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Phenotypic variability of a likely FA2H founder mutation in a family with complicated hereditary spastic paraplegia

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To the Editor

Fatty acid hydroxylase-associated neurodegeneration (FAHN) is caused by mutations in *FA2H* (OMIM 612319) and encompasses a spectrum ranging from complicated spastic paraplegia (SPG35) [1, 2], to leukodystrophy with spastic paraparesis and dystonia [3], to neurodegeneration with brain iron accumulation (NBIA) [4] [5]. *FA2H* encodes fatty acid 2-hydroxylase, an important enzyme in galactolipid synthesis that is essential for neuronal myelin sheath maintenance. To date, only a few patients with *FA2H* mutations have been reported [1, 2, 4, 6, 7].

We describe 2 siblings born to non-consanguineous parents from Montenegro with SPG35 caused by mutation in *FA2H* (figure 1a–b). Patient 1 is a 13 year-old girl who developed normally until 3 years when she started toe walking and had frequent falls. By 4, her legs crossed with ambulation, consistent with spastic diplegia. Lower extremity spasticity progressed, and she lost independent ambulation at 9 years, when she also developed difficulty with handwriting. By 10, she developed dysarthic speech and a head and hand tremor. By 11, she developed scoliosis and head drop. When first seen at 13 years, she was non-ambulatory and unable to write, with unintelligible speech and difficulty chewing. Receptive language, cognition and hearing appeared intact. She had no history of seizures. Brain MRI at 8 years demonstrated an atrophic cerebellum, slightly flat pons, mild thinning

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of the corpus callosum, prominent lateral ventricles, and bilateral posterior periventricular FLAIR hyperintensities. There was no evidence of brain iron accumulation (Figure 1c–f).

Patient 2 is her 5 year-old brother. He developed normally until 2 years, when a labored gait associated with scissoring and clumsiness was noted. By 3 years, he had lower extremity spasticity and slow speech. At 5 years, he had lost independent ambulation, had difficulty gripping a pencil, and developed a head drop and tremor. His decline seemed quicker than his sister's. Brain MRI at 5 years revealed a mildly atrophic cerebellum, normal pons and corpus callosum, and subtle T2 hyperintensities near the posterior horns of the lateral ventricles. There was no brain iron accumulation (Figure 1g–j). Table 1 shows clinical examination findings. Oligonucleotide based microarray analysis (Affymetrix 6.0, >1.8 million probes) revealed two large, contiguous genomic segments (16q21-q23.1, including *FA2H,* and 19q3.12-q13.33) with loss of heterozygosity. Direct sequencing of *FA2H* in the affected siblings identified a homozygous deletion (c.509_510 delAC) resulting in a frameshift and premature stop codon (p.Y170*). The parents and unaffected sister were heterozygous carriers. This mutation was previously reported in two brothers from Albania with NBIA [4], possibly representing a founder mutation from the Balkan region.

Review of the few published cases does not reveal a clear genotype-phenotype correlation, though putative null mutations or deletions causing absence of FA2H may result in a more severe phenotype than missense mutations [1, 3, 7]. Within the spectrum of FAHN, MRI can be unremarkable or show leukodystrophy or subcortical and periventricular T2 white matter hyperintensities, atrophy of the cerebellum, brainstem or cervical spinal cord, thinning of the corpus callosum, or iron accumulation in the globus pallidus. A family with the same c. 509_510 delAC mutation and NBIA has been reported [4]. In contrast, the siblings presented here showed no brain iron deposition, indicating that this mutation may not always result in NBIA. Thus, additional factors may play a role in FAHN phenotypic expression. Imaging studies also indicate that FAHN represents a clinical spectrum rather than a distinct syndrome [5]. The significant supranuclear upgaze palsy seen here has only been reported in a Pakistani patient [1] and adds to oculomotor abnormalities (strabismus and ocular apraxia) reported in other FAHN patients. The clinical spectrum and pathogenic mechanisms of FAHN are still unfolding.

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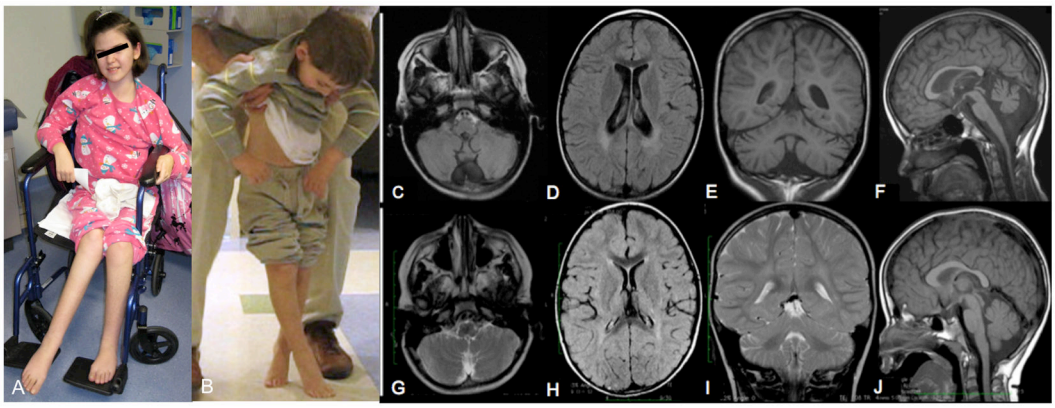

Figure 1.

Table 1

Clinical and examination findings of 2 siblings with SPG35. Ashworth Scale: (0) No increase in muscle tone, (1) Slight increase in tone with a catch and release or minimal resistance at end of range, (2) As 1 but with minimal resistance through range following catch, (3) More marked increase tone through ROM, (4) Considerable increase in tone, passive movement difficult, (5) Affected part rigid.

	Patient 1: 13 year old sister	**Patient 2: 5 year old brother**
Physical Findings	No dysmorphic features. Near constant drooling. Thoracolumbar scoliosis.	No dysmorphic features. Slight ptosis.
Mental status	Pleasant and appears normal but speech is difficult to understand.	Pleasant and appears normal but speech is difficult to understand.
Cranial nerve	Spastic dysarthria, bilateral optic atrophy, intermittent exotropia, broken saccades and supranuclear gaze palsy.	Spastic dysarthria, bilateral optic atrophy, intermittent exotropia, broken saccades and supranuclear gaze palsy.
ROM/Tone	Slow tongue movements. Spastic tetraparesis Ashworth 2. Nondystonic tendency to preferentially keep head laterally flexed to the right.	Slow tongue movements. Mild-moderate contractures in the ankles, knees, and hips. Truncal hypotonia. Spastic tetraparesis Ashworth 1. Nondystonic tendency to preferentially keep head laterally flexed to the right
Gait	Non-ambulatory.	Ambulates only with assistance and demonstrates a spastic diplegic gait.
Cerebellar	Bradykinesia and moderate-to-severe appendicular dysmetria along with an intention tremor. Titubation at rest.	Bradykinesia and moderate-to-severe appendicular dysmetria along with an intention tremor.
Muscle bulk	Atrophy below knees bilaterally.	Atrophy below knees bilaterally.
Strength	Appeared full; testing limited by spasticity.	Appeared full; testing limited by spasticity.
Reflexes	+4/4 throughout with a crossed adductor response and sustained ankle clonus. Babinski sign present bilaterally.	+4/4 throughout with a crossed adductor response and sustained ankle clonus. Babinski sign preset bilaterally. + Jaw jerk.
Electromyography and nerve conduction	Normal	- not performed -
Ophthalmologic exam	Optic nerve head pallor.	Bilateral +1 temporal optic nerve pallor.