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CASE REPORT

Novel *ATL1* mutation in a Chinese family with hereditary spastic paraplegia: A case report and review of literature

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Abstract

BACKGROUND

Hereditary spastic paraplegias (HSPs) refer to a group of heterogeneous neurodegenerative diseases characterized by lower limbs spasticity and weakness. So far, over 72 genes have been found to cause HSP (SPG1-SPG72). Among autosomal dominant HSP patients, spastic paraplegia 4 (*SPG4/SPAST*) gene is the most common pathogenic gene, and atlastin-1 (*ATL1*) is the second most common one. Here we reported a novel *ATL1* mutation in a Chinese spastic paraplegia 3A (SPG3A) family, which expands the clinical and genetic spectrum of *ATL1* mutations.

CASE SUMMARY

A 9-year-old boy with progressive spastic paraplegia accompanied by right hearing loss and mental retardation for five years was admitted to our hospital.

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Past history was unremarkable. The family history was positive, and his grandfather and mother had similar symptoms. Neurological examinations revealed hypermyotonia in his lower limbs, hyperreflexia in knee reflex, bilateral positive Babinski signs and scissors gait. The results of blood routine test, liver function test, blood glucose test, ceruloplasmin test and vitamin test were all normal. The serum lactic acid level was significantly increased. The testing for brainstem auditory evoked potential demonstrated that the right side hearing was impaired while the left was normal. Magnetic resonance imaging showed mild atrophy of the spinal cord. The gene panel test revealed that the proband carried an *ATL1* c.752A>G p.Gln251Arg (p.Q251R) mutation, and Sanger sequencing confirmed the existence of family co-segregation.

CONCLUSION
We reported a novel *ATL1* Q251R mutation and a novel clinical phenotype of hearing loss in a Chinese SPG3A family.

Key words: Hereditary spastic paraplegia; SPG3A; Atlastin-1 (*ATL1*) gene; Hearing loss; Case report

Core tip: Hereditary spastic paraplegias are a group of genetically and clinically heterogeneous neurodegenerative diseases characterized by lower limbs spasticity and weakness. Here we reported a novel *ATL1* Q251R mutation predicted to be pathogenic and a novel clinical phenotype of hearing loss in a Chinese SPG3A family, which expands the clinical and genetic spectrum of *ATL1* mutations.

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INTRODUCTION

Hereditary spastic paraplegias (HSPs), also called spastic paraplegias (SPGs), are a group of genetically and clinically heterogeneous neurodegenerative diseases characterized by lower limbs spasticity and weakness. HSP can be classified into pure and complicated HSP based on symptoms. In pure HSP, the patient simply develops spasticity and weakness in lower limbs, while in complicated HSP, the patient presents with lower limbs spasticity accompanied by other symptoms, such as seizure and ataxia[1]. Over 72 genes have been identified to cause HSP and named by the order of discovery (SPG1-SPG72). HSP can be inherited in autosomal dominant, autosomal recessive or X-linked forms[2].

Among autosomal dominant HSP (AD-HSP) patients, spastic paraplegia 4 (*SPG4/SPAST*) is the most common pathogenic gene while the second most common one is atlastin-1 (*ATL1*)[3,4]. The patients presenting with walking disturbances sometimes initially visit orthopaedic outpatient clinic for treatment. It is crucial to distinguish HSP from other orthopaedic diseases. Drugs, stretching and physiotherapy can reduce spasticity of HSP patients. In some severe HSP cases, orthopaedic surgery is also needed for improving contracture in the lower limbs[5]. Here we reported a novel *ATL1* Q251R mutation in a Chinese family with spastic paraplegia 3A (SPG3A), with a novel phenotype of hearing loss.

CASE PRESENTATION

Chief complaints

A 9-year-old male student was admitted to our hospital orthopaedic outpatient clinic because of progressive spastic paraplegia accompanied by right hearing loss and

mental retardation for five years.

