Identification of a novel mutation in *ATP13A2* associated with a complicated form of hereditary spastic paraplegia

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Abstract

Objective
To establish molecular diagnosis for a family with a complicated form of autosomal recessive hereditary spastic paraplegia with intellectual disability, cognitive decline, psychosis, peripheral neuropathy, upward gaze palsy, and thin corpus callosum (TCC).

Methods
Physical examinations, laboratory tests, structural neuroimaging studies, and exome sequence analysis were carried out.

Results
The 3 patients exhibited intellectual disability and progressive intellectual decline accompanied by psychiatric symptoms. Gait difficulty with spasticity and pyramidal weakness appeared at the ages of 20s–30s. Brain MRI revealed TCC with atrophic changes in the frontotemporal lobes, caudate nuclei, and cerebellum. Exome sequence analysis revealed a novel homozygous c.2654C>A (p. Ala885Asp) variant in the *ATP13A2*, a gene responsible for a complicated form of hereditary spastic paraplegia (SPG78), Kufor-Rakeb syndrome, and neuronal ceroid lipofuscinosis. The predominant clinical presentations of the patients include progressive intellectual disability and gait difficulty with spasticity and pyramidal weakness, consistent with the diagnosis of SPG78. Of note, prominent psychiatric symptoms and extrapyramidal signs including rigidity, dystonia, and involuntary movements preceded the spastic paraparesis.

Conclusions
Our study further broadens the clinical spectrum associated with *ATP13A2* mutations.

Glossary

HSP = hereditary spastic paraplegia; **KRS** = Kufor-Rakeb syndrome; **NBIA** = neurodegeneration with brain iron accumulation; **NPC** = Niemann-Pick disease type C; **PARK9** = Parkinson disease; **SPG78** = spastic paraplegia; **TCC** = thin corpus callosum.

Hereditary spastic paraplegias (HSPs) are neurodegenerative disorders characterized by slowly progressing spasticity and pyramidal weakness of the lower limbs. Clinically, HSPs are classified into pure and complicated forms. Patients with pure HSPs show lower limb spasticity associated with pyramidal weakness alone, whereas patients with complicated forms show additional neurologic signs. To date, SPG1–SPG80 have been described as the genetic loci for HSP.

Mutations in the *ATP13A2* gene were originally identified in patients with Kufor-Rakeb syndrome (KRS), a rare autosomal recessive form of juvenile-onset atypical parkinsonism associated with supranuclear gaze palsy, spasticity, and dementia,[1] and subsequently reported in those with early onset Parkinson disease (PARK9),[2,3] neuronal brain iron accumulation,[4] and neuronal ceroid lipofuscinosis (CLN12).[5] Recently, Estrada-Cuzcano et al.[6] described cases of complicated HSP (SPG78) with c.1550C>T (p.Thr517Ile), c.364C>T (p.Gln122*), or c.1345C>T/c.3418C>T (p.Arg449*/p.Gln1140*) (NM 022089) in the *ATP13A2* gene. Functional analysis of ATP13A2 with the p.Thr517Ile missense variant confirmed the loss of function of *ATP13A2*.[6]

We have recently experienced 3 sibling cases in one family with a complicated form of HSP accompanied by intellectual disability and psychiatric symptoms. Exome sequence analysis of the proband revealed a novel homozygous mutation of c.2654C>A (p.Ala885Asp) in the *ATP13A2* gene. We herein report the detailed clinical presentations of the 3 cases showing considerable overlaps with those described in other *ATP13A2*-related disorders.

# Clinical manifestations of the 3 sibling cases

Patient 1

The pedigree chart of the family is presented in figure 1. The parents of the 3 siblings (patients 1, 2, and 3) were first cousins. Her father died of cerebral infarction at the age of 60 years, and her mother had dementia with anxiety along with lumbar spondylosis around the age of 76 years. Patient 1 (II-1) did not show any abnormalities at birth. Intellectual disability was noticed in her childhood and she went to a special support class. Her motor function, however, developed normally. At the age of 19 years, she experienced relationship and paranoid delusions, leading to the diagnosis of schizophrenia at a local general hospital. She was prescribed several antipsychotics. She developed a gait abnormality at the age of 29 years, and dystonia was observed in the extremities, especially in the upper extremities at the age of 30. There

