A novel KIF5A gene variant causes spastic paraplegia and cerebellar ataxia

Yusen Qiu, Shanshan Zhong, Lu Cong, Ling Xin, Xuguang Gao, Jun Zhang, Daojun Hong

1Department of Neurology, Peking University People’s Hospital, Beijing, China
2Department of Neurology, The First Affiliated Hospital of Nanchang University, Nanchang, China
3Department of Health, Exercise Science, and Recreation Management, University of Mississippi, University, Mississippi

Abstract

Mutations in the kinesin family member 5A (KIF5A) gene are mainly associated with autosomal dominant spastic paraplegia 10 (SPG10). The additional complicated symptoms of SPG10 commonly include a wide spectrum. However, cerebellar ataxia is only noticed in a very few patients. Herein, we described a large autosomal dominant family, in which the affected individuals presented with progressive spastic paraparesis and marked cerebellar ataxia. Exome sequencing revealed that a novel variant in the KIF5A gene might be responsible for the phenotype. The obvious cerebellar ataxia indicated that the KIF5A gene should be included in the expanding gene list for spasticity-ataxia spectrum.

Introduction

Hereditary spastic paraplegias (HSPs) and hereditary spinocerebellar ataxias (SCAs) each are a clinically and genetically heterogeneous group of neurological disorders characterized by progressive degeneration of cerebellum or spinal cord. They have traditionally been designated in distinct clinical entities according to their predominant phenotypic patterns, but they are increasingly recognized to have overlapping phenotypes. Indeed, increasing numbers of genes are assigned to the “spasticity-ataxia spectrum” of genes causing a phenotypic continuum of HSP and SCA.

The kinesin family member 5A (KIF5A) gene encodes a neuronal kinesin heavy chain that acts as a molecular motor. Mutations in this gene can cause autosomal dominant spastic paraplegia 10 (SPG10), neonatal intractable myoclonus, axonal Charcot-Marie-Tooth disease, or amyotrophic lateral sclerosis (ALS). SPG10 was initially considered as a simple form of HSP with infantile onset, but patients with later onset, even asymptomatic carrier, were soon reported to have a complicated phenotype. The complicated symptoms of SPG10 commonly included peripheral neuropathy, atrophy, sensory loss, and facial dyskinesia. However, the cerebellar ataxia was only noticed in three SPG10 cases. Liu et al. in 2014 wrote “K5 and her sister had marked cerebellar ataxia complicating the spasticity.” Nam et al. in 2018 described a “patient with p.R204T mutation showed the CMT2 phenotype with additional symptoms of HSP, ataxia, fatigability, and pyramidal sign.” Recently, we encountered an autosomal dominant family, in which the affected individuals presented with progressive spastic paraparesis and marked cerebellar ataxia. The patients were initially diagnosed as SCA, but a SPG10-related ataxia due to a novel variant in the KIF5A gene was finally established through exome sequencing.
Methods

All patients were examined by at least two neurologists after giving informed consent. Information of the deceased individuals was obtained from their offspring or medical records. Brain and spinal cord MRI were performed. The research was also approved by ethics committee of the Peking University People’s Hospital.

Sural nerve biopsy specimens were routinely processed for histological and ultrastructural examinations. DNA was extracted from peripheral blood of all available family members. Initially, the genetic test was commercially conducted in the index patient through exome next generation sequencing (Myogenetics, Beijing, China). And then DNA from all available family members was directly sequenced for co-segregation analysis. In addition, the dynamic (CAG)n numbers for SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA12, SCA17, and DRPLA were directly detected by PCR amplified fragments. The copy number variation of exons in the SPAST, REEP1, and ATL1 gene were examined by multiplex ligation-dependent probe amplification (MLPA).

