SHORT REPORT

A family with pseudodominant Friedreich’s ataxia showing marked variation of phenotype between affected siblings

Stewart Webb, Kit Doudney, Mark Pook, Susan Chamberlain, Michael Hutchinson

Abstract

A family with pseudodominant Friedreich’s ataxia is described showing marked variation of phenotype between affected siblings. The mother of this family (III-3) developed a spastic ataxic tetraplegia with neuropathy at 34 years of age; her husband, who was unrelated, was clinically normal. Of their nine children, two (IV-2, IV-3), including one with multiple sclerosis (IV-3), developed a mild spinocerebellar degeneration in the third decade. Three in their late 20s had an asymptomatic spinocerebellar degeneration (IV-4, IV-5, IV-6) and one was confined to a wheelchair at 15 years with typical Friedreich’s ataxia (IV-9). Three other siblings (IV-1, IV-7, IV-8) were clinically normal. The father proved to be heterozygous for the triplet repeat expansion at the Friedreich’s ataxia locus and all clinically affected members were homozygous for alleles in the expanded size range. This family confirms that homozygote-heterozygote mating is the genetic basis for some families with apparent autosomal dominant Friedreich’s ataxia. The pedigree is shown in the figure. The father proved to be heterozygous for the triplet expansion at the FRDA locus.

Keywords: Friedreich’s ataxia; pseudodominant; variable phenotype

Friedreich’s ataxia is an autosomal recessive disorder and the most common inherited ataxia. Until recently the diagnosis of Friedreich’s ataxia has been made using strict diagnostic criteria. Primary criteria included autosomal recessive inheritance, age of onset less than 25 years, progressive limb and gait ataxia, areflexia in the lower limbs, neurophysiological evidence of axonal sensory neuropathy followed within 5 years by dysarthria, areflexia of all limbs, distal loss of proprioception and vibration, pyramidal weakness, and extensor plantar responses. Variable features include cardiomyopathy, scoliosis, pes cavus, optic atrophy, diabetes, and sensorineural deafness.

Identification of the mutation responsible for Friedreich’s ataxia has allowed the study of genotype-phenotype correlation. These studies have broadened the diagnostic criteria for Friedreich’s ataxia to include pedigrees with pseudodominant Friedreich’s ataxia, thought to result from either homozygote-heterozygote mating or from partial expression in heterozygote carriers and patients with late onset Friedreich’s ataxia (LOFA), retained reflexes (FARR), and Acadian FRDA, which include members with brisk reflexes and lower limb spasticity.

We describe an Irish pedigree with pseudodominant Friedreich’s ataxia, in which genetically affected members show marked variation in clinical phenotype. This study confirms that the pseudodominant form of the disease may result from homozygote-heterozygote mating with a diversity of clinical features caused by variable expansion at the FRDA locus.

Patient and methods

CLINICAL ASSESSMENT

This study was approved by the ethics committee of St Vincent’s Hospital and informed consent was obtained from all participating family members before inclusion in the study.

All family members were examined by two neurologists. Nine members (III-3, IV-2, IV-3, IV-4, IV-5, IV-6, IV-7, IV-8, and IV-9) had nerve conduction studies performed and four (III-3, IV-3, IV-4, and IV-9) had extensive tests to exclude other causes of spinocerebellar degeneration.

GENETIC STUDIES

Having eliminated expansion within the known dominant spinocerebellar ataxia loci, the family was investigated for expansion at the FRDA locus.

Results

FAMILY PEDIGREE

The pedigree is shown in the figure. The mother (III-3) of this family developed a spastic tetraparesis with peripheral neuropathy at 34 years of age. Her husband (III-4), who was apparently unrelated, showed no evidence of neurological disease except for a benign essential tremor. Two of their daughters (IV-2 and IV-3), including one with multiple sclerosis (IV-3), developed mild spinocerebellar degener-
A pedigree with pseudodominant Friedreich’s ataxia, showing the results of mutation analysis underneath each case. Circles = females; Squares = males; filled symbols = affected member; symbols filled with a spot = asymptomatic affected; half filled symbol = probably affected; horizontal line above the symbol = examined member; diagonal slash = deceased.

Germination in the second decade. Another sister (IV-4) and two brothers (IV-5, IV-6), all in their late 20s, were asymptomatic but similarly affected with a mild spinocerebellar degeneration. A third brother (IV-9) had typical Friedreich’s ataxia, with onset at 7 years of age. Three other siblings (IV-1, IV-7, IV-8) had normal examination.

Their maternal uncle (III-2) was clinically normal but their maternal aunt (III-1), who died at 51 years of age, had been increasingly unsteady for 30 years and was confined to a wheelchair.

