

# World Journal of *Clinical Cases*

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## Novel mutation of *SPG4* gene in a Chinese family with hereditary spastic paraplegia: A case report

Jie Wang, Wei-Ting Bu, Mei-Jia Zhu, Ji-You Tang, Xiao-Min Liu

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### Abstract

#### BACKGROUND

Hereditary spastic paraplegia (HSP) is a group of neurogenetic diseases of the corticospinal tract, accompanied by distinct spasticity and weakness of the lower extremities. Mutations in the spastic paraplegia type 4 (*SPG4*) gene, encoding the spastin protein, are the major cause of the disease. This study reported a Chinese family with HSP caused by a novel mutation of the *SPG4* gene.

#### CASE SUMMARY

A 44-year-old male was admitted to our hospital for long-term right lower limb weakness, leg stiffness, and unstable walking. His symptoms gradually worsened, while no obvious muscle atrophy in the lower limbs was found. Neurological examinations revealed that the muscle strength of the lower limbs was normal, and knee reflex hyperreflexia and bilateral positive Babinski signs were detected. Members of his family also had the same symptoms. Using mutation analysis, a novel heterozygous duplication mutation, c.1053dupA, p. (Gln352Thrfs\*15), was identified in the *SPG4* gene in this family.

#### CONCLUSION

A Chinese family with HSP had a novel mutation of the *SPG4* gene, which is autosomal dominant and inherited as pure HSP. The age of onset, sex distribution, and clinical manifestations of all existing living patients in this family were analyzed. The findings may extend the current knowledge on the existing mutations in the *SPG4* gene.

**Key Words:** Hereditary spastic paraplegia; *SPG4* gene; Mutation; Genetic testing; Autosomal dominant HSP; Adenosine triphosphatases associated with diverse cellular activities; Case report

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**Core Tip:** It is difficult to distinguish hereditary spastic paraplegia (HSP) from other spasticity-related genetic diseases because the different affected genes lead to large differences in the pathogenic mechanisms, clinical features, and imaging abnormalities of HSP. Therefore, genetic testing is important for the diagnosis and typing of HSP. A Chinese HSP male patient was identified, and pedigree surveys of his relatives were performed. Furthermore, genomic DNA was extracted for whole-exome sequencing, and pathogenic variants were screened by bioinformatics methods and verified using Sanger sequencing. A novel heterozygous duplication mutation, c.1053dupA, p. (Gln352Thrfs\*15), was identified in the *SPG4* gene in this family.

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## INTRODUCTION

Hereditary spastic paraplegia (HSP) is a group of neurogenetic diseases caused by degeneration of the corticospinal tract, which is characterized by slow progressive spasms and weakness of the lower limbs. The disease has obvious clinical and genetic heterogeneity[1]. According to their clinical manifestations, HSP is divided into pure and complex types. The pure type presents with slowly progressive lower extremity weakness and spasticity, corticospinal tract signs, disturbance in the vibration sense and proprioception, and possible sphincter disturbances. Complex HSP is characterized by leg spasticity and other complications, such as ataxia, a thin corpus callosum, extrapyramidal signs, chorioretinal dystrophy, peripheral neuropathy, and mental retardation[2,3]. HSP can be inherited by autosomal dominant (AD), autosomal recessive, X-linked, and mitochondrial maternal patterns. More than 80 genes or loci involved in the inheritance of this disease have been identified. Spastic paraplegia type 4 (*SPG4*) is the most common cause of pure HSP, accounting for 45% of pure HSP cases. It is inherited by AD mode and is caused by the mutation of the *SPAST* gene[1,4,5].

## CASE PRESENTATION

### Chief complaints

Seven years before his admission to our hospital, a 44-year-old male (patient V: 4) experienced right lower limb weakness, leg stiffness, and unstable walking. The symptoms appeared without obvious inducement. The patient was from the Han Chinese population in Shandong Province, China.

### History of present illness

Initially, he felt that his symptoms were mild. He was never treated, and his symptoms gradually worsened over time. In the 4<sup>th</sup> year after onset, he began to experience hotness in his right knee joint, his gait became increasingly slow, his legs felt stiff, and lumbago appeared. The patient's lumbago symptoms were most severe at night during sleep and in the morning. Meanwhile, the patient felt that the range of motion of both knees was limited, which aggravated when he was tired. He could not run and had difficulty climbing stairs.

### History of past illness

The patient was healthy before. The patient denied a history of surgery and trauma, diabetes mellitus, cardiac disease, or infectious diseases.

### Personal and family history

His family history revealed that he was born to non-consanguineous parents, but similar symptoms were found in several of his relatives.