Results

The proband was a 49-year-old woman who had clumsy gaits from 15 years old. The gait disturbance was mild and stable from onset to the age of 41, but afterward the symptoms were progressive along dysarthria, tiptoeing, weakness of lower limbs, and numbness of distal lower limbs. Physical examination at age 49 showed spasticity in both legs, brisk reflexes in lower extremities, mild foot dorsi/plantar flexion weakness, and obvious muscle wasting in the distal lower limbs. Jaw reflex was negative. Babinski’s signs were positive bilaterally. Bilateral pes cavus was obvious. Romberg sign was positive in both open and close eye condition. Sensory examination revealed a mild decrease of vibratory sensation at ankles, but other sensations were intact. Evidence of cerebellar ataxia such as horizontal nystagmus, dysarthria, finger-nose dysmetria, and dysdiadochokinesis was identified. Mini-mental state examination (MMSE) and frontal assessment battery (FAB) evaluations revealed normal cognitive and frontal lobe function. MRI showed an atrophy of cerebellum and thoracic spinal cord.
Neurophysiological studies revealed a delayed latency and poor waveform differentiation in somatosensory evoked potentials (SEP). The brainstem potentials showed abnormal conduction. Motor nerve conduction velocity (MNCV) showed severe decrease of compound muscle action potentials (CMAP) in the lower limbs. Sensory NCV only displayed very small potentials in lower limbs.

Several individuals showed similar gait disturbance in this family with four successive generations (Fig. 1). The grandfather of the index patient (II) had severe spastic paraplegia and depended on wheelchair before he died at age 69. The mother of the patient (II4) had an adult onset of dysarthria, spastic gait, and wasting and numbness of lower limbs. The young uncle (II7) presented with spastic gait and dysarthria since 20 years old. Distal muscle wasting, decreased vibratory sensation in the distal legs, and pes cavus were also found. The daughter (IV1) had abnormal gait since 5 years old. Neurological examinations at age 28 revealed spastic gait, brisk knee tendon reflex, and bilateral Babinski’s signs. Wasting of bilateral distal limbs and bilateral pes cavus were also identified. Horizontal nystagmus, dysarthria, and finger-nose dysmetria were also observed. MRI displayed an atrophy of cerebellum and thoracic spinal cord. SEP indicated a delay latency and poor waveform differentiation. NCV showed an axonal sensory-motor neuropathy characterized by markedly decreased CAMP and mildly decreased NCV in the examined nerves. The patient II2 and III2 were reported to have similar clumsy gait and dysarthria, but detailed clinical data were unavailable.

**Figure 2.** Pathological changes of sural nerve of the index patient. Modified Gomori trichrome staining showed a decrease of myelinated fibers without inflammatory infiltrates (A). The toluidine blue semithin staining showed a severe loss of nerve fibers (B). Electron microscopy revealed a severe loss of large myelinated fibers, but small unmyelinated fibers were relatively preserved (C). Clusters of small regenerative axons can be identified (D).
The pathological changes of sural nerve were uniform in different nerve fascicles without inflammatory infiltration (Fig. 2A). The semithin sections showed a severe loss of fibers larger than 8 μm (Fig. 2B). A little bit of myelinated fibers showed thin myelin. Onion-bulb formations and acute axonal degeneration were not found. Electron microscopy revealed a severe loss of large myelinated fibers, but small unmyelinated fibers were relatively preserved (Fig. 2C). Clusters of small regenerative axons were occasionally observed (Fig. 2D).

The exome screening revealed a novel heterozygous missense variant (c.259C>G, p.Q87E) located in exon 3 of the KIF5A gene (Fig. 3). The variant was also identified in family member II4, II7, and IV1, but not in II6, II9, III5, III8, and IV2, which indicated the variant was closely co-segregated with the phenotype (Fig. 1). The variant was not found in 200 healthy Chinese controls, 1000 genomes database, ExAC database, and gnomAD database. A homology search in different species demonstrated that the glutamine at residue 87 was highly evolutionarily conserved. The variant was predicted to be probably damaging with PolyPhen-2 score of 1.00, be deleterious with SIFT score of 0.00, and be disease causing by MutationTaster. No other causative variants associated with SPGs were found in the target genes; no abnormal expansion of nucleotide repeats was identified in SCAs. No copy number variation of exons was found in the SPAST, REEP1, or ATL1 gene.

