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Case Report

Infantile-onset spinocerebellar ataxia type 5 associated with a novel *SPTBN2* mutation: A case report

Tomoko Mizuno [a,*], Ayako Kashimada [a], Toshihiro Nomura [a], Kengo Moriyama [a], Haruna Yokoyama [a], Setsuko Hasegawa [a], Masatoshi Takagi [a], Shuki Mizutani [a,b]

[a] *Department of Pediatrics, Tokyo Medical and Dental University, Japan*
[b] *Kawasaki North Center for Childhood Developmental Disorder, Japan*

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Abstract

Background: Spinocerebellar ataxia type 5 (SCA5), a dominant spinocerebellar ataxia is caused by spectrin beta nonerythrocytic 2 gene (*SPTBN2*) mutation. It typically consists of a slow progressive cerebellar ataxia with an onset principally in adulthood. Here, we report on the first Japanese patient with infantile-onset SCA5 associated with a novel heterozygous *SPTBN2* mutation.

Case report: The patient, a 6-year-old girl, developed delayed motor development and unsteady arm movement during infancy. She also showed gaze-evoked nystagmus, saccadic eye pursuit, dysarthria, dysmetria, intention tremor and mild intellectual disability. Brain MRI revealed moderate cerebellar atrophy and mild pontine atrophy. Comprehensive target capture sequencing to identify the causative gene identified a novel missense mutation in *SPTBN2* (c.1309C<G, p.R437G), which was thought to be pathogenic.

Discussion: Two patients with infantile-onset SCA5 associated with another novel heterozygous *SPTBN2* mutation have recently been reported; these *SPTBN2* mutations, which may have a significant impact on protein function, were located in the second spectrin. Our findings indicate that *SPTBN2* mutations may be associated with infantile-onset cerebellar ataxia accompanied with global developmental delay.

Keywords: Spinocerebellar ataxia; Infantile-onset; SPTBN2; β-III spectrin

1. Introduction

Spinocerebellar ataxias (SCAs) are a heterogeneous group of neurodegenerative disorders characterized by progressive cerebellar ataxia, incoordination, dysarthria, and difficulty in swallowing [1]. Thus far, 38 different genes have been identified to be associated with SCAs [2]. Among these, the SCA type 5 (SCA5) is a dominant type associated with spectrin beta nonerythrocytic 2 gene (*SPTBN2*) mutations [3–6]. SCA5 is clinically described as a slow progressive cerebellar ataxia with little brainstem or spinocerebellar tract or cerebrum involvement and an onset principally in adulthood [4]. Two patients with infantile-onset SCA5 with the same novel heterozygous *SPTBN2* mutation have recently been reported [7,8]; these patients presented a more severe phenotype than usual, with global developmental delay and hypotonia. Here, we report on the first

* Corresponding author at: Department of Pediatrics, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8510, Japan.
E-mail address: tmzn1005@ksh.biglobe.ne.jp (T. Mizuno).

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Japanese patient with infantile-onset SCA5 with a novel heterozygous *SPTBN2* mutation.

2. Case report

The proband was a 6-year-old girl born to non-consanguineous parents at gestational week 39. The neonatal course was unremarkable. The patient displayed delayed motor development and hypotonia from infancy. She acquired head control at 7 months of age and began sitting and standing independently at 2 and 3 years of age, respectively. Brain magnetic resonance imaging (MRI) performed at 10 months and 2 years of age revealed moderate cerebellar atrophy. She was referred to our hospital at 6 years of age. Physical examination revealed gaze-evoked nystagmus, saccadic eye pursuit, dysarthria, dysmetria, and intention tremor. She could take a few steps with ataxic gait. No pyramidal signs were observed; she could speak using simple sentences. Her developmental quotient was 46 according to the Kyoto Scale of Psychological Development. The patient showed no apparent periods of regression.

