

[CASE REPORT]

A Novel *de novo* *KIF1A* Mutation in a Patient with Autism, Hyperactivity, Epilepsy, Sensory Disturbance, and Spastic Paraplegia

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Abstract:

Heterozygous mutations in *KIF1A* have been reported to cause syndromic intellectual disability or pure spastic paraplegia. However, their genotype-phenotype correlations have not been fully elucidated. We herein report a man with autism and hyperactivity along with sensory disturbance and spastic paraplegia, carrying a novel *de novo* mutation in *KIF1A* [c.37C>T (p.R13C)]. Autism and hyperactivity have only previously been reported in a patient with c.38 G>A (R13H) mutation. This case suggests that alterations in this arginine at codon 13 might lead to a common clinical spectrum and further expand the genetic and clinical spectra associated with *KIF1A* mutations.

Key words: *KIF1A*, spastic paraplegia, hereditary sensory and autonomic neuropathies, autism, attention deficit disorder with hyperactivity, psychomotor hyperactivity

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Introduction

Biallelic mutations in *KIF1A* were discovered as a cause of hereditary sensory neuropathy type 2C and hereditary spastic paraplegia type 30 (1, 2), whereas heterozygous mutations in the motor domain of *KIF1A* have been reported to cause pure spastic paraplegia or syndromic intellectual disability presenting with intellectual disability, spastic paraplegia, sensory neuropathy, cerebellar ataxia, and optic atrophy (3-12). Various heterozygous missense mutations, mostly *de novo*, have been reported (3-12). The ages at the onset range from 0 to 24 years, and the intellectual disability ranges from severe to mild or none (3-12). The genotype-phenotype correlations of such mutations have not been fully elucidated.

We herein report a man with autism, hyperactivity, and epilepsy along with mild intellectual disability, sensory disturbance, and spastic paraplegia carrying a novel *de novo*

missense mutation in the motor domain of *KIF1A* [c.37C>T (p.R13C)].

Case Report

An 18-year-old man visited our hospital for evaluation of his spastic paraplegia. The patient had been born to noncon-sanguineous parents after an uncomplicated pregnancy and delivery. Both of his parents of Japanese origin and his sister were unaffected.

From 11 months of age, the patient started to show secondarily generalized tonic seizures lasting 1-2 minutes once a year with a focal onset starting from one side of his upper extremities. At 4 years old, poor social communication skills were noted, and he had difficulty in making friends. At 6 years old, he was unable to sit quiet and concentrate during classes in his elementary school. Frequent violent behavior toward his classmates was also noted. The administration of valproic acid ameliorated his epilepsy and violent behavior.

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At 11 years old, the patient was diagnosed with autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) and attended a special support school. Methylphenidate and risperidone improved his ADHD symptoms and violent behavior. At 12 years old, spastic gait was noted, which gradually worsened. At 18 years old, the patient was still able to walk without assistance but frequently stumbled during walking.

On a neurological examination, the patient showed spastic gait, increased tendon reflexes, extensor plantar responses, mildly decreased touch/pain/vibration sensations in the distal lower extremities, saccadic pursuit, and slurred speech. No limb or truncal ataxia or frontal release signs were noted. The patient's speech was normal, and he could remember recent events but took time conducting complicated tasks. A neuropsychological test using the Wechsler Adult Intelligence Scale - Third Edition showed a full-scale intelligence quotient (IQ) of 62 (Verbal IQ, 71; Performance IQ, 57; Verbal comprehension index, 80; Perceptual organization index, 61; Working memory index, 62; Processing speed index, 57).

All laboratory tests showed normal findings, including those of vitamin B₁₂ and very-long-chain fatty acids. A nerve conduction study conducted in the right upper and lower extremities revealed decreased sensory nerve action potential amplitudes [SNAPs; right median nerve, 7.3 μ V (normal range, 7.5-30.0 μ V); right ulnar nerve, 6.8 μ V (normal range, 4.0-22.0 μ V); right sural nerve, 0.9 μ V (normal range, 1.9-17.0 μ V)] with normal conduction velocities and compound muscle action potential amplitudes. Motor evoked potentials showed an upper-normal-limit central motor conduction time (CMCT) in the upper extremities [right 8.2 ms, left 7.8 ms (normal range 6.2-7.8 ms)] and a prolonged CMCT in lower extremities [right 21.2 ms, left 19.7 ms (normal range 11.9-14.7 ms)]. Sensory evoked potentials conducted in the right upper extremity were normal [central conduction time 6.4 ms (normal range 5.1-6.7 ms)], and in those conducted in right lower extremity, N20 was difficult to detect, and the P38 latency was slightly above the normal limit [42.8 ms (normal range 33.8-42.4 ms)]. Electroencephalograms showed small amounts of spikes and waves in bilateral parietooccipital leads. Although his corrected visual acuity was normal, slight left optic atrophy was noted by optical coherence tomography. Brain magnetic resonance imaging (MRI) revealed mild atrophy of the cerebellum, pontine tegmentum, and body of the corpus callosum (Fig. 1). Spinal cord MRI showed no abnormalities.

