Identification of a Frameshift Mutation in SON Gene via Whole Exome Sequencing in a Patient With ZTTK Syndrome

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Case report

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Abstract

Backgrounds: Since the association between SON gene and Zhu-Tokita-Takenouchi-Kim (ZTTK, OMIM 617140) is formally recognized, the purpose of this study is to detailed report a Chinese girl with clinical features and SON variant. The other aim is to review the previously published papers of ZTTK syndromes to summarize the clinical and genetic characteristics to provide guidance for the ZTTK diagnosis.

Case presentations: We report a Chinese girl with typically clinical features of ZTTK syndrome: intellectual disability, developmental delay, cerebral cortex's aberrations, epilepsy, vision problems, musculoskeletal abnormalities and congenital malformations. Then, the whole exome sequencing (WES) analysis showed that the child had a heterozygous mutation c.5753_5756delTTAG (p. Val1918Glufs*87) in exon 3 of SON gene, which was verified by Sanger sequence, lead to the loss of function of SON protein.

Conclusions: We predicted that the heterozygous mutation c.5753_5756delTTAG (p. Val1918Glufs*87) in exon 3 of SON gene caused the ZTTK syndrome, and also was a very hot-spot mutation of SON gene. Further, the summary of all the patients with ZTTK syndromes in clinical, neuroimaging and genetics characteristics could provide guidance for the ZTTK syndrome's diagnosis.

Background

Zhu-Tokita-Takenouchi-Kim (ZTTK, OMIM 617140) syndrome is a rare and *de novo* autosomal dominant inborn error of metabolism. It was first reported in the study of Zhu et al., in which a 5-year-old girl with intellectual disability (ID), seizures, minor dysmorphisms, brain white matter abnormalities, intestinal atresia and ventricular septal defect in 109 trios was described [1]. So far, about 30 cases with ZTTK syndrome caused by the heterozygous mutations in SON gene have been reported at home and abroad (MIM: 182465).

The description of SON gene was firstly reported in the screening of human embryonic cDNA library [2]. Currently, it is widely accepted that the SON gene locates in chromosome region 21q22.11 and contains 12 exons (GenBank: NM_138927.3). The SON gene mainly possesses the following features: 1) The size of exon 3 accounts for 82% of the entire coding region [3]. 2) The SON gene encodes a 2,426 amino-acid protein that is ubiquitously present in human tissues [4, 5] and highly conserved compare to mouse Son [6] or zebrafish Son [7]. 3) This protein contains an arginine/serine-rich domain (RS domain) and two RNA-binding motifs (G-patch and double-stranded RNA-binding motif (DSRM)) [8–10]. 4) SON is a nuclear speckle-localized protein and is enriched with pre-mRNA splicing factors including small nuclear ribonucleoprotein particles and SR protein family members [6, 10, 11], which is involved in the regulation of cell cycle [9], the maintenance of human embryonic stem cells [5], etc. 5) SON haploinsufficiency can lead to aberrant pre-mRNA splicing in many genes, such as TUBG1, FLNA, PNKP, PCK2, PFKL, IDH2, CAKUT and so on, which are critical for neurodevelopment and metabolism [7], and even for kidney morphogenesis [12].

In this study, the clinical and radiological features of a female patient with ZTTK syndrome were described. Through the whole exome sequencing (WES) of the patient and two unaffected parents, a highly frequent mutation in SON gene, c.5753_5756delTTAG (p. Val1918Glufs*87) was found.

Case Presentation

The patient was a full-term female infant born to an unrelated Chinese couple after an uncomplicated pregnancy and delivery, with the weight of 3,200 g, the length of 50 cm and the head circumference of 34 cm (3rd percentile), and without breathing problems and apparent jaundice (Fig. 1). Her mother took cough medicine and antibiotics due to cold during early pregnancy, and developed shingles with external treatment at 6 months of gestation. In addition, her mother had oligohydramnios in the late pregnancy. Her mother's first pregnancy ended in an induced abortion without abnormalities. Her parents and elder sister are normal.

At the age of 10 months, the proband had a fever of 38.8°C, and then developed convulsion with loss of consciousness, right eyelid's shutter, left-side central facial palsy and rhythmic jitters of left limbs for forty minutes. After a series of examinations, the proband presented with left hemiplegia, status epilepticus, seizures, development delay, hearing defective and bronchopneumonia. Visual evoked potential (VEP) indicated obviously prolonged latency of both-side P100, and the threshold of auditory evoked potential (AEP) was 90dBL. During this time, the patient's convulsion was uncontrolled with oxcarbazepine (10 mg/kg.d). She was discharged to go home, and then was admitted in BaYi Children Hospital at the age of 11 months.

