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CLINICAL REPORT

Genetic analysis and literature review of a Poirier–Bienvenu neurodevelopmental syndrome family line caused by a de novo frameshift variant in *CSNK2B*

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Abstract

Background: Poirier–Bienvenu neurodevelopmental syndrome (POBINDS) is a rare autosomal dominant neurologic disorder caused by a heterozygous variant of *CSNK2B*, which is characterized by early onset epilepsy, hypotonia, varying degrees of intellectual disability (ID), developmental delay (DD), and facial dysmorphism. This study clarifies the molecular diagnosis and causative factors of a Chinese boy with POBINDS.

Methods: The clinical phenotypes and ancillary laboratory tests were collected and analyzed by trio whole exome sequencing (WES) and copy number variant sequencing (CNV-seq) in the follow-up proband's families. The candidate variant was validated by Sanger sequencing and bioinformatics software was used to further explore the effect of the de novo frameshift variant on the protein structure.

Results: The proband carries a de novo frameshift variant c.453_c.454insAC (p.H152fs*76) in *CSNK2B*. According to the ACMG genetic variant classification criteria and guidelines, the locus is a pathogenic variant (PVS1+PS2+PM2) and the associated disease was POBINDS. Protein structure prediction suggests significant differences in amino acid sequences before and after mutation.

Conclusion: A rare case of POBINDS caused by a novel frameshift variant in *CSNK2B* was diagnosed. The novel variant extends the variation spectrum of *CSNK2B*, which provides guidance for early clinical diagnosis, genetic counseling and treatment of this family. A review of the currently reported cases of POBINDS further enriches and summarizes the relationship between genotype and phenotype of POBINDS.

KEYWORDS

CNV-seq, *CSNK2B*, epilepsy, frameshift variant, Poirier–Bienvenu neurodevelopmental syndrome, WES

1 | INTRODUCTION

Poirier–Bienvenu neurodevelopmental syndrome (POBINDS, OMIM #618732) is a rare, autosomal dominant neurologic disorder first reported by Poirier et al. (2017), which is caused by a heterozygous variant of *CSNK2B* (OMIM*115441). The clinical phenotype of POBINDS is diverse, with early onset epilepsy, hypotonia, varying degrees of intellectual disability (ID) and developmental delay (DD) as the main clinical manifestations (Di Stazio et al., 2023; Zhang et al., 2022). In addition, some patients have facial deformities, autism, language, mental, behavioral, and motor disorders features, and a few have other atypical phenotypes. Currently, a total of 81 cases of POBINDS disease (including the present case) have been reported, most of which were treated symptomatically with levetiracetam (LEV) and sodium valproate (VPA) anti-epileptic drug (AED). However, the efficacy of anti-epileptic treatment varies depending on the type of genetic variant, the type of seizure, and the severity of the patient's condition.

CSNK2B is located at 6p21.33 and contains seven exons with a genomic size of 3988 bp, encoding 215 amino acids. Interestingly, *CSNK2B* encodes a regulatory subunit (β) of casein kinase II (CK2) involved in neuronal growth, development, and synaptic transmission (Di Stazio et al., 2023). It has been shown that CK2 is highly expressed in brain and can be involved in the regulation of multiple cellular signaling pathways (Asif et al., 2022; Di Stazio et al., 2023). Accordingly, normal expression of *CSNK2B* plays an important role in neuronal morphology maintenance, normal development, and synaptic transmission. Nevertheless, the pathogenesis and function of this gene variant causing POBINDS epilepsy symptoms are rarely studied and still cannot be clarified (Di Stazio et al., 2023; Yang et al., 2022), and needs to be further investigated and explored. By reviewing the HGMD (http://www.hgmd.org) and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) databases, the variation sites of *CSNK2B* were heterogeneous. The ClinVar database contains 37 missense variants and the HGMD database contains 23 variants of *CSNK2B*, including 10 missense variants, 4 frameshift variants, 5 nonsense variants, 3 classical splices, and 1 initiation.

