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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 progressive 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. 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. 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. 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 13-21.1,2 Normal alleles contain between 6 and 34 GAA repeats, whereas FA alleles carry between 66 and 1700 repeats.3,4 Some individuals are compound heterozygotes with a GAA trinucleotide repeat expansion on one allele and a point mutation on the other, and Bidichandani and colleagues 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,3,5-11 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.5,9

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REPORT OF CASES

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. 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 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.
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. 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 chromosome 9, but the GAA repeat number on the other allele was normal in both subjects. The diffuse polymerase chain reaction product associated with the GAA expansion in subject III:1 overlapped the expansion in subject 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. 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 dysthria, 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. 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 reflexes or a spastic gait.13

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.6

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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