The patient exhibited distinctive facial features including a prominent forehead, curly hair, sparse eyebrows, epicanthal folds, a flat nasal bridge, a short nose, protruding ears and full cheeks (Fig. S1). Further physical examination revealed that she had poor joking, weak light-tracking capability, low interaction ability, diminished left limb power and low muscular tension, and additionally, she lacked the capability of visual fixation and was unable to roll over, sit and crawl. During the age of 16 months to 20 months, there were four main forms of seizures in this patient (Supplementary Table S1) until she was treated with the drugs, that is, oxcarbazepine (40 mg/kg.d), levetiracetam (40 mg/kg.d) and sodium valproate (20 mg/kg.d). After the treatment, her seizure was completely controlled for six months. Her hemiplegia was improved by specialty rehabilitation training and neurotrophic therapy after two months. At the age of 2 years, she could sit, crawl, stand independently, but had no initiative grasping consciousness, and she could only emit the "baba" and "mama" sounds with apparent language cognition retardation. Meantime, her interaction ability was still poor and did not respond to being called by her name, and her developmental quotient was 30 according to the Gesell Developmental Schedules.

In addition, another 21 adjuvant examinations were also conducted (Supplementary Table S2), and the results were normal except video electroencephalogram (VEEG) and cranial magnetic resonance imaging (MRI) (Fig. S2 and Fig. 2). At the age of 10 months, her VEEG result showed discontinuous low-medium slow waves in bilateral posterior head, continuous low-medium slow waves in right brain, a large of low-

medium spike waves, spike and slow wave complex and multiple spike waves in right posterior head during the intermission (the result was not shown). At the age of 1 year and 16 days, the VEEG reexamination result was still aberrant and displayed slowing background rhythm, discontinuous waves in bilateral hemispheres with the asymmetry in the right side lower than that in the left side and more significant in the temporal region, and multiple sporadic, clustered or non-rhythmic and long-path frequently sharp waves in the left-central, parietal and middle-posterior temporal regions, which even sometimes generalized in the left brain (Fig. S2A and S2B). At the age of 1 year and 7 months, the VEEG result showed slow background rhythm, discontinuous and asymmetry waves in bilateral hemispheres which was the same as the waves mentioned above, few low-medium wave amplitude and sporadic sharp waves in the left front, central, and pre-temporal region during sleep, and few medium-high wave amplitude and sporadic slow waves in the left occipital lobe and mid-posterior temporal gyrus (Fig. S2C and S2D).

When the patient was 10 months old, the MRI result was also abnormalities (Fig. 2). The result showed long signal intensity on T1W1 and T2W1, and high signal intensity on DWI in the right temporal, parietal, occipital and thalamus, which was the same as the result of enhanced MRI. Moreover, both the results of cranial magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) were normal (data is not shown). Therefore, the patient was suspected of cerebral infarction depending on the MRI result and clinical consequence. At the age of 10 months and 13 days, her MRI result presented long signal intensity on T1W1 and T2W1, and high signal intensity on DW1 in the right temporal, parietal, and occipital lobe and thalamus, and the lesion shrunk, frontal sulcus and outer cerebral space were significantly widened. In addition, when the patient was 12 months and 14 days old, the MRI result showed the signal of gliosis in the right temporal and occipital cortex, additionally, her right brain shrunk, the gap outside the brain widened and both lateral ventricles broadened slightly.

Genomic DNA was isolated from the peripheral blood of the patient and her parents, and then sequenced using WES. After the filtering process with default parameters, a *de novo* and heterozygous mutation c.5753_5756delTTAG (p. Val1918Glufs87) was found in exon 3 of SON gene of this proband, while the SON genes of her parents were normal (Fig. 1A), which were validated by Sanger sequencing (Fig. 1B). This variant caused the loss-of-function (LoF) of SON gene (Fig. 1C). No other pathogenic variants were found in other exomes. This mutation was the same as that in previously published reports [1, 7, 13, 14].