History of present illness
Five years ago, the patient began to have difficulty in walking and climbing stairs progressively accompanied by right hearing loss and mental retardation.

History of past illness
His medical history was not remarkable.

Personal and family history
His family history was positive for spastic paraplegia (Figure 1). His grandfather (subject I:1 Figure 1) developed unsteady walking at 3 years old, while his mother presented the same symptoms (subject II:2 Figure 1) at 8 years old. His mother had no other symptoms, while his grandfather had mental retardation (Table 1).

Physical examination upon admission
Vital signs were in the normal ranges: Body temperature, 37.0 °C, respiratory rate, 21 breaths/min, pulse rate, 92 bpm and blood pressure, 98/60 mmHg. Neurological examinations revealed hypermyotonia in his lower limbs, hyperreflexia in knee reflex, and bilateral positive Babinski signs. He had scissors gait when walking. His lower limbs' muscle strengths were grade 5-/5.

Laboratory examinations
The results of blood routine test, urine routine test, stool routine test, liver function test, renal function test, serum creatase, serum electrolyte, plasma ammonia, blood glucose, ceruloplasmin test and vitamin test were all within normal ranges. The serum lactic acid level was significantly raised to 4.36 mmol/L (normal range: 1.42-1.90 mmol/L). The gene panel included 72 known pathogenic genes associated with spastic paraplegia (Supplement Table 1). Genetic testing revealed that the proband carried an *ATL1* c.752A>G p.Gln251Arg (p.Q251R) mutation, and Sanger sequencing confirmed the existence of family co-segregation (Figure 2).

Imaging examinations
Magnetic resonance imaging (MRI) of the proband showed mild atrophy of the spinal cord (Figure 3), while the MRI results of his grandfather and mother were normal.

FINAL DIAGNOSIS
A diagnosis of autosomal-dominant SPG3A was made based on previously published criteria[6].

TREATMENT
Mecobalamine 0.5 mg three times a day, coenzyme Q10 400 mg twice a day and baclofen 5 mg three times a day were administrated to the patient.

OUTCOME AND FOLLOW-UP
No adverse effects were observed. The patient's symptoms deteriorated gradually in a follow-up visit after two months.

DISCUSSION
To date, 68 *ATL1* pathogenic mutation types have been identified, most of which are missense mutations, followed by small insertions, small deletions and whole exon deletions. The mutation types were located in exon 12 (n = 29, 42.65%), exon 4 (n = 12, 17.65%), exon 8 (n = 8, 11.77%), exon 10 (n = 6, 8.82%), exon 7 (n = 4, 5.88%), exon 5 (n = 2, 2.94%), exon 11 (n = 2, 2.94%), exon 3 (n = 1, 1.47%), exon 6 (n = 1, 1.47%), exon 9 (n = 1, 1.47%), exon 13 (n = 1, 1.47%), and intron 1 (n = 1, 1.47%). The most common mutation genetic model is autosomal dominant (AD) inheritance (n = 57, 83.82%) while the sporadic is the second most common one (n = 7, 10.30%), and autosomal recessive (AR) inheritance is rare (n = 2, 2.94%) while two mutations' types are not available (n = 2, 2.94%) (Table 2)[4,7-12]. Most *ATL1* mutation carriers develop pure

Table 1 Clinical characteristics of the patient and affected family members

Characteristics	I:1	II:2	III:1
Gender	Male	Female	Male
Age at onset (yr)	3	8	4
Past history	Lumbar disc herniation	None	None
Clinical presentations	Walking disturbance, mental retardation	Walking disturbance	Walking disturbance, mental retardation, right hearing loss
Physical examination			
Muscle strength	Normal	Normal	Lower limbs: grade 5-
Muscle tension	Lower limbs: increase	Lower limbs: increase	Lower limbs: increase
Sensory	Normal	Normal	Normal
Tendon reflex	Bilateral knee reflex[1]	Bilateral knee reflex[1]	Bilateral knee reflex[2]
Babinski signs	Positive	Positive	Positive
Gait	Scissors gait	Scissors gait	Scissors gait
Auxiliary examination			
MRI	Normal	Normal	Mild atrophy of the spinal cord
EMG/NCS	NA	Normal	Right tibial nerve's F wave: Wide
BAEP	NA	NA	Right side hearing was impaired