In this study, *CSNK2B* variant c.453_c.454insAC (p.H152fs*76) was detected using WES in a 21-month-old Chinese boy with POBINDS who mainly presented with generalized seizures, DD and hypotonia, autistic features, and less interaction with people. Although different groups (Bonanni et al., 2021; Orsini et al., 2022; Yang et al., 2022) have elaborated and studied the relationship between genotype and phenotype of POBINDS, expanding the POBINDS genotype and phenotype spectrum, the relationship is still unclear (Di Stazio et al., 2023), and needs further analysis and exploration. In this study, the genotype–phenotype relationship of POBINDS was further studied and analyzed by reviewing 80 reported cases of POBINDS and the cases in this study to expand its genetic and phenotypic spectrum.

2 | MATERIALS AND METHODS

The study was conducted according to the principles of the Declaration of Helsinki established by the World Medical Association (WMA), and the study protocol was approved by the Ethics Committee of Gansu Provincial Maternal and Child Health Hospital (Gansu, China) (No. (2021) GSFY Ethics Review [65]). Written informed consent was obtained from all participants or their legal guardians who took part in this study.

2.1 | Patient report

The proband was a 21-month-old boy, G_2P_2, born full term with a birth weight of 3.3 kg. He presented to our hospital at 5 months of age with intermittent convulsions and generalized seizures with no apparent cause, and was treated with PB, DAP sedation, and vitamin B6 nutritional maintenance therapy, which was ineffective, while during the intermittent seizures. At the same time, he had fever, cough, pneumonia, furuncle rash, and hypotonia phenotype. Additionally, he could only babble and communicate at 5 months of age, could not pronounce bama, could actively grasp objects with both hands, could lift his head, could not roll over, and had weak muscle tone in all four limbs. At 18 months of age, he had only five teeth, could pronounce ba, could not pronounce ma, had delayed dental and speech development, had poor cognitive skills, and had no facial, finger, or heart deformities. He also had autistic features with little interaction with others. The proband had a 6-year-old healthy older brother whose parents were not consanguineously married and had neither phenotypic abnormalities nor familial history of genetic or metabolic disorders (Figure 1).

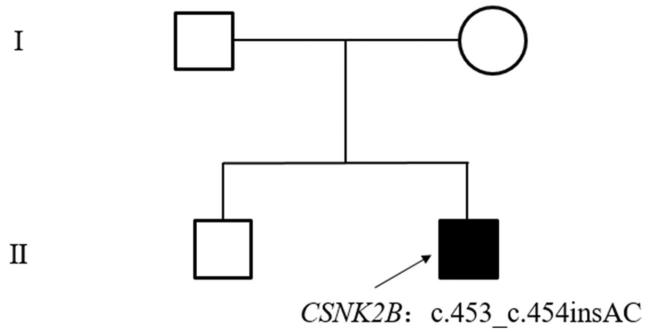

FIGURE 1 Family tree of the proband.

2.2 | Genomic DNA preparation

EDTA anticoagulation tubes were used to draw 2–3 mL of peripheral venous blood from the proband, his brother and parents, and DNA extraction was performed according to the instructions of the Tiangen Biotechnology DNA Extraction Kit (Beijing, China). DNA purity and concentration were determined by Nanodrop 2000 Nucleic Acid quantification apparatus. DNA concentration was controlled at 50–250 ng/μL and stored at −20°C.

2.3 | Whole-exome sequencing (WES)

WES was performed by applying high-throughput sequencing target sequence capture technology. After genomic library construction, the whole exome target region was captured and sequenced using IDT's xGen® Exome Research Panel v2.0 capture probe, and the gene data were analyzed using bioinformatics and clinical information analysis techniques. This capture sequencing provides approximately 99% coverage of the target sequence, with an average depth >20× coverage of 99%.

2.4 | Sanger sequencing

The primers were designed with reference to the nucleic acid sequence of *CSNK2B* (NM_001320.7) by applying Primer3 Input software (v.0.4.0, https://bioinfo.ut.ee/primer3-0.4.0/) against the candidate variant c.453_c.454insAC. The forward primer is 5′-CTTCTTTACATCTACCTGCCAACC-3′, and the reverse primer is 5′-CTCAGAGCTAAAGCCTCGTGGTTC-3′, fragment length 682 bp. The amplification was carried out according to the PCR reaction system: 2× PCR Mix 12.5 μL, ddH20 10 μL, DNA 1.5 μL, upstream and downstream primers 0.5 μL each and reaction conditions as follows: 96°C for 3 min, 94°C for 30 s, 60°C for 30 s, 72°C for 1 min, 20 cycles; 94°C for 30 s, 60°C for 30 s, 72°C for 1 min, 15 cycles; 72°C for 10 min; 4°C at constant temperature. The PCR amplification products were purified with purification kits, then amplified using ABI 3500DX Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) and the SeqMan software (v7.1.0) was applied to compare the sequencing results with the standard sequences.