were neither cerebellar signs nor nystagmus. She was noticed to have rigidity in her extremities and supranuclear gaze palsy at the age of 33. Later, she exhibited spasticity in the lower limbs. Her intellectual impairment and gait disturbance gradually deteriorated, and she became bedridden around the age of 40. Partial seizures and generalized tonic seizures appeared around the age of 52. Later, she was diagnosed as having HSP at our hospital. She exhibited spasticity and muscle atrophy in the lower limbs, generalized increased tendon reflexes, extensor plantar reflexes, and involuntary movement in her upper trunk. Brain MRI taken at the age of 48 showed thin corpus callosum (TCC) and atrophic changes in frontotemporal lobes, caudate nuclei, cerebellum, and brainstem (figure 2A). Brain MRI did not show iron accumulation in the putamen or caudate nucleus. Routine blood test results were within the normal limits. There were no lesions in the spinal X rays. There was no hepatosplenomegaly.
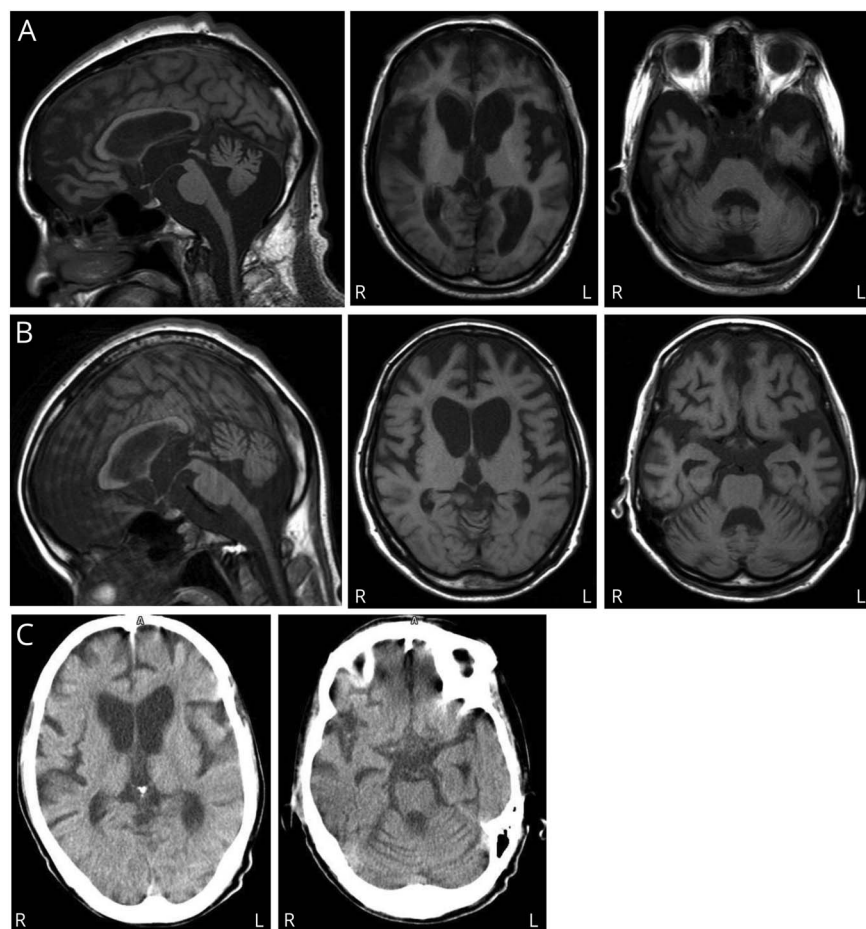
Patient 2

Patient 2 was the younger sister of the patient 1. She had no abnormalities at birth. Intellectual disability was noticed in her childhood and she went to a special support class. Her motor function developed normally. At the age of 31, she talked to herself, exhibited forced laughing, and became increasingly irritable. She developed gait abnormality at the age of 32. She showed horizontal gaze nystagmus and rigido-akinetic clinical presentations but did not show tremor. She exhibited spasticity and muscle atrophy in the lower limbs, increased tendon reflexes in her 4 extremities, and extensor plantar reflexes. Her symptoms of intellectual impairment and gait disturbance gradually worsened, and she became bedridden at the age of 34. She was diagnosed as having HSP. At the age of 44, neurologic

