Compound heterozygous mutations in the TPP1 gene causes the rare Autosomal recessive spinocerebellar ataxia type 7: A case report and review

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Case Report

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Abstract

Background: Spinocerebellar ataxia type (SCA) type 7 is an inherited neurological disorder that can be inherited as autosomal dominant, autosomal recessive, X-linked, or mitochondrial. In clinical practice, the most common type of SCA7 is autosomal dominant, and the autosomal recessive spinocerebellar ataxia 7 (SCAR7) has been rarely reported. Here, we report the first case of SCAR7 from China with compound heterozygous missense mutations in the Tripeptidyl peptidase-I (TPP1) gene.

Case presentation: A 25-year-old female patient presented with difficulty in walking, easy falling, accompanied by limb shaking, unstable holding objects, slurred speech, choking and coughing when drinking water, palpitations, easy hunger, and hyper-eating without obvious causes 12 years ago. She was admitted to a tertiary general hospital for a cranial MRI examination, which showed cerebellar atrophy. The patient had dysarthria, and had horizontal nystagmus in both eyes for left vision. She was not stable and precise enough in the bilateral finger-nose test and heel and knee shin test and showed Romberg's sign (+). Wechsler Adult intelligence test suggested mild intelligence defect. Genetic testing showed that there were two compound heterozygous mutations in the TPP1 gene. The patient was diagnosed as SCAR7.

Conclusions: The results of autosome testing and sequencing showed that the SCAR7 case was caused by compound heterozygous mutations of the TPP1 gene (c.1468G>A p.Glu490Lys and c.1417G>A p.Gly473Ary). This mutation has not been reported in the Chinese population and is a rare novel mutation. This finding provides a new starting point for the study of the SCAR7 gene.

Background

Autosomal recessive spinocerebellar ataxia 7 (SCAR7) is an atypical tripeptidyl peptidase-I (Tripeptidyl peptidase-I; TPP1) enzyme lacking phenotype. TPP1 is an extra-lysosomal peptidase that sequentially removes tripeptides from the N-terminal of a protein and has weak endopeptidase activity, which is synthesized as a non-catalytic enzyme that is activated and automatically goes through proteolysis when acidified. SCAR7 is characterized by childhood to adolescent ataxia, with or without pyramidal signs, posterior column involvement and nystagmus, and pontine and cerebellar atrophy in the radiograph[1]. The progression of patient's condition often causes significant physical, mental, and economic burdens. The most common type of SCA7 is autosomal dominant inheritance, while SCAR7 has been rarely reported previously. Only two individuals and one family were reported in the world. Given the large global population, although the disease may indeed be rare in the population, this scarcity is also most likely due to misdiagnosis of the disease. We report the first case of SCAR7 from China with missense compound heterozygous mutations in the TPP1 gene. This article summarizes and analyzes the literature to improve the clinicians' understanding of this disease. The SCAR7 case diagnosed and treated in our hospital is reported as follows.

Case Presentation
A female patient aged 25 years old was admitted to the hospital due to "walking difficulty for 12 years and progressively exacerbated". Her symptoms included walking difficulties without obvious inducements, easy falling, manifested as unable to walk independently, showing a "wide basal gait", accompanied by shaking of limbs, unstable holding, unclear speech, coughing when drinking water, palpitations, easy hunger, and excessive eating. She had no difficulty swallowing and no vision loss. The symptoms were progressively exacerbated in the past 10 years. In 2011, the patient was admitted to the Affiliated Hospital of Jining Medical College due to "tremors in the limbs". Cranial MRI was performed and showed cerebellar atrophy. Anti-TG was 667.10 IU/ml. The patient was admitted to the hospital with "Hashimoto's encephalopathy and cerebellar ataxia".

The patient had no history of hypertension, diabetes, or heart disease, nor any family history of similar disorders. Her neurologic examination revealed severe dysarthria, horizontal nystagmus in the left vision of both eyes, slightly elevated muscle tone, unstable alignment in bilateral finger-nose and heel-knee-tibia test, and showed Romberg's sign (+). The other physical examinations were normal. The neuropsychological Wechsler Adult Intelligence Test showed that the patient had a mild mental deficit, with an MMSE score of 9, and a MOCA score of 7.

