**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 57892

**Manuscript Type:** CASE REPORT

**Compound heterozygous mutations in the neuraminidase 1 gene in type 1 sialidosis:** **A case report and review of literature**

Cao LX *et al*. Clinical and genetic features of type 1 sialidosis

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**Author contributions:** Zhang BR played a major role in the acquisition of data; Liu Y interpreted the patient data; Cao LX analyzed the data and was a major contributor in writing the manuscript; Zhao GH and Long WY revised the manuscript for intellectual content; All authors read and approved the final manuscript.

**Supported by** the Research Foundation of Zhejiang Health, No. 2020RC061.

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**Received:** July 12, 2020

**Revised:** December 2, 2020

**Accepted:** December 10, 2020

**Published online:**

**Abstract**

BACKGROUND

Type 1 sialidosis, also known as cherry-red spot-myoclonus syndrome, is a rare autosomal recessive lysosomal storage disorder presenting in the second decade of life. The most common symptoms are myoclonus, ataxia and seizure. It is rarely encountered in the Chinese mainland.

CASE SUMMARY

A 22-year-old male presented with complaints of progressive myoclonus, ataxia and slurred speech, without visual symptoms; the presenting symptoms began at the age of 15-years-old. Whole exome sequencing revealed two pathogenic heterozygous missense variants [c.239C>T (p.P80L) and c.544A>G (p.S182G) in the neuraminidase 1 (NEU1) gene], both of which have been identified previously in Asian patients with type 1 sialidosis. All three patients identified in Mainland China come from three unrelated families, but all three show the NEU1 mutations p.S182G and p.P80L pathogenic variants. Increasing sialidase activity through chaperones is a promising therapeutic target in sialidosis.

CONCLUSION

Through retrospective analysis and summarizing the clinical and genetic characteristics of type 1 sialidosis, we hope to raise awareness of lysosomal storage disorders among clinicians and minimize the delay in diagnosis.

**Key Words:** Sialidosis; Myoclonus; Ataxia; Neuraminidase 1; Case report; Mucolipidoses

Cao LX, Liu Y, Song ZJ, Zhang BR, Long WY, Zhao GH. Compound heterozygous mutations in the neuraminidase 1 gene in type 1 sialidosis: A case report and review of literature. *World J Clin Cases* 2020; In press

**Core Tip:** Type 1 sialidosis is a rare autosomal recessive lysosomal storage disorder. Very few cases of this condition have been reported in mainland China, which may be partly attributed to an inadequate awareness of lysosomal storage diseases among neurology physicians. This study reports the clinical and molecular characteristics of a Chinese patient with type 1 sialidosis confirmed by genetic testing. Neuraminidase 1 mutations p.S182G and p.P80L are common pathogenic variants of all three patients identified in Mainland China, coming from three unrelated families.

**INTRODUCTION**

Sialidosis is a progressive lysosomal storage disease that exhibits an autosomal recessive inheritance pattern, with an incidence of 0.04 in 100000[1]. This condition is caused by mutations in the neuraminidase 1 (NEU1) gene, leading to alpha-N-acetylneuraminidase (sialidase) deficiency and abnormal tissue accumulation and urinary excretion of sialylated oligosaccharides and glycolipids[2]. Sialidosis can be classified into types 1 and 2, according to the clinical presentation. Type I sialidosis has a relatively late onset (predominantly ages 10-30 years) and a milder phenotype[3], whereas type 2 sialidosis is a severe form with earlier onset and is further subdivided into congenital, infantile and juvenile forms, which show abnormalities *in utero*, within 1 year of birth and after the age of 2 years, respectively[3].

The clinical characteristics of type I sialidosis include myoclonus, seizures, ataxia, visual symptoms and cognition impairment presenting in the second decade of life[4]. This condition is also known as cherry-red spot-myoclonus syndrome[5]. Tibial somatosensory evoked potentials (commonly known as SSEP), suggesting giant cortical potential, in addition to abnormal electroencephalography (commonly referred to as EEG) and brain magnetic resonance imaging (commonly referred to as MRI) provide strong evidence for sialidosis diagnosis[4,6,7]. To date, 55 genetically-confirmed patients have been reported in various regions of the world and more than 30 NEU1 mutations have been shown to be responsible for type 1 sialidosis[6-8].

Here, we describe the clinical manifestations of a 22-year-old man with type 1 sialidosis carrying two known pathogenic missense variants that have been identified previously in Chinese and Japanese patients.

