CLINICAL REPORT

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A Novel *WDR45* Mutation in a Patient With Static Encephalopathy of Childhood With Neurodegeneration in Adulthood (SENDA)

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Static encephalopathy of childhood with neurodegeneration in adulthood (SENDA) is an X-linked dominant neurodegenerative disorder, and is classified as a subtype of neurodegeneration with brain iron accumulation. Recently, de novo heterozygous mutations in *WDR45* at Xp11.23 have been reported in patients with SENDA. We report the clinical and neuroradiological findings of a patient with SENDA with a novel c.322del mutation in *WDR45*. In this patient, characteristic MRI findings were useful for diagnosis.

Key words: static encephalopathy of childhood with neurodegenartion in adulthood (SENDA); *WDR45*; magnetic resonance imaging (MRI)

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INTRODUCTION

Neurodegeneration with brain iron accumulation (NBIA) are a clinically and genetically heterogeneous group of neurodegenerative diseases characterized by extrapyramidal movement disorder, intellectual deterioration, and a characteristic deposition of iron in the basal ganglia. Static encephalopathy of childhood with neurodegeneration in adulthood (SENDA) is an X-linked dominant neurodegenerative disorder and is classified as a subtype of NBIA [Gregory and Hayflick, 2011; Kruer et al., 2012; Schneider and Bhatia, 2012]. The SENDA phenotype is characterized by global developmental delay in early childhood that is essentially static. In early adulthood, affected individuals develop progressive parkinsonism, dystonia, spasticity, and intellectual deterioration resulting in severe disability [Gregory and Hayflick, 2011; Haack et al., 2012; Kruer et al., 2012; Schneider and Bhatia, 2012; Hayflick et al., 2013; Kasai-Yoshida et al., 2013; Saitsu et al., 2013]. To date, all affected individuals with SENDA have been sporadic with no family history, and most of them are female [Haack et al., 2012; Hayflick et al., 2013; Saitsu et al., 2013]. Recently, two independent groups have reported that de novo heterozygous mutations in *WDR45* at Xp11.23 cause SENDA [Haack et al., 2012; Saitsu et al., 2013]. *WDR45* (also known as WIPI4) is one of the four mammalian homologs of yeast Atg18, which has an important role in autophagy [Saitsu et al., 2013]. We report here on the clinical and neuroradiological findings of a patient with SENDA with a novel c.322del mutation in *WDR45*.

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The patient was a 39-year-old female. She had no family history of neurological disease. Her symptoms began at the age of 3 months with febrile seizures. The seizures were usually triggered by fever,

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and decreased in frequency from the age of 5 years. She presented with psychomotor developmental delay; even at 3 years old, she could only walk unsteadily and was able to speak only simple words. She went to special classes for the education of physically or mentally handicapped children. Her condition was stable until the age of 28 when her gait disturbance began to worsen. Thereafter, intellectual deterioration, dysphagia, dystonia, and spasticity of the limbs developed with such rapid progression that she became unable to walk at the age of 31. Percutaneous endoscopic gastrostomy was performed at the age of 35. At the age of 39, she was bedridden and unable to communicate.

Routine laboratory findings showed no abnormality. Cranial magnetic resonance imaging (MRI) showed severe cerebral atrophy, particularly that of the frontotemporal lobes. T2-weighted and T2 star-weighted images showed low signal intensities in the substantia nigra and globus pallidus, indicating iron accumulation. The T1-weighted images showed high signal intensities with central linear hypointensities in the substantia nigra and cerebral peduncles, which are known to be a unique radiological feature of SENDA. Similar changes were also observed in the globus pallidus, namely high signal intensities surrounding the central hypointensity (Fig. 1).