### Physical examination

Neurological examination showed that the cranial nerves of the proband were not abnormal. The proximal and distal muscle strength and muscle tone of double upper extremities were normal. Biceps reflexes, triceps reflexes, and radial reflexes were normal, and bilateral Hoffman signs were negative. The proximal and distal muscle strength of both lower limbs was normal. Lower limb hypermyotonia and bilateral knee reflex were enhanced. Bilateral Chaddock's sign, Oppenheim sign, and Gordon sign were negative, while Babinski sign was positive. There was no muscle atrophy or abnormal involuntary movement.

### Laboratory examinations

The proband was initially suspected of having myelopathy. Further laboratory examinations, such as cerebrospinal fluid sample analysis and determination of the serum vitamin B12 level, were conducted. No inflammatory or immune lesions were detected. Neuro-electrophysiological examination suggested normal motor nerve conduction, sensory nerve conduction, and needle electromyography.

### Imaging examinations

The magnetic resonance imaging of the cervical spinal cord, thoracic spinal cord, and lumbar spinal cord revealed only intervertebral disc herniation of the cervical and lumbar spine. No obvious swelling, atrophy, or compression of the spinal cord was found.

### Family structure and description of deceased and living patients

After obtaining written informed consent from the proband and his relatives, a detailed investigation of this Han Chinese family from Shandong Province, China was conducted. This family was traced back to the sixth generation, with a total of 11 people suffering from the disease, with an AD genetic pattern (Figure 1A). Five deceased individuals had spastic paraplegia in their lifetime, including four males (patients I: 1, II: 1, II: 2, and IV: 6) and one female (patient III: 2). Of the six living patients, five were male (patients IV: 2, IV: 4, V: 4, VI: 1, and VI: 3), and one was female (patient V: 3).

Other living and symptomatic patients initially showed weak legs or unstable walking. They developed different clinical symptoms as they grew older and the course of the disease progressed. The proband's father (patient IV: 4) and uncle (patient IV: 2) were affected by the illness in middle age, with a long course of disease, severe symptoms, difficulty in lifting the legs, and a scissor gait. Neurological examination revealed the increased lower limb hypermyotonia and tendon hyperreflexia, and bilateral Babinski signs were positive. They started using crutches to assist walking approximately 20 years and 10 years after onset, respectively. The proband's nephew (VI: 1), now 20 years old, developed a gait disturbance at the age of 10-years-old. Although there was obvious difficulty in walking, he did not need the assistance of appliances. The proband's cousin (V: 3) was a female patient with an onset age of 46-years-old and a disease course of 2 years who presented with mild weakness of both lower limbs. The son (VI: 3) of the proband, aged 19-years-old, was an asymptomatic mutation carrier. The mean age of onset of symptoms was  $36.6 \pm 14.1$ -years-old. The disease course was  $14.8 \pm 10.9$  years. All the surviving patients were intellectually normal with no cognitive impairment, peripheral neuropathy, bladder dysfunction, and claw-feet. No scoliosis was detected. Their age of onset, course of disease, sex, spastic paraplegia rating scale[6], and disability stage were recorded and evaluated. The spastic paraplegia rating scale is a composite measurement modality. It includes walking distance without pause, gait speed, quality of gait, climbing stairs, arising from chair, spasticity quality, weakness and contractures, pain caused by spastic paraplegia-related symptoms, and bladder dysfunction. The score for each item ranged from 0 (no dysfunction) to 4 (the most severe dysfunction), and the highest total score of all items is 52. Thus, higher spastic paraplegia rating scale scores represent heavier dysfunction. Additional data are presented in Table 1.

