Received: 18 June 2022 | Revised: 23 October 2022 | Accepted: 22 February 2023

DOI: 10.1002/mgg3.2188

Molecular Genetics & Genomic Medicine Open Access WILEY

CLINICAL REPORT

Expanding the mutational spectrum of ZTTK syndrome: A de novo variant with global developmental delay and malnutrition in a Chinese patient

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Funding information
Support Scheme of Guangzhou for Leading Talents in Innovation and Entrepreneurship, Grant/Award Number: 2019005

Abstract

Background: Zhu-Tokita-Takenouchi-Kim (ZTTK, OMIM 617140) syndrome is a severe multisystem developmental disorder characterized by intellectual disability, developmental delay, cortical malformations, epilepsy, visual problems, musculoskeletal abnormalities, and congenital malformations. ZTTK syndrome is caused by a heterozygous pathogenic variant of the *SON* gene (NM_138927) at chromosome 21q22.1. The purpose of this study was to investigate the pathogenesis of a 6-month-old Chinese child who exhibited global developmental delay, muscle weakness, malnutrition, weight loss, and strabismus, brain abnormality, immunological system abnormalities.

Methods: The little girl was tested for medical exome sequencing (MES) and mtDNA sequencing in trio. And, the mutation was validated by Sanger sequencing.

Results: A novel de novo frameshift variant, c.1845_1870del26 (p.G616Sfs*61), in the *SON* gene was found in the proband.

Conclusion: We described a 6-month-old Chinese child with global developmental delay caused by pathogenic de novo mutation c.1845_1870del26 (p.G616Sfs*61) in the *SON*. Apart from a founder mutation, we reviewed the phenotypic abnormalities and genotypes in 79 individuals. The data showed that global developmental delay is accompanied by other system disorders. Our findings expanded the mutational spectrum of ZTTK syndrome and provide genetic counseling of baby with global developmental delay.

KEYWORDS

genetics, global developmental delay, multiple phylogenetic disorders, muscle weakness, *SON*, Zhu-Tokita-Takenouchi-Kim syndrome

1 | INTRODUCTION

Patients with genetic disorders mainly with intellectual disabilities, developmental delay, and multiple malformations impose a heavy financial burden on families and society (Mithyantha et al., 2017). After more than a decade of efforts, scientists have established a series of genetic testing techniques to diagnose patients with suspected chromosomal aberrations and monogenic diseases. Developmental delay is a very common clinical manifestation of genetic disorders, namely, physical developmental delay, motor developmental delay, speech delay, and intellectual developmental delay (Mithyantha et al., 2017). However, causes of developmental delay could be exogenous, hereditary (nonmetabolic), or hereditary (metabolic) that make it difficult to diagnose it clinically (Mithyantha et al., 2017). In recent years, the rapid development of high-throughput sequencing has brought hope for early diagnosis (Kushary et al., 2021), treatment, and intervention for patients and families with developmental delay.

There are many disorders associated with developmental delay, one of which is the *SON* gene-related disorder, ZTTK syndrome (ZTTK, OMIM 617140). It is a severe multisystem developmental disorder characterized by physical and psychomotor development delayed, with clinical manifestations similar to those of mitochondrial diseases, which typically involve multiple organ systems. Patients have dysmorphic facial features, hypotonia, malnutrition, global dysplasia, hearing abnormalities, and eye or visual abnormalities. Most patients also have musculoskeletal abnormalities, and some have congenital cardiac and genitourinary defects (Dingemans et al., 2021; Kushary et al., 2021). Brain imaging usually showed developmental abnormalities such as altered brain gyrus, cortical and/or cerebellar atrophy, and thin corpus callosum (Kim et al., 2016). The disease was first reported in 2015 with the identification of a mutation in *SON* gene (Zhu et al., 2015), which encodes a ubiquitously expressed and conserved DNA-binding protein. SON is able to shear DNA and RNA and regulates the transcription of genes involved in cell cycle progression and pluripotency (Ahn et al., 2013). The first de novo truncated mutation in the *SON* gene was identified in a large cohort of patients with severe intellectual disability (Gilissen et al., 2014).