The genetic analysis

The index patient and his healthy parents were enrolled in the study after their written informed consent was obtained. The study was approved by the institutional review board of The University of Tokyo.

Genomic DNA was extracted from peripheral blood leukocytes collected from the participants. Whole-exome sequencing was conducted using SureSelect V5+UTRs (Ag-

ilent, Santa Clara, USA) and a HiSeq2500 sequencer (Illumina, San Diego, USA). Short-read alignment to the reference genome (hg19) and variant calling were performed using the BWA v0.5.9 (13) and SAMtools v0.1.18 (14) software programs with default parameter settings. Annotation of variants with RefSeq (<https://www.ncbi.nlm.nih.gov/refseq/>) and dbSNP (<https://www.ncbi.nlm.nih.gov/projects/SNP/>) was performed as previously described (15). *In silico* functional prediction of the variants was performed using the Polyphen2 (Polymorphism Phenotyping v2; <http://genetics.bwh.harvard.edu/pph2/>), SIFT (Sorting Intolerant From Tolerant; <http://sift.jcvi.org/>), Mutation Taster (<http://www.mutationtaster.org/>), and CADD (Combined Annotation-Dependent Depletion; <http://cadd.gs.washington.edu/>) software programs. The primer sequences described by Rivière et al. (2) were used for Sanger sequencing.

Results of genetic analyses

An exome analysis was carried out for the index patient. From the 11,270 non-synonymous or splice-site variants, the 249 rare variants whose allele frequencies were less than 0.001 in our in-house database of 1,261 Japanese control subjects were further analyzed. There were no rare biallelic variants in genes relevant to spastic paraplegia. *KIF1A* (NM_001244008.1) c.37C>T (p.R13C) was the only rare variant found within a gene known to cause spastic paraplegia with a heterozygous state. The mutation was confirmed by Sanger sequencing of *KIF1A*. The mutation was not found in his parents (Fig. 2A); thus, it was considered to be a *de novo* mutation. To further confirm the *de novo* mutation, the exome data of the proband and the parents were analyzed in detail, which showed the following read depths corresponding to the reference and c.37C>T reads: proband: reference 59 reads, c.37C>T 66 reads; father: reference 120 reads, c.37C>T 0 read; mother reference 109 reads, c.37C>T 0 read. This confirmed the *de novo* origin of the mutation. The exome sequence data further confirmed that the parents were his biological parents. The mutation was located in the motor domain of its protein, where pathogenic mutations have often been found (Fig. 2B). The mutation was not found in the gnomAD database (<https://gnomad.broadinstitute.org/>) or in our in-house database. The mutation substitutes cysteine for an evolutionally conserved arginine (Fig. 2C) and was predicted to be deleterious using Polyphen2 (probably damaging), SIFT (deleterious), Mutation Taster (disease-causing), and CADD (35). Given these findings, we concluded that this novel *de novo* mutation was the causative mutation in this patient.

Discussion

We herein report a novel *de novo* missense mutation in the motor domain of *KIF1A* in a man with autism, hyperactivity, and epilepsy, along with typical symptoms associated with *KIF1A* mutations, including mild intellectual disability, sensory disturbance with diminished SNAP amplitudes, and

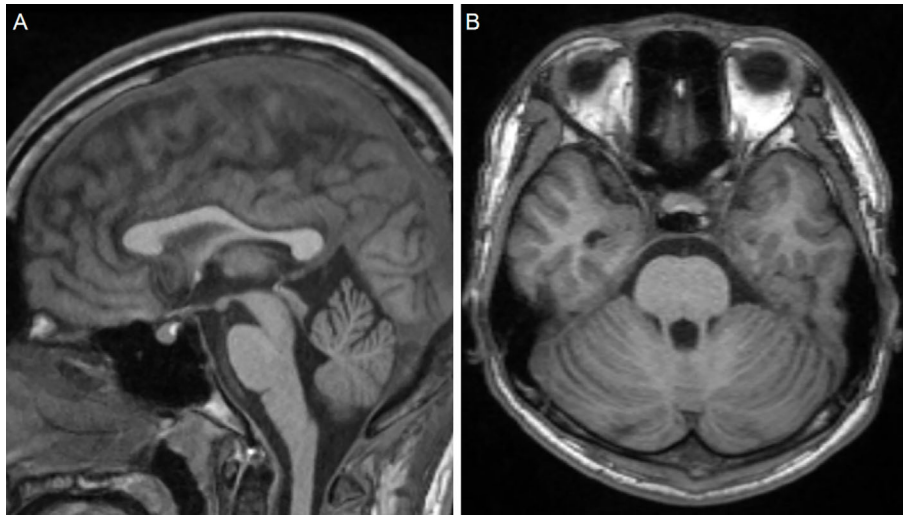


Figure 1. Brain magnetic resonance images obtained at 18 years old. (A) Sagittal T1-weighted image. (B) Axial T1-weighted image. Mild atrophy of the cerebellum, pontine tegmentum, and body of the corpus callosum is noted.

