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Intrafamilial Phenotypic Variability in Friedreich Ataxia Associated With a G130V Mutation in the *FRDA* Gene

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Background: Most patients with Friedreich ataxia (FA) have a GAA trinucleotide repeat expansion in intron 1 of the FA gene (*FRDA*) on both arms of chromosome 9. However, some patients are compound heterozygotes and harbor a GAA expansion on one allele and a point mutation on the other. Compound heterozygous patients with FA who have a GAA expansion and a G130V mutation have been reported to have an atypical phenotype with a slow disease progression, minimal or no ataxia, or gait spasticity.

Objective: To describe intrafamilial phenotypic variability in a GAA expansion/G130V mutation compound heterozygous family with FA.

Setting: Tertiary referral university hospital setting.

Patients and Methods: A 34-year-old man presented to our hospital with a 24-year history of stiff legs and mild unsteadiness of gait. Clinical examination showed a spastic paraparesis with normal to pathologically brisk deep tendon reflexes and mild left upper limb ataxia. His 27-year-old sister presented with a slowly pro-

gressive early-onset ataxic syndrome. She had ataxia of gait, mild to severe limb ataxia, and reduced or absent deep tendon reflexes, but no evidence of spasticity on examination.

Results: Neurophysiologic investigations showed evidence of a sensory axonal neuropathy, and molecular genetic analysis showed that both siblings were compound heterozygotes with a GAA expansion and a G130V mutation.

Conclusions: This report confirms that compound heterozygous patients with FA who have a GAA expansion and a G130V mutation may present with an ataxic phenotype and that intrafamilial phenotypic variability in these pedigrees can occur. It also emphasizes the importance of performing molecular genetic analysis for the GAA trinucleotide expansion in patients presenting with a spastic paraparesis of undetermined etiology, especially when there is neurophysiologic evidence of a sensory axonal neuropathy.

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FRIEDREICH ATAXIA (FA) is a progressive neurodegenerative disorder with a prevalence of approximately 1 in 50 000 in European populations.¹ According to Harding's mandatory clinical diagnostic criteria for FA, affected individuals should have an age at onset younger than 25 years and definitely younger than 27 years, ataxia of gait, ataxia of all 4 limbs, lower limb areflexia, and a mode of inheritance consistent with an autosomal recessive disorder.^{2,3} Dysarthria was present in all patients with a disease duration of at least 10 years, and 96% of patients had neurophysiologic evidence of a sensory axonal neuropathy in Harding's original series.² The majority of patients with FA, including some individuals with an atypical phenotype,

have a GAA trinucleotide repeat expansion in intron 1 of the FA gene (*FRDA*) on both arms of chromosome 9q 13-21.1.^{1,3-5} Normal alleles contain between 6 and 34 GAA repeats, whereas FA alleles carry between 66 and 1700 repeats.^{1,3,4,6,7} Some individuals are compound heterozygotes with a GAA trinucleotide repeat expansion on one allele and a point mutation on the other,^{3,4,7-12} and Bidichandani and colleagues⁸ identified one such missense mutation, the G130V mutation, in exon 4 of the *FRDA* gene in 1997. Although the phenotype may vary between family members harboring 2 GAA expansions,^{3,13} intrafamilial phenotypic variability has rarely been described in compound heterozygous FA pedigrees with a GAA expansion on one allele and a G130V mutation on the other.^{8,9}

Author affiliations are listed at the end of this article.

CASE 1

A 34-year-old right-handed man (subject III:1; **Figure, A**) presented to our hospital with a 24-year history of stiff legs and unsteadiness while walking; his clinical history has been briefly alluded to previously.³ He was the offspring of two unrelated Irish parents who had no symptoms of ataxia or neurologic disease.