So far, ZTTK syndrome caused by mutations in *SON* identified from only 79 patients all over the world. In this report, we described a case of global developmental delay and multiple phylogenetic disorders caused by *SON* heterozygous frameshift mutation (*SON*: c.1845_1870del26, p.G616Sfs*61) in a 6-month-old Chinese girl. The genotype and clinical characteristics were discussed and the literature was reviewed in this study.

2 | MATERIALS AND METHODS

2.1 | Study subject

The project was approved by the ethics committee of Hunan Children's Hospital. A 6-month-old female infant went to gastroenterology, and ultrasound revealed abdominal distention. There was loss of subcutaneous fat, and there was a 2-month history of slow weight gain. Her abdomen and extremities were found to have low muscle tone. Malnutrition, growth retardation, and a weak neck with inability to lift her head were observed. Cardiac enzymes (lactate dehydrogenase (LD) 456.0 IU/L; creatine kinase isoenzyme (CK-MB) 51.60 IU/L; lactate were high (4.86 mmol/L)). Her cardiac ultrasound did not show any significant abnormalities in cardiac morphology and structure, and left heart systolic function was in the normal range. She also had hypoglycemia and the milk-specific IgG antibody level 2. Her cranial MRI showed bilateral widening of the anterior horn of the ventricle and suspicious gray matter ectopia at the edge of the right anterior horn of the ventricle (Figure 1a). Moreover, the Denver Developmental Screening Test (DDST) showed failure of fine motor-adaptive, language, and gross motor skills. The fetus had a low birth weight (2.25 kg). Her parents did not show any clinical signs.

Her treatment history started after admission when the child was given a combination of vitamins, montelukast, and zinc sulfate syrup to repair the intestinal mucosa and *Saccharomyces boulardii* to regulate the intestinal flora.

On discharge, the proband displayed no diarrhea, no vomiting, no abdominal pain, and good nourishment. Physical examination showed that the abdomen was flat and soft and had no pressure pain or rebound pain. Upon follow-up, currently, the 2 years old had strabismus with hearing abnormalities when she did not respond to the content of sounds. She also had motor development delay and was able to lift her head but was unable to sit or walk. The child's weight gain was slow, and her intellectual and motor development was lagging compared to her peers.

2.2 | DNA extractions, library preparation, and medical exome sequencing

After obtaining informed consent from her parents, the peripheral blood samples from the couple were sent to the independent laboratory (AmCare Genomics Laboratory) for MES. We used a SolPure Blood DNA kit (Magen, Guangzhou, China) to extract genomic DNA according to the manufacturer's instructions. Then, 1 μg genomic DNA was fragmented by an ultra sonicator Q800R (Qsonica), at