Discussion And Conclusions

ZTTK syndrome is a severe multisystem developmental disorder characterized by delayed psychomotor development and ID. In addition to case indexing, the reported patients with ZTTK syndrome were also reviewed. The clinical symptoms and neuroimaging results of the patients with ZTTK syndrome were described in Table 1 and the further detailed information was shown in Supplementary Table S3.

At present, a total of 31 patients with ZTTK syndrome have been reported worldwide. The clinical manifestations of the disease are often different in the patients with distinct genotype, even in the

patients with the same genotype and different race. However, ZTTK syndrome is most likely to occur in the early childhood of the patients. All the patients showed developmental delay (DD) (29/29), ID (31/31), facial dysmorphism (29/29), eye/vision abnormality (24/24), pregnancy abnormal of mater (13/13) and hearing defect (15/15). The majority of cases presented with failure-to-thrive (26/28; 92%), mouth abnormalities (10/11; 90%), musculoskeletal abnormalities (23/29; 79%), feeding difficulties (22/28; 78%), C-section (7/10; 70%) respiratory failure of born (6/10; 60%) and short stature (17/30; 56%). The remaining patients with ZTTK syndrome exhibited urogenital malformations (12/29; 41%), congenital heart defects (8/27; 29%), gastrointestinal malformations (7/29; 24%), autism spectrum disorder (7/27; 25%), craniosynostosis (2/22; 9%) and hands and feet abnormalities. Premature delivery (12/29; 41%) is inclined to be a warning. Moreover, dysplastic kidney including single kidney and horseshoe kidney is the major cause of urogenital malformations.

Neuroimaging findings were performed by VEEG and/or MRI for the patients with ZTTK syndrome. Brain abnormalities were observed in most patients (23/28; 82%). 17 of 27 cases (62%) developed enlarged ventricular. Corpus callosum abnormalities occurred in nearly half of the patients (12/28; 42%). 6 of 28 cases (21%) developed cortex malformation. In addition, 4 of 28 cases showed white-matter abnormalities and cerebellar abnormalities (14%), respectively. And more notably, 14 of 28 patients (50%) presented with seizures and most of the cases (21/28; 75%) showed hypotonia.

ZTTK syndrome is regarded as a severe multisystem developmental disorder and caused by a heterozygous mutation in SON gene. The mutations in SON gene that have been reported in previously published papers are summarized and depicted in Table 2 and Fig. 3, respectively. There are 28 different variants in SON gene have been reported, which mainly result in 4 molecular consequence including frameshift, nonsense, non-frameshift and missense. Due to that the size of the exon 3 in SON gene accounts for 82% of the entire coding region, the majority of these mutations localize on this exon, thus forming the repeat domain and RS-rich domain [8–10]. Interestingly, almost all the variants occur only once except that c.5753_5756delTTAG (p.Val1918Glufs*87) mutant occur 8 times in different patients, which suggested it is extremely hot-spot mutation of SON gene. To explore the effect of this mutation on the phenotype of the patients with ZTTK syndrome, the difference of the clinical features and neuroimaging findings among the patients with this mutation and other mutations were analyzed and compared (Supplementary Table S4). Most of the clinical and neuroimaging findings of the patients maintain consistent, such as DD, ID, facial dysmorphism and so on. However, the clinical symptoms including hypermetropia, cleft palate, horseshoe kidney, joint contractures, scoliosis/kyphosis, hemivertebrae, small hands and arachnodactyly belonged in hands aberrant, cerebellar abnormalities and craniosynostosis did not occur in the patients with the variant c.5753_5756delTTAG. This mutation was continuously compared with other variants in RS-domain and it was found that age of birth, short stature, strabismus, congenital heart defects, urogenital malformations, hand and feet abnormalities were distinction but the other features, especially neuroimaging findings and musculoskeletal abnormalities were similar (Supplementary Table S4). Currently, no suitable conclusion can be obtained due to the limited number of cases.

SON haploinsufficiency leads to defective RNA splicing of multiple genes that are critical for brain development, neuronal migration, metabolism and heterogeneous renal phenotypes [7, 12]. All the patients with ZTTK syndrome present with ID and DD (Table 1 and Supplementary Table S3) caused by the *de novo* LoF mutations in SON gene, which were further ascertained by the exome sequencing of 2104 trios [15] and 66 neonatal patients [16], respectively. At present, the mutations in more than 1,500 genes have been found to participate in ID and/or DD [17–21], a few of which were indeed significantly down-regulated in the individuals with SON haploinsufficiency through qPCR analysis [7]. These phenomena confirm that the *de novo* LoF mutations in SON gene are the main cause of a complex neurodevelopmental disorder associated with ID and/or DD and severe brain malformations [7].

