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CLINICAL REPORT

Phosphoserine aminotransferase deficiency diagnosed by whole-exome sequencing and LC–MS/MS reanalysis: A case report and review of literature

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Abstract

Background: Phosphoserine aminotransferase deficiency (PSATD) is an autosomal recessive disorder associated with hypertonia, psychomotor retardation, and acquired microcephaly. Patients with PSATD have low concentrations of serine in plasma and cerebrospinal fluid.

Methods: We reported a 2-year-old female child with developmental delay, dyskinesia, and microcephaly. LC–MS/MS was used to detect amino acid concentration in the blood and whole-exome sequencing (WES) was used to identify the variants. PolyPhen-2 web server and PyMol were used to predict the pathogenicity and changes in the 3D model molecular structure of protein caused by variants.

Results: WES demonstrated compound heterozygous variants in *PSAT1*, which is associated with PSATD, with a paternal likely pathogenic variant (c.235G>A, Gly79Arg) and a maternal likely pathogenic variant (c.43G>C, Ala15Pro). Reduced serine concentration in LC–MS/MS further confirmed the diagnosis of PSATD in this patient.

Conclusions: Our findings demonstrate the importance of WES combined with LC–MS/MS reanalysis in the diagnosis of genetic diseases and expand the *PSAT1* variant spectrum in PSATD. Moreover, we summarize all the cases caused by *PSAT1* variants in the literature. This case provides a vital reference for the diagnosis of future cases.

Jiaci Li, Xinping Wei, and Yuchen Sun are joint first author.

KEYWORDS

LC–MS/MS, microcephaly, phosphoserine aminotransferase deficiency, *PSAT1* gene, serine concentration, whole-exome sequencing

1 | INTRODUCTION

Phosphoserine aminotransferase deficiency (OMIM#610936) (PSATD) is an autosomal recessive disorder that is usually caused by dysfunction of serine biosynthetic enzyme (Brassier et al., 2016; Debs et al., 2021; Hart et al., 2007; Shapira Zaltsberg et al., 2020). Serine and glycine concentrations are low in the plasma and cerebrospinal fluid (CSF) of patients (Brassier et al., 2016; Debs et al., 2021; Hart et al., 2007; Shapira Zaltsberg et al., 2020).

Serine is a non-essential amino acid, and its action is vital to maintain physical and mental health (Glinton et al., 2018; Maugard et al., 2021; Ngo et al., 2020). Serine helps form phospholipids needed by the body, which involves fat and fatty acid metabolism, muscle formation, etc. In particular, it plays an important role in the brain and central nervous system (Glinton et al., 2018; Maugard et al., 2021; Ngo et al., 2020). Myelin sheaths used to protect and nourish nerves contain serine (Glinton et al., 2018; Maugard et al., 2021; Ngo et al., 2020). The main source of serine is the de novo serine biosynthesis pathway. Serine can be synthesized from 3-phosphoglycerate in the central nervous system. The biosynthetic pathway of serine includes three enzymes: phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase (PSAT), and phosphoserine phosphatase (PSPH) (El-Hattab, 2016; Shen et al., 2022; Svoboda et al., 2018). This deficiency of three enzymes is believed to lead to complications observed in serine biosynthesis defects (El-Hattab, 2016; Shen et al., 2022; Svoboda et al., 2018).

Defects in serine biosynthesis resulting from loss of function variants in *PSAT1* gene, cause a set of rare, autosomal recessive diseases known as PSATD. Most of the clinical phenotypes resulting from patients with *PSAT1* are intractable seizures, acquired microcephaly, hypertonia, developmental delay, and neurological abnormalities. *PSAT1* variants can also cause skin lesions such as ichthyosis, and malformations such as brain malformations and foot deformities. In the literature, *PSAT1* variants were first reported in two siblings identified by low concentrations of serine and glycine in plasma and CSF, and the index patient presented with intractable seizures, microcephaly, hypertonia, and psychomotor retardation (Hart et al., 2007). So far, *PSAT1* variants were found in 32 individuals as Table 1 (Abdelfattah et al., 2020; Acuna-Hidalgo et al., 2014; Brassier et al., 2016; Debs et al., 2021; Gieldon et al., 2018; Glinton et al., 2018; Hart et al., 2007; McRae et al., 2017; Monies et al., 2017; Ni et al., 2019; Shapira Zaltsberg et al., 2020; Shen et al., 2022).

In the study, we reported a 2-year-old female child with developmental delay, dyskinesia, and microcephaly. MRI showed mild white matter signal abnormalities. The diagnosis was eventually made with WES combined with LC–MS/MS reanalysis of the patient, showing that the combination of two experimental techniques is helpful for genetic disease diagnosis.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

The study was approved by the ethics committee of the Tianjin Children's Hospital. Written informed consent was obtained from the patient's parents before performing WES.