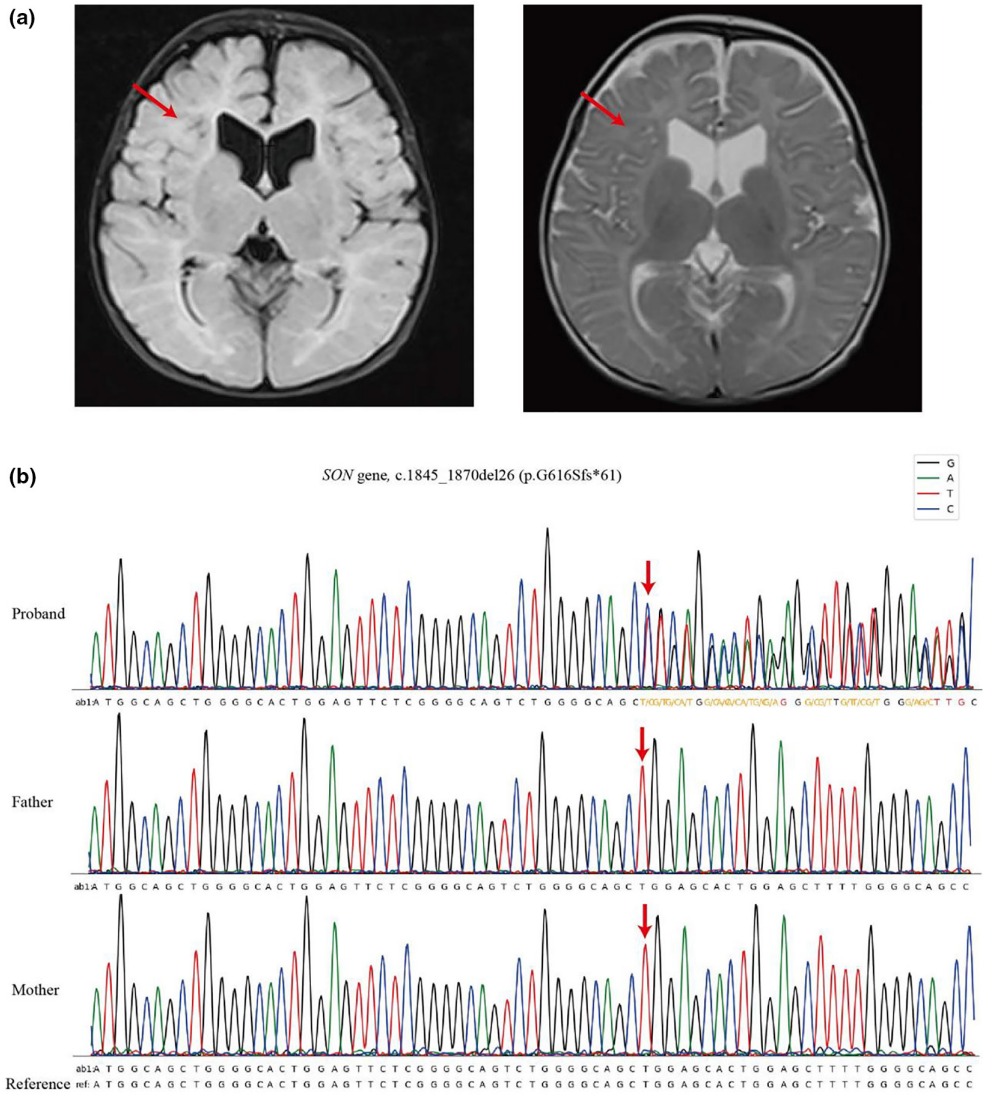

FIGURE 1 Brain MRI of proband and Sanger sequencing analysis of the family. (a), The brain MRI of proband which showed parallel bilateral lateral ventricles, ventricular enlargement, and thin corpus callosum. (b), Upper panel: segments of genomic DNA sequences of the proband showing a variation (*SON*: c.1845_1870del26; p.G616Sfs*61) which the region indicated by the red arrows; middle panel: segments of genomic DNA sequences of the proband's father; lower panel: segments of genomic DNA sequences of the proband's mother.