2.5 | Data analysis

The results obtained from WES were compared with the reference genome (GRCh37/hg19), and the detected high-quality variants were annotated with mutation information according to the Pgenomics platform (https://pgenomics.cn), a national shared service platform for human genetic resources. Moreover, the Pgenomics platform can combine information on the clinical phenotype, inheritance pattern, family codisjunction, and pathogenicity of the variation point of the affected children to screen the detected candidate variation point and score them comprehensively by bioinformatics software; the higher the score, the higher the correlation.

2.6 | CNV-seq

Genomic DNA was extracted using DNeasy Blood & TissueKit DNA extraction kit (QIAGEN, Germany), purified using Genomic DNA Clean & Concentrator purification kit, and the eluate was fully dissolved, and concentration and purity were determined using Qubit 3.0, and stored at −20°C. Genomic DNA fragmentation reagents from Beijing Berry Genetics were used to fragment 50 ng of genomic DNA, and the library was constructed using end-fill, splice ligation and polymerase chain reaction amplification, and sequenced on an Illumina NextSeq CN500 sequencer with a precision of 100 kb and a depth of 0.1×. The clinical significance of the detected and localized copy number variants (CNV) was analyzed and interpreted using public databases (including OMIM, DECIPHER, DGV, PubMed, ClinGen, etc.), after sequencing was completed, and pathogenicity was analyzed and assessed according to ACMG guidelines.

2.7 | Protein sequence analysis and protein structure prediction

The amino acid sequence analysis of *CSNK2B* variant c.453_c.454insAC (p.H152fs*76) was performed by using the Mutalyzer software 2.0.35 (https://v2.mutalyzer.nl/), and the wild-type and mutant protein sequences were compared to clarify the specific changes in amino acid

sequence due to the shift variant. The PSIPRED software (http://bioinf.cs.ucl.ac.uk/psipred) was used to predict and analyze the secondary structure of the shift variant c.453_c.454insAC wild-type and mutant protein, and SWISS-MODEL (https://swissmodel.expasy.org/) predicted the tertiary structure of the proteins, clarifying the differences in protein structure before and after the variation.

3 | RESULTS

3.1 | Patient follow-up and ancillary test results

The proband first presents with generalized tonic–clonic (GTC) seizure at 5 months of age, followed by intermittent seizures lasting up to 5 min, which usually resolve in 1–2 min. The symptoms were unconsciousness, eyes rolled up, cyanosis around the mouth, flexion, and shaking of the limbs, without incontinence, fever, and foaming at the mouth during the seizure. DAP injection (2 mg) and PB (0.035 g) were given during the seizure for sedation and symptomatic treatment, which was ineffective.

The proband was evaluated as vitamin D insufficiency because 25-hydroxyvitamin D was measured at 20.48 ng/mL (deficiency: <20 ng/mL; insufficiency: 20–30 ng/mL; sufficiency: 30–100 ng/mL; toxicity: >100 ng/mL). Meanwhile, the C4DC_C5OH was elevated to 1.12 μmol/L (reference range: 0.09–0.55 μmol/L) by tandem mass spectrometry and remained at 0.94 μmol/L after re-examination, which was considered as biotinase deficiency. After regular vitamin AD and B6 supplementation, 1–2 seizures/day still occurred intermittently at 5.5 and 6 months of age, followed by drowsiness and lethargy. Consequently, hypocalcemia, febrile convulsions, and convulsive symptoms due to biotinidase deficiency could be excluded. At 6 months of age, 1.5 mL of LEV oral solution (specification: 150 mL:15 g/bottle) was given for treatment and low-frequency pulse electrotherapy with poor epilepsy control. At 6.5 months, symptoms were the same as before, 4–5 times/day, and 80 mg/120 mg VPA was given for 4 months. The seizure of proband was well controlled at 10.5 months of age and the proband has not had a seizure since.

