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Letter to the Editor

A *de novo* mutation in the *NALCN* gene in an adult patient with cerebellar ataxia associated with intellectual disability and arthrogryposis

To the Editor:

Mutations in *NALCN* cause either a recessive or dominant condition. Recessive mutations predominantly cause hypotonia and severe intellectual disabilities like infantile neuroaxonal dystrophy (1, 2). Meanwhile, dominant mutations are all *de novo*, and cause congenital contractures of the limbs and face, hypotonia, and global developmental delay syndrome, or intellectual disability, ataxia and arthrogryposis (3–5). Thus, both recessive and dominant mutations might cause a severe phenotype in childhood. In contrast, we report here the first adult patient with a relatively mild phenotype with a *de novo* *NALCN* mutation.

A 33-year-old Japanese woman presented with cerebellar ataxia associated with intellectual disability and arthrogryposis. She was able to run and ride a bicycle until age 18. After that, her movement balance worsened. At age 26, she first visited our hospital because of unsteadiness of gait. Neurological examination revealed mild limb and truncal cerebellar ataxia. Cerebellar ataxia was not episodic. She showed an ataxic gait, but she could walk about 2 km without assistance. Mild slurred speech was noted. Wechsler Adult Intelligence Scale-Revised showed an intelligence quotient (IQ) of 40, a verbal IQ (VIQ) of 45, and a performance IQ (PIQ) of 45. She had minor dysmorphisms including a broad nasal bridge, large nares, and camptodactyly. She showed ulnar deviation of the wrists, mild camptodactyly of the digits of the hands (Fig. 1a), and clubfoot with dorsal flexion of the first toes (Fig. 1b). Brain

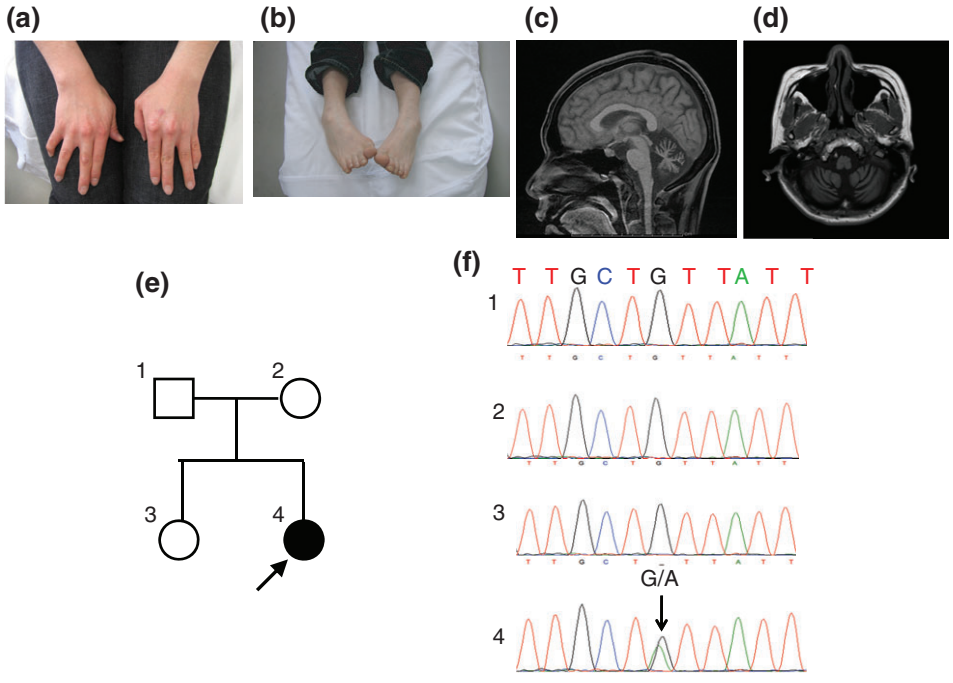

Fig. 1. Both hands show mild camptodactyly of the digits and ulnar deviation of the wrists. (**a**) Both feet show clubfoot and dorsal fexion of the first toes. (**b**) T1-weighted brain magnetic resonance imaging (MRI) revealed cerebellar atrophy (**c**, saggittal slice and **d**, axial slice). Pedigree of the present family. (**e**) Sanger sequencing revealed that the patient had a heterozygous missense mutation in the *NALCN* gene (c.1789G > A, p. V597I) (4), but that the unaffected parents (1 and 2) and sister (3) did not have (**f**).

magnetic resonance imaging (MRI) revealed cerebellar atrophy (Fig. 1c,d). Molecular analysis of the patient excluded spinocerebellar ataxia (SCA)1, SCA2, MJD, SCA6, SCA7, SCA8, SCA12, SCA17, SCA31, SCA36 and DRPLA. We have followed her as an outpatient and the neurological deficits have shown no remarkable changes over the past 7 years.

Through whole-exome sequencing, we identified 12977, 12986 and 13079 variations in the patient, and her father and mother, respectively. Once anonymous open reading frames were excluded and genes associated with SCAs were prioritized, the results revealed no known causative gene associated with SCAs. Because her parents and sister did not show any symptoms similar to hers, we speculate that the patient's mutation is homozygous, compound heterozygous or *de novo*. We found one candidate variation (*ZFHX3*) in a homozygous condition, none in a compound heterozygous condition, and six *de novo* variants (*NALCN*, *AMDHD2*, *SAFB2*, *EML2*, *ZNF865*, and *ZSCAN18*). However, HGVD revealed that five (*ZFHX3*, *AMDHD2*, *SAFB2*, *EML2*, and *ZSCAN18*) of them occur at a high rate in Japanese. Meanwhile, Mutation Taster and SIFT predicted that the variant of *ZNF865* was polymorphism and tolerated, respectively. Furthermore, ZNF865 was conserved only in some species.

The detected variant of *NALCN* (c.1789G > A, p.V597I) with a *de novo* condition is strongly considered to be responsible for our patient's disease for the following four reasons. First, patients reported with mutations in *NALCN* have similar clinical features to our patient (3–5). Second, Sanger sequencing confirmed that the patient had this missense mutation, and that the unaffected parents and sister did not have (Fig. 1e,f). Third, the protein is conserved in various species. Fourth, bioinformatic analyses including Mutation Taster and SIFT predicted that the detected variant of *NALCN* was disease causing and damaging, respectively.

Thus, we identified a *de novo* missense mutation in *NALCN* in an adult patient with cerebellar ataxia associated with intellectual instability and arthrogryposis. To date, 19 *de novo* heterozygous *NALCN* mutations in 21 patients, and four homozygous ones in 11 patients have been reported. Two of the three patients with recessive transmission and three of the 14 *de novo* patients died before the age of 5 years (2, 3). Because respiratory insufficiency was noted in 8 of the 10 *de novo* cases (3), and a 7.5-year-old patient with a *de novo* mutation used a walker for long distances because of frequent falls (4), at least some *de novo* patients might show a severer phenotype than that of our patient. Thus, our patient with a *de novo NALCN* mutation shows relatively mild phenotype, which broadens the clinical spectrum of *NALCN* abnormalities. This study clearly shows that we should analyze the *NALCN* gene even in an adult case of cerebellar ataxia associated with intellectual disability and arthrogryposis.

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