an ultrasonic amplitude of 30% for 7.5 min, into DNA fragments of less than 500 bp with most at 350 bp. Then, DNA fragments are modified by adding an "A" base at the 3 'end and ligated to the adaptors. The library with the adaptors was amplified with the Pre-Capture LM-PCR, and the fragment size of the library was checked by agarose gel electrophoresis. The Qubit 4 Fluorometer (Thermo Fisher Scientific, MAN0017210) and the Applied Biosystems 7500 Real-Time PCR System (Life Technologies) were used to detect the concentration of the library. The library was diluted and then sequenced on NovaSeq6000 sequencing platform. A custom-designed NimbleGen SeqCap probe (Roche NimbleGen) was used to hybridize and enrich DNA sequences of the targeted region, which included all exonic regions of approximately 5000 OMIM-associated targeted genes and 30 bp each upstream and downstream intronic regions and known intron variants (Meng et al., 2017), followed by NGS performed on the Illumina NovaSeq 6000 platform. Sequenced reads were aligned to the human reference genome (GRCh37/hg19) sequence using the NextGENe software. Single nucleotide variation (SNV/indels) analysis and copy number variations (CNVs) analysis methods were detailed in our previous report (Qi et al., 2020), and high-frequency variants were filtered by population frequency databases and our internal database of variants (dbSNP, ExAC, gnomAD) with reference to dbSNP, OMIM HGMD, ClinVar, DGV, DECIPHER, and various other databases as well as reviewing the peer-reviewed literature to evaluate pathogenic variants. The internal database currently has

100,000 Chinese clinical patients and has collected nearly 5000 rare diseases in children and adults. The pathogenicity of SNV and CNV variants was classified according to the American College of Medical Genetics (ACMG) guidelines (Richards et al., 2015).

2.3 | MTDNA sequencing

The child had high lactate and clinical manifestations involving multiple system involvement including neurological, digestive, and muscular systems, and the possibility of mitochondrial disease could not be excluded. After obtaining informed consent from her parents, peripheral blood was drawn from the child and her mother for mitochondrial genome sequencing. Three to five μg of the genome was extracted with a DNA extraction kit (Mike Bio, China). The methods of mitochondrial amplification, libraries construction, sequencing, and data analysis were completed according to our previous publication (Ouyang et al., 2021).

2.4 | PCR and sanger sequencing

We used Sanger sequencing (ABI 3730xl sequencers) to confirm the candidate gene variants in the patient and her parents and used Primer-BLAST (https://www.ncbi.nlm.nih.gov/tools/primer-blast/) to design the primers. The human reference genome was GRCh37/hg19. Following a commercial PCR reagent (TaKaRa), PCR amplification was performed in a thermalcycler®6333 (Eppendorf AG).

3 | RESULTS

Medical exome sequencing results showed no chromosome number abnormalities or pathogenic copy number variants, and the mt-DNA sequencing results were negative. A de novo heterozygous frameshift variant (*SON*: c.1845_1870del26, p.G616Sfs*61) was identified in the proband patient that was confirmed by Sanger sequencing (PVS1, Figure 1). In addition, the patient's parents did not carry this variant (PS2 + PM2). The gnomAD database population frequency was zero, and the variants had not been seen in our internal database (PM2). The proband had typical clinical features of ZTTK syndrome including global developmental delay, muscle weakness, malnutrition, weight loss, and strabismus, brain abnormality, and immunological system abnormalities. According to the American College of Medical Genetics and Genomics (ACMG) criteria, this novel variant was classified as pathogenic variant (PVS1 + PS2 + PM2), combined with the clinical manifestations and pedigree analysis of the proband. This *SON* mutation was predicted to the cause of this patient.

4 | DISCUSSION

In this study, we described a 6-month-old Chinese child with ZTTK syndrome due to the pathogenic de novo mutation c.1845_1870del26 (p.G616Sfs*61) in the *SON* gene, who had global developmental delay, muscle weakness, malnutrition, weight loss, and strabismus, brain abnormality, and immunological system abnormalities. ZTTK syndrome is a severe multisystem developmental disorder characterized by delayed psychomotor development and intellectual disability. In addition to the index case, a review of reported patients with ZTTK syndrome was presented. The clinical symptoms and neuroimaging findings of patients with ZTTK syndrome were shown in Table 1, and further details were provided in Table S1.