Figure 1 Pedigree chart of the family
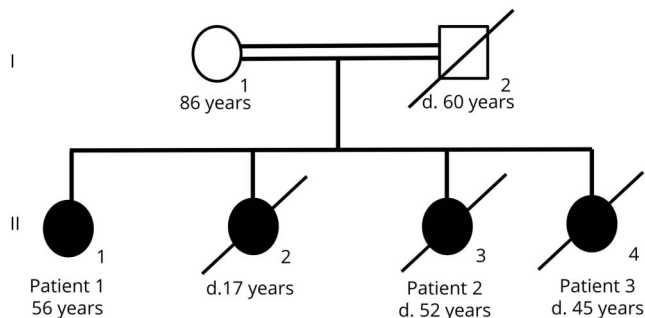
Squares and circles indicate men and women, respectively. A diagonal line through a symbol indicates a deceased individual. Affected individuals are indicated by filled symbols. II-2 had intellectual disability and gait disturbance at the age of 13 and died at age of 17.

Figure 2 Neuroimaging studies of the patients

(A) T1-weighted brain MRI scans of patient 1 at the age of 48. TCC and atrophic changes in frontotemporal lobes, caudate nuclei, cerebellum, and brainstem are shown. (B) T1-weighted brain MRI scans of patient 2 at the age of 46. TCC and atrophic changes in frontotemporal lobes, caudate nuclei, cerebellum, and brainstem are shown. Brainstem atrophy was also observed. (C) Brain CT scans of patient 3 at the age of 45. Atrophic changes in frontotemporal lobes, caudate nuclei, cerebellum, and brainstem are shown. TCC = thin corpus callosum.

examination revealed severe intellectual disability and euphoria and an upward gaze limitation. She could not speak because of progressing dementia. She exhibited an involuntary movement of extending her right elbow, and her legs were in flexed positions with contracture of knee and ankle joints. She was diagnosed as having a complicated form of HSP. Brain MRI taken at the age of 46 showed TCC and atrophic changes in frontotemporal lobes, caudate nuclei, cerebellum, and brainstem (figure 2B). Brain MRI did not show iron accumulation in the putamen or caudate nucleus. Routine blood test results were within the normal limits. There were no lesions in the spinal X rays. There was no hepatosplenomegaly.