Laboratory analysis revealed normal levels of α-fetoprotein and amino acids in the serum and organic acids in the urine. Levels of lactate and pyruvate in the serum and cerebrospinal fluid were normal. Giemsa banding revealed a normal karyotype. Brain MRI revealed moderate cerebellar atrophy and mild pontine atrophy (Fig. 1). Electroencephalography revealed occasional spikes or spike and wave complexes that predominantly occurred over the left central and middle temporal areas. Comprehensive target capture sequencing was performed using TruSight One sequencing panels (Illumina, San Diego, CA) to identify the causative gene. A written informed consent was obtained from her parents, and the analysis was approved by the ethical committee at Tokyo Medical and Dental University. The analysis identified a novel missense mutation in *SPTBN2* (c.1309C<G, p.R437G). Upon investigation, we discovered that the mutation occurred *de novo* in the patient and that it was not registered in the Human Genetic Variation Database or the Japanese Genome Variation Database, which includes genetic variations determined via exome sequencing of 1208 Japanese individuals. Evolutionary conservation analysis using PhyloP program indicated that the arginine at 437 was highly conserved among multiple species. The pathogenicity of this missense mutation was predicted using two programs: Sorting Intolerant from Tolerant (0, intolerant) and Polymorphism Phenotyping v2 database (0.926, probably damaging).

3. Discussion

Here, we present the first Japanese patient with infantile-onset SCA associated with a novel *SPTBN2* mutation. In humans, heterozygous mutations in *SPTBN2* have been designated as SCA5 [3–6]. Clinical symptoms of SCA5 are described to be slow progressive cerebellar ataxia with little brainstem or spinocerebellar tract or cerebrum involvement, and disease onset has been reported in patients as young as 10 years and as old as 68 years [4]. Two other patients with infantile-onset SCA5 associated with a novel heterozygous *SPTBN2* mutation have recently been reported [7,8]. Jacob et al. reported the case of a 12-year-old girl with congenital onset accompanied by hypotonia and early evidence of tremor and ataxia [7]. She exhibited a progressive clinical course, which included nystagmus development, tremor worsening, hyperreflexia, clonus, and facial myokymia. Neuroimaging performed at 9 years of age revealed diffuse cerebellar atrophy with a normal brainstem. During the most recent clinical examination, she could independently take approximately 10 steps, and had mild intellectual disability. Schnekenberg et al. reported the case of a 5-year-old girl who demonstrated symptoms of head nodding and unsteady arm movement within few weeks after birth [8]. Apart from cerebellar ataxia, she demonstrated failure of abduction of the eyes on lateral gaze. When examined at 5 years of age, she could take a few steps with assistance. Her brain MRI revealed cerebellar atrophy.

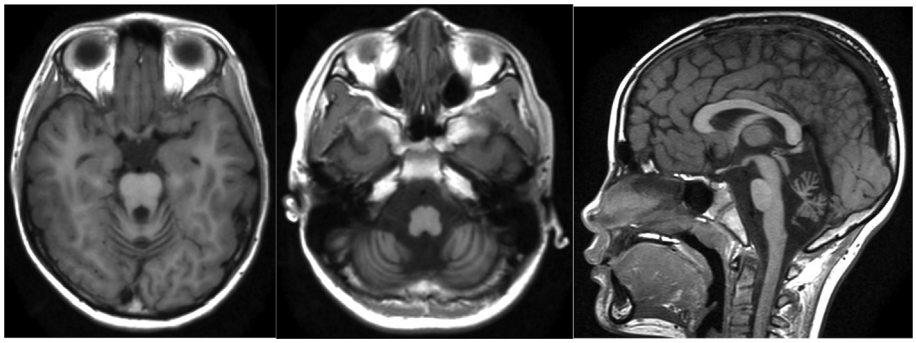

Fig. 1. Brain MRI of the patient at 6 years of age. Moderate cerebellar atrophy and mild pontine atrophy are indicated.

The above-mentioned patients had the same novel heterozygous mutation in *SPTBN2* (c.1438C>T, p.R480W). *SPTBN2* encodes β-III spectrin, which comprises an N-terminal actin-binding domain, 17 spectrin repeats, and a pleckstrin homology domain at the C-terminus [4,9]. The β-III spectrin is primarily expressed in the central nervous system, with its highest level of expression in the Purkinje cells of the cerebellum. Furthermore, β-III spectrin is involved in trafficking and anchoring of crucial neurotransmitter transporters and ion channels to neuronal cell membranes [4,9]. Schnekenberg et al. reported that voltage-gated sodium currents in cultured hippocampal neurons were lower in the presence of R480W β-III spectrin than in the presence of wild-type β-III. This finding provided an evidence for pathogenicity of this mutation [8]. The R480W mutation in *SPTBN2* is located in the second spectrin, which may be involved in dimer formation prior to self-association into a tetramer; therefore, this mutation is likely to have a significant impact on protein function. The clinical phenotype of our patient is highly similar to that of the two above-mentioned patients (Table 1). Similar to the R480W mutation, the R437G mutation in *SPTBN2* is also located in the second spectrin; therefore, the R437G mutation may also have a significant impact on protein function.