**CASE PRESENTATION**

***Chief complaints***

A 22-year-old male (II:3; Figure 1A) from Southwest China was admitted to the Second Affiliated Hospital, Zhejiang University School of Medicine to address involuntary movements of the four extremities and dysarthria lasting for several years.

***History of present illness***

Aged 16 years, the patient experienced involuntary shaking of the bilateral upper limbs, with gradual lower limb involvement over the next few years, resulting in disruption of his walking balance. Three years previously, the patient experienced an inability to speak clearly and fluently and he achieved only a junior middle school education. Despite numerous visits to his doctors, the patient did not obtain a definitive diagnosis nor effective treatment. When he presented to our clinic, he exhibited worsening ataxia and myoclonus resulting in impaired walking ability and difficulties with communication.

***History of past illness***

The patient had a free previous medical history.

***Personal and family history***

The patient’s parents were in a nonconsanguineous marriage and neither they nor his elder sister complained of the same symptoms.

***Physical examination***

The neurological examination revealed slurred speech, intention tremor, ataxia, and marked hyperreflexia. His cognition was normal. He had normal eye movement, no nystagmus, and denied visual symptoms, such as blurred vision and visual field defects.

***Laboratory examinations***

His routine laboratory test results were unremarkable and there were no abnormalities in his EEG. Electromyography and nerve conduction velocity examination of the patient indicated reduced motor nerve conduction velocity and prolonged motor latency in the left peroneal nerve.

***Imaging examinations***

Cranial MRI showed slight atrophy of the bilateral cerebellum (Figure 1B). Fundus photographs of both eyes showed absence of a cherry-red spot (not shown).

**FINAL DIAGNOSIS**

The diagnosis of type 1 sialidosis was confirmed by identification of compound heterozygous known mutations in the NEU1 gene: c.239C>T (p.Pro80Leu) and c.544A>G (p.Ser182Gly).

**TREATMENT**

The patient was treated with 5 mg of buspirone and 30 mg of idebenone three times per day.

**OUTCOME AND FOLLOW-UP**

The patient did not continue to take medicine not long after he was discharged from the hospital. Six months after his discharge, involuntary shaking of the four extremities and dysarthria persisted without significant improvement or aggravation.

**DISCUSSION**

Type 1 sialidosis is a rare, autosomal recessive disorder. Here, we describe a 22-year-old male who exhibited cerebellar ataxia, myoclonus, hyperreflexia, slurred speech, and mild cerebellar atrophy. The diagnosis of type 1 sialidosis was confirmed by identification of compound heterozygous known mutations in the NEU1 gene, namely c.239C>T (p.Pro80Leu) and c.544A>G (p.Ser182Gly). Very few cases of this condition have been reported in mainland China, which may be partly attributed to an inadequate awareness of lysosomal storage diseases among neurology physicians. In recent years, the widespread use of next-generation sequencing technologies in clinical settings has improved the accuracy and sensitivity of diagnosis of lysosomal storage diseases.

Previous reports indicate that myoclonus is the most common symptom of type 1 sialidosis and was detected in almost all the genetically diagnosed patients[4,7,9]. Overall, 88.3% of patients present with ataxia and 72.5% with seizures[8]. Visual disturbances, such as blurred vision and visual field deficits, occur in only 68.4% of all cases[8]. Although type 1 sialidosis is also known as cherry-red spot-myoclonus syndrome, is noteworthy that this feature was observed in less than half of all the reported patients, indicating that this is not an accurate naming of this disease[10]. Furthermore, cherry-red spots are seen more frequently in Caucasian patients than in Asian patients (61.1% *vs* 40.7%)[8], suggesting that this feature should not be listed as an indispensable sign of type 1 sialidosis diagnosis, especially in Asian patients. The possible reasons for this lack of cherry-red spots include late appearance, residual enzymatic activity, and potential effects of various mutations[11,12]. Macular cherry-red spot is caused by deposition of material in the ganglion cells of the macula in the retina. Because ganglion cells are several layers thick in this area and absent from the fovea, the fovea remains relatively transparent and contrasts with the surrounding opaque retina[13]. Moreover, prolonged visual evoked potential latency and giant cortical potential SSEP are also helpful for early diagnosis[6,8,14]. In neuroimaging, diffuse brain atrophy (particularly the cerebellum) can be evident in the advanced stage of type 1 sialidosis[15]. In addition, accumulation of sialyloligosaccharides can be observed in the central nervous system of sialidosis patients by pathological examination[15].

