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Letter to the Editor

A Japanese family with a novel nonsense mutation in the *spastin* gene associated with both cerebellar ataxia and cognitive impairment

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Dear Editor,

Hereditary spastic paraplegias (HSPs) are a group of neurodegenerative disorders characterized by spasticity and weakness of the lower extremities. Among HSPs, the *spastin* mutation with SPG4 is the most common genetic abnormality, and usually causes a pure form of HSP with autosomal dominant transmission [1,2]. We report here a novel nonsense mutation in the *spastin* gene in a Japanese SPG4 family presenting as a complicated form of HSP. Our patients showed spastic paraplegia associated with both cerebellar ataxia and cognitive impairment, which are rarely reported in SPG4.

1. Case report

A 48-year-old right-handed Japanese male (proband) visited our hospital because of unsteadiness of gait. At age 46, he began to fall easily. Dysuria appeared at age 47. The symptoms gradually worsened. The family pedigree is shown in Fig. 1A.

Neurological examination at age 48 revealed leg spasticity and weakness, cognitive impairment, slurred speech and cerebellar ataxia. Eye movements were normal and nystagmus was absent. Sensation was normal and involuntary movements were not observed. The tendon reflexes of all limbs were exaggerated with bilateral ankle clonus and positive Babinski's signs. The assessment and rating of ataxia (SARA) score was 11/40. His gait was spastic and ataxic. He frequently urinated, and sometimes showed urinary incontinence. Urological examination revealed no prostatic hyperplasia or tumor, and so he was diagnosed as having neurogenic bladder dysfunction.

Conventional cognitive evaluation revealed his attentional issues. He showed scores of 20/30 for the Japanese version of the Montreal Cognitive Assessment scale, 22/30 for the Mini Mental State Examination (MMSE), 19/30 for the the revised Hasegawa's dementia scale (HDS-R), and 9/18 for the Frontal Assessment Battery. The Wechsler Adult Intelligence Scale-Third Edition showed a verbal IQ of 59, a performance IQ of 65, and a full-scale IQ of 59. In the Standard Language Test of Aphasia, information processing disability and decreased understanding of language, paraphasia, and difficulty of word recall were observed. Furthermore, he had more problems with longer words. These tests indicated difficulty in speech based on aprosexia, a decrease in frontal lobe function, and attentional issuea. The Hamilton Depression Rating Scale score was 1.

Basic laboratory tests including TSH, vitamin B1 and B12, HTLV-1 antibody, syphilis, and very-long-chain fatty acid were normal. Brain MRI revealed mild cerebral and cerebellar atrophy, but thinning of the corpus callosum or hippocampal atrophy was absent (Fig. 1B). ^{123}I-IMP SPECT imaging revealed unremarkable findings.

His mother noted gait disturbance and forgetfulness at age 62. At age 72, she could not walk due to contractures of the knee joints. Neurological examination revealed severe dementia and cerebellar dysarthria, so we could not perform HDS-R or MMSE evaluation. The SARA score was 17/40. Eye movements were normal and nystagmus was absent. Sensation was normal and involuntary movements were not observed. The tendon reflexes were exaggerated in the upper limbs, but were absent in the lower limbs due to the severe leg contractures.

We performed gene analysis for HSPs by means of whole exome sequencing of the proband. The mean depth in the target region was 98.66, and the coverage of the target region was 99.77%. We identified a novel heterozygous nonsense mutation in the *spastin* gene (NM_014946.3 (SPAST): c. 1136 T > A [p.Leu379*]) in the proband. This variant was not seen in ExAC (http://exac.broadinstutute.org/) or HGVD (http://www.hgvd.genome.med.kyoto-u.ac.jp/). Whole exome sequencing did not reveal any mutation in the causative genes for SPG1–79 or SCA 1–47 (variations of the genes except for repeat expansions for HSP and autosomal dominant cerebellar ataxia are shown in the Supplemental Table). Furthermore, molecular analysis in the proband excluded repeat expansion diseases including SCA1, SCA2, MJD/SCA3, SCA6, SCA7, SCA8, SCA12, SCA17 and DRPLA by Sanger sequencing. We confirmed the mutation in the proband by Sanger sequencing. This nonsense mutation, which leads to premature termination of exon 8 in the *spastin* gene, cosegregated with the disease phenotype in this family (Fig. 1C).

The present study was approved by the institutional review board of Yamanashi University, and written informed consent was obtained from all individuals.