The proband had a normal ultrasound bone mineral density examination at 5 months of age, and the Gecell Developmental Schedules (GDS) suggested mild DD (Figure 2). The rehabilitation evaluation showed a forward sitting position, unsupported standing position, poor head control, and assisted turning. Cerebrospinal fluid examination did not show any abnormalities. A cranial CT examination showed mucosal thickening of the maxillary and nasal septal sinuses bilaterally, with no abnormalities in cranial morphology, brain parenchyma, ventricles, or brain pools. The cranial magnetic resonance imaging (MRI) showed that the process of brain myelination formation was equal to that of the same age group, and there was no abnormality in the brain parenchyma. No abnormalities were seen in the electroencephalogram (EEG) during both seizures and non-seizures.

3.2 | Genetic variant detection analysis

A de novo shift variant c.453_c.454insAC (p.H152fs*76) of *CSNK2B* was detected in the proband (Figure 3), the variant was not detected in his parents and brother. No pathogenic or likely pathogenic CNV were detected in the proband. The variant c.453_c.454insAC (p.H152fs*76) is a novel variant that is not included in HGMD and Clinvar databases and has not been reported in the literature.

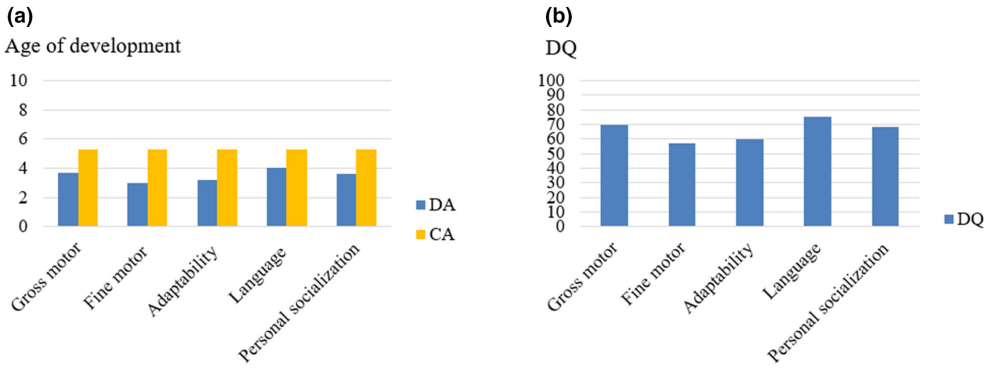

FIGURE 2 Gecell Developmental Schedules (GDS) at 5 months of age. (a) Age of development (DA) perspective assessment. CA, chronological age. (b) Development quotient (DQ) perspective assessment. The patients had a mean DA of 3.5 months and a DQ score of 66, with scores of 60 for adaptation, 70 for gross motor, and 57 for fine motor, 75 for language, and 68 for personal socialization. The overall assessment was mild DD.

3.3 | Analysis of the pathogenicity of variable sites

Pathogenicity analysis of the variant was performed according to the ACMG genetic variant classification criteria and guidelines: c.453_c.454insAC (p.H152fs*76) of *CSNK2B* is a shift variant due to insertion of two bases, and the LOF variant results in possible loss of gene function (PVS1); the variant was verified as de novo by both parents of the family (PS2); the variant was in the frequency of this variant in the database of all normal populations was less than 0.0005 (PM2). The variant was determined to be pathogenic according to the ACMG guidelines (PVS1+PS2+PM2).

3.4 | Protein sequence analysis and secondary structure prediction

The amino acid sequence prediction of *CSNK2B* before and after the mutation at the c.453_c.454insAC (p.H152fs*76) locus by Mutalyzer software 2.0.35 revealed that the mutation resulted in the change of histidine (H) to threonine (T) at position 152, encoding 75 amino acids followed by a stop codon at position 227. Compared to the wild-type amino acid sequence, which has a stop codon at position 216, the mutant increased by 11 amino acids (Figure 4). The prediction of the secondary structure of wild-type (Figure 5a) and mutant (Figure 5b) proteins using PSIPRED software revealed significant differences