2.2 | Whole-exome sequencing

Peripheral blood was collected from the patient and her parents, and genomic DNA was extracted using a Blood Genomic DNA Mini kit. WES was commercially supported by Guangzhou KingMed Diagnostics Group Co., Ltd. The specific steps are as follows (Alrayes et al., 2020): Genomic DNA samples passing the quality control (DNA concentration ≥100 ng/μL, DNA amount ≥3 μg, and OD260/280 value between 1.8 and 2.0) were randomly interrupted into 150–200 bp fragments. After end repair and A-tail addition, the two ends of the fragments were connected with adapters, respectively. The ligated products were purified to remove the unconnected adapters. The DNA fragments with adapters were amplified by PCR and purified to construct the library. Exons were captured using magnetic beads. DNA fragments were captured by PCR amplification. Captured DNA enrichment was assessed with an Agilent 2100 Bioanalyzer (Agilent, USA). Qualified DNA libraries were tested and sequenced using a Hiseq2500 (Illumina, USA). The sequencing raw data were compared with the hg19 human

TABLE 1 Summary table of *PSAT1* variants.

Publication	No	Sex	Age	POP	Variant	AAC	TOV	Phenotype
Debs (2021)	1	F	38 Years	Chinese	c.497C>T	p.Thr156Met	Mis	PSATD
					c.43G>C	p.Ala15Pro	Mis	
Shapira Zaltsberg et al. (2020)	2	F	4 Months	–	c.432delA	p.Pro144fs	Frs	PSATD
Brassier et al. (2016)	3	M	5.5 Years	Turkish	c.129T>G	p.Ser43Arg	Mis	PSATD
Hart et al. (2007)	4	M	7 Months	British	c.299 A>C	p.Asp100Ala	Mis	PSATD
					c.107delG	p.Gly36Ala_fs*5	Frs	
	5	F	3 Years	British	c.299 A>C	p.Asp100Ala	Mis	PSATD
					c.107delG	p.Gly36Ala_fs*5	Frs	
Glinton et al. (2018)	6	F	7 Months	–	c.432delA	p.D145Mfs*49	Frs	PSATD
					c.44C>T	p.Ala15Val	Mis	
Shen et al. (2022)	7	M	19 Years	–	c.43G>C	p.Ala15Pro	Mis	PSATD
	8	M	17 Years	–	c.43G>C	p.Ala15Pro	Mis	
Acuna-Hidalgo et al. (2014)	9	M	Died	–	c.1023_1027delinsAGACCT	p.Arg342Aspfs*6	Frs	NLS
	10	M	Died	–	c.296C>T	p.Ala99Val	Mis	NLS
	11	M	Died	–	c.296C>T	p.Ala99Val	Mis	NLS
	12	F	Died	–	c.296C>T	p.Ala99Val	Mis	NLS
	13	M	Died	–	c.536C>T	p.Ser179Leu	Mis	NLS
	14	F	Died	–	c.296C>T	p.Ala99Val	Mis	NLS
					c.536C>T	p.Ser179Leu	Mis	
Gieldon et al. (2018)	15	F	–	–	c.181C>T	P.Arg61Trp	Mis	–
	16	–	–	–	c.235G>T	p.Gly79Trp	Mis	–
Monies et al. (2017)	17	–	–	Saudi Arabian	c.233G>C	p.Gly78Ala	Mis	–
McRae et al. (2017)	18	-	–	–	c.637C>T	p.Arg213Cys	Mis	–
El-Hattab (2016)	19	M	–	–	c.296C>T	p.Ala99Val	Mis	–
Ni et al. (2019)	20	M	–	–	c.208T>A	p.Tyr70Asn	Mis	NLS
					c.1024C>T	p.Arg342Trp	Mis	
	21	M	–	–	c.208T>A	p.Tyr70Asn	Mis	NLS
					c.1024C>T	p.Arg342Trp	Mis	

(Continues)

TABLE 1 (Continued)

Publication	No	Sex	Age	POP	Variant	AAC	TOV	Phenotype
Abdelfattah et al. (2020)	22	F	Died	–	c.1A>G	–	–	–
	23	F	Died	–	c.1A>G	–	–	–
	24	M	–	–	c.129T>G	p.Ser43Ala	Mis	–
	25	M	–	–	c.129T>G	p.Ser43Ala	Mis	–
	26	M	Died	–	c.181C>T	p.Ala61Thr	Mis	–
					c.296C>T	p.Ala99Val	Mis	–
	27	F	–	–	c.181C>T	p.Ala61Thr	Mis	–
					c.296C>T	P.Ala99Val	Mis	–
	28	M	Died	–	c.733T>C	p.Cys245Ala	Mis	–
	29	F	Died	–	c.463G>C	p.Glu155Gln	Mis	–
					c.8701G>T	–	–	–
	30	F	–	–	c.8701G>T	–	–	–
	31	M	Died	–	c.955delAp	p.Arg319Aspfs*14	Frs	–
	32	M	Died	–	c.955delAp	p.Arg319Aspfs*14	Frs	–