She suffered from bacterial meningoencephalitis at the age of 46 but recovered by treatment with antibiotics. After this event, partial and generalized tonic seizures appeared. Later, she exhibited involuntary movement, shaking her head from side to side. Her condition gradually deteriorated, and she died of pneumonia at the age of 52.
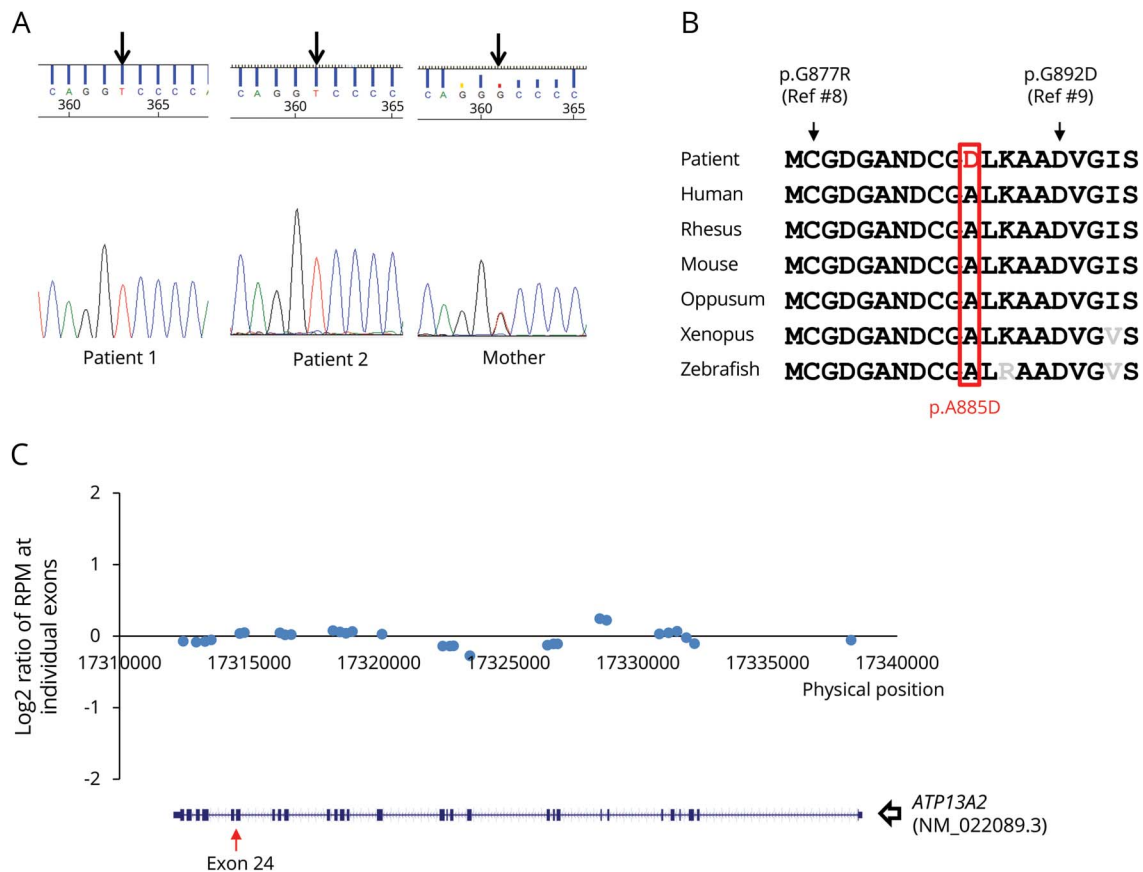
Patient 3

Patient 3 was the youngest sister of patients 1 and 2. She had no abnormalities at birth. Intellectual disability was noticed in her childhood and she went to a special support class. Her motor function developed normally. At the age of 33, she experienced hallucinations and delusions. She presented with spastic tetraparesis and spastic gait at the age of 35. She became unable to walk in a few years. Her intellectual impairment deteriorated. At the age of 42, she had euphoria and exhibited dysarthria. She did not have any abnormal eye movements. She presented with spasticity and muscle atrophy in the lower limbs, generalized increased tendon reflexes, and extensor plantar reflexes. There was mild dysmetria in her upper limbs, and she exhibited stereotypic movements in her upper limbs and face. Owing to these movements, she frequently hit her arm against the bed fence. She was diagnosed as having a complicated form of HSP. Brain CT scan taken at the age of 45 showed atrophic changes in frontotemporal lobes, caudate nuclei, cerebellum, and brainstem (figure 2C). Routine blood test results were within normal limits. There were no lesions in the spinal X rays. There was no hepatosplenomegaly. Her condition gradually deteriorated and she died of respiratory failure at age 45.

Mutational analysis

We received approval from the National Hospital Organization, Hokuriku National Hospital Clinical Research Ethics

Figure 3 Mutational analysis of the family

(A) Direct nucleotide sequence analysis of the PCR products obtained from patients 1, 2, and their mother showing c.2654C>A (p.Ala885Asp). Nucleotide sequence analysis of the reverse complementary strand is shown. (B) The c.2654C>A (p.Ala885Asp) involves alanine residue at codon 885 that is highly conserved among species. Conserved amino acid residues are shown by black, whereas those showing a strong conservation among species are shown by gray. Other previously reported causative variants (p.G877R and p.G892D) are shown above the amino acid sequences. (C) Comparison of RPM (reads per million mapped reads) in individual exons of *ATP13A2* calculated using the results of exome sequence analysis. Log2 ratio of RPM at individual exons is shown on the y-axis, whereas the physical position of *ATP13A2* on human chromosome 1 (GRCh37/hg19) is shown on the x-axis. There are no significant differences in the RPM values of individual exons including exon 24, where the variant is located, confirming the homozygosity of the c.2654C>A (p.Ala885Asp) variant in the patients.