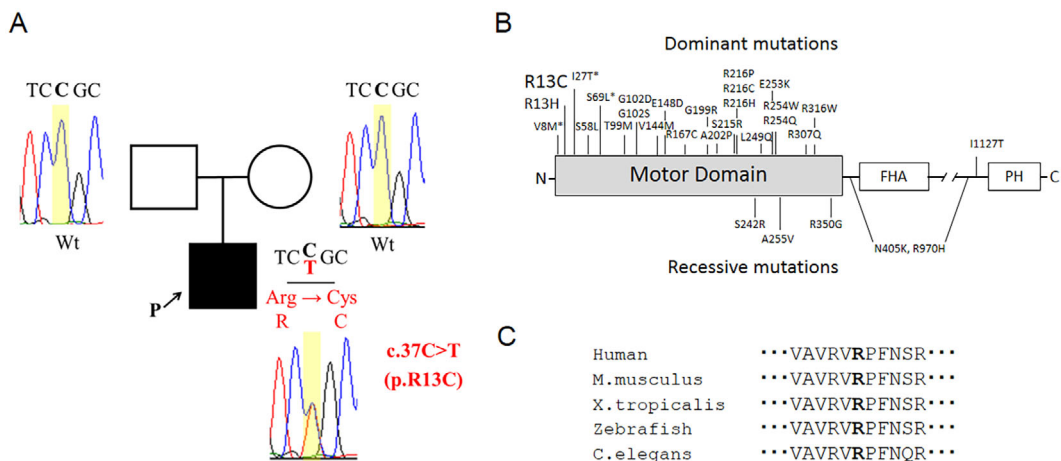


Figure 2. (A) Pedigree chart and electropherograms of Sanger sequencing of PCR products showing the *de novo* *KIF1A* mutation [c.37C>T (p.R13C)]. (B) Schematic structure of *KIF1A* protein and reported mutations. Twenty-four of the 25 dominant mutations reported so far are in the motor domain. Asterisk: mutations causing an autosomal dominant family presenting with pure spastic paraplegia. (C) Cross-species conservation of R13 and the surrounding amino acids of *KIF1A* in various species. FHA: fork-head associated domain, PH: pleckstrin homology domain

spastic paraplegia.

Overall, 24 heterozygous *KIF1A* mutations in the motor domain have been reported to cause neurological diseases. Three of the 24 mutations (marked with asterisks in Fig. 2B) with autosomal dominant transmission showed a similar phenotype within the family with pure spastic paraplegia, suggesting genotype-phenotype correlations (7, 8). The remaining mutations were considered to be *de novo*, and 90% (28/31) of the patients showed intellectual disability, 94% (29/31) showed spastic paraplegia, 52% (16/31) showed sensory neuropathy, and 58% (18/31) showed optic atrophy (3-12).

Although intellectual disability is a frequently reported symptom in *KIF1A*-related disorders, clinical features sug-

gesting ASD and ADHD have been reported in only two and one patient, respectively (5, 12). One patient who was reported to have features of both ASD and ADHD carried c.38G>A (p.R13H), substituting histidine for the arginine at the same codon 13 (12). Thus, our case further raises the possibility that these mutations involving R13 are associated with autism and hyperactivity. Epilepsy was reported in two of the four patients with c.296C>T (p.T99M) (4, 5), two of the three patients with c.757G>A (p.E253K) (4), and one patient with c.647G>A (p.R216H) (5), but not in the patient with c.38G>A (p.R13H) (12). Reported seizure types are varied and include myoclonic, tonic, partial complex, and generalized tonic-clonic seizures as well as infantile spasm (4, 5). Thus, the genotype-phenotype correlation re-

garding epilepsy has not been clarified.

KIF1A encodes a neuron-specific motor protein that plays an important role in anterograde axonal transport of synaptic vesicle precursors (16). Impairment of this anterograde axonal transport is believed to be the cause of spastic paraplegia and sensory neuropathy in patients with pathogenic mutations (1, 2, 17). Length-dependent axonal impairment of upper motor neurons or primary sensory neurons seems to explain the patient's symptoms that started from the distal extremities. However, why most of the heterozygous *KIF1A* mutations also cause neurodevelopmental disorders while others do not is unclear. Studies have shown that the *KIF1A* protein also plays a role in synaptogenesis and learning enhancement via presynaptic bouton formation (18) or the dendritic transport of cargo vesicles containing postsynaptic proteins, including AMPA glutamate receptors (19-21), which are impaired in neurodevelopmental disorders, such as intellectual disability, autism, and hyperactivity (22).

In conclusion, we found a novel *de novo* missense mutation in the motor domain of *KIF1A* [c.37C>T (p.R13C)] in a patient with autism, hyperactivity, and epilepsy, along with mild intellectual disability, sensory disturbance with a selective decrease in SNAP amplitudes, and spastic paraplegia. This case suggests that alterations in this specific amino acid at codon 13 lead to a common clinical spectrum and further expands the genetic and clinical spectra of *KIF1A* mutations.

The authors state that they have no Conflict of Interest (COI).

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