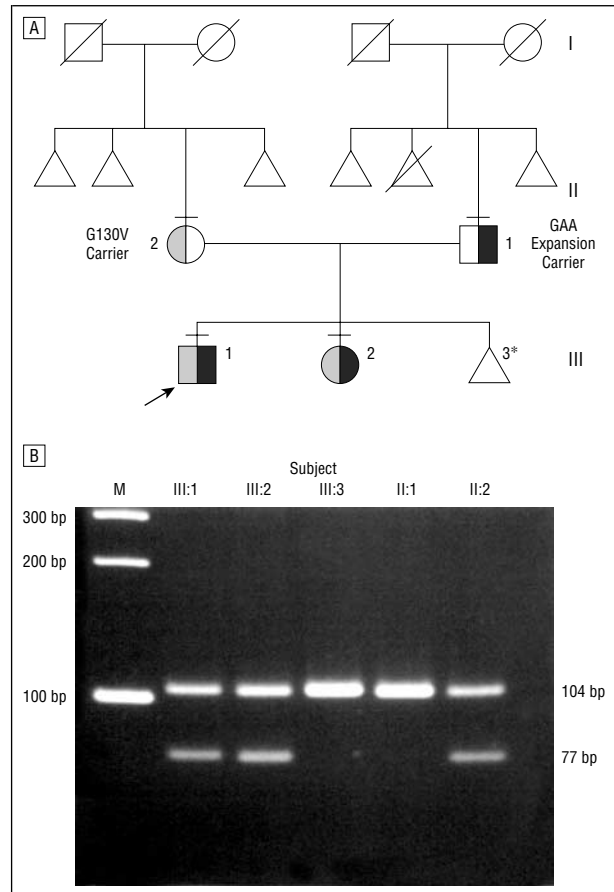
He had been well until 10 years of age, when he developed a febrile illness with vomiting, nocturnal confusion, agitation, and arthralgia during a 3-week period. He was treated with a course of oral amoxicillin, and although his symptoms improved within weeks, he complained of lower limb aching pains for the following 2 months. Subsequently, he noted stiffness in both legs and incoordination of the left more than right leg, with difficulty correcting his posture if pushed over. He had no subjective limb weakness, sensory symptoms, or sphincter disturbance. The unsteadiness while walking gradually increased, so that he required assistance to walk within 6 years and began using crutches 10 years after symptom onset. Although his leg stiffness subjectively increased during the 5-year period before the current examination, he was still ambulatory with the aid of 2 crutches. He had no cardiac symptoms and no history of diabetes and was not taking any medication at the time of assessment. One of his sisters had been given a clinical diagnosis of FA at 20 years of age (patient III:2), but there was no other family history of ataxia.

General physical examination disclosed a very mild thoracic scoliosis, fixed flexion contractures at the left knee and hip joints, and pes planus, but was otherwise normal. The findings on neurologic examination are outlined in the **Table**; the patient had a spastic paraparesis with normal to pathologically brisk reflexes throughout, bilateral extensor plantar responses, and minimal ataxia. He did not fulfill all of Harding's mandatory clinical diagnostic criteria for FA, and he did not have dysarthria 24 years after disease onset.

Results of routine hematologic and biochemical investigations were normal, as were levels of blood glucose, vitamin E, vitamin B₁₂, and folate. Thyroid function test results, autoantibody screening results, and treponemal serologic findings were normal or negative. His electrocardiogram was generally of low amplitude and showed p mitrale, but was otherwise normal, and a 2-dimensional transthoracic echocardiogram was normal. Magnetic resonance images of the brain were normal, but magnetic resonance images of the cervical spine showed a right-sided posterior disc protrusion at C4-5, posteriorly displacing the cord at this level, but without evidence of signal abnormality within the cord.

CASE 2

The sister (subject III:2; **Figure, A**) of subject III:1 was assessed at 27 years of age. She had had normal developmental milestones, but had transient ataxia and vomiting for a few days associated with a febrile illness at 5



A, Family tree of the compound heterozygous patients with Friedreich ataxia (subjects III:1 and III:2). Squares indicate males; circles, females; horizontal line above symbols, examined family members; diagonal slash, deceased; shading, G130V mutation; solid sections, GAA expansion; and arrow, index case with the G130V mutation. Some unaffected family members are represented as triangles to preserve anonymity. Asterisk indicates GAA repeat number within normal range and G130V point mutation testing negative. **B**, The 2.5% agarose gel showing polymerase chain reaction amplification products from the G130V mutation analysis of the pedigree. M indicates 100-base pair (bp) ladder showing 3 size markers of 100, 200, and 300 bp. The positions of the 104-bp and 77-bp fragments are indicated on the right.

years of age. Ten years later, she developed a sore throat, arthralgia, and fever and was diagnosed as having rheumatic fever. Subsequent to this illness, she had mild persistent left leg weakness and mild ataxia of gait, but was able to run and continued to play sports. The ataxia of gait increased slowly until 19 years of age, and after a recurrence of rheumatic fever at 20 years of age, she was clinically diagnosed as having FA. Her unsteadiness while walking increased during the 7-year period before presentation, but she was still able to walk without assistance at the time of assessment.

General physical examination showed a mild thoracic scoliosis and left pes cavus, but was otherwise normal. Her neurologic findings are outlined in the **Table**. In contrast to her clinically affected brother (subject III:1), she had no evidence of spasticity or limb weakness, and she had reduced or absent deep tendon reflexes and more pronounced ataxia of gait and limbs. It was of interest that she did not have dysarthria at least 12 years after disease onset either.