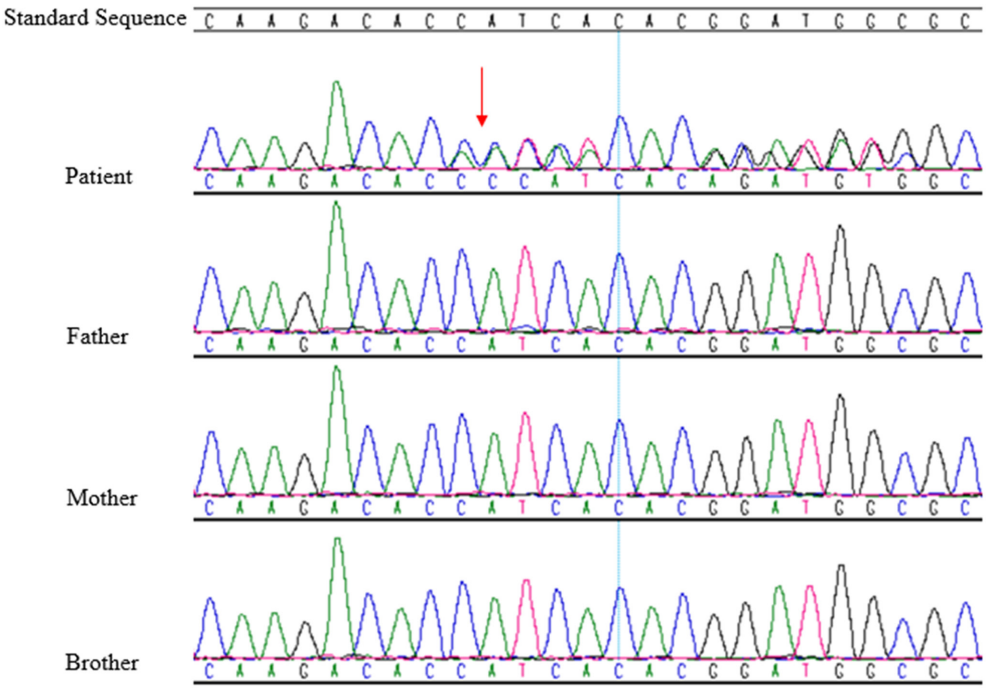

FIGURE 3 Sanger sequence of the affected family, with the sequencing validation sites shown by red arrows.

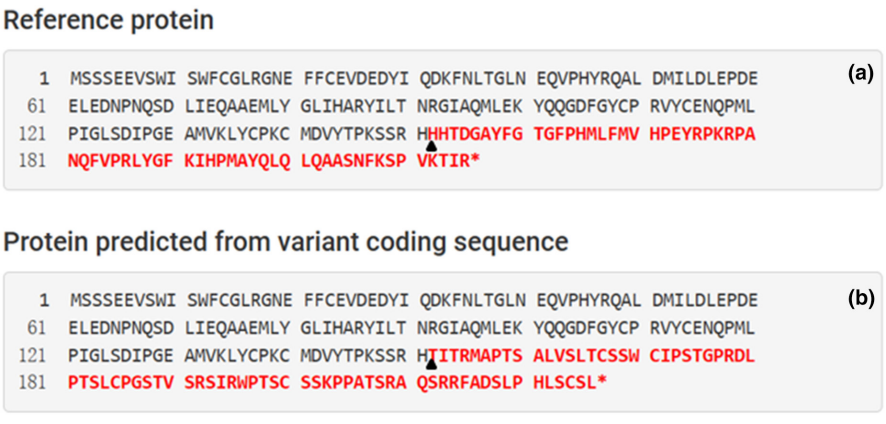

FIGURE 4 Predicted amino acid sequence before and after mutation, the black triangle shows the starting variant amino acid position. (a) Wild-type amino acid sequence. (b) Mutant amino acid sequences.

in their secondary structure folding forms. The wild-type had more β-folds than the mutant type, and conversely, the mutant type had more irregular and loose structures than the wild-type. Both software predictions indicate that the *CSNK2B* gene c.453_c.454insAC (p.H152fs*76) variant severely affects the structure of the encoded protein and thus its normal function (Figure 6).