[1]Active;
[2]Hyperreflexia. MRI: Magnetic resonance imaging; EMG: Electromyography; NCS: Nerve conduction study; BAEP: Brainstem auditory evoked potential; NA: Not available.

HSP[4,13,14], while a few of them present with complicated phenotypes, such as seizure, optic atrophy, mental retardation and ataxia[15]. In China, the most common phenotype of *ATL1* mutation carriers is pure HSP while only one complicated phenotype was observed, namely muscular atrophy[16-21].

The impairments of the upper motor system can lead to spastic paraplegia, including cerebral palsy, brain injury, spinal cord infection, spinal cord tumor, and spinal cord injury[22-26]. Among them, the most common cause of spastic paraplegia in children is cerebral palsy, which can mimic HSP[27]. Consequently, it is important to identify HSP in orthopedic patients presenting with spastic paraplegia. Lumbosacral dorsal rhizotomy, botulinum toxin, and physiotherapy are effective ways to treat spasticity in children[28,29].

In the present study, we detected a novel *ATL1* Q251R mutation, which is located in exon 8. *ATL1* Q251R was considered as a novel mutation, as it is absent in the Human Gene Mutation Database (HGMD) (http://www.hgmd.cf.ac.uk/ac/index.php) and clinvar database (www.ncbi.nlm.nih.gov/clinvar/). Besides, no previous case has been reported with *ATL1* Q251R by searching it in PubMed and Web of Science. Protein Variation Effect Analyzer (PROVEN), Mutation Taster and Mutation Assessor were utilized to predict the pathogenicity of *ATL1* Q251R, and the results were described as deleterious, disease-causing and medium credible pathogenic, respectively. The amino-acid substitution replaced a neutrally charged glutamine for a positively charged arginine. Besides, *ATL1* Q251K was also reported to be a disease-causing mutation in HSP[30]. Consequently, the above evidence suggests that *ATL1* Q251R is likely to be a pathogenic mutation of HSP. Further functional studies are warranted to confirm its pathogenicity.

ATL1 was firstly identified and reported to be pathogenic in five HSP kindreds[31]. It encodes for atlastin-1 (ATL1) protein that belongs to the dynamin family of guanosine triphosphatases (GTPases). ATL1 protein has a vital role in homotypic endoplasmic reticulum fusion, which is likely to be the underlying mechanism in the pathogenesis of HSP[32].

In our SPG3A family, we found that the proband and affected family members exhibit different clinical manifestations despite having the same mutation. The proband developed progressive walking disturbance accompanied by hearing loss and mental retardation, while his mother exhibited pure HSP symptoms and his grandfather also had mental retardation but no hearing dysfunction. This clearly indicates that SPG3A is clinically heterogeneous. The intra-family variable penetrance may result from environmental modifiers as well as regulatory variants[33]. Furthermore, sex and mutation types are of great importance in modifying the penetrance in HSP[34]. In our SPG3A family, regulatory variants, gender differences and environmental factors may be the underlying contributors to different phenotypes.

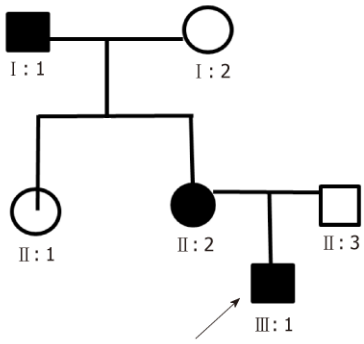

Figure 1 The pedigree of the SPG3A family. The patient is indicated with arrow (III:1) and the affected families are indicated by solid boxes (I:1 and II:2).