SON, a nuclear speckle-localized protein, consists of 2,426 amino acids (Fig. 3). The N-terminal region of SON contains a Lysine-rich region and an extensive amino-acid repeat region that might serve as a scaffold for loading accessory proteins [6, 8, 9, 22, 23]. The RS domain and the G-patch in the C-terminal domain of SON are the core motifs necessary for the activity of SON during splicing process. However, the DSRM domain, which has been found in diverse proteins involved in RNA metabolisms and RNA interference (RNAi), such as dsRNA-dependent protein kinase (PKR) and Dicer [24, 25], is dispensable [8–10]. During the splicing process of constitutive RNA, SON ensures the efficient removal of intron from the transcripts containing suboptimal splice sites. Importantly, SON-mediated splicing is required for the proper processing of the selective transcripts related to cell cycle, microtubules, centrosome maintenance, genome stability and heterogeneous renal phenotypes [9, 10, 12, 26].

Due to the regulation effect of SON on RNA splicing and transcription, the heterozygous loss-of-function mutations in SON gene can reduce the gene expression of PKD1 and PKD2 through impairing the intron removal process at multiple splice sites during their pre-mRNA splicing [9, 27]. It has been demonstrated that the expression PKD1 and PKD2 mRNAs can be moderated and diffused in the neural tube, anterior horn of the spinal cord, neural ganglia and heart et al during the 5- to 6-week human embryo [28]. Subsequently, PKD1 mRNAs mainly express in brain and kidney as well as PKD1 mRNAs in lung and kidney during fetal issues [28]. In addition to the CAKUT, PKD1 and PKD2 gene, there are many genes of which the splicing process is regulated by SON, such as OSR1, PAX8, FRAS1, GDNF and BMP4, and WNT4 [12]. *Osr1*, a known transcription factor, homologizes with human OSR1 and plays a role in the second heart field (SHF) together with *Tbx5* and *Pcks6* gene, in which the mutation can cause common atrium in mouse embryos [29–31]. Furthermore, the function of both *Osr1* and *Osr2* gene is required for the maintenance of the expression of the signaling molecules critical for joint formation besides *Gdf5*, *Wnt4* and *Wnt9b* [32]. By multiple tissue expression array analysis, it has been also demonstrated that PAX8 expresses in developing central nervous system and kidney, including ureteric bud and main collecting ducts [33, 34], and the expression of FRAS1 is relatively high in fetal kidney and heart [35]. The heterozygous missense mutations in FRAS1 gene cause non-syndromic CAKUT in humans [36]. BMP4 is a vital regulatory molecule that can play a role during the developmental process including mesoderm induction, tooth development, limb formation, bone induction, fracture repair, orofacial cleft and microphthalmia, even can regulate heart development [37–39]. In general, the hypothesis that the

clinically aberrant features of ZTTK syndrome patients are regulated by the genes mentioned above due to the loss-of-function mutations in SON gene will be further certified in the future.

ZTTK syndrome is regarded as an extremely rare genetic disorder, and until recently, there is no known effective method to prevent the progression of this disease, which imposes great importance on the accurate DNA diagnosis and prenatal screening to this rare disease.

In summary, this study provided a female patient with ID, DD, facial dysmorphism, brain malformation and seizures caused by the mutation c.5753_5756delTTAG (p. Val1918Glufs*87) in SON gene, which can produce a truncate variant and disrupt RNA splicing of the genes associated with brain development and metabolism. Then, all the reported patients with ZTTK syndrome and the mutations in SON gene were systematically reviewed and analyzed. We found that the clinical manifestations of all the patients with ZTTK syndrome are somewhat variable, but the typical clinical symptoms presented in every patient. Furthermore, the variant c.5753_5756delTTAG (p.Val1918Glufs*87) is extremely hot-spot mutation of SON gene. These results obtained from the present study are hoped to provide guidance for the early diagnosis of ZTTK syndrome.

Abbreviations

AEP: auditory evoked potential; DD: developmental delay; ID: intellectual disability; LoF: loss-of-function; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; MRV: magnetic resonance venography; PKR: dsRNA-dependent protein kinase; RNAi: RNA interference; SHF: second heart field; VEEG: video electroencephalogram; VEP: Visual evoked potential; WES: whole exome sequencing; ZTTK: Zhu-Tokita-Takenouchi-Kim.