Abbreviations: AAC, amino acid change; F, female; M, male; NLS, Neu-Laxova syndrome; POP, population; PSATD, phosphoserine aminotransferase deficiency; TOV, type of variant.

reference genome using BWA software and were annotated with ANNOVAR software and 1000 Genomes Project, dbSNP, OMIM, and other databases. The variant pathogenicity classification of the screened gene variants was identified according to the criteria for the American College of Medical Genetics (ACMG) guidelines. The functional effect prediction and changes in the 3D model molecular structure of protein caused by variants were obtained by PolyPhen-2 web server and Pymol. Prediction of variant protein stability based on the variations in free energy values (ΔΔG) by FoldX software (Martín-Doncel et al., 2019).

2.3 | LC–MS/MS

Blood screening for genetic metabolic diseases in the patient was performed by LC–MS/MS, which was commercially supported by the Matsumoto Institute of Life Science Co., Ltd (Johnson, 2011). Peripheral venous blood was collected from the patient in the fasting status and dropped on a dried blood spot collection card (Matsumoto Institute of Life Science Co., Ltd, Japan). Filter paper blood spots were collected. Methanol containing amino acids and acylcarnitine isotopes was added. Amino acids and acylcarnitine in blood were extracted, and treated with derivatization method.

2.4 | Literature review

We searched in PubMed, China National Knowledge Infrastructure, and Wanfang Database for articles published before June 2023. Articles selection criteria included: (1) case reports of *PSAT1* variants, (2) the individual has both defined variants and clinical manifestations, and (3) language was limited to English and Chinese.

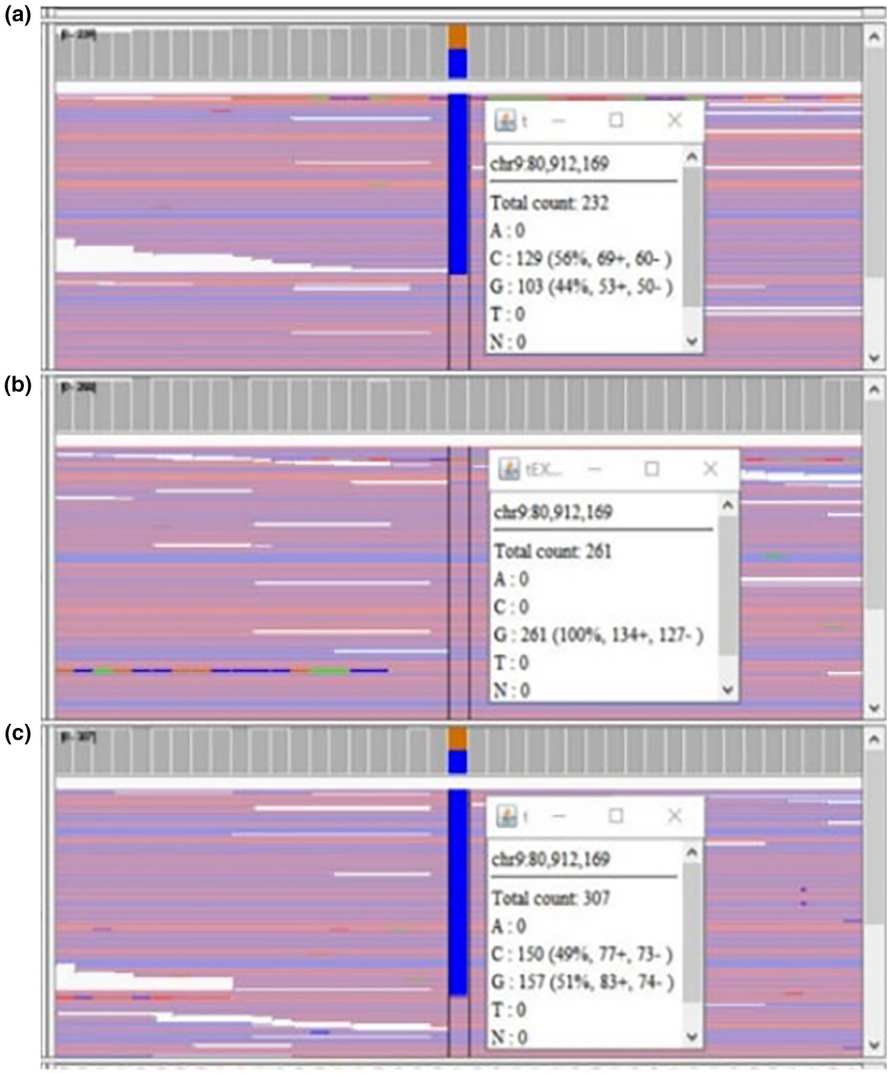

FIGURE 1 WES sequencing results of c.43G>C missense variant in *PSAT1* gene. (a) The patient; (b) The patient's father; (c) The patient's mother.