Committee, to conduct this study and obtained written informed consent from the family for genetic testing and protocol. Exome sequence analysis was performed as described previously.[7]

NM 022089 was used as the reference sequence for *ATP13A2* in this study. The disease-causing variant was confirmed by primer pairs (5′-GCCCAGCTGTCATCATTTC and 5′-CCCACGTCATCTATTCTGGG).

Data availability

The raw data are available upon request.

Results

Identification of causative variant

We searched exome sequence data of patient 1 for rare variants in the known causative genes for HSP (the gene list for HSP is shown in the supplementary data, links.lww.com/NXG/A319) and identified an apparently homozygous c.2654C>A (p.Ala885Asp) variant in *ATP13A2* in patients 1 and 2 (figure 3A). Analysis of the number of reads from individual exons excluded the possibility of large deletions involving exons including exon 24 in one allele (figure 3C) confirming the homozygosity of the c.2654C>A (p.Ala885Asp) variant.

The variant was neither registered in gnomAD (gnomad.broadinstitute.org/) nor in the in-house database consisting of 1,261 control subjects. The variant was only registered in the integrative Japanese Genome Variation Database (ijgvd.megabank.tohoku.ac.jp/) at a very low allele frequency (0.00015). The amino acid, Ala, at codon 885 is evolutionarily conserved among species (figure 3B). In silico prediction revealed a combined annotation dependent depletion score of 28.1, supporting its pathogenicity (cadd.gs.washington.edu/home)."

Table Clinical characteristics of patients with SPG78

	This study			Estrada-Cuzcano et al.[6]					van de Warrenburg et al.[9,10]	Erro et al.[11]	Estiar et al.[12]		
	Patient 1	Patient 2	Patient 3	HSP84/II-1	HSP84/II-3	HSP84/II-4	HIH21480/II-3	HIH22132/II-1	Patient 17	NAPO-7	Patient A	Patient B	Patient C
Mutation (coding DNA)[a] [NM_022089]	c.[2654C>A]; [2654C>A]	c.[2654C>A]; [2654C>A]	Not examined	c.1550C>T(;) (1550C>T)	c.1550C>T(;) (1550C>T)	c.1550C>T(;) (1550C>T)	c.364C>T(;) (364C>T)	c.1345C>T(;) (3418C>T)	c.2675G>A(;) (2675G>A)	c.2629G>A(;) (2629G>A)	c.insAAdelC(;) (2473 2474)	c.2126G>C(;) (2126G>C)	c.2158G>T(;) (2158G>T)
Mutation (predicted protein)[a]	p.[(Ala885Asp)]; [(Ala885Asp)]	p.[(Ala885Asp)]; [(Ala885Asp)]	Not examined	p.(Thr517Ile) (;) (Thr517Ile)	p.(Thr517Ile) (;) (Thr517Ile)	p.(Thr517Ile) (;) (Thr517Ile)	p.(Gln122*) (;) (Gln122*)	p.(Arg449*) (;) (Gln1140*)	p.(Gly892Asp) (;) (Gly892Asp)	p.[(Gly877Arg)] [(Gly877Arg)]	p.(leu825Asnfs*32) (;) (leu825Asnfs*32)	p.(Arg709Thr) (;) (Arg709Thr)	p.(Gly720Trp) (;) (Gly720Trp)
Gender	Female	Female	Female	Male	Male	Male	Female	Female	Male	Male	Female	Male	Male
Age at onset of psychiatric symptom (y)	19	30	33	n.a.	n.a.	n.a.			None	31	40	31	12
Age at onset of gait difficulty (y)	29	30	35	30	33	30	36	32	11	31	31	18	32
Age at examination (y)	49	45	42	50	40	50	47	39	37	n.a.	44	31	32
Cognitive deficits	Intellectual disability, severe dementia	Intellectual disability, severe dementia	Intellectual disability, severe dementia	Slight verbal memory deficit	None	Slight verbal memory deficit	Severe dementia	Severe frontotemporal dementia	Cognitive decline	Intellectual disability	Cognitive decline	Mild intellectual disability, cognitive decline	Learning difficulty
Behavioral and psychiatric symptoms	Delusion	Irritability, empty smile	Hallucination, delusion	None	None	None	Labile motivation	Aggression acoustic hallucinations	None	None	Laughing excessively, aggressive	Delusion, hallucination	Psychotic episode, paranoid delusions
Pyramidal and peripheral motor system													
UL/LL spasticity	-/+	-/+	-/+	-/+	-/+	-/+	-/+	-/+	+/+	+/+	-/+	-/+	-/+
UL/LL weakness	+/+	+/+	+/+	-/+	-/+	-/+	-/+	+/+	+/+	n.a.	-/+	-/+	-/+
Increased tendon reflexes UL/LL	+/+	+/+	+/+	+/+	+/+	+/+	-/+	+/+	n.a.	+/+	-/+	+/+	n.a.
Muscle atrophy	+	+	+	-	-	-	-	-	n.a.	n.a.	n.a.	+	n.a.
Babinski sign	Extensor	Extensor	Extensor	Extensor	Extensor	Extensor	-	Extensor	Extensor	Extensor	Extensor	Extensor	Extensor
Extrapyramidal motor system	+	+/-	-	-	-	-	-	+	+	+	+	n.a.	-
Other involuntary movement	+ (upper body)	+ (head)	+ (Rt upper limb)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	Action tremor	n.a.	n.a.
Supranuclear palsy	+	(Upgaze limitation)	-	-	-	-	Vertical	Horizontal and vertical	(Upgaze limitation)	n.a.	n.a.	n.a.	n.a.
Seizure	Partial and generalized tonic seizure	Partial and generalized tonic seizure	-	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	Seizures	n.a.	n.a.