**Discussion**

Our patients were initially misdiagnosed as SCA prior to genetic screening, because they presented with spastic gait, cerebellar ataxia, and possible anticipation in the autosomal dominant inherited family. However, the definite age at onset was difficult to determine exactly due to the insidious onset of a chronic course. Therefore, the ascertainment bias should be kept in mind. Overall, negative genetic results of the dynamic (CAG)n numbers for SCAs made us reconsider the possibility of HSP. Through exome sequencing, we finally found that a novel variant in the KIF5A gene was closely co-segregated with the individuals in the family.

**Figure 3.** Exome screening revealed a novel c.259C>G variant (p.Q87E) which is located in the motor domain of the N-terminal KIFA5. A homology search in different species demonstrated that the glutamine at residue 87 was highly evolutionarily conserved. The causative variants for SPG10/CMT2/ataxia were missense mutations and mainly located at the N-terminal motor domain, but the causative variants for ALS were truncated mutations and concentrated at the C-terminal cargo binding domain. The red font indicated that the KIF5A variants associated with ataxia only included p.R204W in previous reports, and p.Q87E in this report.
Most previously reported KIF5A missense mutations were associated with the phenotype of SPG10 (Fig. 3), which can range from pure HSP to complicated HSP with a wide spectrum. However, marked cerebellar ataxia along with spasticity was only described in a few patients. Significant horizontal nystagmus was also observed in a baby with c.2934delG in the KIF5A gene, but neonatal intractable myoclonus overwhelmed the symptoms of cerebellar ataxia in the case. Our patients presented with multiple signs of cerebellar ataxia, which were in agreement with the atrophy of cerebellum. The pathogenesis of cerebellar ataxia might be associated with degeneration of the cerebellar Purkinje cells and spinocerebellar tracts between brainstem and cerebellum.

Our patients displayed typical SPG symptoms along with signs of cerebellar ataxia, which made it difficult to differentiate from SCA due to the overlap between their clinical presentations. Interestingly, ataxia and spasticity frequently co-occur in patients whose spinocerebellar tracts are affected, which led to the designation of a group of disorders termed spastic ataxia (SPAX). More and more genes have been identified in association with these conditions (Table S1). Therefore, the expanding number of genes assigned to the “spasticity-ataxia spectrum” should also include the KIF5A gene according to our observations.

The phenotypic spectrum associated with KIF5A mutations can exhibit pure axonal Charcot-Marie-Tooth disease. Sural nerve biopsy revealed a moderate loss of large myelinated fibers in accordance with the clinical features and neurophysiological results. These findings confirmed that the “mixed” central-peripheral involvements were the most common features of KIF5A-related SPG10. The sensory abnormalities of lower extremities might contribute to the observation of ataxia, but the ataxia symptoms mainly located in upper extremities and brain stem territory. Therefore, the mild sensory loss in the lower extremities might not be primary cause of the ataxia dysfunction in our patients.

Although the variant appears to qualify as variant uncertain significance (VUS) according to the American college medical genetics genomics (ACMG) criteria, the p.Q87E variant is located in the nucleotide binding site corresponding to the N-terminal residues of the motor domain, which is essential for binding microtubule and ATP. Therefore, p.Q87E, like other missense variants such as p.Y63C and p.D73N, might disrupt the important role in supplying the ATP to motor process. However, the exact mechanism how variants can either selectively or simultaneously affect the corticospinal and spinocerebellar tracts still needs further investigation.

In conclusion, we described a novel KIF5A variant involved in SPG10 phenotype with spastic paraplegia and cerebellar ataxia. The obvious cerebellar ataxia indicated that the KIF5A gene should be included the expanding gene list for “spasticity-ataxia spectrum”, and should be considered in the diagnostic workflow of SCA.

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Author Contribution
Q. Y. contributed to research execution and manuscript composition; Z. S. and C. L. contributed to radiological, pathological, and genetic evaluation. X.L. G. X. and Z. J. contributed to critical review and revision of manuscript; H. D. contributed to design, conception, and manuscript composition.

Conflicts of Interest
None.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. List of genes causing ataxia-spasticity spectrum disease.