We performed other relevant tests after the patient was admitted to the hospital. The abnormal laboratory tests are as follows: serum ammonia: 68umo/L, thyroid function: free triiodothyronine: 5.81pmol/L, free thyroxine: 20.6pmol/L, thyrotropin: 2.16uIU/mL, anti-thyroglobulin antibody: 433.4IU/mL, anti-thyroid peroxidase antibody: 33.32IU/mL, and thyroglobulin: 11.04ng/mL. Other screening tests were normal, including erythrocyte sedimentation rate, coagulation series, ceruloplasmin, liver and kidney function, blood glucose, external blood flow, urine organic acid, etc. In addition, electromyography showed normal sensorimotor features. However, thyroid ultrasound showed multiple thyroid nodules (TI-RADS category: 3), cardiac ultrasound showed mild tricuspid regurgitation, and brain MRI showed cerebellar atrophy (Fig. 1).

We also tested the patient for inherited metabolic disease by tandem mass spectrometry. The patient's arginine concentration was 57.32umol/L, threonine was 108.10umol/L, and ornithine/ citrulline was 8.97umol/L. The above indexes deviated from the reference range, but no specific changes were found. Subsequent SCA8 subtype testing showed that the number of repeats of (CTA.TAG) n (CTG.CAG) in the ATXN8OS gene was within the normal range (the number of repeats in normal people is not more than 50). Finally, gene detection of the whole exon group + mitochondrial group showed that two compound heterozygous mutations were detected in the TPP1 gene. Further, her parents and brother also underwent genetic testing. Genetic sequencing confirmed that the patient's father carries a heterozygous mutation 1 and the patient's mother carries a heterozygous mutation 2. The patient carries the compound heterozygous mutations. In contrast, the younger brother, who had inherited only mutation 2 from his mother, was unaffected (Fig. 2, 3). After admission, the patient was given neurotrophic treatment and cell metabolism improvement for 2 weeks. The patient was discharged after the symptoms slightly improved. The 6-month follow-up showed the patient had worsening symptoms and increased dependence on family members.
Discussion And Conclusions

Hereditary spinocerebellar ataxia type (SCA) is a heterogeneous group of inherited neurological disorders characterized by gait ataxia, cerebellar atrophy, and impaired speech, and impaired eye and hand movements. Autosomal dominant SCA is usually caused by repeated trinucleotides cytosine-adenine-guanine amplification, and usually manifests in adulthood, whereas autosomal recessive SCA usually occurs in adolescence\(^2\). Regarding the case in our study, SCAR7 is caused by autosomal recessive inheritance. The locus of SCAR7 was previously associated with chromosome band 11p15\(^3\). Sun et al.\(^4\) determined that TPP1 is the causal gene for SCAR7 by exon sequencing. TPP1 is a member of the serine-carboxypeptidase family that releases N-terminal tripeptides from peptides and is involved in the processing of neuron-specific nutritional factors\(^5\). TPP1 is also the causal gene for late infantile neuronal ceroid lipofuscinosis 2 (CLN2). Lack or very low TPP1 activity usually results in severe classical CLN2, characterized by neurodevelopmental degeneration at age 2–4 years, epileptic seizure, cognitive impairment, language difficulties, vision loss, spasms, ataxia, and eventually death in the second decade. A higher residual TPP1 gene activity leads to a prolonged course of late-onset juvenile CLN2\(^6\). Rarely, CLN2 patients with TPP1 gene deficiency may not have epileptic seizures. Patients with SCAR7, on the other hand, showed ataxia, dysarthria, and higher residual TPP1 enzyme activity. The disease has an onset in adolescence and the phenotypes are more restricted. Radiographical examinations showed pontine and cerebellar atrophy, and patients showed no epilepsy and ophthalmic abnormalities\(^5\). Furthermore, biallelic mutations of the TPP1 gene are generally ineffective in classical CLN2, and are generally less severe in juvenile CLN2 and other atypical phenotypes\(^1\). We performed the whole exosome + mitochondrial genome sequencing for the patient and his family and found two mutations of TPP1 on the patient's genome (c.1468G > A p.Glu490Lys and c.1417G > A p.Gly473Ary), a group of compound heterozygous mutations.

According to the database: HGMD Pro, PubMed, ClinVar, c.1468G > A mutation has not been reported in the literature. c.1417G > A mutation was reported in CLN2. The first mutation of this patient was that the G base at position 1468 of the gene was replaced by the A base, which is a missense mutation and results in the substitution of amino acid at position 490. The second variant is that the G base at position 1417 of the gene is replaced by the A base resulting in the substitution of amino acid at position 473, a missense mutation. The two mutations were inherited from heterozygotes carrying father and mother, respectively. The patient's brother is also a heterozygous carrier, inheriting only the mother's c.1417G > A. The phenotype observed in our study is more consistent with SCAR7 but not CLN2 in differential diagnosis, based on the results of genetic testing, radiographical imaging, and clinical manifestations.