Continued

Table Clinical characteristics of patients with SPG78 *(continued)*

	This study			Estrada-Cuzcano et al.[6]					van de Warrenburg et al.[9,10]	Erro et al.[11]	Estiar et al.[12]		
	Patient 1	Patient 2	Patient 3	HSP84/II-1	HSP84/II-3	HSP84/II-4	HIH21480/II-3	HIH22132/II-1	Patient 17	NAPO-7	Patient A	Patient B	Patient C
Imaging	Diffuse cerebral and cerebellar atrophy, TCC	Diffuse cerebral and cerebellar atrophy, TCC	Diffuse cerebral and cerebellar atrophy	Cerebellar > cortical atrophy	Mild cortical atrophy periventricular white matter changes, "ear of lynx sign"	Cerebellar > cortical atrophy	Cerebellar > cortical mesencephalic atrophy, TCC, Hydrocephalus, periventricular white matter changes	Cerebellar > cortical atrophy, "ear of lynx sign"	Cerebral and cerebellar atrophy	Generalized atrophy	Diffuse cerebellar atrophy	Diffuse cerebral and cerebellar atrophy, hypoplasia of the corpus callosum	Cortical and cerebellar atrophy with signs of leukoencephalopathy in semioval centers, especially on the right side
Nerve conduction studies	Minimally decreased MCV/CMAP and SCV/SNAP	Minimally decreased MCV/CMAP and SCV/SNAP	Minimally decreased MCV/CMAP and SCV/SNAP	Axonal motor and sensory polyneuropathy	Normal	Axonal motor and sensory polyneuropathy	Mixed axonal-demyelinating motor polyneuropathy	Mild axonal sensory polyneuropathy	n.a.	n.a.	n.a.	n.a.	n.a.

Abbreviations: CMAP = compound muscle action potential; MCV = motor nerve conduction velocity; n.a. = not available; SCV = sensory nerve conduction velocity; SNAP = sensory nerve action potential; TCC = thin corpus callosum; UL/LL = upper limb/lower limb.
[a] Nomenclature of DNA and protein variants is based on the Guidelines by Human Genome Variation Society (hgvs.org/).