## GENETIC TESTING

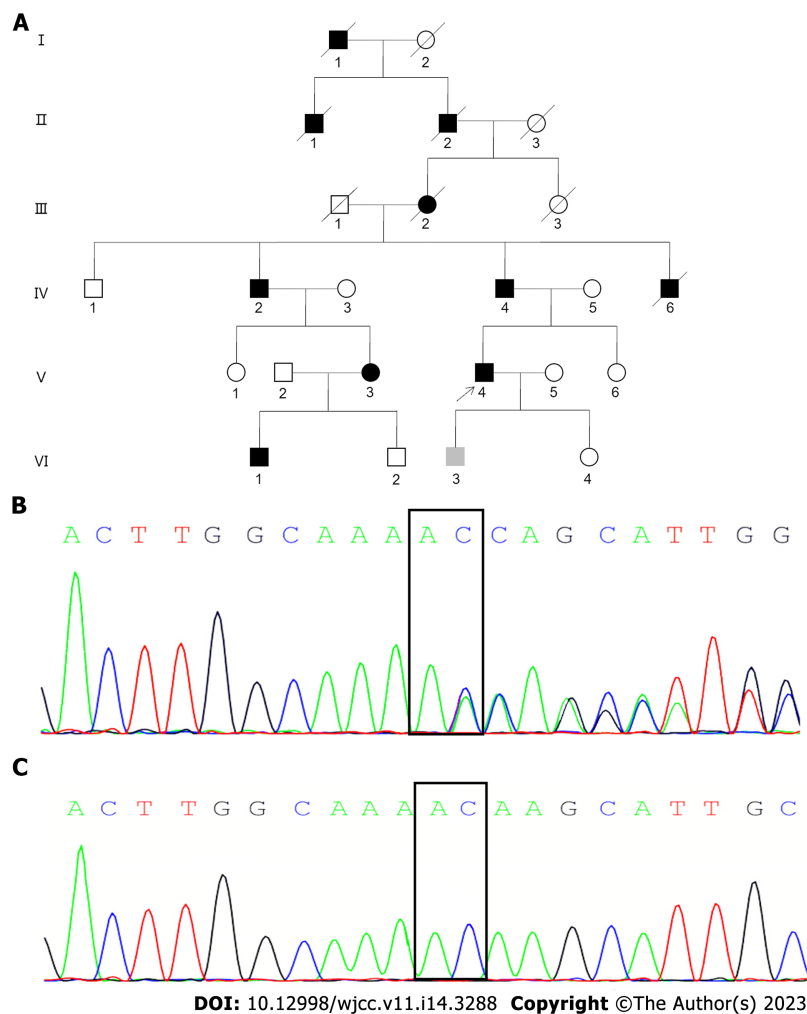
After obtaining written informed consent from participants, DNA was extracted from seven peripheral blood samples, including the proband (V: 4), his father (IV: 4), his mother (IV: 5), his wife (V: 5), his sister (V: 6), his son (VI: 3), and his daughter (VI: 4). Whole-exome sequencing was first performed, pathogenic variants were analyzed by bioinformatics methods, and were then verified using Sanger sequencing. It was found that the proband (V: 4) and the patient (IV: 4, VI: 3) carried a pathogenic heterozygous variant of the *SPG4* gene, namely c.1053dupA, p. (Gln352Thrfs\*15), located at the shear site of the *SPG4* exon 7 (Figures 1B and C). This mutation has not previously been reported. It was also not registered in the Clinvar, dbSNP, and HGMD databases.



**Table 1 Clinical features of patients with a c.1053dupA mutation of the *SPG4* gene**

| Patient | Sex    | Age at onset, yr | Duration of the disease, yr | Hyperreflexia | Spasticity | Decreased vibration sense | Sensory impairment | Stages <sup>a</sup> | SPRS |
|---------|--------|------------------|-----------------------------|---------------|------------|---------------------------|--------------------|---------------------|------|
| IV: 2   | Male   | 50               | 24                          | +             | +          | -                         | N                  | 4                   | 28   |
| IV: 4   | Male   | 40               | 31                          | +             | +          | -                         | N                  | 4                   | 30   |
| V: 3    | Female | 46               | 2                           | -             | -          | -                         | N                  | 1                   | 3    |
| V: 4    | Male   | 37               | 7                           | +             | +          | -                         | N                  | 3                   | 20   |
| VI: 1   | Male   | 10               | 10                          | +             | +          | -                         | N                  | 2                   | 16   |
| VI: 3   | Male   | -                | -                           | -             | -          | -                         | N                  | 1                   | 0    |

<sup>a</sup>The following stages were defined: (1) Normal or very slight stiffness in the legs; (2) Moderate gait stiffness; (3) Unable to run while able to walk alone; (4) Able to walk on crutches or with help; and (5) Wheelchair-bound. -: Absent; +: Present; N: Normal; SPRS: Spastic paraplegia rating scale.



**Figure 1 Pedigree of the patient and mutation analysis of the *SPG4* gene.** A: The family with hereditary spastic paraplegia (HSP). The proband is indicated by an arrow. A square indicates male, a circle for female, a shadow symbol for an HSP individual, including a black shadow for a symptomatic patient and a gray shadow for an asymptomatic patient, a non-shadowing symbol for a non-HSP individual, and a slash symbol for a deceased individual; B: Sequence analysis identified a c. 1053dupA mutation in the *SPG4* gene in this family. Black frames delineate the C. 1053dupA nucleotides; and C: Wild-type sequence.

## FINAL DIAGNOSIS

Referring to the Harding diagnostic criteria[7] and based on genetic testing, the proband and other related relatives were finally diagnosed with SPG4 HSP.

## TREATMENT

The proband was given an intravenous injection of methylcobalamin (500 µg/d) for 2 wk; then the route was changed to oral administration (1.5 mg/d) for 3 mo. He also took baclofen orally (15 mg/d at the initial stage, which then increased to 30 mg/d) for 6 wk.

## OUTCOME AND FOLLOW-UP

Although his low back pain was resolved somewhat, his slow walking and stiffness in both lower limbs were not significantly improved. He still could not run, and he had difficulty climbing the stairs.

