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Case Report

Hereditary spastic paraplegia type 35 caused by a novel FA2H mutation

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Hereditary spastic paraplegia type 35 (SPG35) is a rare disorder characterized by progressive spasticity. Mutations in the fatty acid 2-hydroxylase (*FA2H*) gene in different loci are responsible for phenotypic variability. We aimed to define the phenotype of SPG35 linked to a novel homozygous mutation c.160_169dup (p.Asp57Glyfs*48) in the *FA2H* gene, and compared with the clinical characteristics and neuroimaging findings of the patients with mutation in the *FA2H* gene. We describe a 5-year-old boy presenting with spastic paraplegia. He developed a rapid progressive spastic paraplegia and loss of ambulation at an early age, despite the absence of accompanying seizure, neuropathy, cognitive impairment, speech disturbance, and optic atrophy. Neuroimaging revealed white matter changes without brain iron accumulation. A duplication variation; leading to a truncated protein c.160_169dup in the *FA2H* gene was found on the homozygous state. A homozygous mutation c.160_169dup in the *FA2H* gene, which resulted in SPG35 phenotype, may present with rapid progressive spastic paraplegia at an early age.

Key words: child, hereditary spastic paraplegia, genetic.

Hereditary spastic paraplegias (HSPs), a heterogeneous group of neurodegenerative disorders, are characterized by progressive spasticity of the lower extremities. HSPs demonstrate variability in terms of age of onset, disease progression rate, and phenotypic features. The clinical features such as, speech and cognitive impairments, optic atrophy, seizures, and neuropathy occurring in HSP overlap with other neurodegenerative disorders. Over 40 different genes with more than 70 loci, which are inherited in autosomal dominant, autosomal recessive or X-linked patterns, have been associated with HSPs[1].

The spectrum of HSPs was expanded by the identification of a mutation in the fatty acid 2-hydroxylase (*FA2H*) gene, which has been recently associated with a novel form of brain iron accumulation[2]. The *FA2H* gene mutation associated with spastic paraplegia has been defined as HSPs type 35 (SPG35)[3].

Here, we describe the phenotype of SPG35 caused by a novel homozygous mutation c.160_169dup (p.Asp57Glyfs*48) in the *FA2H* gene, and compare the clinical characteristics and brain imaging findings of the patients with mutations in different loci of the *FA2H* gene.

Case Report

A 5-year-old boy presented with progressive spastic paraplegia. He was born from healthy consanguineous parents after normal gestation and delivery. Early developmental milestones were normal. He was able to walk at the age of 1 year, and had no history of seizures. At the age of 4 years, he developed a recognizable gait abnormality that had been progressed for 3 months, followed by falling flat on the ground while walking. He had a healthy older sister. Two familial antecedents with similar clinical characteristics were reported to have died aged 15 and 17 years. The genetic data of them is

unknown. Pedigree is shown in Figure 1.

His anthropometric measurements (weight, height, and head circumference) were placed between 10-25 centile. He had no dysmorphic features. A neurological examination revealed muscle weakness, spasticity, hyperreflexia with ankle clonus in the lower limbs, and positive Babinski sign. The tests of cerebellar function were in normal range. He was unable to walk without support and had urinary incontinence. The cognitive status according to Stanford-Binet Intelligence Scale, and visual examination were within the normal range. Biochemical and metabolic screening (including analysis of plasma lactate, creatine kinase, ammonia, amino acids, very-long-chain fatty acids, and urinary organic acids), electromyography, and motor and sensory nerve conduction studies were unremarkable. Sleep electroencephalography (EEG) showed normal background activity and