3 | RESULTS

3.1 | Case report

The patient was a 2-year-old female child and was admitted to Tianjin Children's Hospital. She had acquired microcephaly, accompanied by global developmental delay and dyskinesia. At present, the patient cannot walk. She had increased muscle tension and ankle joint contracture. Her tendon reflexes, skin, and facial features were normal. Her karyotypes were normal. Brain magnetic resonance imaging (MRI) showed mild white matter signal abnormalities. LC–MS/MS assays of blood were within the normal range in the fasting status of the patient.

3.2 | Variation detection

The results of WES showed that the patient was compound heterozygous for *PSAT1* variants. No pathogenic variants were found in the other genes tested. The maternal variant c.43G>C in exon 1 of *PSAT1* gene changed the 15th amino acid from Ala to Pro. The paternal variant c.235G>A in exon 4 of *PSAT1* gene changed the 79th amino acid from Gly to Arg (Figures 1 and 2).

The variant pathogenicity classification by ACMG showed that c.43G>C (PM2_Supporting+PM3_mederate+PS3+PM5+PP3_moderate) and c.235G>A (PM2_Supporting+PM3_moderate+PP3_strong) for *PSAT1* variants were both of likely pathogenic (Richards et al., 2015). The variant of c.235G>A (p.Gly79Arg) was not included in HGMD, 1000 Genomes, and gnomAD databases.

The functional effect prediction of *PSAT1* variants showed the c.43G>C variant and the c.235G>A variant were probably damaging (Figure 3). Amino acid sequence alignment by the PolyPhen-2 web server (Du et al., 2021; Jalilvand et al., 2022; Zhang et al., 2020) showed that two variants both occurred at a highly conserved residue in *PSAT1*, and the surrounding amino acid residues were highly conserved between species (Figure 4). Protein 3D structures drawn with Pymol (Kagami et al., 2020; Rosignoli & Paiardini, 2022) showed that the variants (p.Ala15Pro and p.Gly79Arg) were damaging to the stability of the PSAT1 protein triple helix (Figures 5 and 6).

