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Compound heterozygous mutations in *TPP1* cause rare autosomal recessive spinocerebellar ataxia type 7: a case report

A case report of SCAR7

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Abstract

BACKGROUND

Spinocerebellar ataxia recessive type 7 (SCAR7) is a rare clinical manifestation beginning in childhood or adolescence. SCAR7 is caused by tripeptidyl peptidase 1 (*TPP1*) gene mutations, and presents with cerebellar ataxia, pyramidal signs, neurocognitive impairment, deep paresthesia, and cerebellar atrophy.

CASE SUMMARY

Here, we describe a 25-year-old female patient in China who presented with increasing difficulty walking, falling easily, shaking limbs, instability holding items, slurred speech, coughing when drinking, palpitations, and frequent hunger and overeating. Magnetic resonance imaging showed cerebellar atrophy. Whole exome sequencing detected two compound heterozygous mutations in the *TPP1* gene: c.1468G>A p.Glu490Lys and c.1417G>A p.Gly473Arg. Considering the patient's clinical presentation and genetic test results, we hypothesized that complex heterozygous mutations cause *TPP1* enzyme deficiency, which may lead to SCAR7.

CONCLUSION

We report the first case of SCAR7 from China. We also identify novel compound heterozygous mutations in the *TPP1* gene associated with SCAR7, expanding the range of known disease-causing mutations for SCAR7.

Key Words: Spinocerebellar ataxia recessive type 7; Tripeptidyl peptidase 1; Compound heterozygous variant

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Core Tip: A Chinese woman presented with progressive walking difficulties, falling easily, slurred speech, and coughing when drinking. Magnetic resonance imaging revealed cerebellar atrophy. Whole exome sequencing detected novel compound heterozygous mutations in the tripeptidyl peptidase 1 (*TPP1*) gene. Clinical manifestations and bioinformatics analysis showed that the mutations caused spinocerebellar ataxia recessive type 7 (SCAR7).

INTRODUCTION

Spinocerebellar ataxia (SCA) type 7 is an inherited neurological disorder and its inheritance including autosomal dominant, autosomal recessive, X-linked, and mitochondrial manner ^[1]. The most common type of SCA7 is autosomal dominant, while autosomal recessive SCA7 (also known as SCAR7) has rarely been reported.

SCAR7 is caused by low activity of tripeptidyl peptidase 1 (TPP1) and presents from childhood to adolescence with cerebellar ataxia, pyramidal signs, deep sensory loss, and pontine and cerebellar atrophy ^[2]. As the disease progresses, it will cause serious damage to the patient's body and spirit, and cause a serious financial burden to the patient's family.

Studies have found that pathogenic mutations in *TPP1* cause SCAR7 [1]. Typically, *TPP1* mutations lead to neurotic cerebrum ceroidosis type 2 (CLN2), which is characterized by ataxia, seizures, progressive motor and cognitive decline, and visual impairment. CLN2 first presents at 2 to 4.5 years of age, and often leads to death before the age of 20 [3]. Of the more than 100 pathogenic mutations in *TPP1*, only 1% clinically manifest as SCAR7 [3]. To date, <10 patients with SCAR7 have been reported worldwide [24].

This is the first SCAR7 patient reported in China due to missense ¹compound heterozygous mutations in the *TPP1* gene

CASE PRESENTATION

Chief complaints

A 25-year-old female patient was admitted to the hospital with progressive walking difficulties that had been ongoing for 12 years.

History of present illness

The patient had normal development from birth to pre-adolescence. Thirteen years ago, she developed upper and lower limb tremors. Then 12 years ago, she exhibited unstable walking, inarticulate speech, and coughing when consuming fluids. At present, the patient's symptoms include walking difficulties and falling easily, which have left her inability to walk independently, wide basal gait, shaking limbs, unsteady holding, slurred speech, and choking on drinking water. She often experiences palpitations and feels hungry.

⁴

History of past illness

The patient had no abnormal birth history.

Personal and family history

The patient's parents are healthy and not consanguineous. The patient had a gestational age of 39 wk, head circumference of 34 cm, birth weight of 2.75 kg and body length of 49 cm. The rooting reflex, sucking reflex, grip reflex and embrace reflex were normal. The patient has a younger brother. Neither the patient's parents nor her younger brother have clinical manifestations of SCAR7.

Physical examination

Neurological examination revealed severe dysarthria, horizontal nystagmus² of both eyes, mildly elevated muscle tone, unstable alignment in bilateral finger-nose and heel-knee-tibia tests, and positive Romberg sign. The neuropsychological Wechsler Adult Intelligence Test showed that the patient had mild intellectual disability. The minimal state examination (9 points) , Montreal Cognitive Assessment (7 points) and cerebellar cognitive affective syndrome (CCAS) scale (failure score of 6) all indicated cognitive impairment. The patient did not have vision problems and other physical tests showed no abnormalities.

Laboratory examinations

Laboratory findings were within normal limits.

Imaging examinations

Cranial magnetic resonance imaging (MRI) T1-weighted sequence cross-sectional image showed obvious cerebellar atrophy and T2-weighted sequence sagittal image showed obvious cerebellar atrophy, deepening sulcus widening, and enlarged cerebral cistern, suggesting cerebellar atrophy (Figure 1).⁵

Genetic analysis

Genomic DNA was isolated from the peripheral blood of the patient for whole exome sequencing. Candidate mutation sites were detected by Sanger sequencing; peripheral blood from the patient's parents and younger brother was used for Sanger sequencing.