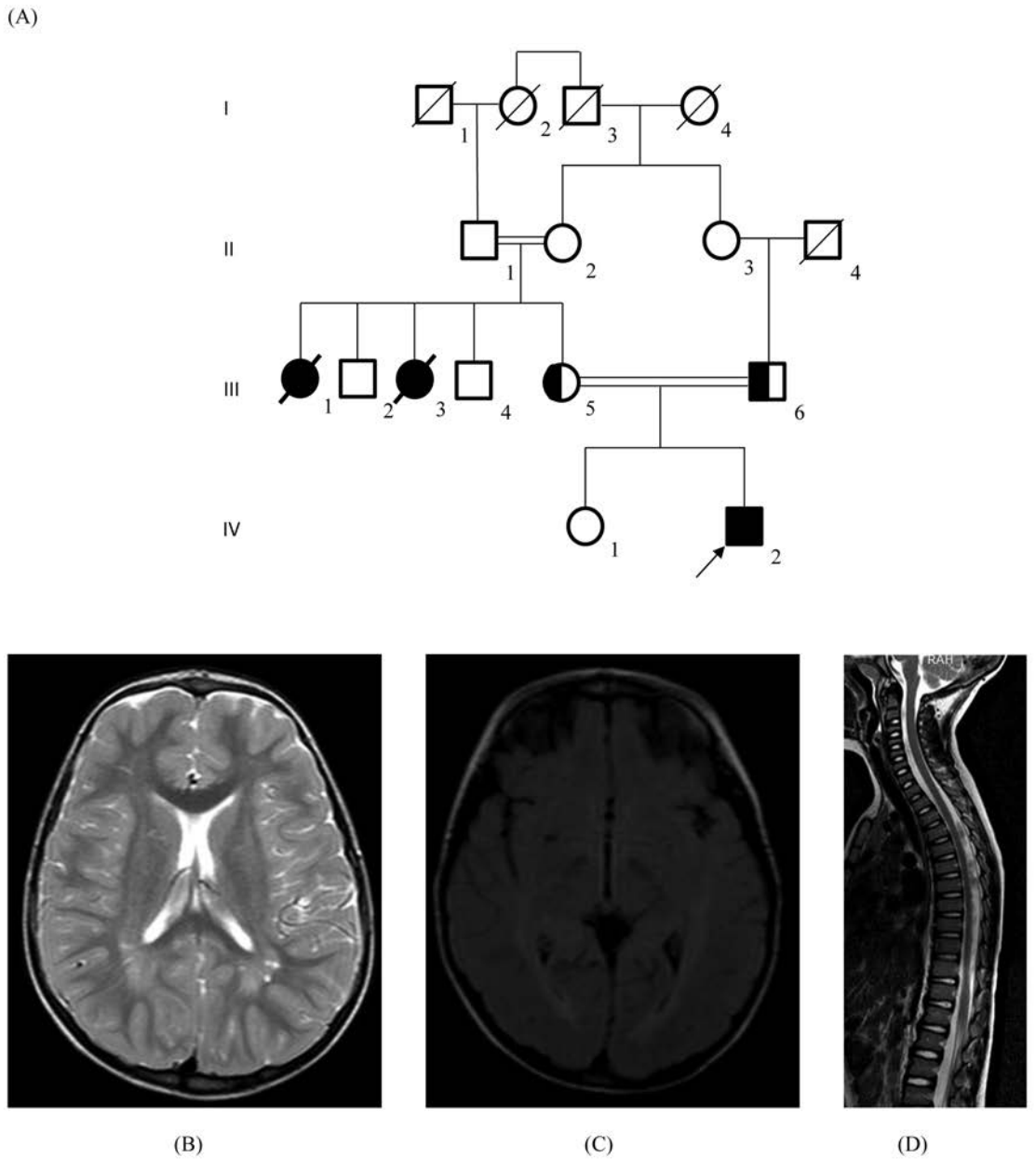

Fig. 1. (A) Pedigree of the patient with homozygous mutation c.160_169dup (p.Asp57Glyfs*48) in the FA2H gene, (B, C) axial T2-weighted and FLAIR images demonstrates white matter hyperintensities in periventricular region, and (D) spinal magnetic resonance imaging is unremarkable.

generalized multiple spike discharges. Brain magnetic resonance imaging (MRI) showed white matter hyperintensities in the posterior periventricular areas on T2/FLAIR sequences. The brain iron accumulation was not found. Spinal MRI was normal (Fig. 1).

After obtaining the parents' written informed consent, genomic DNA from peripheral blood was extracted using standard techniques. The samples were enriched for 4813 genes with known associated clinical phenotypes by the TruSight One Sequencing Panel kit on Illumina NextSeq500 platform. Generated variants were reduced by filtering out those with a minor allele frequency greater than 1% according to various population data. Homozygous rare variants were then filtered due to consanguinity at first step. All candidate variations were evaluated according to clinical inspection. A duplication variation; leading to a truncated protein c.160_169dup (p.Asp57Glyfs*48) in the *FA2H* gene was found on the homozygous state, which is caused to a loss of function of the *FA2H* gene. Confirmation and segregation analysis of both parents was performed by Sanger sequencing and revealed a heterozygous c.160_169dup (p.Asp57Glyfs*48) change showing their carrier status for the relevant mutation. The carrier status of the sibling was not known. Genetic counseling to the patient and his family were provided.