Currently, 79 patients with ZTTK syndrome have been reported worldwide (Dingemans et al., 2021; Gilissen et al., 2014; Indelicato et al., 2022; Kim et al., 2016, 2019; Kushary et al., 2021; Mahler et al., 2019; Mena et al., 2020; Peng et al., 2021; Qiao et al., 2020; Quintana Castanedo et al., 2020; Slezak et al., 2020; Takenouchi et al., 2016; Tan et al., 2020; Tokita et al., 2016; Xin et al., 2022; Yang et al., 2019; Yang & Yang, 2020; Yi et al., 2022; Zhu et al., 2015). The patients included 36 males (45.57%), 37 females (46.84%), and 6 with an unknown gender (7.59%). It can be seen that the inheritance of the ZTTK syndrome has nothing to do with sex, and the chance of the disease is equal for both men and women. The inheritance was mainly de novo (89.87%). ZTTK syndrome is most likely to occur in the early years of patients: 39.97% under 5 years old, 48.1% between 5 and 15 years old, and 8.86% above 15 years old (Table S1). All patients exhibit developmental delay (79/79, 100%) and intellectual disability (79/79, 100%). Most cases exhibited facial dysmorphisms (52/79, 65.82%), skeleton abnormalities (53/79, 67.09%), brain malformations (49/79, 62.03%), and neurological symptoms (57/79, 72.15%). The variant types included frameshift (64/79, 81.01%), nonsense (9/79, 11.39%), deletion (3/79, 3.80%), and missense (3/79, 3.80%) variants. The remaining patients with ZTTK syndrome exhibited short stature (23/79, 29.11%), eye abnormalities (38/79, 48.10%), hearing abnormalities (11/79, 13.92%), heart abnormalities (9/79, 11.39%), urogenital system abnormalities (15/79, 18.99%), gastrointestinal abnormalities (16/79, 20.25%), skin abnormalities (11/79, 13.92%), immunological system abnormalities (12/79, 15.19%), feeding difficulties (25/79, 31.65%), low birth weight (20/79, 25.32%), and behavioral problems (14/79, 17.72%) (Table 1 and

TABLE 1 Clinical features of subjects with *SON* variants.

	Case ($n = 79$)	Percentage
Sex		
Male	36	45.57%
Female	37	46.84%
Unknown	6	7.59%
Variant		
Frameshift	64	81.01%
Nonsense	9	11.39%
Deletion	3	3.80%
Missense	3	3.80%
Inheritance		
De novo	71	89.87%
Unknown	8	10.13%
Clinical characteristics		
Developmental delay	79	100%
Intellectual disability	79	100%
Short stature	23	29.11%
Facial dysmorphism	52	65.82%
Eye abnormality	38	48.10%
Hearing abnormality	11	13.92%
Heart abnormality	9	11.39%
Urogenital system abnormality	15	18.99%
Skeleton abnormality	53	67.09%
Gastrointestinal abnormalities	16	20.25%
Skin abnormality	11	13.92%
Immunological system abnormalities	12	15.19%
Feeding difficulties	25	31.65%
Brain malformation	49	62.03%
Neurological abnormality	57	72.15%
Low birth weight	20	25.32%
Behavioral problems	14	17.72%

Table S1). The data showed that developmental delay and intellectual disability were accompanied by other system symptomology and that *SON* mutations were mainly de novo frameshift variants. According to Table 1, each patient had developmental delay and skeleton abnormality and neurological abnormality affect more than half of the patients with this disease. However, in this report, the proband has no skeleton abnormality and seizures currently. Therefore, she needed to further follow-up and multiple system evaluation in the future. Unfortunately, there is very little literature describing drug treatment and subsequent treatment effects in ZTTK syndrome. In this case, only the digestive system was treated. After admission when the child was given a combination of vitamins, montelukast, and zinc sulfate syrup to repair the intestinal mucosa, and *Saccharomyces boulardii* to regulate the intestinal flora. At discharge, the patient had no diarrhea, vomiting, abdominal pain, normal mental and eating performance, flat and soft abdomen, no tenderness, and rebound pain.

