Mathieu Anheim, MD, PhD; Louise-Laure Mariani, MD; Patrick Calvas, MD, PhD; Emmanuel Cheuret, MD; Fabien Zagnoli, MD; Sylvie Odent, MD; Claire Seguela, BS; Cecilia Marelli, MD; Marlene Fritsch, BS; Jean-Pierre Delaunoy, PhD; Alexis Brice, MD, PhD; Alexandra Dürr, MD, PhD; Michel Koenig, MD, PhD

Background: Friedreich ataxia (FA) is the most frequent type of autosomal recessive cerebellar ataxia, occurring at a mean age of 16 years. Nearly 98% of patients with FA present with homozygous GAA expansions in the FXN gene. The remaining patients are compound heterozygous for an expansion and a point mutation. Patients who are compound heterozygous for an exonic deletion and an expansion are exquisitely rare.

Objectives: To describe 6 patients affected with FA due to an exonic deletion mutation (FAexdel) and to compare these 6 patients with FAexdel with 46 patients consecutively diagnosed with typical FA due to homozygous GAA expansion and whose small expansions were within the same range as that of the expansions of the patients with FAexdel.

Design: Description of a series.

Setting: Academic research.

Patients: Six patients with FAexdel and 46 patients with typical FA.

Intervention: FXN gene analysis, including assessments of GAA expansion and exon sequencing and determination of exonic copy numbers using multiplex ligation-dependent probe amplification.

Results: We identified 6 patients with FA who presented with the combination of 1 GAA expansion and 1 FXN exonic deletion. The mean (SD) age at onset of the disease was earlier for patients with FAexdel (7 [4] years [range, 3-12 years]) than for patients with typical FA (15 [5] years [range, 6-30 years]) (P = .001), and the median time to confinement to wheelchair was shorter for patients with FAexdel (20 years) than for patients with typical FA (28 years) (P = .002). There was no difference between the mean (SD) size of the expansion for the patients with FAexdel (780 [256] GAA triplet repeat sequences [range, 340-1070 GAA triplet repeat sequences]) and the mean (SD) size of the short expansion for the patients with typical FA (634 [163] GAA triplet repeat sequences [range, 367-1000 GAA triplet repeat sequences]) (P = .10). The mean disease duration before becoming wheelchair bound was shorter for patients with FAexdel (9 years) than for patients with typical FA (13 years), and the incidence of cardiomyopathy was higher for patients with FAexdel (84%) than for patients with typical FA (68%). However, these differences were not significant, probably owing to the small size of the FAexdel group. The other extraneurological signs, such as scoliosis or diabetes mellitus, were particularly frequently observed in the FAexdel group. One patient presented at 9 years of age with severe angina and marked cardiomyopathy that confined her to a wheelchair. Three patients had disabling autonomic disturbances. It appears that exonic deletion significantly contributes to the clinical picture of patients with FA.

Conclusions: Friedreich ataxia due to an exonic deletion mutation corresponds to an early onset and severe variant of FA. FXN should be investigated for exonic deletion in patients with early-onset FA in which only 1 GAA expansion without a point mutation is found. Patients with FAexdel have to be carefully observed using cardiological, orthopaedic, endocrinological, gastroenterological, and ophthalmological data. Friedreich ataxia due to an exonic deletion mutation should be suspected in young patients presenting with severe scoliosis.


Friedreich ataxia (FA) is the most frequent type of autosomal recessive cerebellar ataxia. First signs usually occur at a mean age of 16 years old (mostly between 10 and 25 years). Friedreich ataxia is clinically characterized by the combination of both cerebellar and proprioceptive ataxia, sensory neuronopathy with loss of deep tendon reflexes, extensor plantar responses, scoliosis, hypertrophic cardiomyopathy, and, less frequently, diabetes mellitus. Nearly 98% of patients with FA present with ho-
mosozygous GAA expansions in the FXN gene encoding the frataxin protein. About 2% of these patients have both 1 GAA expansion and 1 point mutation in FXN. Patients compound heterozygous for an exonic deletion and an expansion are exquisitely rare. Although the clinical phenotype of FA due to GAA expansion or point mutations has been well described, the clinical spectrum of patients with FA due to an exonic deletion mutation (FAexdel) remains unknown. We report 6 patients with FAexdel who presented with the combination of 1 GAA expansion and 1 FXN exonic deletion responsible for early-onset FA with precocious neurological disability and cardiomyopathy.