Discussion

We described the phenotype of SPG35 caused by a novel homozygous mutation c.160_169dup (p.Asp57Glyfs*48) in the gene encoding *FA2H*. The *FA2H* gene encodes an essential protein for the permanence of the myelin sheath around axons[3]. The c.160_169dup (p.Asp57Glyfs*48) duplication variation resulted in a truncated protein in the *FA2H* gene. A compound heterozygous insertion; c.169_170insGCGGGCCAGG (p.Asp57Glyfs*66) leading to a stop codon mutation similar to c.160_169dup (p.Asp57Glyfs*48) was defined in a recent report. The mutation c.169_170insGCGGGCCAGG predicted as deleterious through the results of computational algorithms, indicating that stop codon mutations were critical for the activity of *FA2H*[4]. A homozygous frameshift mutation; c.160_169dup (p.Asp57Glyfs*48) in the *FA2H* gene has been identified for the first time. Other mutations in the *FA2H* gene with distinct clinical manifestations are listed in Table I.

The differential diagnosis of progressive spastic paraplegia; adrenomyeloneuropathy, abetalipoproteinemia, mitochondrial disorders, hereditary motor-sensory neuropathy, and spinal cord lesions, were ruled out in line with laboratory and neuroimaging findings. The phenotype of SPG35 shows variability depending on mutated gene. Early age of onset following a normal development and gait disturbance are common features in SPG35. In our patient, the initial symptoms developed at the 4 years of age. The age of onset was around 4 years in the literature, while there are a few reports indicating a late onset at adulthood[1,9]. Our patient developed spastic paraplegia at an early age of onset as compared with the patient with compound heterozygous mutation c.169_170ins(p.Asp57Glyfs*66) and c.117C>A, and became non-ambulatory at 5 years[4]. The loss of ambulation occurred earlier than the most of the patients with SPG35 caused by *FA2H* mutation. This phenotype of the mutation c.160_169dup (p.Asp57Glyfs*48) demonstrated a rapid progression of spastic paraplegia.

Speech and cognitive impairments, optic atrophy, seizures, and neuropathy have also been described in SPG35[1]. Speech impairment existed in almost all of the patients. The occurrence of optic atrophy and peripheral neuropathy were not correlated, neuropathy was defined in only two reports[8, 13]. The presence of seizure and cognitive decline were also not correlated. Cognitive and speech impairment, optic atrophy, strabismus, seizures, and neuropathy were not yet existent in our case. However, EEG revealed epileptiform discharges indicating the probability of seizure occurrence. While describing the phenotype caused by the mutation c.160_169dup (p.Asp57Glyfs*48), the absence of accompanying features should cautiously be interpreted in view of early age of our patient.

White matter changes; cerebral, cerebellar, brainstem atrophy; and thin corpus callosum were detected in MRI of patients with the *FA2H* gene mutation. Periventricular white matter changes defined in our patient are

Table I. Clinical Features and Brain Imaging Findings of Patients with Mutation in the *FA2H* Gene in Different Loci.