INVESTIGATION RESULTS
The nerve conduction studies in all clinically affected members showed absent sensory action potentials and normal motor nerve conduction. The nerve conduction studies in two clinically unaffected members (IV-7, IV-8) were normal. Brain MRI showed characteristic changes of multiple sclerosis in IV-3 and atrophy of the medulla, pons, and midbrain in IV-9. Visual evoked responses were normal in III-3, normal sinus rhythm in IV-3, and atrial fibrillation and right axis deviation in III-3, normal sinus rhythm with left anterior hemiblock in IV-9. A nerve biopsy in IV-9 showed changes consistent with a severe axonal neuropathy. The ECG showed normal sinus rhythm with left anterior hemiblock in III-3, normal sinus rhythm in IV-3, and atrial fibrillation and right axis deviation in IV-9. All other tests including an echocardiogram in IV-9 were normal.

GENETIC RESULTS
Having eliminated expansion within the known dominant spinocerebellar ataxia loci, the family was investigated for expansion at the FRDA locus. Six clinically affected (III-3, IV-2, IV-3, IV-4, IV-6, and IV-9) and five clinically unaffected members (III-2, III-4, IV-1, IV-7, IV-8) were analysed. The mother of the family, who was clinically affected, had comparatively small expansions on both alleles (300/300 repeats). Her husband (III-4) and brother (III-2), who were both clinically normal, proved heterozygous for the expansion, consistent with carrier status (1100/N and 300/N repeats respectively). Two affected offspring (IV-2 and IV-3) with mild spinocerebellar degeneration proved homozygous for alleles in the expanded size range (770/300 and 800/300 repeats respectively), two asymptomatic but clinically affected offspring (IV-4 and IV-6) were also homozygous for alleles in the expanded size range (800/300 and 300/280 repeats respectively), one offspring (IV-9) with typical Friedreich’s ataxia had a very large homozygous expansion (1100/900) and three clinically unaffected offspring (IV-1, IV-7, and IV-8) had heterozygote expansions (300/N, 430/N and 1100/N repeats respectively).

Discussion
Friedreich’s ataxia is an autosomal recessive disorder; however, families have been rarely described with affected members over two generations. In this family the father (III-4) was clinically normal but had a large expanded allele. The mother (III-3), who was clinically affected, had relatively small expansions of both alleles. Her dead sister (III-1) had a history of a progressive gait disorder. This family confirms that homozygote-heterozygote mating is the genetic basis for some families with apparent autosomal dominant Friedreich’s ataxia.

The mother of this family (III-3) showed homozygosity for alleles at the lower end of the expanded size range (300/300), consistent with a comparatively late and mild phenotype. Five of the eight offspring who were available for analysis also showed homozygosity for alleles within the expanded size range. Three of the affected offspring (IV-2, IV-3, and IV-4) had apparently inherited an allele containing 800 repeats from their father, who was heterozygous for the expansion consistent with carrier status. Contraction of the expansion on transmission from the father (1100 repeats) to each of the three female offspring (770–800 repeats) was found. The inheritance of the larger expanded allele from the father seems to correlate with an earlier age of onset in the offspring, when compared with the mother. The fourth offspring (IV-6) also inherited an allele which had contracted upon transmission from

\[
\text{symbols} = \begin{cases} 
\text{a} & \text{_examined member;} \\
\text{V} & \text{diagonal slash = deceased.}
\end{cases}
\]
the father but which was smaller (280 repeats) than that seen in the other affected siblings and seemed to correlate with a milder phenotype; this sibling remained asymptomatic with evidence of only a mild spinocerebellar degeneration at 28 years of age. The fifth offspring (IV-9) inherited a maternal allele which seemed to expand on transmission (900 repeats). The large size of both alleles (1100/900) was consistent with manifestation of a more typical Friedreich’s ataxia phenotype.

This family shows the variable nature of Friedreich’s ataxia but also the consistent findings in all affected members, of upper and lower limb ataxia and neurophysiological evidence of axonal sensory neuropathy. In three recent genotype-phenotype studies with a total of 213 affected members (homozygous for GAA expansion) the same two primary criteria were present in 98.0% of affected members.478 Patients who fulfil the strict diagnostic criteria previously proposed by Harding and Geoffroy et al are likely to have Friedreich’s ataxia.1 Patients who lack several of the diagnostic criteria but who have progressive ataxia and neurophysiological evidence of axonal sensory neuropathy should be screened for the FRDA gene. Based on our findings in this family we also recommend that molecular testing for Friedreich’s ataxia should be considered in families with affected members in two generations.

Clinical details of all affected members

<table>
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<tr>
<th>Members</th>
<th>III-3</th>
<th>IV-2</th>
<th>IV-3</th>
<th>IV-4</th>
<th>IV-5</th>
<th>IV-6</th>
<th>IV-9</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>63</td>
<td>33</td>
<td>31</td>
<td>30</td>
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<td>21</td>
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<td>Asym</td>
<td>Asym</td>
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<td>+</td>
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<td>N</td>
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<tr>
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<td>−</td>
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<td>WF</td>
<td>Mild ataxia</td>
<td>Mild ataxia</td>
<td>Asym</td>
<td>Asym</td>
<td>Asym</td>
<td>WC</td>
</tr>
</tbody>
</table>

Asym=Asymptomatic; NK=not known; N=normal; Ab=absent; WC=wheelchair; WF=walking frame.

*Sensory loss confined to dorsal columns.


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