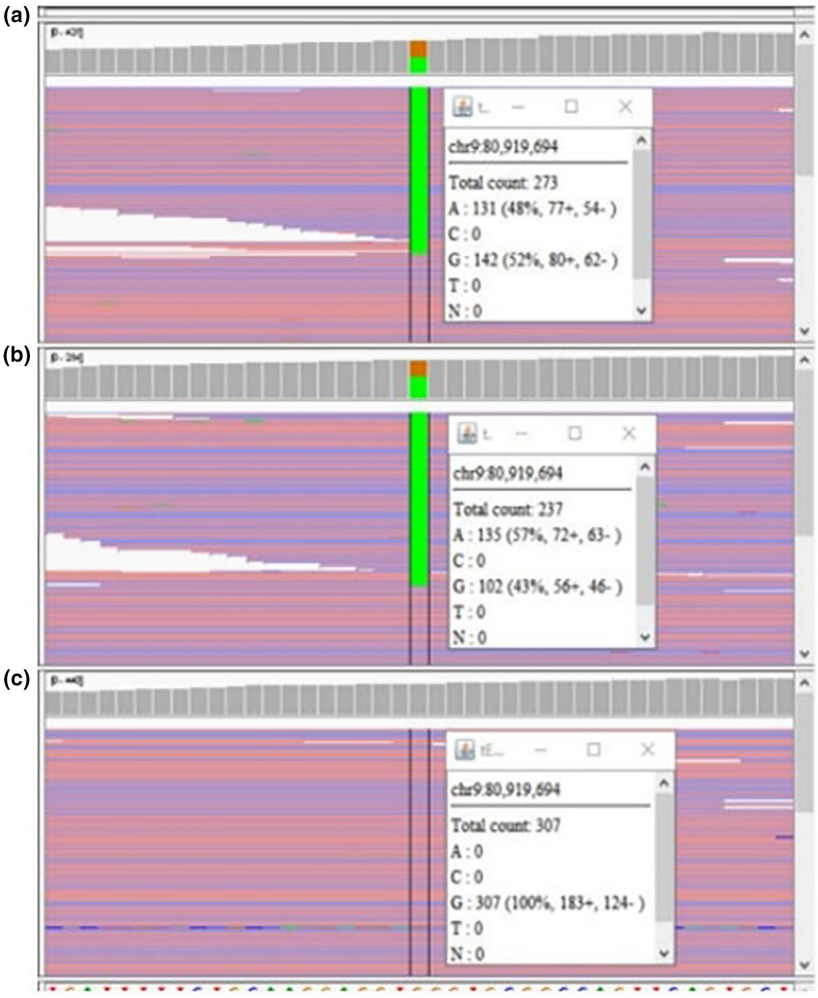

FIGURE 2 WES sequencing results of c.235G>A missense variant in *PSAT1* gene. (a) The patient; (b) The patient's father; (c) The patient's mother.

The results of protein stability showed that the ΔΔG of c.43G>C (Ala15Pro) variant was 6.39 kcal/mol and the variant had a high destabilizing effect. The c.235G>A (Gly79Arg) variant was 0.29 kcal/mol and the variant had a neutral effect.

3.3 | LC–MS/MS reanalysis

As the patient's WES result and clinical phenotype were consistent with PSATD, we reanalyzed the result of the LC–MS/MS assay. The testing showed that serine and glycine concentrations in the patient (24.00 and 92.52 μM, respectively) were decreased compared with those in 127 children aged 1–3 years previously seen at Tianjin Children's Hospital (50.65 and 106.43 μM, respectively) (Figure 7). Therefore, the diagnosis was eventually made with WES combined with LC–MS/MS reanalysis of the patient.

4 | DISCUSSION AND CONCLUSIONS

The patient in our study presented with hypertonia, psychomotor retardation, and acquired microcephaly. The

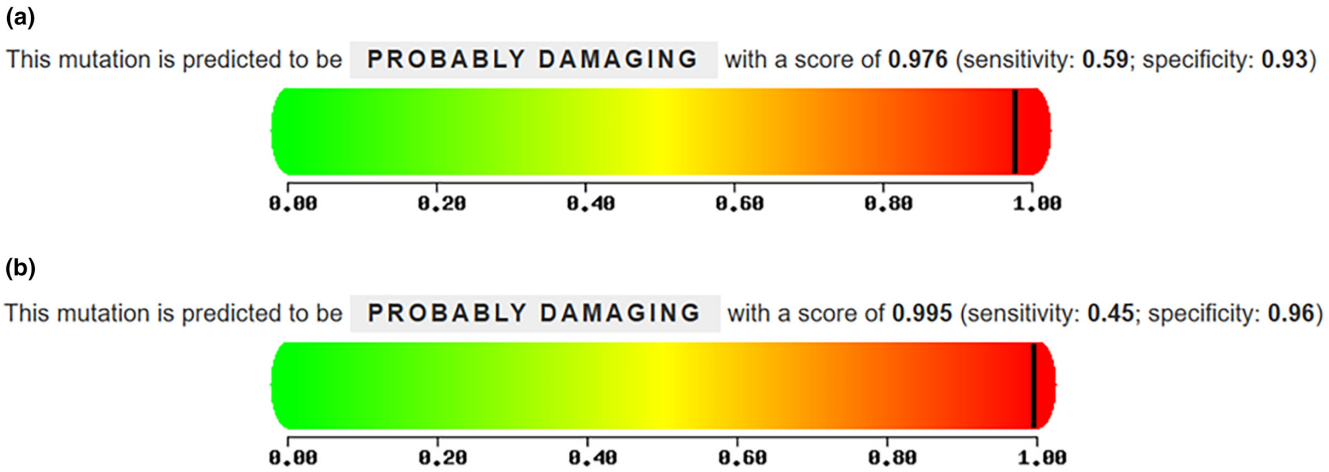

FIGURE 3 Functional effect prediction of PSAT1 protein variants. Amino acid positions of variants are highlighted by thick black lines. (a) Exon1 c.43G>C p.Ala(A)15Pro(P); (b) Exon4 c.235G>A p.Gly(G)79Arg(R).

