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

Yasuko Odake, MD, Kishin Koh, MD, PhD, Yoshihisa Takiyama, MD, PhD, Hiroyuki Ishiura, MD, PhD, Shoji Tsuji, MD, PhD, Masahito Yamada, MD, PhD, and Mitsuhiro Yoshita, MD, PhD

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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.
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, and subsequently reported in those with early onset Parkinson disease (PARK9), neuronal brain iron accumulation, and neuronal ceroid lipofuscinosis (CLN12). Recently, Estrada-Cuzcano et al. described cases of complicated HSP (SPG78) with c.2654C>A (p.Ala885Asp) in the ATP13A2 gene. Functional analysis of ATP13A2 showed the loss of function of ATP13A2.

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. Functional analysis of ATP13A2 with the p.Ala885Asp missense variant confirmed the loss of function of ATP13A2.

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-kinetic 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
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 meningocencephalitis 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
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 $\text{ATP13A2}$ 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 $\text{ATP13A2}$ 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 in the patients.

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 evolutionally 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).8

![Figure 3 Mutational analysis of the family](image-url)
<table>
<thead>
<tr>
<th></th>
<th>This study</th>
<th>Estrada-Cuzcano et al.</th>
<th>van de Warrenburg et al.</th>
<th>Erro et al.</th>
<th>Estiar et al.</th>
<th>Patient 17</th>
<th>NAPO-7</th>
<th>Patient A</th>
<th>Patient B</th>
<th>Patient C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mutation (coding DNA)</strong></td>
<td>c.[2654C&gt;A]; (2654C&gt;A)</td>
<td>c.[2654C&gt;A]; (2654C&gt;A)</td>
<td>Not examined</td>
<td>c.1550C&gt;T (1550C&gt;T)</td>
<td>c.1550C&gt;T (1550C&gt;T)</td>
<td>c.364C&gt;T; (3418C&gt;T)</td>
<td>c.2675G&gt;A; (2675G&gt;A)</td>
<td>c.2629G&gt;A; (2629G&gt;A)</td>
<td>c.2126G&gt;C; (2126G&gt;C)</td>
<td>c.2159G&gt;T; (2159G&gt;T)</td>
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<tr>
<td><strong>Mutation (predicted protein)</strong></td>
<td>p.[(Ala885Asp)]; [(Ala885Asp)]</td>
<td>p.[(Ala885Asp)]; [(Ala885Asp)]</td>
<td>Not examined</td>
<td>p.(Thr517Ile) (Thr517Ile)</td>
<td>p.(Thr517Ile) (Thr517Ile)</td>
<td>p.(Gly892Asp)(Gly877Arg)</td>
<td>p.[(Gly325Arg)]; [(Gly325Arg)]</td>
<td>p.(Arg709Thr); (Arg709Thr)</td>
<td>p.[(Gly720Trp)]; [(Gly720Trp)]</td>
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<td><strong>Gender</strong></td>
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<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
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<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
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<tr>
<td><strong>Age at onset of psychiatric symptom (y)</strong></td>
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<td>30</td>
<td>33</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>None</td>
<td>40</td>
<td>31</td>
<td>12</td>
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<tr>
<td><strong>Age at onset of gait difficulty (y)</strong></td>
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<td>30</td>
<td>35</td>
<td>30</td>
<td>33</td>
<td>30</td>
<td>36</td>
<td>32</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td><strong>Age at examination (y)</strong></td>
<td>49</td>
<td>45</td>
<td>42</td>
<td>50</td>
<td>40</td>
<td>50</td>
<td>47</td>
<td>39</td>
<td>37</td>
<td>44</td>
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<tr>
<td><strong>Cognitive deficits</strong></td>
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<td>Intellectual disability, severe dementia</td>
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<td>None</td>
<td>None</td>
<td>None</td>
<td>Severe frontotemporal dementia</td>
<td>Cognitive decline</td>
<td>Intellectual disability</td>
<td>Cognitive decline</td>
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<td><strong>Behavioral and psychiatric symptoms</strong></td>
<td>Delusion</td>
<td>Irritability, empty smile</td>
<td>Hallucination, delusion</td>
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<td>None</td>
<td>None</td>
<td>Labile motivation</td>
<td>Agression</td>
<td>Acoustic hallucinations</td>
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<tr>
<td><strong>Pyramidal and peripheral motor system</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ul/Ll spasticity</td>
<td>–/+</td>
<td>–/+</td>
<td>–/+</td>
<td>–/+</td>
<td>–/+</td>
<td>–/+</td>
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<tr>
<td>Ul/Ll weakness</td>
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<td>+/+</td>
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<td>+/+</td>
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<tr>
<td>Increased tendon reflexes Ul/Ll</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
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<tr>
<td>Muscle atrophy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Babinski sign</td>
<td>Extensor</td>
<td>Extensor</td>
<td>Extensor</td>
<td>Extensor</td>
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<td>Extensor</td>
<td>–</td>
<td>Extensor</td>
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<tr>
<td>Extopyramidal motor system</td>
<td>+</td>
<td>+/+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Other involuntary movement</td>
<td>(upper body)</td>
<td>(head)</td>
<td>(ft. upper limb)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
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<td>Supranuclear palsy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Seizure</td>
<td>Partial and generalized tonic seizure</td>
<td>Partial and generalized tonic seizure</td>
<td>–</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
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Continued
Clinical characteristics of patients with SPG78 (continued)

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<th>Imaging</th>
<th>Nerve conduction studies</th>
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<tr>
<td>Patient 1</td>
<td>Patient 2</td>
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<tr>
<td>Diffuse cerebral and cerebellar atrophy, TCC</td>
<td>Diffuse cerebral and cerebellar atrophy, TCC</td>
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<tr>
<td>NAPD-7</td>
<td>Patient A</td>
</tr>
<tr>
<td>Minimally decreased MCV/CMAP and SCV/SNAP</td>
<td>Axonal motor and sensory polyneuropathy</td>
</tr>
</tbody>
</table>

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.

* 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 the table. Prominent psychiatric symptoms preceding gait disturbance were observed in the 3 patients, including one patient with KRS or PARK9, who did not present psychiatric symptoms. Intrafamilial and interfamilial variations in the clinical presentation were noted in 3 siblings within the same family, and the same clinical presentation was observed in at least 2 of the 3 siblings. The occurrence of psychiatric symptoms, including hallucination, delusion, or increased irritability over one to 10 years before the onset of gait disturbance, was noted in patients with KRS or PARK9, whereas the psychotic symptoms associated with the ATP13A2 mutation were not observed in patients with KRS or PARK9. The clinical presentation of psychiatric symptoms in patients with KRS or PARK9 was associated with the ATP13A2 mutation, whereas the psychiatric symptoms in patients with SPG78 were not associated with the ATP13A2 mutation. Therefore, it is suggested that multiple genetic factors may be involved in the occurrence of psychiatric symptoms in patients with parkinsonism-related disorders. Further investigation is necessary to determine the role of psychiatric symptoms in patients with KRS or PARK9.
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Disclosure
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Appendix Authors

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

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<th>Name</th>
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<tbody>
<tr>
<td>Mitsuhiro Yoshita, MD, PhD</td>
<td>Department of Clinical Research, National Hospital Organization, Hokuriku National Hospital, Nanto, Japan</td>
<td>Clinical characterization, revision of the manuscript, study supervision and coordination</td>
</tr>
</tbody>
</table>

References
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