### Methods

Approximately 600 patients, recruited from French centers during the period from 1988 to 2010, received a diagnosis of FA, which was determined by use of a genetic test. The DNA samples of 13 ataxic patients whose clinical phenotypes were compatible with FA but who were heterozygous for a GAA expansion and had no point mutation were assessed for large FXN molecular analysis.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of ataxia, y</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>5</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>First sign</td>
<td>Unsteadiness</td>
<td>Scoliosis</td>
<td>Unsteadiness</td>
<td>Unsteadiness</td>
<td>Unsteadiness</td>
<td>Unsteadiness</td>
</tr>
<tr>
<td>Spino cerebellar degeneration functional score</td>
<td>3/7 at 4 y, 6/7 at 12 and 14 y</td>
<td>6/7 at 9 and 30 y</td>
<td>6/7 at 24 y, 7/7 at 64 y, deceased at 69 y</td>
<td>2/7 at 9 y (ICARS score, 19/100)</td>
<td>12 at 9 y</td>
<td>12 at 9 y</td>
</tr>
<tr>
<td>SARA score</td>
<td>28 at 14 y</td>
<td>36 at 30 y</td>
<td>Unknown</td>
<td>12 at 9 y</td>
<td>NA</td>
<td>34 at 46 y</td>
</tr>
<tr>
<td>Disease duration before becoming wheelchair bound, y</td>
<td>9</td>
<td>6</td>
<td>17</td>
<td>NA</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>FXN molecular analysis</td>
<td>1070 GAA triplet repeat sequences (exons 4 and 5 deleted)</td>
<td>800 GAA triplet repeat sequences (exons 4 and 5 deleted)</td>
<td>970 GAA triplet repeat sequences (exons 4 and 5 deleted)</td>
<td>670 GAA triplet repeat sequences (exons 2 and 3 deleted)</td>
<td>340 GAA triplet repeat sequences (exons 4 and 5 deleted)</td>
<td>830 GAA triplet repeat sequences (exon 4 deleted)</td>
</tr>
<tr>
<td>Cerebellar ataxia?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Extensor plantar response?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Areflexia and/or vibration sense loss?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Motor deficit?</td>
<td>Severe hypotonia</td>
<td>Yes (LL, areflexia)</td>
<td>Yes (UL and LL, areflexia)</td>
<td>No</td>
<td>No</td>
<td>Yes (LL, areflexia)</td>
</tr>
<tr>
<td>Dysarthria?</td>
<td>Yes</td>
<td>Yes (48 y)</td>
<td>Yes (9 y)</td>
<td>No</td>
<td>Yes</td>
<td>Yes (31 y)</td>
</tr>
<tr>
<td>Diabetes (age at diagnosis)?</td>
<td>Yes (11 y)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cardiomyopathy (age at diagnosis)?</td>
<td>Yes (4 y)</td>
<td>Yes (at 9 y) and severe angor</td>
<td>Yes (48 y)</td>
<td>Yes (9 y)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Pes cavus (age at diagnosis)?</td>
<td>Yes (4 y)</td>
<td>Yes (and equinovarus)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>Scoliosis?</td>
<td>Yes, arthrodesis at 14 y</td>
<td>Yes, operated on at 13 y</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Loss of visual acuity?</td>
<td>Myopia, optic atrophy</td>
<td>No</td>
<td>Yes (bilateral 10-20 dB sensorineural hearing loss)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hearing loss?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Movement disorder?</td>
<td>Yes (cerebellar tremor)</td>
<td>Yes (cerebellar tremor)</td>
<td>No</td>
<td>Yes (head tremor)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Autonomic disturbance?</td>
<td>Repeated ileus at 11 y</td>
<td>No</td>
<td>NA</td>
<td>No</td>
<td>Ileus at 49 y</td>
<td>NA</td>
</tr>
<tr>
<td>Fundus examination findings (age at diagnosis)</td>
<td>Optic neuropathy (24 y)</td>
<td>Asymptomatic optic neuropathy suspected</td>
<td>NA</td>
<td>Normal</td>
<td>Normal</td>
<td>NA</td>
</tr>
<tr>
<td>EMG findings (age at diagnosis)</td>
<td>Sensory neuronopathy (4 y)</td>
<td>Sensory neuronopathy (10 y)</td>
<td>NA</td>
<td>Sensory neuronopathy</td>
<td>Sensory neuronopathy</td>
<td>Sensory neuronopathy</td>
</tr>
<tr>
<td>MRI findings of the brain</td>
<td>Normal</td>
<td>Normal</td>
<td>NA</td>
<td>Normal</td>
<td>Normal</td>
<td>NA</td>
</tr>
<tr>
<td>MRI findings of the medulla oblongata</td>
<td>Spinal cord atrophy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Treatment with idebenone?</td>
<td>Yes (10 mg/kg/d)</td>
<td>NA</td>
<td>NA</td>
<td>Yes (mg/kg/d)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: EMG, electroneuromyography; ICARS, International Cooperative Ataxia Rating Scale; LL, lower limbs; MRI, magnetic resonance imaging; NA, not available; SARA, Scale for the Assessment and Rating of Ataxia; UL, upper limbs.