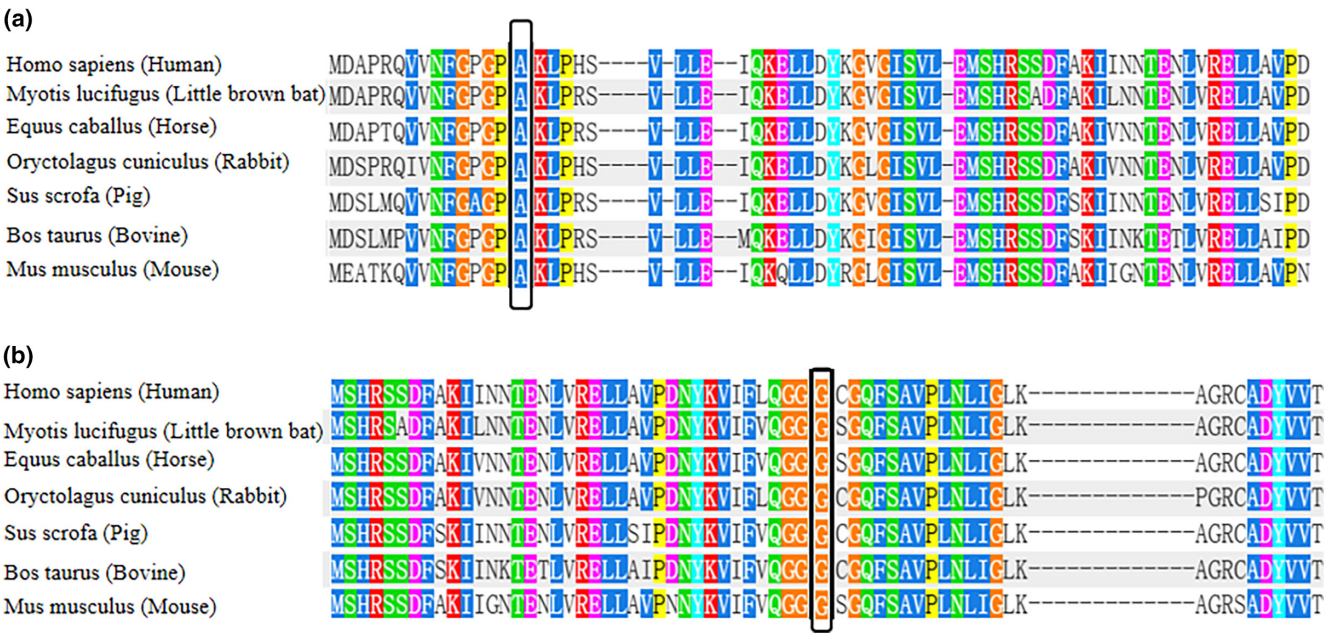

FIGURE 4 Conservation analysis of *PSAT1* variants in different species. (a) Exon1 c.43G>C p.Ala(A)15Pro(P); (b) Exon4 c.235G>A p.Gly(G)79Arg(R).

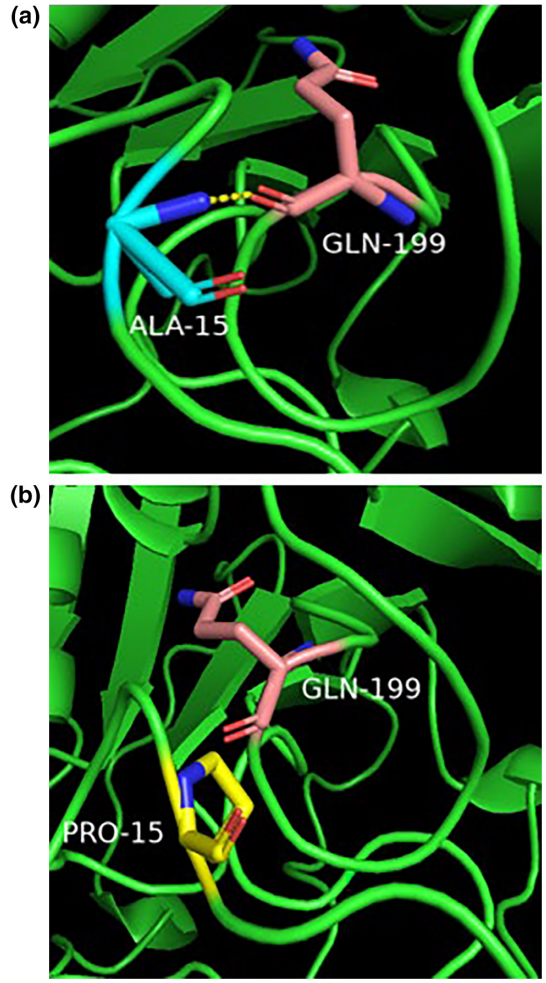

FIGURE 5 Three-dimensional structure model of PSAT1 protein at position 15. (a) Native (Ala) side-chains; (b) mutant (Pro) side-chains. The H-bonds are indicated by yellow dashed lines.