Previous literature has reported only 2 cases of individuals and 1 family worldwide with SCAR7. Breedveld et al.\(^3\) previously reported a unique Dutch family with slowly progressive SCAR7 of childhood-onset with pyramidal signs and posterior column involvement and postural tremor but without other neurologic phenotypes. Neuroimaging revealed atrophy of the cerebellum, vermis, pons, and medulla oblongata. The causative gene was mapped to a region 5.9 cM on chromosome band 11p15 by genome-
wide linkage study. Because ataxia genes mostly have different functions and characteristics, ultimately no obvious candidate gene could be assigned. Subsequently, Sun et al. performed exon sequencing of the DNA of patients and relatives of the Dutch family and found that SCAR7 was related to the TPP1 gene. A 17-year-old female SCAR7 patient was reported in India, who exhibited typical SCAR7 features, including cerebellar ataxia with pyramidal signs, and brain MRI showing diffuse cerebellar atrophy. Two complex heterozygous mutations were identified in the TPP1 gene by genetic testing: a novel single-base pair deletion mutation (Variant-1, chr11:g.6636749delA; c.1190delT; p.Phe397SerfsTer30; NM_000391.4) and a missense mutation (Variant-2, chr11:g.6636213G > C; c.1435C > G; p.Pro479Ala; NM_000391.4) [1].

Recently developed genomic technologies, such as exome sequencing that only targets the coding sequence of the genome, provide an alternative strategy for rapidly and comprehensively sequencing all genes [7]. In summary, SCAR7 is caused by a complex heterozygous variant in TPP1, but clinical symptoms are mostly unexpected, thus we will increasingly apply new technologies such as whole exome sequencing to reduce misdiagnosis of the disease [4]. Because there is currently no treatment to slow or stop SCA, clinical care for patients with SCA focuses on curbing symptoms through physiotherapy, occupational therapy, and speech therapy [8]. Sun et al. [4] found that mutations that reduce TPP1 enzyme activity cause SCAR7, so we infer that treatments that increase TPP1 enzyme activity in the brain may alter the course of the disease, but whether it can cure the disease requires further investigation. Researchers found that gene-editing techniques such as CRISPRCas9 may help with the treatment of SCAR7 [9].

In summary, this report introduces a case of SCAR7 caused by TPP1 compound heterozygous mutations (c.1468G > A p.Glu490Lys and c.1417G > A p.Gly473Ary) and describes SCAR7 in detail. This finding expands the spectrum of mutations that cause SCAR7 and highlights the importance of genetic testing for the diagnosis of early-onset ataxia. Hopefully, this report will provide clinical data for further clinical and scientific research of SCAR7 to increase clinicians’ understanding of the disease and help the diagnosis and treatment of the disease.

**Abbreviations**

SCA Spino cerebellar ataxia type  SCAR7 Autosomal recessive spinocerebellar ataxia 7  TPP1 Tripeptidyl peptidase-I  MRI: Magnetic resonance imaging. CLN2 the causative gene for late infantile neuronal ceroid lipofuscinosis 2  MMSE Mini-mental State Examination  MoCA Montreal Cognitive Assessment.

**Declarations**

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Authors’ contributions
XYW and XCW gathered and evaluated the patient’s clinical data and drafted the manuscript. RHL, XM, NQ, YYJ participated in literature screening and evaluation. QXK guided the revision of the thesis and provided financial support. All authors have read and approved the manuscript.

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Availability of data and materials
All data related to this case report are documented within this manuscript.

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare that they have no known conflict of interest or personal relationships that could have appeared to influence the work reported in this paper.

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References


Figures
Figure 1

Cranial MRI showed reduced cerebellar volume (red arrow), widened and deepened sulci, and enlarged cisterna magna. There was no obvious abnormal signal in the brain parenchyma.
Gene sequencing chromatogram variants TPP1:c.1468G>A (red arrow) and TPP1:c.C.1417G>A (blue arrow) in compound heterozygous state in the patient variant TPP1:c.1468G>A (red arrow) in heterozygous carrier state with wild type at TPP1:c.1417G (purple arrow) in the father variant TPP1:c.1417G>A (blue arrow) in heterozygous carrier state with wild type at TPP1:c.1468G (green arrow) in the mother variant TPP1:c.1417G>A (blue arrow) in heterozygous carrier state with wild type at TPP1:c.1468G (green arrow) in the mother.
Figure 3

Pedigree chart of the family. The back shade represents c.1417G>A, the grey shade represents c.1468G>A; wt denotes wild-type.

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