To date, more than 30 NEU1 mutations have been identified as responsible for type 1 sialidosis (Table 1)[4,7,8,11-27]. Missense variants are the most common pathogenic mutations, and few exonic duplications or deletions have been reported[11]. The symptoms and severity of the disease are closely related to the type of NEU1 variants and the levels of residual enzyme activity[16]. The missense mutation c.544A>G (p.S182G) was previously reported to be pathogenic and is a common missense mutation in the Taiwanese population[4,8]. Lai *et al*[4] reported that macular cherry-red spots were present in three of 17 Taiwanese patients with type 1 sialidosis who carried the NEU1 c.544A>G (p.S182G) mutation. Patients harboring the Ser182Gly mutation may have relatively high enzymatic activity (~40% of normal) compared with other known mutations (for instance, Phe260Tyr and Leu270Phe mutants showed 10%-20% of normal enzymatic activity), and they may have a slower rate of lysosomal sialic acid accumulation in retinal cells, resulting in moderate symptoms and absence of macular cherry-red spots[28]; this feature is consistent with our patient. A review of all the type I sialidosis cases reported in the Chinese population (Table 2[4,8,20,29-31]) revealed that p.S182G and p.P80L are the common pathogenic variants of all three patients identified in Mainland China from three unrelated families[29,30]. Unlike the patient in this study, however, the other two cases previously reported in China had visual symptoms and cherry-red spots.

Currently, available therapies for sialidosis are limited to symptom management. The myoclonus can be alleviated by drugs such as clonazepam and valproic acid, as well as piracetam in some cases. The most common type of seizures in type 1 sialidosis are generalized tonic-clonic seizure and myoclonic seizures, which can be significantly controlled within 1 year by anti-epileptic drugs, with seizures subsequently occurring at low frequency[4]. A longitudinal study revealed that both of these primary symptoms deteriorate during the first 5 years after onset and then remain stable, suggesting a more rapid progression in the early stages of this disorder[4]. Further longitudinal studies of patients with different mutations and geographical origin are needed to verify this pattern. The limitation of this case report is the absence of long-term follow-up and reexamination of the patient to assess the progress of the disease.

The underlying pathological mechanism of type 1 sialidosis is still unclear, and finding specific therapeutic approaches remains a significant challenge. Studies have implicated proteosomal regulation as a potential therapeutic target. Proteasomal inhibitors (*e.g.*, MG132) combined with chemical chaperones (*e.g.*, celastrol) have been shown to rescue misfolded sialidase and increase enzyme expression[32]. In addition, protective protein/cathepsin A (known as PPCA)-chaperone-mediated gene therapy has shown positive effects in protecting against severe phenotypes in a mouse model of type 1 sialidosis carrying a NEU1 variant (a V54M amino acid substitution). Enzyme activity was successfully increased in the systemic tissues of mice following injection with a liver-tropic recombinant AAV2/8 vector expressing PPCA, which is a NEU1 binding chaperone that maintains lysosomal compartmentalization, stability and catalytic activation[33]. These results provide promising evidence that increasing sialidase activity through chaperones is a promising therapeutic target in sialidosis.

**CONCLUSION**

Type 1 sialidosis is a rare autosomal recessive lysosomal storage disorder. Very few cases of this condition have been reported in mainland China, which may be partly attributed to an inadequate awareness of lysosomal storage diseases among neurology physicians. NEU1 mutations p.S182G and p.P80L are the shared pathogenic variants among all three patients identified in Mainland China, although from three unrelated families. Increasing sialidase activity through chaperones is a promising therapeutic target in sialidosis.

**ACKNOWLEDGEMENTS**

We are thankful to the patients who agreed to participate in this study.

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**Footnotes**

**Informed consent statement:** Written informed consent was obtained from each participant for publication of this case report.

**Conflict-of-interest statement:** The authors declare that they have no competing interests.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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**Manuscript source:** Unsolicited manuscript

**Peer-review started:** July 12, 2020

**First decision:** November 26, 2020

**Article in press:**

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Gingras M **S-Editor:** Gao CC **L-Editor:** Filipodia **P-Editor:**

**Figure Legends**



**Figure 1 Clinical and genetic information of the patient.** A: Pedigree of the family with compound heterozygous neuraminidase 1 (NEU1) mutations; B: Cranial magnetic resonance imaging of the patient demonstrated slight atrophy of bilateral cerebellum; C and E: Normal control sequences; D: Variant in exon 2 (c.239C>T); F: Variant in exon 4 (c.544A>G). Family member I:1 was the carrier of c.239C>T and family member I:2 was the carrier of c.544A>G. Family member II:3 harbored the compound heterozygous NEU1 mutations.