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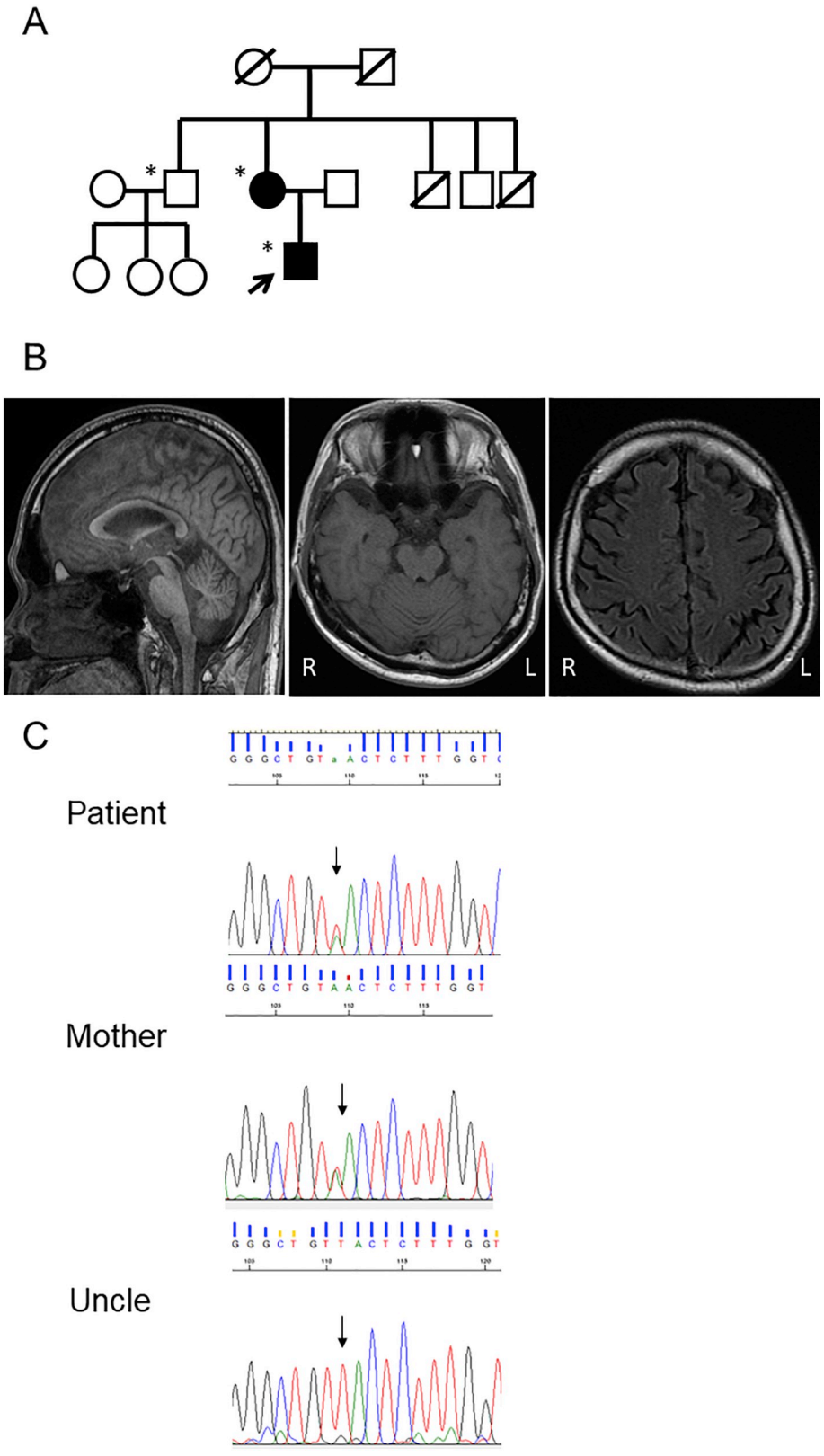

Fig. 1. Family pedigree. Squares and circles indicate males and females, respectively. Filled symbols indicate affected individuals, and open symbols unaffected individuals. Asterisks indicates individuals who underwent gene analysis. The slashes indicate deceased. A. Left: T1-weighted, sagittal slice. Middle and Right: T1-weighted, axial slice. Brain MRI of the proband revealed mild cerebral and cerebellar atrophy, but thinning of the corpus callosum or hippocampal atrophy was absent. B. Sanger sequencing revealed a novel heterozygous nonsense mutation in the *SPAST* gene (c. 1136 T > A, p. L379*) (arrows) in the proband and mother. However, it revealed no mutation (arrow) in his unaffected uncle.

2. Discussion

We described two SPG4 patients in a Japanese family associated with both cerebellar ataxia and cognitive impairment. Although most patients with SPG4 show a pure HSP phenotype, a mild cerebellar syndrome in the upper limbs was diagnosed in four of 224 SPG4 patients [3]. Similarly, we estimated that 9.0% of 100 Japanese SPG4 patients showed cerebellar ataxia through the Japan Spastic Paraplegia Research Consortium [2].

Cognitive impairment is also an atypical symptom observed in nine of 224 SPG4 patients [3]. Since cognitive problems have been reported later in the course of the disease, typically after the age of 70 [4–6], it is

noteworthy that the proband showed young-onset cognitive impairment with spastic paraplegia. Similarly, a SPG4 patient with cognitive impairment before the age of 40 has been reported [7]. Thus, we should consider SPG4 even in a case with early-onset cognitive impairment with spastic paraplegia.

To date, only one SPG4 patient with both cerebellar ataxia and cognitive impairment has been reported [8]. However, since the patient reported had depression, the cognitive impairment would have been caused by the depression [8]. Meanwhile, our patients did not present depression and SPECT imaging did not indicate treatable dementia or neurodegenerative dementia such as Alzheimer disease, diffuse Lewy body disease, or frontotemporal dementia. Thus, the cognitive impairment might have been due to SPG4, and this is the first family with SPG4 associated with both cerebellar ataxia and cognitive impairment.

In the present study, we found a novel heterozygous mutation in the *spastin* gene in two patients. A lot of missense, nonsense, and splice-site mutations, and ones with deletions and insertions in the *spastin* gene have been identified so far. Cognitive decline and dementia have been reported to be features of SPG4 due to deletion of exon 17 in the *spastin* gene [6]. Furthermore, patients with young-onset cognitive impairment exhibited deletion of exons 4–9 in the *spastin* gene [7], and had mutations in two genes, i.e., *spastin* and the neighboring *DPY* gene [9]. However, what kind of *spastin* mutation causes cerebellar ataxia remains unknown. Comparison of the phenotypes observed in patients carrying a missense mutation versus patients with truncated spastin failed to reveal any differences in the clinical sign frequency, disease severity or age at onset [3]. The present study might broaden the clinical and genetic spectrum of SPG4, and provide an opportunity to study the genotype-phenotype correlation in SPG4.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2018.12.025.

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Conflicts of interest

None.

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