On the other hand, autosomal recessive spinocerebellar ataxia 14 (SCAR14) which is caused by homozygous mutation in *SPTBN2* gene, is reported [10]. SCAR14 is characterized by delayed psychomotor development, severe early-onset ataxia, and eye movement abnormalities. Although we can not deny the possibility that our patient has an undetected secondary *SPTBN2* mutation in trans, the clinical features of our patient are more similar to that of the two above-mentioned patients with infantile-onset SCA5.

Furthermore, this comprehensive target capture sequencing is not able to detect the repeat expansion. The SCA patients with trinucleotide repeat expansion have almost always degenerative course, and early-onset type is more severe. So we think that the clinical course of our patient is different from that of the SCA patients with trinucleotide repeat expansion.

Fig. 2 shows the structure of *SPTBN2* and localization of mutations, as reported in previous patients with SCA5. The T472M mutation, which is also located in the second spectrin, has been reported in patients with adult-onset pure cerebellar ataxia. The reasons underlying different mutations in the same second spectrin resulting in different types of SCA5 remain unknown. Hence, further confirmation pertaining to this aspect

Table 1
Detailed clinical summary and neuroimaging findings of our patient and previously reported patients.

	Our case	Jacob et al.	Parolin Schnekenberg et al.
Age of onset	10 months	Early infancy	Neonatal period
Early symptoms	Hypotonia	Poor head control	Head nodding
	Motor retardation	Hypotonia	Unsteady arm movements
		Motor retardation	Motor retardation
Intellectual disability	+	+	NA
Brain MRI	Cerebellar atrophy	Cerebellar atrophy	Cerebellar atrophy
	Mild pontine atrophy		
SPTBN2 mutation	c.1309C>G	c.1438C>T	c.1438C>T
	p.R437G	p.R480W	p.R480W
Prognosis	Take a few steps independently	Take 10 steps independently	Stand independently
	(7 years old)	(12 years old)	(4 years old)

NA: not applicable.

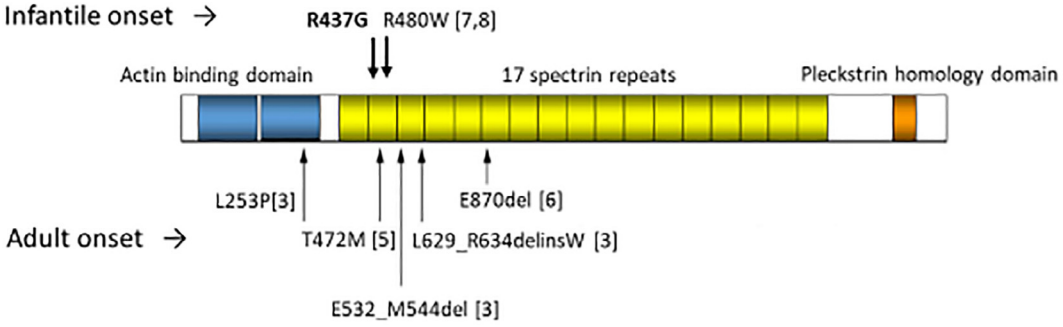

Fig. 2. Structure of *SPTBN2* and localization of mutations in previously reported patients with SCA5. The mutations in the upper line are associated with cases of infantile-onset, whereas those in the lower line are associated with cases of adult-onset.

by functional genetic analysis or identification of additional cases is needed.

Our findings indicate that *SPTBN2* mutations may be associated with infantile-onset cerebellar ataxia accompanied with global developmental delay. Hence, we should consider the possibility of SCA5 in patients with above-mentioned clinical features although slow progressive cerebellar ataxia, with an onset in adulthood, is the typical clinical feature of SCA5.

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