Declarations

Ethics approval and consent to participate

Written consents were obtained from the patient's guardians and parents. All clinical and experimental steps in this study were approved by the Ethical Committee of the Seventh Medical Center of PLA General Hospital, number 2019-8.

Consent for Publication

Consent for publication of the case was obtained for the patient's parents, including case description, clinical data and images. The publication about parents' clinical and genetic contents were obtained the agreement with them.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no competing financial interests.

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Authors' contributions

Conceptualization: XM; Methodology: FP and XM; Formal analysis and investigation: FP, YH, RG, YW and XW; Writing - original draft preparation: FP, LZ, YH, RG and YW; Writing - review and editing: XM; Funding acquisition: LZ; Resources: LZ and XM; Supervision: TJ and XM. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Tables

Table 1

Clinical features of the patients with ZTTK syndrome reported so far in previously published papers.

SON mutations (n = 31)	
Sex	F (18), M (13)
Age	< 1y (1), 1 ~ 12y (22), 12 ~ 18y (4), > 18y (4)
Gestation premature [†]	41% (12/29)
Respiratory failure	60% (6/10)
Pregnancy abnormal	100% (13/13)
C-section	70% (7/10)
Feeding difficulties	78% (22/28)
Developmental delay	100% (29/29)
Intellectual disability	100% (31/31)
Short stature	56% (17/30)
Failure to thrive	92% (26/28)
Facial dysmorphism	100% (29/29)
Eye/vision abnormality	100% (24/24)
Hypermetropia	17% (5/28)
Strabismus	57% (16/28)
Mouth abnormalities	90% (10/11)
Thin lips	60% (6/10)
Cleft palate	37% (3/8)
Hearing defect	100% (15/15)
Congenital heart defects	29% (8/27)
Gastrointestinal malformations	24% (7/29)
Urogenital malformations	41% (12/29)

Abbreviations: ASD, autism spectrum disorder; C-section, cesarean section; F, female; M, male; y, years.

†: less than 37 weeks pregnant.

SON mutations (n = 31)	
Dysplastic kidney	24% (7/29)
Single kidney	10% (3/29)
Horseshoe kidney	6% (2/29)
Others	27% (8/29)
Musculoskeletal abnormalities	79% (23/29)
Joint contractures	10% (3/29)
Joint hypermobility	48% (14/29)
Scoliosis/Kyphosis	17% (5/29)
Hemivertebrae	10% (3/29)
Hand abnormalities	39% (11/28)
Small hands	7% (2/28)
Arachnodactyly	14% (4/28)
Feet abnormalities	35% (10/28)
Small feet	14% (4/28)
Flat feet	21% (6/28)
Short toes	10% (3/28)
Neurological features	
Seizures	50% (14/28)
Hypotonia	75% (21/28)
Brain malformation	82% (23/28)
Ventricular enlargement	62% (17/27)
Corpus callosum abnormality	42% (12/28)
Cortex malformation	21% (6/28)
White-matter abnormalities	14% (4/28)
Cerebellar abnormalities	14% (4/28)
Abbreviations: ASD, autism spectrum disorder; C-section,	
cesarean section; F, female; M, male; y, years.	
†: less than 37 weeks pregnant.	

SON mutations (n = 31)	
Others	32% (9/28)
Craniosynostosis	9% (2/22)
ASD	25% (7/27)
Abbreviations: ASD, autism spectrum disorder; C-section,	
cesarean section; F, female; M, male; y, years.	
†: less than 37 weeks pregnant.	

Table 2
Mutations of SON gene in the ZTTK syndrome patients.