Knockdown of the *SON* gene results in exon skipping of pre-mRNAs of chromatin-modifying enzymes including *ADA, HDAC6,* and *SetD8* (Sharma et al., 2011). *SON* interacts with *SNIP1,* which causes psychomotor retardation, epilepsy, and craniofacial dysmorphism (OMIM 614501), showing overlap with the presentation in our patient. There is a hot zone for de novo mutations (Zhu et al., 2015). In 2016, 28 individuals with pathogenic variants in *SON* were reported, who mainly presented with intellectual disability and psychomotor retardation (Takenouchi et al., 2016; Tokita et al., 2016; Zhu et al., 2015). In addition, SON was knocked down in a renal cell line, resulting in abnormal pre-mRNA splicing, leading to several established congenital malformations of the kidney and urinary tract (CAKUT) gene (Kim et al., 2019). These may be the reasons why individuals with heterozygous variants in *SON* exhibit such severe clinical manifestations.

In this study, we identified a de novo variant, *SON*: c.1845_1870del26 (p.G616Sfs*61), in a Chinese girl by MES. This frameshift variant was located in exon 3 and resulted in the deletion of the G-patch structural domain and the double-stranded RNA-binding motif (DSRM) structural domain. The G-patch structural domain is found in several RNA-binding proteins and proteins containing RNA-binding structural domains (Marchler-Bauer et al., 2017). The DSRM structural domain is highly specific for double-stranded RNA and is found in a variety of proteins, including dsRNA-dependent protein kinases, RNA helicases, and dsRNA-dependent adenosine deaminases (Marchler-Bauer et al., 2017). Thus, relatives exhibiting such severe symptoms may be due to RNA splicing defects in multiple genes critical for brain development, neuronal migration, and metabolism.

The limitation of this study is that we only probed the exonic region of disease-causing genes. Other types of mutations and noncoding locations need to be further studied by whole-genome sequencing or other microarray-based technologies. In the MES analysis, some deep intronic and promoter mutations were not included. In addition, genes that have not been associated with diseases were not included in this study. And it is worth noting that the possibility of somatic or gonadal mosaicism in the parents of the proband could not be ruled out, and it is recommended to address parental mosaicism with deep next-generation sequencing of the de novo mutation.

In conclusion, MES detection was performed to help the 6-month-old baby to find the global developmental delay caused by a pathogenic mutation c.1845_1870del26 (p.G616Sfs*61) of *SON* gene. Our finding provide novel information in the molecular diagnosis and genetic counseling of patient with developmental delay.

AUTHOR CONTRIBUTIONS

ST, JY, LL, HO, NJ and HZ performed the research, JD, CL, YL and WT extracted genomic DNA for medical exome sequencing, MZ, CL, GL and WZ contributed in study design. ST and HZ analysed the exome sequencing data and wrote the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

We thank the patient's parents for participating in this study and their cooperation.We greatly appreciate all of the hospital staff for their efforts in recruiting and treating patients. We thank Victor Wei Zhang and other staffs at AmCare Genomics Lab for their expert technical assistance.

FUNDING INFORMATION

We thanked the Support Scheme of Guangzhou for Leading Talents in Innovation and Entrepreneurship (No:2019005).The national natural Science Foundation of Hunan province(2019JJ40155)

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data in this article are not publicly available because concerns regarding patient's anonymity. Requests to access the data should be directed to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Tang, S., You, J., Liu, L., Ouyang, H., Jiang, N., Duan, J., Li, C., Luo, Y., Zhang, W., Zhan, M., Liu, C., Lyu, G.-Z., Zhang, V. W., & Zhao, H. (2023). Expanding the mutational spectrum of ZTTK syndrome: A de novo variant with global developmental delay and malnutrition in a Chinese patient. *Molecular Genetics & Genomic Medicine*, *11*, e2188. https://doi.org/10.1002/mgg3.2188