## DISCUSSION

HSP is a nervous system disease, accompanied by diverse clinical manifestations and complex genetic etiology and pathogenesis. The onset age ranges from infancy to senility, and the functional impairment is highly variable[4]. The onset age span of patients in the present study was large, in which the largest age span between two relatives was 40 years. The majority of patients developed the disease in middle age.

According to the clinical symptoms, it was revealed that the pure HSP type was dominant in the proband's family, including progressive weakness of the lower extremities and spasticity[1-4]. Notably, in this family, male patients were more affected by the disease than female patients, with a male to female ratio of 9:2, which is consistent with the findings of another study[8]. Earlier reports have also confirmed that patients with *SPG4* gene mutation-related diseases were mostly male, suggesting that in some cases sex is a stronger contributing factor to the time of onset of disease symptoms than age[9]. This may be associated with the higher levels of estrogen and progesterone in female patients[10,11]. Due to the genetic and clinical heterogeneity of HSP, its phenotype is complex, and the diagnosis is difficult, which may be attributed to the effects of genetic factors, environmental modifiers, penetrance, and sex[8,12,13].

In the present study, a novel mutation, c.1053dupA, p. (Gln352Thrfs\*15), was detected in the *SPG4* gene in the family with HSP. This variant is a frameshift mutation that results in a Gln 352-to-Thr substitution and a new reading frame and is terminated at codon 15 downstream of the amino acid at position 352, causing early translation termination compared with the wild-type protein. This may lead to truncation of the coding protein synthesis, thereby losing its normal function. This novel variant was predicted to be deleterious by Mutation Taster analysis ([http://www.mutationtaster.org/MT69/MutationTaster69.cgi?bases\\_inserted=A&end\\_insdel=1054&start\\_insdel=1053&transcript\\_stable\\_id\\_text=ENST00000315285&sequence\\_type=CDS&gene=spast](http://www.mutationtaster.org/MT69/MutationTaster69.cgi?bases_inserted=A&end_insdel=1054&start_insdel=1053&transcript_stable_id_text=ENST00000315285&sequence_type=CDS&gene=spast)). The DNA sequence variants were named following the guidelines of the Human Genome Variation Society (<https://varnomen.hgvs.org/recommendations/general/>).

In 2009 and 2010, two mutations of the *SPG4* gene were reported in two families, including c.1055A > C, p. (Gln352Pro) and c.1054C > T, p. (Gln352X), respectively[14,15]. Both are mutations caused by a single-base substitution, one being a missense mutation and the other being a nonsense mutation. These two previously detected mutations and our newly identified mutation are located within the conserved adenosine triphosphatases associated with diverse cellular activities cassette, resulting in changes in activity of the spastin protein and loss of function. The findings of the present study suggest that mutations in this region are not uncommon. To date, at least 80 genes and several variants have been found to be associated with HSP, of which those of *SPG4* cause the most common type of HSP[9,16,17]. Most of the mutations of the *SPG4* gene are missense (33%), frameshift (24%), splice-site (16%), nonsense variants, and deletions (12%)[4].

The *SPG4* gene encodes a microtubule (MT)-severing protein, namely spastin, which is an MT-severing enzyme containing an MT-binding domain and adenosine triphosphatases associated with diverse cellular activity domains with adequate severing activity, playing an important role in axon development, synaptic formation, and spinal cord maturation[18-20]. A number of factors lead to mutations in the *SPG4* gene and the onset of related disease symptoms, of which the main factor is a decrease in the level of the functional spastin protein, resulting in insufficient MT cutting[18-21]. Another study found that aggregation of the mutant spastin protein caused toxicity, while it could not explain the underlying mechanisms and possible consequences[21]. Qiang *et al*[22] demonstrated that the function acquisition mechanism of *SPG4* gene is more meaningful than its function loss mechanism.

Only symptomatic treatment of HSP is currently available. In the present study, the proband was treated with methylcobalamin and baclofen, which only relieved his low back pain, while the other symptoms were not improved significantly. Therefore, it is critically important to find an effective treatment for this disease. A recent study proposed a new direction of targeted therapeutic application [23]. The results of this investigation showed that the mutation of the *SPG4* gene was not only associated with haploinsufficiency causing decreased spastin function but also could be one of the important

pathogenic factors of spastin function dysregulation. The phosphorylation of S268 mediated by HIPK2 may contribute to the stability of the spastin protein and rescue HSP neurite defects.

## CONCLUSION

In conclusion, a newly pathogenic mutation was proposed, expanding the existing knowledge of the spectrum of mutations of the *SPG4* gene. The findings may provide a reliable basis for further research on the genetic etiology and pathogenesis of HSP. The diagnosis and typing of HSP through genetic analysis can control and treat the disease as well as avoid the transmission of pathogenic genes in the family.

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