Discussion

The clinical presentations of the 3 patients are summarized in table. Prominent psychiatric symptoms preceding gait abnormality commonly observed in the 3 patients in this family was one of the characteristic clinical presentations. In particular, all the patients presented psychiatric symptoms such as hallucination, delusion, or increased irritability over one to 10 years before the onset of gait disturbance. Although psychiatric symptoms have previously been frequently reported in patients with KRS or PARK9,[2,3,13,14] they usually develop several years after the onset of gait disturbances or administration of antiparkinsonian drugs. Among the patients with PARK9, the one patient reported by Schneider et al.[4] is an exceptional case presenting with the psychiatric symptoms before the onset of parkinsonism. Among the patients with the clinical diagnosis of HSP with *ATP13A2* mutation (SPG78), only one case of Estiar et al.[12] presented with psychiatric symptoms preceding spastic paraparesis.

Psychiatric symptom is also observed in patients with neurodegeneration with brain iron accumulation (NBIA) presenting with progressive dystonia/parkinsonism.[15,16] Although we did not observe iron deposition in our patients, NBIA or NBIA-related diseases should also be included in a differential diagnosis for patients presenting with psychiatric symptoms accompanied by dystonia/parkinsonism. Supranuclear gaze palsy is also a characteristic finding in *ATP13A2*-related diseases. In addition to progressive supranuclear palsy and parkinsonism linked to chromosome 17 (FTDP-17), supranuclear gaze palsy is also observed in patients with Niemann-Pick disease type C (NPC) presenting with dystonia, cognitive decline, and psychiatric symptoms,[17–19] thus NPC should also be included in a differential diagnosis.

TCC is an important finding in the differential diagnosis of HSP and is observed in SPG1, SPG11, SPG15, SPG21, SPG44, SPG46, SPG47, SPG49, SPG50, SPG54, SPG63, SPG66, and SPG71.[20] Becuase MRI scans revealed TCC in patients 1 and 2 in this study and one patient with SPG78 showed TCC,[6] SPG78 should also be included in the differential diagnosis of HSPs with TCC.

Patient 1 initially manifested extrapyramidal symptoms. Indeed, she was initially tested for possible Wilson disease, but spastic paraparesis appeared later and became predominant over time. Patient 2 had pallidopyramidal syndrome (rigidoakinetic plus spasticity), and patient 3 had spastic tetraparesis with cognitive decline. In contrast to previous reports showing the similar clinical presentations among the siblings with the *ATP13A2* variants,[6] the 3 siblings in this family exhibited similar but considerable variation in the complex clinical presentations. Thus, the present 3 sibling case falls in the continuum between the 2 extremities (HSP78 and KRS).[6,21] Intrafamilial and interfamilial variations in the clinical presentations associated with *ATP13A2* mutation should be further investigated.

Disclosure

The authors report no disclosures. Go to Neurology.org/NG for full disclosures.

Appendix Authors

Name	Location	Contribution
Yasuko Odake, MD	Department of Clinical Research, National Hospital Organization, Hokuriku National Hospital, Nanto, Japan	Drafting of the manuscript and clinical characterization
Kishin Koh, MD, PhD	Department of Neurology, Graduate School of Medical Science, University of Yamanashi, Tyuo, Japan	Genetic tests, assessment and revision of the manuscript
Yoshihisa Takiyama, MD, PhD	Department of Neurology, Graduate School of Medical Science, University of Yamanashi, Tyuo, Japan	Genetic tests, assessment and revision of the manuscript
Hiroyuki Ishiura, MD, PhD	Department of Neurology, The University of Tokyo, Tokyo, Japan	Genetic tests, assessment, major role in the acquisition of data and revision of the manuscript
Shoji Tsuji, MD, PhD	Department of Molecular Neurology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; Institute of Medical Genomics, International University of Health and Welfare	Genetic tests, assessment, major role in the acquisition of data and revision of the manuscript
Masahito Yamada, MD, PhD	Department of Neurology and Neurobiology of Aging, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan	Clinical characterization and revision of the manuscript

Appendix *(continued)*

Name	Location	Contribution
Mitsuhiro Yoshita, MD, PhD	Department of Clinical Research, National Hospital Organization, Hokuriku National Hospital, Nanto, Japan	Clinical characterization, revision of the manuscript, study supervision and coordination

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