**Table 1 Mutations in the neuraminidase 1 gene causing type 1 sialidosis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Mutation** | **Nucleotide change** | **Exon** | **Origin** | **Ref.** |
| R6Qfs\*21 | c.15\_16del | 1 | Korean | Ahn *et al*[7] |
| V54M | c.160G>A | 1 | German | Bonten *et al*[17] |
| Q55X | c.163C>T | 1 | Taiwanese | Lai *et al*[4] |
| S67I | c.200G>T | 2 | Italian | Canafoglia *et al*[18] |
| P80L | c.239C>T | 2 | Japanese, Chinese | Sekijima *et al*[15] |
| A106\_G118 del | c.314\_352del | 2 | Taiwanese | Fan *et al*[8] |
| L111P | c.332T>C | 2 | French | Seyrantepe *et al*[11] |
| D135N  | c.403G>A | 3 | Japanese | Sekijima *et al*[15] |
| G136E | c.407G>A | 3 | French | Seyrantepe *et al*[11] |
| D177V | c.530A>T | 3 | Italian | Hu *et al*[20] |
| S182G | c.544A>G | 3 | Chinese, Taiwanese | Lai *et al*[4], Fan *et al*[8], Mohammad *et al*[12], Bonten *et al*[17], and Hu *et al*[20] |
| Q207X | c.619C>T | 3 | Taiwanese | Hu *et al*[20] |
| E209Sfs\*94 | c.625delG | 3 | Turkish | Gultekin *et al*[21] |
| P210L | c.629C>T | 3 | Ecuadorian | Aravindhan *et al*[14] |
| V217M | c.649G>A | 4 | Japanese | Naganawa *et al*[16] |
| G218A | c.654G>A | 4 | African-American | Bonten *et al*[17] |
| G219A | c.656G>A | 4 | African, American | Bonten *et al*[17] |
| G227R | c.679G>A | 4 | Greek, Italian, East-Asian, Dutch | Mohammad *et al*[12], Bonten *et al*[17], Canafoglia *et al*[18], Schene *et al*[22] |
| L231H | c.692T>A | 4 | African | Bonten *et al*[17] |
| S233R | c.699C>A | 4 | German | Mütze *et al*[23] |
| D234N | c.700G>A | 4 | Portuguese | Sobral *et al*[13] |
| G243R | c.727G>A | 4 | Japanese | Naganawa *et al*[16] |
| G248C | c.742G>T | 4 | Indian | Gowda *et al*[24] |
| Y268C  | c.803A>G | 5 | German | Mütze *et al*[23] |
| V275A | c.824T>C | 5 | French | Seyrantepe *et al*[11] |
| R280Q | c.839G>A | 5 | Italian | Caciotti *et al*[19] |
| R294S, R294C | c.880C>A, c.880C>T | 5 | African, Indian, Hispanic | Bonten *et al*[17] |
| R305C | c.913C>T | 5 | Italian | Canafoglia *et al*[18] |
| D310N | c.928G>A | 5 | Turkish, Korean | Ahn *et al*[7], Gultekin *et al*[21] |
| P316S | c.946C>T | 5 | Japanese | Itoh *et al*[25] |
| A319V | c.956C>T | 5 | Taiwanese | Lai *et al*[4] |
| G328S | c.982G>A | 5 | Italian | Palmeri *et al*[26] |
| H337R | c.1010A>G | 5 | Italian | Caciotti *et al*[19] |
| R341X | c.1021C>T | 5 | Portuguese | Sobral *et al*[13] |
| T345I | c.1034C>T | 6 | Czech | Seyrantepe *et al*[11] |
| E377X | c.1129G>T | 6 | German | Canafoglia *et al*[18] |
| N398Tfs\*90 | c.1191delG | 6 | Indian | Ranganath *et al*[27] |
| H399\_Y400dup | c.1195\_1200dup | 6 | Dutch | Schene *et al*[22] |