a Score from 0 (no cerebellar sign) to 7 (bedridden), with 6/7 indicating that the patient is wheelchair bound.

b Motor deficit was defined by a score of 3/5 or less in muscle strength from the Oxford scale.
deletion or duplication using a multiplex ligation-dependent probe amplification kit (SALSA MLPA kit P316-A1 Recessive Ataxias; MRC-Holland) according to the manufacturer’s recommendations. We retrospectively reviewed the clinical, molecular, electrophysiological, and morphological data of the patients with FAexdel and of 46 patients consecutively diagnosed with typical FA due to homozygous GAA expansion and whose small expansions were within the same range as that of the expansions of the patients with FAexdel.

Data, reported as mean (SD) values along with minimum and maximum values (ie, range), were analyzed by use of the Mann-Whitney test. When percentages were compared, the Fisher exact test was used. For the median time to confinement to a wheelchair and for the median disease duration before confinement to a wheelchair, the Kaplan-Meier method was performed.

**RESULTS**

Seven patients had a normal FXN exonic copy number dosage, excluding the diagnosis of FA. These patients, whose molecular diagnosis remains unknown, presented with late-onset ataxia (ranging from 30 to 58 years of age) and had large expansions (from 700 to 1100 GAA triplet repeat sequences). Some had atypical presentation because they had cerebellar atrophy and/or a lack of sensory neuropathy. They were assumed to be heterozygous carriers of the expansion by chance, given the high frequency of the GAA expansion in the European population (= 1 in 90 individuals). The remaining 6 patients were found to be affected with FA due to heterozygous FXN exonic deletion. Three of them (patients 1, 2, and 3) were previously reported in a series of patients with an FA-like disease who presented with only 1 GAA repeat expansion and no point mutation. The main findings are summarized in Table 1 and Figure 1, and the comparison between patients with FAexdel and patients with typical FA are presented in Table 2 and Figure 2. Cardiomyopathy was diagnosed at 4 years of age in patient 1 but was particularly stable until the patients turned 24 years of age. Patient 2 presented with severe angina and cardiomyopathy with a left ventricular ejection fraction of 52% at 9 years of age that confined her to a wheelchair. Interestingly, patient 3 was the grandaunt of patient 2 (Figure 1); therefore, autosomal dominant cerebellar ataxia was first suspected in this family. The high frequency of GAA expansion in heterozygous carriers led to a pseudodominant inheritance of FA in this family because the expansion of the 2 patients was transmitted by 2 unrelated individuals (Figure 1). The 6

![Pedigree showing 4 generations of a family that included patient 2 (IV1) and patient 3 (II3) with pseudodominant inheritance of Friedreich ataxia. The squares represent male individuals; circles, female individuals; filled circles, affected female individuals; diagonal line, deceased individual; arrow, proband. Genotypes are indicated as follows: E, GAA expansion; exdel, exonic deletion; WT, wild type. ND indicates analysis was not done.](image1)