Clinical Characteristics of the 2 Affected Patients

Clinical Details	Subject III:1	Subject III:2
Age at examination, y	34	27
Disease duration, y	24	12†
Gait	Spastic scissoring	Ataxic
Titubation	No	Mild
OA/SP*	Right SP	No
Nystagmus	Very mild horizontal gaze-evoked	No; jerky pursuit movements
Dysarthria	No	No
Upper limb tone	Normal	Normal
Lower limb tone	Severe spasticity	Normal
Pyramidal weakness	Not in arms/severe in legs	No
Upper limb reflexes	++ to +++	Absent
Lower limb reflexes	++++ Right and left knee jerks, +++ left ankle jerk/++ right ankle jerk	+ Right knee jerk (reinforced), absent left knee/ankle jerks
Extensor plantar response	Bilateral	Bilateral
Upper limb ataxia	Mild left	Mild right and left
Lower limb ataxia	Indeterminate; spasticity	Severe right and left
Cerebellar rebound	Bilateral	Bilateral
Sensation in upper limbs	Impaired vibration	Normal
Sensation in lower limbs	Impaired pinprick, temperature, vibration	Impaired vibration and joint position
Distal amyotrophy	Legs	No
Pes cavus	No; pes planus	Left and varus deformity
Nerve conduction studies	Sensory axonal neuropathy	Sensory axonal neuropathy

*OA indicates optic atrophy; SP, suspicious pallor of the optic disc; +, reduced deep tendon reflex; ++, normal deep tendon reflex; +++, brisk deep tendon reflex; and +++++, brisk deep tendon reflex with clonus. Subject III:2 was considered to have had an age at onset of the disease at 15 years because of the presence of persistent symptoms after this age.

†Subject III:2 was considered to have onset at age 15 years because of the presence of persistent symptoms after this age.

Results of routine hematologic and biochemical investigations were normal, and levels of blood glucose, vitamin B₁₂, and folate and treponemal serologic findings were normal or negative. Vitamin E levels were mildly reduced at 10.7 μmol/L (reference range, 11.5-35 μmol/L). An electrocardiogram showed T-wave inversion in leads III and V₁, but no other signs of cardiomyopathy. Two-dimensional transthoracic echocardiography at age 23 years had shown concentric left ventricular hypertrophy with good left ventricular function.

MOLECULAR GENETIC ANALYSIS

In view of the clinical diagnosis of FA in subject III:2, polymerase chain reaction (PCR) analysis for the GAA trinucleotide repeat expansion was performed by means of established techniques.^{3,5,14} Subject III:1 was estimated to have approximately 954 GAA repeats and subject III:2 was estimated to have 917 GAA repeats on one allele of chromosome 9, but the GAA repeat number on the other allele was normal in both subjects. The diffuse PCR product associated with the GAA expansion in subject III:2 overlapped the expansion in subject III:1 on agarose gel electrophoresis (data not shown). Because both patients were presumed to be compound heterozygotes, G130V point mutation testing was performed with the following primers: FRDA G130Vf: 5'-AAG-CAATGATGACAAAGTGCTAAC; FRDA G130Vr: 5'-CTCCACCCAGTTTGACAGTTAAGTCA. The 25-μL reaction contained 200 ng of DNA, 100 ng of each primer, 200 μM deoxynucleotide mixture (dNTP), and standard PCR buffer containing 1.5 mM magnesium chloride and 1 U of *Taq* polymerase (Gibco BRL, Life

Technologies, Paisley, Scotland). The PCR conditions were 94°C for 5 minutes; followed by 35 cycles of 30 seconds at 94°C, 59°C, and 72°C, respectively, and a final extension at 72°C for 5 minutes. The underlined T in the FRDA G130Vr primer results in the generation of a *HincII* site in the presence of the G130V mutation. After PCR, 10 μL of the PCR product was digested for a minimum of 2 hours with 10 U of *HincII* (New England Biolabs Inc, Beverly, Mass) with the use of conditions recommended by the manufacturer. The digestion products were visualized on a 2.5% agarose gel containing ethidium bromide, 0.5 μg/μL (Figure, B). Wild-type sequences from subjects not carrying the G130V mutation result in an uncut PCR product of 104 base pairs (bp). The G130V mutation results in 2 additional products of 77 and 27 bp, but the 27-bp product is generally not visible on the agarose gel. This analysis showed a G130V mutation within exon 4 of the *FRDA* gene in both patients (subjects III:1 and III:2). Subsequent screening of the unaffected parents confirmed that the father (subject II:1) was a carrier of the GAA expansion and the mother (subject II:2) carried the G130V mutation. The remaining sibling (subject III:3) was phenotypically and genotypically normal.