Nucleotide	locus	Protein	Function	References
c.268delA	exon2	p.Ser90Valfs*59	frameshift	5
c.286C > T	exon2	p.Gln96*	nonsense	3
c.384delA	exon3	p.Lys128Asnfs*21	frameshift	8
c.394C > T	exon3	p.Gln132*	nonsense	7
c.999_5013del	exon3	p.Ala333Alafs*15	frameshift	8
c.1881_1882delAG [†]	exon3	p.Val629Alafs*56	frameshift	1, 5
c.2076_2078TAC	exon3	p.Thr694del	non-frameshift	8
c.2365delA	exon3	p.Ser789Alafs*8	frameshift	5
c.3073dupA	exon3	p.Met1025Asnfs*6	frameshift	3
c.3334C > T	exon3	p.Arg1112*	nonsense	5, 6
c.3556C > T	exon3	p.Gln1186*	nonsense	8
c.3597_3598dupCG	exon3	p.Pro1200Argfs*17	frameshift	5
c.3852_3856delGGTAT	exon3	p.Met1284Ilefs*2	frameshift	3, 5
c.4055delC	exon3	p.Pro1352Glnfs*14	frameshift	5
c.4151_4174del24	exon3	p.Leu1384_Val1391del	non-frameshift	5
c.4358_4359delCA	exon3	p.Thr1453Serfs*11	frameshift	5
c.4549dupG	exon3	p.Glu1517Glyfs*6	frameshift	5
c.4640delA	exon3	p.His1547Leufs*76	frameshift	5
c.4678delG	exon3	p.Glu1560Lysfs*63	frameshift	6
c.4909A > T	exon3	p.Thr1637Ser	missense	3
c.4999_5013delGATTTAC CATCTAAT	exon3	p.Asp1667_Asn1671del	non-frameshift	5
c.5031_5032insAA	exon3	p.Asp1678Lysfs*9	frameshift	5
Note: All the SON variants aligned to the reference sequence (Genbank: NM_138927.3, NP_620305.2). †: the same person with different papers				
References: 1. Gilissen et al. 2014; 2. Zhu et al. 2015; 3. Tokita et al. 2016; 4. Takenouchi et al. 2016; 5. Kim et al. 2016; 6. Kim et al. 2019; 7. Yang et al. 2019; 8. Clivar database.				

Nucleotide	locus	Protein	Function	References
c.5528C > A	exon3	p.Ser1843Tyr	missense	3
c.5549_5550delGA	exon3	p.Arg1850Ilefs*3	frameshift	5
c.5753_5756delTTAG	exon3	p.Val1918Glu fs*87	frameshift	2, 3, 4, 5, this study
c.6002_6003insCC	exon3	p.Arg2002Gln fs*5	frameshift	5
c.6087delC	exon3	p.Ser2029Arg fs*22	frameshift	5
c.6233delC	exon4	p.Pro2078His fs*4	frameshift	3
Note: All the SON variants aligned to the reference sequence (Genbank: NM_138927.3, NP_620305.2). †: the same person with different papers				
References: 1. Gilissen et al. 2014; 2. Zhu et al. 2015; 3. Tokita et al. 2016; 4. Takenouchi et al. 2016; 5. Kim et al. 2016; 6. Kim et al. 2019; 7. Yang et al. 2019; 8. Clivar database.				

Figures

Figure 1

Pedigree of a family with ZTTK syndrome. (A) Family pedigree. The proband is indicated by filled symbols (●), normal persons are indicated by fill white (○). The mark (X) means manual abortion without abnormalities. (B) Analysis of SON c.5753_5756delTTAG (NM_138927.3, p.Val1918Glufs*87) in a non-related Chinese family. (C) The variant generates a frameshift variant in RS domain, which can disrupt the RNA splicing of genes. Abbreviations: RS domain, arginine/serine-rich domain; DSRM, double-stranded RNA-binding motif.

Figure 2

Brain magnetic resonance imaging (MRI) of the proband with ZTTK syndrome. (A-C) At the age of 10 months, MRI presented long signal intensity on T1W1 and T2W1, and high signal intensity on DWI in the right temporal, parietal, occipital and thalamus, which was the same as the result of enhanced MRI. This patient was diagnosed with cerebral infarction. (D-F) At the age of 10 months 13 days, MRI revealed long signal intensity on T1W1 and T2W1, and high signal intensity on DW1 in the right temporal, parietal, and occipital lobe and thalamus. The lesion shrunk, frontal sulcus and outer cerebral space significantly

were widened. (G-I) At the age of 12 months and 14 days, MRI result showed the signal of gliosis in the right temporal and occipital cortex, and her right brain shrunk, the gap outside the brain widened and the brain widened and both lateral ventricles broadened slightly.

Figure 3

Mutations in the SON gene (NM_138927.3) in ZTTK syndrome. Abbreviations: RS domain, arginine/serine-rich domain; DSRM, double-stranded RNA-binding motif; pt, patients.

Supplementary Files

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