Our group previously analyzed the clinical spectrum of HSP in China and found that most of cases were pure one, whereas a few showed complicated phenotypes like atrophy in extremities[35]. Only a few HSP patients develop deafness or hearing loss in the course of the disease, however, none of SPG3A patients with deafness or hearing loss has been reported[36]. The patient we presented here developed progressive walking disturbance accompanied by hearing loss. Therefore, we also presented a novel clinical phenotype in SPG3A, hearing loss.

Furthermore, both neurological defects and orthopaedic diseases can result in movement abnormalities[5]. In fact, orthopaedic surgeons are usually the first doctors who are visited by patients with walking disturbances or gait abnormalities, including HSP patients presenting with progressive spasmodic paraplegia. For example, a Caucasian girl was misdiagnosed with cerebral palsy and a final correct diagnosis of SPG3A was made by genetic testing[12]. Consequently, careful medical history inquiry and physical examination are extremely important for diagnosis. In some cases, no definite diagnosis can be established by an orthopaedic surgeon alone. The evaluation of a neurologist or multidisciplinary team including a neurologist is essential for correct diagnosis. Besides, the treatments of HSP also involve appropriate orthopaedic therapies, such as surgery in severe HSP patients[37].

CONCLUSION

In conclusion, we reported a novel *ATL1* Q251R mutation which is likely to be pathogenic and a clinically novel phenotype of hearing loss in a Chinese SPG3A family, which expands the clinical and genetic spectrum of *ATL1* mutations. SPG3A was clinically heterogeneous even with the same pathogenic mutation. In addition, this report emphasizes the importance of distinguishing HSP patients from other patients in orthopaedic outpatient clinic.

Table 2 *ATL1* pathogenic mutations in hereditary spastic paraplegia

Exon	Nucleotide changes	Amino acid changes	Genetic model
3	G353A	R118Q	AR
4	T452C	F151S	AD
4	G458C	S153T	AD
4	C460G	Q154E	AD
4	C467T	T156I	AD
4	T470G	L157W	AD
4	T470C	L157S	AD
4	G473C	R158T	AD
4	G481C	A161P	AD
4	A484C	T162P	AD
4	T488C	V163A	AD
4	G493A	A165T	AD
5	C565G	H189D	AD
5	A572G	Q191R	AD
6	A587G	Y196C	AD
7	C649T	R217*	AR
7	G650A	R217Q	AD
7	C715T	R239C	AD
7	G716T	R239L	AD
8	A740C	H247P	AD
8	T749C	L250P	AD
8	C751A	Q251K	AD
8	G757A	V253I	AD
8	A773G	H258R	AD
8	C777A	S259Y	AD
8	C776T	S259Y	AD
8	T776G	S259F	AD
9	T944G	I315S	AD
10	C1006T	Y336H	AD
10	C1025A	P342Q	AD
10	C1030T	P344S	S
10	T1036G	S346A	AD
10	T1040C	M347T	AD
10	G1048T	A350S	AD
11	A1064T	N355I	S
11	C1065A	N355K	S
12	T1123C	C375R	AD
12	C1193A	S398Y	AD
12	C1193T	S398F	S
12	T1202C	L401P	S
12	A1220G	K407R	AD
12	A1222G	M408V	AD
12	T1223C	M408T	AD
12	A1222G	M408T	AD
12	G1226A	G409D	S
12	G1228A	G410R	AD
12	A1237C	F413V	AD
12	T1239C	F413L	AD
12	C1242G	S414R	AD
12	C1243T	R415W	AD
12	A1244G	R415Q	AD
12	C1246T	R416C	AD

12	G1247A	R416H	AD
12	T1308A	N436K	S
12	A1319C	N440T	AD
12	A1376G	Y459C	AD
12	G1406C	G469A	AD
12	G1445T	G482V	AD
12	C1483T	R495W	AD
13	G1556A	S519N	AD
12	1306-1308delAAT	N436del	AD
4	Exon 4 del	140-174del	NA
Intron 1	c.35-3C>T	G13fsX16	AD
12	1462_1463insTG	T490Afs	NA
12	1466-1467insTG	T490fsX508	AD
12	1474insG	A492fsX522	AD
12	1504-1505insG	E502fsX522	AD
12	1520insA	I507fsX522	AD

AR: Autosomal recessive; AD: Autosomal dominant; S: Sporadic; NA: Not available.