4 | DISCUSSION

POBINDS (OMIM #618732), first reported by Poirier et al. (2017), about 81 cases currently reported (including the present case, searched in PubMed), is a rare autosomal dominant neurological disorder caused by heterozygous variants of *CSNK2B*. POBINDS mostly characterized by different degrees of early onset epilepsy (including GTC, myoclonic seizures, febrile epilepsy, partial-onset epilepsy, and so on), ID, DD and hypotonia (Di Stazio et al., 2023; Zhang et al., 2022). Some patients have facial dysmorphism, autistic features, learning disabilities (LD), attention deficits, etc. A few patients show vascular, lymphatic, skeletal, ectodermal, and other abnormalities. It has been suggested that the phenotypic diversity of POBINDS may be associated with variant types of *CSNK2B* (Orsini et al., 2022). Different teams (Bonanni et al., 2021; Ernst et al., 2021; Orsini et al., 2022; Yang et al., 2022; Zhang et al., 2022) have studied the genotype and phenotype of

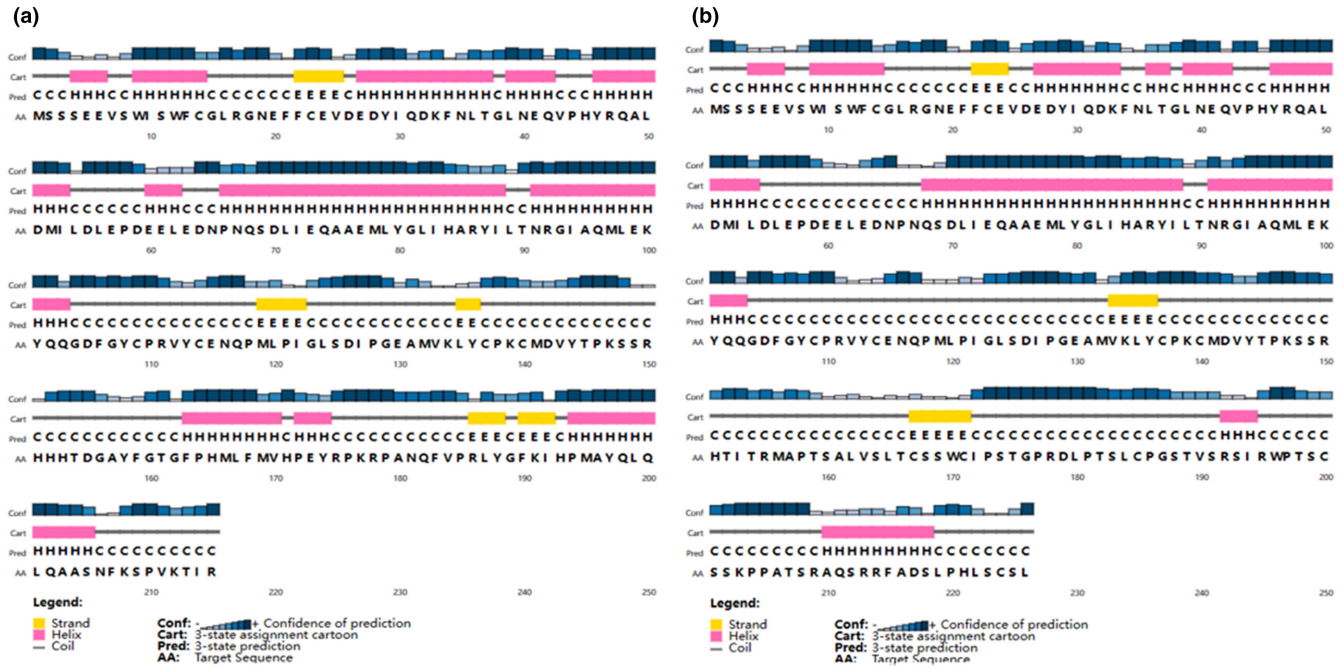

FIGURE 5 Predicted protein secondary structure before and after mutation. (a) Wild-type secondary structure prediction. (b) Mutant secondary structure prediction.