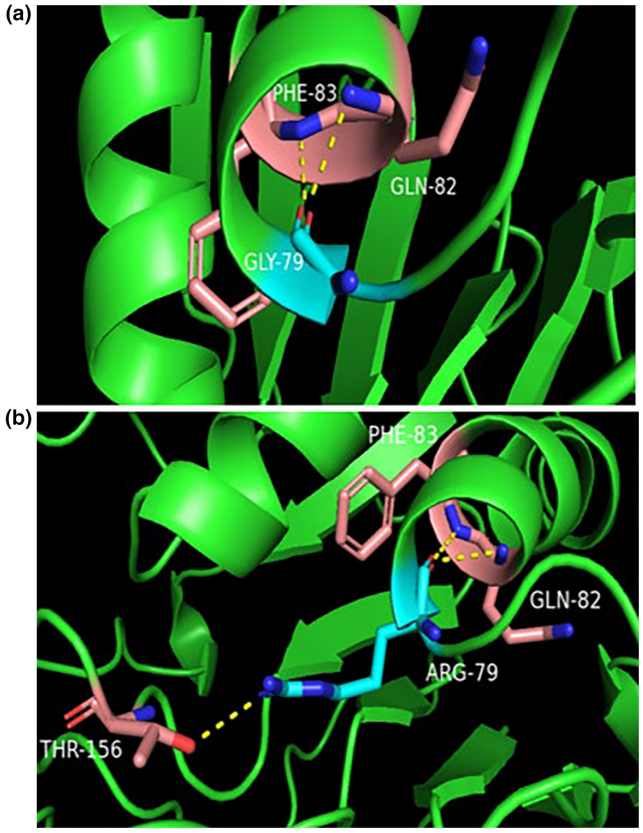

FIGURE 6 Three-dimensional structure model of PSAT1 protein at position 79. (a) Native (Gly) side-chains; (b) mutant (Arg) side-chains. The H-bonds are indicated by yellow dashed lines.

diagnosis of genetic disease was suspected upon the association of microcephaly and severe psychomotor retardation.

To further clarify the diagnosis of the disease, we performed WES in the patient. WES can efficiently detect coding sequences and capture variations in the coding region and flanking intron regions of all known genes (Aggarwal, 2021; Bomba et al., 2022; Li et al., 2022). Although the human exome length accounts for approximately only 2% of the length of the human genome, the exome regions contain about 85% of known disease-causing variants. WES has a large advantage in confirming the association of genes with rare genetic diseases (Funk et al., 2022). In our study, WES sequencing revealed heterozygous variants in the *PSAT1* gene of the patient: a paternal likely pathogenic variant in exon 4 (c.235G>A, p.G79R) and a maternal likely pathogenic variant in exon 1 (c.43G>C, p.A15P) (Figures 1 and 2).

PSAT1 encodes a member of the class-V pyridoxal-phosphate-dependent aminotransferase family (Abdelfattah et al., 2020; Ni et al., 2019; Wang et al., 2023). Variants in the *PSAT1* gene can cause two genetic diseases associated with serine deficiency, new-laxova syndrome (NLS), and PSATD. Among previously reported cases, NLS usually onsets in utero, it is accompanied by more severe clinical phenotypes such as ichthyosis and foot deformities (Acuna-Hidalgo et al., 2014; Gieldon et al., 2018; McRae et al., 2017; Monies et al., 2017). And clinical features of PSATD are microcephaly and psychomotor retardation (Brassier et al., 2016; Debs et al., 2021; Glinton et al., 2018; Hart et al., 2007; Shapira Zaltsberg et al., 2020; Shen et al., 2022), which are consistent with our patient. In Table 1, we summarize the clinical features and identified *PSAT1* variants for previously reported cases (Abdelfattah et al., 2020; Acuna-Hidalgo et al., 2014; Brassier et al., 2016; Debs et al., 2021; Gieldon et al., 2018; Glinton et al., 2018; Hart et al., 2007; McRae et al., 2017; Monies et al., 2017; Ni et al., 2019; Shapira Zaltsberg et al., 2020; Shen et al., 2022). In addition to the one patient in this study, *PSAT1* variants have been reported in 32 additional patients. Most of the patients with *PSAT1* variants showed severe developmental delay and neurological abnormalities in utero or at birth, while a few patients showed a

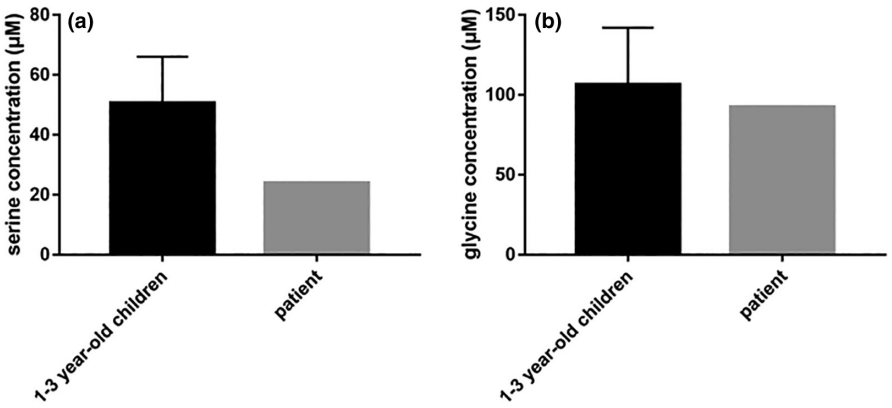

FIGURE 7 Serine and glycine concentrations by LC–MS/MS assay. (a) Serine concentration; (b) Glycine concentration.

