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.
 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 \textit{ATL1} c.752A>G p.Gln251Arg (p.Q251R) mutation, and Sanger sequencing confirmed the existence of family co-segregation.

**CONCLUSION**

We reported a novel \textit{ATL1} Q251R mutation and a novel clinical phenotype of hearing loss in a Chinese SPG3A family.

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

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**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 \textit{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 \textit{ATL1} mutations.

**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 (\textit{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 \textit{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 criteria⁶.

**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)⁶⁻⁸. 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 reflex¹ | Bilateral knee reflex¹ | Bilateral knee reflex²         |
| 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 |

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

HSP⁶[¹⁳,1⁴], while a few of them present with complicated phenotypes, such as seizure, optic atrophy, mental retardation and ataxia¹⁵. In China, the most common phenotype of ATL1 mutation carriers is pure HSP while only one complicated phenotype was observed, namely muscular atrophy⁶[²⁰].

The impairments of the upper motor system can lead to spastic paraplegia, including cerebral palsy, brain injury, spinal cord injury, spinal cord tumor, and spinal cord infection²²[²⁶]. Among them, the most common cause of spastic paraplegia in children is cerebral palsy, which can mimic HSP²⁷. 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 children²⁸[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 HSP³⁰. 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 kindreds³¹. 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 HSP³².

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 variants³³. Furthermore, sex and mutation types are of great importance in modifying the penetrance in HSP³⁴. In our SPG3A family, regulatory variants, gender differences and environmental factors may be the underlying contributors to different phenotypes.
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\cite{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\cite{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\cite{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\cite{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\cite{37}.

CONCLUSION

In conclusion, we reported a novel \textit{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 \textit{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.
| 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    | C481C             | A161P             | AD            |
| 4    | A484C             | T162P             | AD            |
| 4    | T488C             | V163A             | AD            |
| 5    | G493A             | A165T             | AD            |
| 5    | C565G             | H189D             | AD            |
| 5    | A572G             | Q191R             | AD            |
| 6    | G481C             | A165T             | AD            |
| 6    | A587G             | Y196C             | AD            |
| 6    | 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            |
| 9    | T776G             | S259F             | AD            |
| 10   | C791A             | Y336H             | AD            |
| 10   | C1006T            | P342Q             | AD            |
| 10   | C1025A            | P342Q             | AD            |
| 10   | C1030T            | P342Q             | AD            |
| 10   | T1056G            | 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 |
| 12 | G1406C | G469A | AD |
| 12 | A1376G | Y459C | AD |
| 12 | G1445T | G482V | AD |
| 12 | C1483T | R495W | AD |
| 13 | G1556A | S539N | AD |
| 12 | 1308-1308delAAT | 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.
ACKNOWLEDGEMENTS

The authors are grateful to all subjects for participation in our study.

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