**Table 2 Clinical and molecular genetic features of type 1 sialidosis patients in the Chinese population**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Family** | **Case** | **Geographical distribution** | **Mutation 1** | **Mutation 2** | **Age at onset, yr** | **Age at diagnosis, yr** | **Symptoms (presenting age)** | **Cherry-red spot** | **Ref.** |
| 1 | 1 | Taiwan | p.S182G | p.S182G | 27 | 42 | S (27), M (28), A (29) | 0 | Lai *et al*[4], 2009 |
| 1 | 2 | Taiwan | p.S182G | p.S182G | 19 | 34 | S (19), M (19), A (19), V (29), SD | 0 | Lai *et al*[4], 2009 |
| 2 | 3 | Taiwan | p.S182G | p.S182G | 14 | 39 | M (14), S (14), V (14), A (16), SD | 0 | Lai *et al*[4], 2009 |
| 2 | 4 | Taiwan | p.S182G | p.S182G | 26 | 36 | V (26), M (27), A (27), SD | 0 | Lai *et al*[4], 2009 |
| 3 | 5 | Taiwan | p.S182G | p.S182G | 16 | 31 | M (16), A (17), V (19), S (21) | 0 | Lai *et al*[4], 2009 |
| 3 | 6 | Taiwan | p.S182G | p.S182G | 12 | 29 | M (12), A (13), S (16), V (18) | 0 | Lai *et al*[4], 2009 |
| 4 | 7 | Taiwan | p.S182G | p.S182G | 20 | 51 | M (20), Fall (20), S (26), SD | 0 | Lai *et al*[4], 2009 |
| 4 | 8 | Taiwan | p.S182G | p.S182G | 33 | 45 | V (33), M (34), A (34), S (37) | 0 | Lai *et al*[4], 2009 |
| 5 | 9 | Taiwan | p.S182G | p.S182G | 20 | 39 | M (20), A (21), SD | 0 | Lai *et al*[4], 2009 |
| 5 | 10 | Taiwan | p.S182G | p.S182G | 15 | 35 | M (15), A (15), V (25), SD | 0 | Lai *et al*[4], 2009 |
| 6 | 11 | Taiwan | p.S182G | p.S182G | 18 | 42 | M (18), Fall (18), S (20), A (24), V (28) | 0 | Lai *et al*[4], 2009 |
| 7 | 12 | Taiwan | p.S182G | p.S182G | 28 | 47 | S (28), M (29), A (29), V (39) | 0 | Lai *et al*[4], 2009 |
| 8 | 13 | Taiwan | p.S182G | p.A319V | 14 | 25 | M (14), A (19), S (25), V (20), SD | 1 | Lai *et al*[4], 2009 |
| 9 | 14 | Taiwan | p.S182G | p.Q55X | 12 | 27 | M (12), A (14), V (14), S (15) | 1 | Lai *et al*[4], 2009 |
| 10 | 15 | Taiwan | p.S182G | p.S182G | 19 | 49 | M (19), A (24), V (29) | 0 | Lai *et al*[4], 2009 |
| 11 | 16 | Taiwan | p.S182G | p.S182G | 18 | 33 | V (18), M (20), A (20), S (33), SD | 0 | Lai *et al*[4], 2009 |
| 12 | 17 | Taiwan | p.S182G | p.S182G | 14 | 43 | V (14), M (31), A (32), S (40) | 1 | Lai *et al*[4], 2009 |
| 13 | 18 | Mainland | p.S182G | p.P80L | 11 | 17 | V (11), S (15), M (15), A (15) | 1 | Baojingzi *et al*[30], 2015 |
| 14 | 19 | Taiwan | p.S182G | p.Gln207\* | 12 | 15 | S (12), A (12), M (12), dysarthria | 1 | Hu *et al*[20], 2018 |
| 15 | 20 | Taiwan | p.S182G | p.A106\_G118 deletion | 13 | 16 | M (13), A | 0 | Fan *et al*[8], 2020 |
| 16 | 21 | Mainland | p.S182G | p.P80L | 10 | 12 | Limb pain (10), Fall (10), M (11), V (11), S (11) | 1 | Liu *et al*[29], 2019 |
| 17 | 22 | China | p.S182G | p.S182G | NA | 24 | M, dysphagia | NA | Carey *et al*[31], 1997 |
| 18 | 23 | Mainland | p.S182G | p.P80L | 16 | 22 | M (16), A (19) | 0 | Current study |

A: Ataxia; M: Myoclonus; S: Seizure; SD: Sensory defect; V: Visual defect. 0: Absent; 1: Present; NA: Not available.