milder phenotype, mainly characterized by microcephaly and dyskinesia. So far, this phenotype has only been identified in four patients (three reported and one in this study). Besides, most of the patients were initially associated with ichthyosis and seizures, and a few of them had intrauterine growth restriction. Fortunately, the patients show great improvement after treatment.

As PSATD is usually characterized by low concentrations of serine and glycine in plasma and CSF (Brassier et al., 2016; Debs et al., 2021; Hart et al., 2007; Shapira Zaltsberg et al., 2020), we reanalyzed the result of the LC–MS/MS assay in the patient's blood. The result showed that serine and glycine concentrations of the patient were decreased (Figure 7). Serine is a precursor of many essential compounds in protein synthesis (Glinton et al., 2018; Maugard et al., 2021; Ngo et al., 2020). However, the de novo serine biosynthesis pathway remains the main source of serine. The serine biosynthesis pathway is as follows (El-Hattab, 2016; Shen et al., 2022; Svoboda et al., 2018): First, 3-phosphoglycerate is converted to 3-phosphohydroxypyruvate by PHGDH (El-Hattab, 2016; Shen et al., 2022; Svoboda et al., 2018). Second, 3-phosphopyruvate is converted to o-phosphoserine by PSAT (encoded by *PSAT1*) (El-Hattab, 2016; Shen et al., 2022; Svoboda et al., 2018). This reaction is accompanied by the conversion of glutamate to α-ketoglutarate and requires the assistance of pyridoxal phosphate (El-Hattab, 2016; Shen et al., 2022; Svoboda et al., 2018). Finally, serine, the final product of this pathway, is produced catalytically by PSPH (El-Hattab, 2016; Shen et al., 2022; Svoboda et al., 2018). All three identified genes are associated with serine deficiency and are characterized by distinct neurological manifestations. The lack of serine suggests errors in the serine synthesis pathway, further indicating abnormalities in genes or enzymes involved in the pathway. Combined with the results of WES and LC–MS/MS reanalysis, we diagnosed the 2-year-old female child with PSATD.

Reviewing the literature, we found that PSATD is usually treated with serine (Brassier et al., 2016; Hart et al., 2007; Shapira Zaltsberg et al., 2020). Although there is no consensus on the dose of serine, serine supplementation is necessary for the treatment of PSATD, especially in the early ages. It has been documented that serine treatment in patients with PSATD, led to an improvement of spasticity (Brassier et al., 2016). Hart et al found the patient's sister with a diagnosis of PSATD started serine supplementation within the first 24 h of life, and is normal for growth and development at age 3 years (Hart et al., 2007). It has been suggested that if serine is started early before nerve damage occurs, it may help prevent or improve symptoms. This suggests that there may be better outcomes if treatment is started soon after birth. However, due to several factors, the diagnosis of PSATD is often delayed. On the one hand, some PSATD patients have a mild clinical phenotype and can easily be overlooked, resulting in clinical diagnosis too late. On the other hand, in the absence of fasting, serine and glycine concentrations of plasma are normal in serine biosynthesis defects. In contrast, serine and glycine concentrations of CSF are not affected by diet, but CSF testing is usually not performed without seizures and CSF acquisition is invasive for the patients. Nevertheless, in our patient, oral serine supplementation was also recommended.

In conclusion, we report a case of PSATD diagnosed with WES and LC–MS/MS reanalysis. When a genetic disease is highly suspected on clinical grounds, the combination of WES and LC–MS/MS may become an important means of genetic disease diagnosis.

AUTHOR CONTRIBUTIONS

Jiaci Li and Xinping Wei performed the literature search, analyzed data, and wrote the draft of the manuscript. Yuchen Sun put forward constructive revision suggestions, added important references, and revised the draft of the manuscript. Xiaofang Chen, Ying Zhang, Xiaoyu Cui, and Jianbo Shu collected the information of

the patient, confirmed the final diagnosis, and reviewed the manuscript. Dong Li and Chunquan Cai performed the conception and design of this case report. All authors read, edited, and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Our article was published with the consent of the patient's parents and approved by the Ethics Committee of Tianjin Children's hospital.

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SUPPORTING INFORMATION

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