![Data on patients with Friedreich ataxia due to an exonic deletion mutation (FAexdel) and patients with typical FA who were not wheelchair bound (determined by use of the Kaplan-Meier method).](image2)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical FA (n = 46)</th>
<th>FA exdel (n = 6)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, mean (SD) [range], y</td>
<td>15.4 (5) [6-30]</td>
<td>7 (4) [3-12]</td>
<td>.001</td>
</tr>
<tr>
<td>Time to confinement to wheelchair, median, y</td>
<td>28</td>
<td>20</td>
<td>.002</td>
</tr>
<tr>
<td>DD before confinement to wheelchair, median, y</td>
<td>13</td>
<td>9</td>
<td>.42</td>
</tr>
<tr>
<td>Age at last follow-up, mean (SD) [range], y</td>
<td>31 (10) [14-57]</td>
<td>33 (22) [9-69]</td>
<td>.92</td>
</tr>
<tr>
<td>SARA score–to–DD ratio at last follow-up,a mean (SD) [range]</td>
<td>1.5 (0.6) [0.5-3]</td>
<td>1.9 (0.8) [1-3]</td>
<td>.33</td>
</tr>
<tr>
<td>Cardiomyopathy, % of patients</td>
<td>68</td>
<td>90</td>
<td>.66</td>
</tr>
<tr>
<td>GAA triplet repeat sequences, mean (SD) [range], No.</td>
<td>634 (163) [367-1000],b</td>
<td>780 (256) [340-1070],c</td>
<td>.34,c</td>
</tr>
</tbody>
</table>

Abbreviations: DD, disease duration; FA, Friedreich ataxia; FAexdel, FA due to an exonic deletion mutation; SARA, Scale for the Assessment and Rating of Ataxia.

aThis ratio calculation gives a good indication of the severity of the disease progression.
bShort expansion vs 780 (256) [340-1070].
cLarge expansion vs 780 (256) [340-1070].

©2012 American Medical Association. All rights reserved.
patients with FAexdel in our series are all of French an-
cesty: 2 patients are from southern France, and the other 4 patients, with a deletion of exons 4 and 5, were origi-
nally from Brittany, which suggests that the multiple oc-
currence of this deletion is the consequence of a founder
effect.

**COMMENT**

To our knowledge, we report the first series of 6 pa-
tients affected with FAexdel, which is characterized by a
particularly young age at onset in comparison with the
age at onset of typical FA. This comparison holds true be-
cause there is no difference between the 2 groups re-
garding the size of GAA expansion (Table 2). The dis-
ease is more severe in patients with FAexdel, mainly be-
cause of the early onset of the disease and the early age
at which the patients become confined to a wheelchair
but also because there appears to be a trend toward a faster
progression of disability and a higher incidence of car-
diomyopathy in FAexdel. So far, only 1 patient with
FAexdel (with a deletion surrounding exon 5a) had been
reported with the disease at 9 years, sensory axonal neu-
ropathy, foot deformity, loss of independent walking at
15 years, and cardiomyopathy at 21 years. Early-onset
FA is a rare variant of FA, and patients whose age at on-
set is younger than 7 years represent approximately 12%
of all patients. We found that FAexdel is exquisitely rare
and accounts for approximately 1% of cases of FA diag-
nosed in France.

It appears that extensor plantar reflexes are an op-
ional finding in FAexdel. Moreover, the incidence of ex-
terneurological signs is particularly high in such pa-
tients. All but 1 of our 6 patients were affected with
hypertrophic cardiomyopathy, albeit this is not signifi-
cantly different from the 60% of patients with typical FA
who have cardiomyopathy. However, the cardio-
myopathy may be particularly disabling in FAexdel, as
it lead to severe angina and early loss of ambulation in
patient 2. The incidence of diabetes mellitus was higher
in our patients with FAexdel (half of our patients were
affected) than in previously reported series of patients
with FA (about 30%). The incidence of scoliosis in our
patients with FAexdel seems to be the same as in pa-
tients with typical FA, but the severity of scoliosis could
be higher in FAexdel because 2 patients needed spine sur-
gery only a few years after onset of the disease. More-
over, scoliosis may reveal FAexdel (patient 2). Interest-
ingly, 3 patients had autonomic disturbances, especially
repeated ileus, which is an unusual finding in FA. The
severe phenotype associated with exonic deletion mu-
tation is in agreement with the predicted absence of func-
tional frataxin made from the deleted allele.

