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

Dominick J. H. McCabe, MRCPI; Nicholas W. Wood, FRCP; Fergus Ryan, PhD; Michael G. Hanna, MD; Sean Connolly, MD; David P. Moore, MRCPI; Janice Redmond, MD; David E. Barton, PhD; Raymond P. Murphy, FRCP

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.
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 planter 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 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: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-
deficiency contributed to a more pronounced ataxic phenotype in her disease course. Conversely, one 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. 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, 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. It has been proposed that the G130V mutation leads to the production of an abnormal frataxin protein with modified or reduced function. 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.

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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From the Departments of Neurology (Drs McCabe and Murphy) and Cardiology (Dr Moore), The Adelaide and Meath Hospital, incorporating The National Children’s Hospital, Dublin, Ireland; Department of Clinical Neurology, Institute of Neurology, National Hospital for Neurology and Neurosurgery, London, England (Drs McCabe, Wood, and Hanna); Department of Biological Sciences, Dublin Institute of Technology (Dr Ryan); Departments of Clinical Neurophysiology (Dr Connolly) and Neurology (Dr Redmond), St James’s Hospital, and National Centre for Medical Genetics (Drs Ryan and Barton) and University College Dublin Department of Paediatrics (Dr Barton), Our Lady’s Hospital for Sick Children, Dublin.

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Corresponding author and reprints: Dominick J. H. McCabe, MRCP, Department of Clinical Neurology, Institute of Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, England (e-mail: d.mccabe@ion.ucl.ac.uk).
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