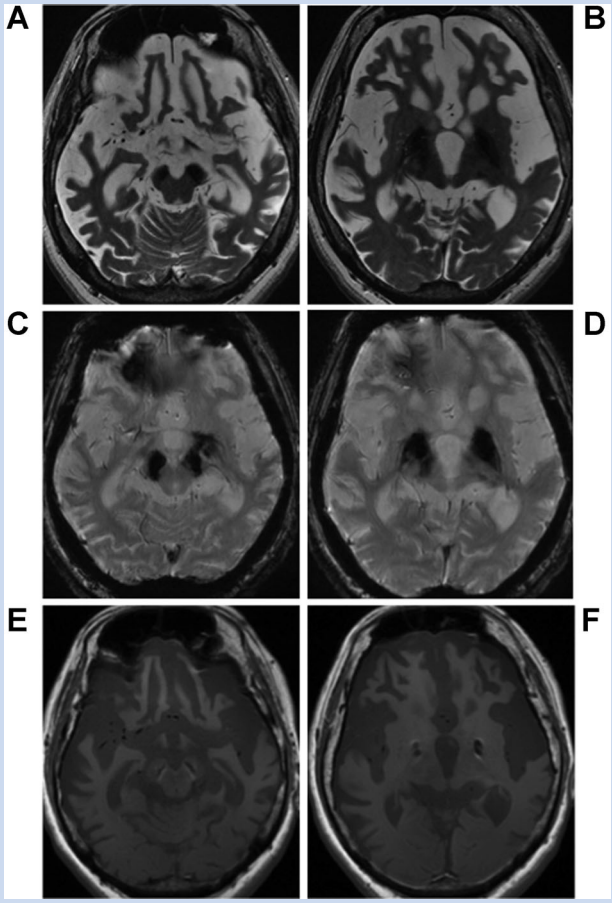

FIG. 1. Cranial MRI images obtained at the age of 39 show severe cerebral atrophy. Markedly low signal intensities are observed in the globus pallidus and substantia nigra on fast-spin-echo T2-weighted (Panel A, B: repetition time [TR]/echo time [TE] = 4781.0/105.5 ms) and gradient-echo T2 star-weighted (Panel C, D: TR/TE = 860.0/20 ms) images. High signal intensities with central low-signal-intensity portions are observed in the substantia nigra and globus pallidus on spin-echo T1-weighted images (Panel E, F: TR/TE = 540.0/9.0 ms). This patient underwent MRI using a 3.0 Tesla MR system (Discovery MR750, GE Healthcare, Fuchu-City, WI) with a standard head coil.

Molecular genetic analysis of *WDR45* was performed using the patient's genomic DNA after obtaining written informed consent from patient's family. Sequence analysis (Fig. 2) identified a novel heterogeneous frameshift mutation (c.322del) in *WDR45* (transcript variant 1, NM 007075.3), producing a premature stop codon at amino acid position 118 (p.Ser108Leufs*10). The mutation was not found in her parents, and we conclude that it is apparently de novo (Fig. 2).

This study was approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

DISCUSSION

The MRI findings of patients with SENDA are highly characteristic: (1) iron deposition in the globus pallidus and substantia nigra, (2) high signal intensities in the substantia nigra and the cerebral peduncles with central linear hypointensities on T1-weighted images, and (3) severe cerebral atrophy in adolescence [Kruer et al., 2012; Kimura et al., 2013]. Similar to the previous reports, MRI findings, particularly those on T1-weighted images are very characteristic in the present patient, and might be a key to the prompt diagnosis of SENDA.

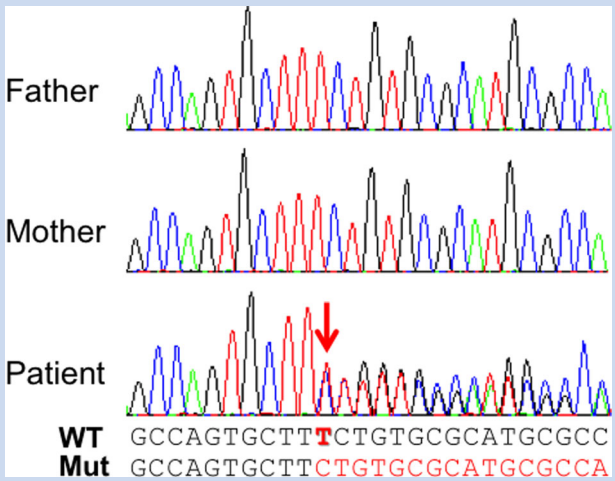

FIG. 2. Direct sequence analysis of *WDR45* showed heterogeneous c.322 deletion mutation in this patient, leading to frameshift mutation (p.Ser108Leufs*10). The mutation was not found in her parents.

Only a few genetically confirmed patients with SENDA have been reported [Haack et al., 2012; Hayflick et al., 2013; Saitsu et al., 2013]. This condition, however, has only been recognized very recently; therefore, there is a possibility that our identification of the unique clinical features and MRI findings of this condition may lead to the discovery of more patients who are currently undiagnosed.

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