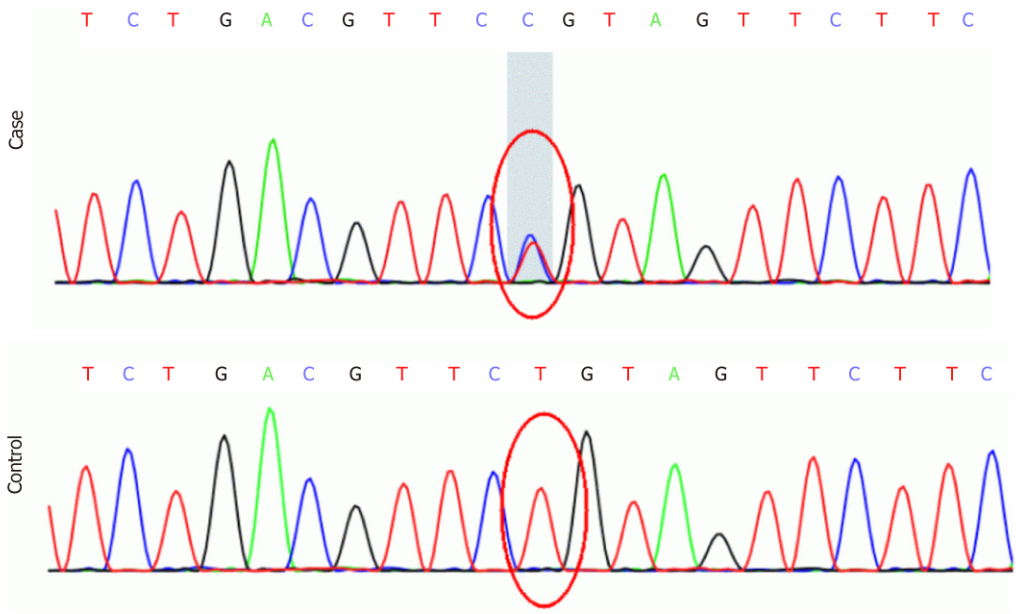

Figure 2 DNA sequencing identified a novel *ATL1* c.752A>G, p.Q251R mutation (top: sequence of the patients; bottom: sequence of healthy individuals).

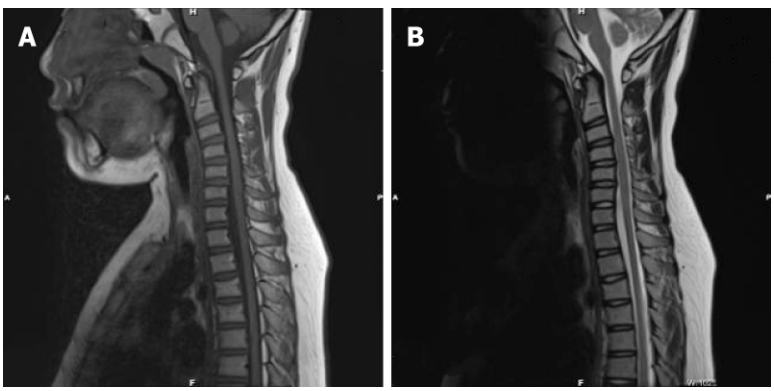

Figure 3 Magnetic resonance imaging showed the mild atrophy the spinal cord. A: T1 sagittal view B: T2 sagittal view.

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