	Exon	Mutation	Protein	Age at onset (y)	Age at last physical examination (y)	Progressive spastic paraplegia	Independent ambulation	Speech impairment	Ocular symptom/signs	Seizures	Cognitive impairment	MRI findings	Neuropathy
Pedroso et al. [4]	1 1	c.169_169dup10 c.117C>A	p.F39L	7	21	+	+	+	strabismus	NR	NR	white matter changes, iron accumulation	NR
Garone et al. [5]	1	c.270+3A>T	splice-site	7	24	+	-	+	optic atrophy	rare	severe	white matter changes, iron accumulation, cerebellar, brainstem, and cervical cord atrophy	-
Soehn et al. [14]	4	c.527G>A	p.W176C	3	12	+	-	NR	NR	NR	moderate severe	NR	NR
Soehn et al. [14]	1	c.131C>A	p.P44Q	4	9	+	-	NR	NR	NR	-	NR	NR
Soehn et al. [14]	1	c.133G>T	p.G45W	4,5	6	+	+	NR	NR	NR	mild	NR	NR
Soehn et al. [14]	6	c.785A>C	p.K262T	4	18	+	-	NR	NR	NR	mild	NR	NR
Edvardson et al. [3]	1	c.103G>T	p.D35Y	4	12	+	+	-	NR	NR	-	NR	-
Edvardson et al. [3]	6	c.786+1G>A	splice-site	4 to 6	7 to 20	+	-	+	NR	+/-	+	white matter changes, cerebellar atrophy	-
Rupps et al. [6]	1 6	c.209C>T c.968C>T	p.S70L p.P323L	3	5	+	-	+	-	-	mild	white matter changes	-
Liao et al.[7]	1	c.230 T>G	p.L77R	4	5	+	NR	+	strabismus papilledema	+	mild	NR	-
Liao et al.[7]	3 3	c.388C>T c.506+6C>G	p.L130F splice-site	10 to 17	26	+	-	+	nystagmus	-	- / mild	white matter changes, cerebellar atrophy	-
Zaki et al. [8]	1	C.265 C>T	p.Q89*	3 to 5	6 to 14	+	NR	+	nystagmus optic atrophy	- /+	- / mild	white matter changes, cerebellar atrophy, iron accumulation	- /+

Kruer et al. [2]	3	c.460C>T	p.R154C	4 to 5	15 to 20	+	-	+	strabismus optic atrophy nystagmus	+	-	white matter changes, iron accumulation, cerebellar, brainstem and cervical cord atrophy	-
Kara et al. [1]	7 3 3 5 6 1	c.1051A>C c.486G>C c.460C>T c.620C>T c.798C>G c.782dupA c.157_174del	p.S351R p.E162D p.R154C p.T207M p.D266E H261Qfs*52 **	3 to 38	NR	+	NR	+	optic atrophy	- /+	NR	white matter changes cortical, cerebellar and brainstem atrophy, thin corpus callosum	-
Tonelli et al. [9]	3	c.509A>G	p.Y170C	38 to 40	-	+	-	+	nystagmus optic atrophy	-	mild	iron accumulation, cerebellar and cerebral atrophy	-
Novarino et al. [15]	4 6	c.528 G>C c.806 G>T	p.W176C p.R269L	NR	NR	+	NR	NR	NR	NR	NR	NR	NR
Aguirre-Rodriguez et al. [10]	4	c.565 C>T	p.R189*	3	NR	+	NR	NR	optic atrophy	NR	mild	cerebellar atrophy	NR
Cao et al. [11]	5 6	c.688 G>A c.968_976delCG CACAAGGinsA GCACAAGA	p.E230K p.P323Q, p.G326S	4	35	+	-	+	nystagmus	+	+	white matter changes, cortical, cerebellar and brainstem atrophy	NR
Dick et al. [12]	5 1	c 703 C>T c.159_176del18	p.R235C **	6	31	+	-	+	optic atrophy	+	mild	white matter changes	-
Pierson et al. [13]	5	c.707C>T	p.F236S	3	10	+	-	+	-	-	moderate	white matter changes	+
Kruer et al. [2] Donkervoort et al. [16]	4	c.510_511delCA	p.Y170X	3	13	+	-	+	NR	-	-	white matter changes, cerebellar atrophy, thin corpus callosum	NR
Present case	1	c.160_169dup	p.D57Gfs*66	4	6	+	-	-	-	-	-	white matter changes	-

NR = not reported; **=Deletion of more than 2 amino acid

common among SPG35[1-13]. Clinical features and periventricular white matter changes can mimic neurodegenerative disorders such as adrenoleukodystrophy. However, the family history, inheritance pattern, disease course, and negative biochemical and metabolic screening can be indicative of HSPs. Recently, identification of the neurodegeneration with brain iron accumulation expanded the phenotypic spectrum of the disorders associated with the *FA2H* gene mutation[2,4,5,8,9]. Brain iron accumulation was not shown in the patient with homozygous mutation c.160_169dup (p.Asp57Glyfs*48) in the *FA2H* gene. However, while describing the phenotype caused by the mutation c.160_169dup (p.Asp57Glyfs*48), the absence of accompanying clinical and neuroimaging features should cautiously be interpreted in view of early age of our patient.

In conclusion, the present study identified a novel homozygous mutation c.160_169dup (p.Asp57Glyfs*48) in the *FA2H* gene resulting in a rapid progressive spastic paraplegia, and an early loss of ambulation.

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