Compound heterozygous mutations in the *TPP1* gene were detected: a missense mutation c.1468G>A p.Glu490Lys (present in the father; Figures. 2, 3), and a missense mutation c.1417G>A p.Gly473Arg (present in the mother; Figures. 2, 3). The younger brother had only inherited the maternal mutation.

These two missense mutations were considered ⁸likely pathogenic according to the American College of Medical Genetics and Genomics criteria (PM1, PM2, PM3, PP3) [5]. SIFT, PolyPhen2, and Mutation Taster software analyses indicated that both c.1468G>A and c.1417G>A mutations are likely to be “deleterious”, “probably damaging”, and “disease-causing” mutation.

FINAL DIAGNOSIS

On the basis of the clinical characteristics, genetic test results, and bioinformatics analysis, the the patient was diagnosed with SCAR7.

TREATMENT

Idebenone, 30mg each time, 3 times a day after meals and N-acetylglycinamide, 400mg each time, once a day, slowly intravenously.

OUTCOME AND FOLLOW-UP

The patient was discharged after a slight improvement in symptoms. At 6 months of follow-up after discharge, the patient's symptoms worsened and the dependence on family members increased significantly

DISCUSSION

Hereditary SCAs are a heterogeneous group of inherited neurological disorders, with *TPP1* being the causative gene of SCAR7. The *TPP1* enzyme is produced as a proenzyme that is processed in the lysosome into active enzymes, which then cuts proteins into tripeptides. Deficiency of *TPP1* Leads to the accumulation of autofluorescent ceroid lipofuscin within cells, causing neuronal death and eventually

brain and retinal degeneration [6]. *TPP1* gene mutations can lead to differing degrees of change in TPP1 activity. Loss of function abolishing TPP1 enzyme activity results in classical CLN2, presents with delayed language development and neurodevelopmental degeneration onset at 2-4 years of age, and followed by loss of motor and language skills, epileptic seizures epileptic seizures, vision loss and eventually death before the early teenage years. Slightly higher retention of TPP1 activity leads to late-onset juvenile CLN2 with a prolonged course [7]. SCAR7 patients have higher TPP1 enzyme activity compared with CLN2 patients. SCAR7 presents from childhood to adolescence as ataxia with or without pyramidal signs, posterior column involvement, and nystagmus. Patients with SCAR7 typically have a late age of onset, fewer phenotypes, and less severe degree. MRI shows obvious cerebellar and pontine atrophy, and patients do not have epilepsy, cognitive impairment, photosensitivity, or ophthalmic abnormalities [8]. On the basis of the clinical manifestations and radiographical imaging, the patient's diagnosis is more consistent with SCAR7 than CLN2.

Among *TPP1* mutations, mutations that cause early termination of protein translation, such as nonsense mutations and frameshift mutations, as well as missense mutations that change the splice site and reading frame, can lead to the loss or significant reduction of TPP1. Mutations that do not cause serious splice changes, such as missense mutations, retain some TPP1 activity [1]. This patient has two missense mutations that are not located at a splice site, which may allow TPP1 to retain partial activity, thereby causing the patient to present with SCAR7 instead of CLN2.

At the age of 13, the patient presented with progressive and aggravated walking difficulties, bilateral upper limb trembling, slurred speech, dysphagia, and no epilepsy or retinopathy. Cerebral MRI showed cerebellar atrophy. Whole exome sequencing revealed complex heterozygous missense mutations in *TPP1* gene. According to the patient's clinical manifestations and gene sequencing results, the patient was given a diagnosis of SCAR7. Enzyme replacement therapy with cerliponase alfa was approved in the United States and Europe in 2017 to treat CLN2. It was found that

giving cerliponase alfa treatment significantly reduced the rate of motor and speech function decline in patients with CLN2 [6]. We suspect that cerliponase alfa may also be effective in patients with SCAR7, but further confirmation is needed.

Only two individuals and one family have been reported with SCAR7 worldwide. Breedveld *et al.*, reported a Dutch family with a pure spinocerebellar phenotype that diagnosed as SCAR7 of childhood-onset, manifested as cerebellar ataxia, pyramidal signs, posterior column involvement with deep sensory loss, and atrophy of the cerebellum, vermis, pons, and medulla oblongata in neuroimaging [9]. Subsequently, Sun *et al.* performed exon sequencing of the Dutch family and their relatives and found that SCAR7 was associated with mutations in the *TPP1* gene [1]. A 17-year-old Indian female patient with typically SCAR7 was reported to be characterized by cerebellar ataxia with pyramidal sign, diffuse cerebellar atrophy on head MRI, and two compound heterozygous mutations in the *TPP1* gene [10]. Taken together, SCAR7 has a variety of clinical manifestations and can be easily confused with CLN2 and other SCAs, which can lead to missed diagnosis and misdiagnosis. Therefore, SCAR7 should be suspected and genetic testing performed for patients with childhood or adolescence onset slow-progressing spastic ataxia syndrome.

In this paper, our team reported a patient with SCAR7 caused by compound heterozygous mutations in *TPP1* gene (c.1468G>A p.Glu490Lys and c.1417G>A p.Gly473Arg). The discovery of this mutations expanded the spectrum of genetic variants that cause SCAR7 and highlighted the importance of genetic testing in the diagnosis of early-onset ataxia. This report will inform further clinical and scientific research on SCAR7, improve clinicians' understanding of the disease, and aid in the diagnosis and treatment of the disease.

CONCLUSION

Hereditary SCAs are a very rare hereditary neurological disorder. Patients with ataxia, dysarticulation, and cerebellar and pontine atrophy on neuroimaging, presence or absence of pyramidal signs, posterior column involvement, nystagmus, should be suspected of having SCAR7 and undergo genetic screening.

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