COMMENT

The first family reported to be heterozygous for the GAA trinucleotide repeat expansion and a G130V mutation exhibited an atypical FA phenotype.⁸ Although the clinical details of the 3 affected members were not published in detail, the 2 older siblings presented with leg weakness in the early teens, with a gradual disease progres-

sion so that they were able to walk with assistance at least 20 years after disease onset. They did not have dysarthria, they had minimal or no ataxia, and their deep tendon reflexes were either reduced or absent. The authors reported "little intrafamilial phenotypic variation." A subsequent collaborative study of the phenotypic expression of compound heterozygous patients with FA included 6 patients from 3 families who were compound heterozygotes with a GAA expansion and a G130V mutation.⁹ Four of these 6 patients had a more spastic than ataxic gait. There was some intrafamilial phenotypic variability in one family with 2 affected siblings, in which one sibling had mild gait ataxia, retained upper limb reflexes, and brisk knee jerks, whereas the other had a spastic gait without ataxia, retained upper limb reflexes, and absent lower limb reflexes. Ataxia of the limbs was not commented on in that article. Two recent reviews have emphasized that compound heterozygotes harboring a GAA expansion and a G130V mutation all have an atypical FA phenotype, but they stated that all patients have brisk knee reflexes⁷ or a spastic gait.¹⁵

We report an additional compound heterozygous FA family with a GAA trinucleotide repeat expansion on one allele and a G130V mutation on the other allele of chromosome 9. This is the second report of a G130V mutation in a family of Irish descent with FA, and all cases described to date are of European origin (Irish, English, or French).¹⁶ Although the difference in disease duration between the 2 affected siblings may have influenced the clinical findings, there was definite intrafamilial phenotypic variability in this family, with a more spastic than ataxic phenotype in the brother (subject III:1) and a more ataxic phenotype, without limb spasticity, in the sister (subject III:2). The presence of cervical cord compression on magnetic resonance imaging may have contributed to the spastic paraparesis in subject III:1, but this finding would not account for the preservation of deep tendon reflexes that are typically absent in the lower limbs in FA. If the phenotype had been consistent within the family, one would have expected lower limb hyporeflexia or areflexia in subject III:1 at 24 years after disease onset, in view of these findings in his younger sibling earlier in her disease course. Conversely, one cannot completely exclude the possibility that borderline vitamin E deficiency contributed to a more pronounced ataxic phenotype with hyporeflexia or areflexia in subject III:2.¹⁷ This patient is unavailable for follow-up, so we cannot comment on whether her clinical condition has stabilized with vitamin E replacement therapy. However, because the size of the GAA trinucleotide repeat expansion in peripheral blood lymphocytes was comparable in the 2 affected siblings, the variation in phenotype is most likely to be secondary to somatic mosaicism in the size of the GAA expansion.¹⁸ The influence of other modifier genes cannot be excluded.

The GAA trinucleotide repeat expansion is believed to interfere with messenger RNA transcription in the *FRDA* gene,^{4,8,19} thus leading to reduced levels of functional frataxin protein in affected individuals. The extent of reduction in the levels of frataxin appears to be inversely proportional to the size of the expansion.⁹ It has been proposed that the G130V mutation leads to the production

of an abnormal frataxin protein with modified or reduced function.⁹ The resulting combination of "frataxin deficiency," caused by a GAA expansion, and "frataxin dysfunction," secondary to a G130V mutation, may account for the difference in phenotypic expression between patients with FA who are compound heterozygotes with a GAA expansion and a G130V mutation and those with 2 GAA expansions. In addition, the degree of frataxin dysfunction may vary depending on the point mutation present in the *FRDA* gene. It has been postulated that the G130V mutation causes more subtle loss of frataxin function than another missense mutation (I154F) that is associated with a typical FA phenotype.⁸

Although compound heterozygotes with FA who have a GAA expansion and a G130V mutation commonly present with a predominantly spastic phenotype, this report confirms that these patients may present with an ataxic phenotype instead, with reduced or absent deep tendon reflexes. In addition, intrafamilial phenotypic variability in these pedigrees may occur. It also emphasizes the importance of performing molecular genetic analysis for the GAA trinucleotide repeat expansion in patients presenting with a spastic paraparesis of undetermined etiology, especially when there is neurophysiologic evidence of sensory axonal neuropathy that is typically seen in FA.

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