It appears that exonic deletion significantly con-
tributes to the clinical picture of patients with FA, es-
specially to the young age at onset of the disease, whereas
the FA phenotype and the age at onset are usually con-
ditioned by the size of the smaller GAA expansion (in
case of homozygous expansions). For instance, pa-
tients with a short size of the smaller expansion may present
with an FA variant such as late-onset FA or very-late-onset FA,
defined by an age at onset of the disease of older than 25 and 40 years, respectively. Within
our series, it seems that the size of the GAA expansion
also contributes to the phenotype. Indeed, the 3 pa-
tients with the larger expansions (patients 1, 3, and 6,
presenting with 1070, 970, and 830 GAA triplet repeat
sequences, respectively) are those affected with both dia-
abetes mellitus and autonomic disturbances, and patient
2 (800 GAA triplet repeat sequences) had had the first
signs at 2 years of age, a severe cardiomyopathy at 4 years
with angina at 9 years, and the shorter disease duration
before becoming wheelchair bound. Moreover, patient
5, with the shortest expansion (340 GAA triplet repeat
sequences) and deletion of exons 4 and 5, does not show
symptoms of an extensor plantar response, cardiomy-
opathy, or diabetes mellitus.

FXN should be investigated for exonic deletion in pa-
tients with early-onset FA in which only 1 GAA expa-
sion without a point mutation is found. In clinical prac-
tice, patients with FAexdel have to be carefully observed
using cardiological, orthopaedic, endocrinological, gas-
troenterological, and ophthalmological data. Moreover,
FAexdel should be suspected in young patients present-
ing with severe scoliosis.

**Accepted for Publication:** August 10, 2011.

**Published Online:** March 12, 2012. doi:10.1001
/ARCHNEUROL.2011.834

**Author Affiliations:** Université Pierre et Marie Curie, Cen-
tre de Recherche de l’Institut du Cerveau et de la Moelle épinière, Institut National de la Santé et de la Recherche Médicale (INSERM), and Centre National de la Recherche Scientifique (CNRS) (Drs Anheim, Marelli, Brice, and Durr), Assistance publique–Hôpitaux de Paris, Pitié–Salpêtrière Hospital, Department of Genetics and Cyto-
genetics (Drs Anheim, Mariani, Marelli, Brice, and Durr), and Centre de Référence des Maladies Neurogénétiques de l’Enfant et de l’Adulte (Drs Anheim, Marelli, Brice, and Durr), Paris, Service de Génétique Médicale, Université de Toulouse, Hôpital Purpan (Dr Calvas), and Service de neuropédiatrie, Hopital des enfants (Dr Cheuret), Tou-
louse, Neurologie Hôpital d’Instruction des Armées Cler-
mont-Tonnerre, Brest (Dr Zagnoli), Service de Géné-
tique clinique CHU de Rennes, Université Rennes 1, CNRS
(Dr Odent), Laboratoire de Diagnostic Génétique, Nou-
vél Hôpital Civil, Strasbourg (Mesdames Seguela and Fritsch and Drs Delaunoy and Koenig), and Institut de Génétique et de Biologie Moléculaire et Cellulaire, CNRS,
Université de Strasbourg, INSERM, Illkirch (Dr Koenig),
France.

**Correspondence:** Mathieu Anheim, MD, Assistance publi-
que–Hôpitaux de Paris, Pitié–Salpêtrière Hospital, De-
partment of Genetics and Cytogenetics, Bâtiment Pinel,
Groupe Hospitalier de la Pitié–Salpêtrière, 47-83, bd de l’Hôpital, 75651 Paris, France (mathieu.anheim@psl .aphp.fr).

**Author Contributions:** Dr Anheim had full access to all the
data in the study and takes responsibility for the in-
tegrity of the data and the accuracy of the data analysis.

**Study concept and design:** Anheim, Mariani, and Koenig.

**Acquisition of data:** Anheim, Mariani, Calvas, Cheuret,
Zagnoli, Odent, Seguela, Marelli, Fritsch, Delaunoy, Brice,
and Durr. Analysis and interpretation of data: Anheim, Mariani, Seguela, Delaunoy, and Koenig. Drafting of the manuscript: Anheim, Mariani, Calvas, Cheuret, Zagnoli, Odent, Seguela, Fritsch, Delaunoy, and Koenig. Critical revision of the manuscript for important intellectual content: Anheim, Mariani, Marelli, Brice, Durr, and Koenig. Statistical analysis: Anheim and Mariani. Obtained funding: Anheim, Mariani, Calvas, Cheuret, Zagnoli, Odent, Seguela, Fritsch, Delaunoy, and Koenig. Study supervision: Anheim and Koenig.

Financial Disclosure: None reported.

Previous Presentation: Presented in part at the Journées de Neurologie de Langue Française; April 28, 2011; Paris, France (abstract and poster).

REFERENCES