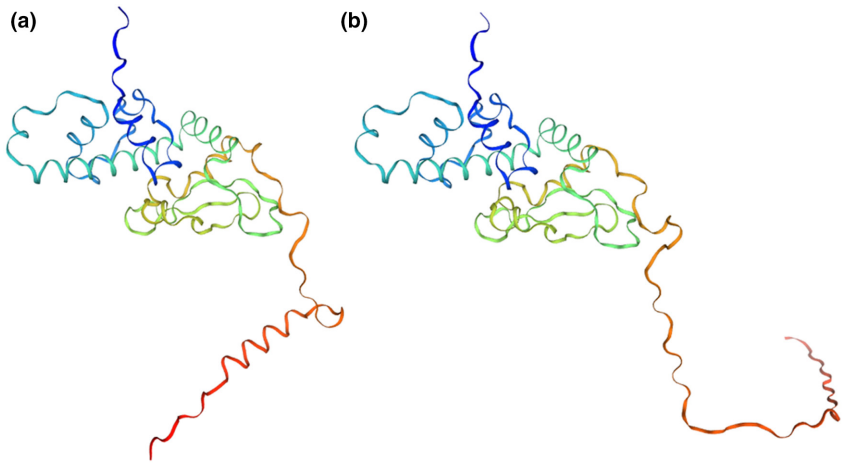

FIGURE 6 Predicted protein tertiary structure before and after mutation. (a) Wild-type tertiary structure prediction. (b) Mutant tertiary structure prediction.

reported cases and elucidated the relationship, which has expanded the genotype and phenotype spectrum and laid the foundation for studying the phenotypic heterogeneity of POBINDS.

Unfortunately, the relationship is still unclear and the specific mechanism of epilepsy in POBINDS due to *CSNK2B* variants is unknown (Orsini et al., 2022), but may be related to CK2-mediated calmodulin phosphorylation enhancing the firing amplitude of KCNQ2 channel neurons (Kang et al., 2014), which needs to be confirmed and explored in further studies. Currently, POBINDS is mostly diagnosed by genetic testing based on clinical symptoms and phenotype.

CSNK2B is located at 6p21.33 and contains seven exons with a genomic size of 3988 bp, encoding 215 amino acids. *CSNK2B* encodes the casein kinase II (CK2) regulatory subunit β (CK2β), an important component of CK2 that contributes to the regulation of enzyme activity, substrate recognition and stability of the whole enzyme complex (Nakashima et al., 2019). CK2 is a ubiquitous and constitutively active serine/threonine protein kinase, a heterotetramer composed of two identical (α/α or α′/α′) or dissimilar (α/α′) catalytic subunits and two regulatory subunits (β), with different genes encoding the different subunits (Di Stazio et al., 2023; Nakashima et al., 2019). CK2 can use ATP or GTP as phosphate donor and participate in various signaling pathways) (Ballardin et al., 2022; Borgo et al., 2021; Di Stazio et al., 2023; Niefind et al., 1999; Orsini et al., 2022), playing important roles in various cellular processes such as cell proliferation, differentiation, apoptosis, migration, adhesion (Lettieri et al., 2019), DNA damage and repair (Gotz & Montenarh, 2017), gene expression, cell signaling, metabolism (Li et al., 2019), immunity (Hong & Benveniste, 2021), angiogenesis, and tumor (Gotz & Montenarh, 2017). It has been suggested that CK2 deficiency may lead to dopamine signaling dysregulation (Poirier et al., 2017; Rebholz et al., 2009; Selvam et al., 2021) suggested that POBINDS patients exhibiting thermal intolerance may be due to a defect in dopamine signaling caused by c.139C>T (p.R47*) of *CSNK2B*, consistent with the finding that CK2 deficiency may affect dopamine signaling dysregulation, but further confirmation is needed.

Furthermore, CK2 is highly expressed in the brain (Selvam et al., 2021) and highly conserved (Niefind et al., 1999) during evolution, and is also critical in neural development, axon generation, synaptic transmission, and plasticity (Lettieri et al., 2019). In recent years, *CSNK2B* variants encoding CK2β have been found to cause POBINDS. The central part of CK2β contains a zinc finger structural domain consisting of four cysteine residues (C109, C114, C137, and C140), ligated with Zn^{2+}, which is highly conserved and establishes an effective dimeric structure for CK2β (Yang et al., 2021). CK2β regulates the substrate specific targeting of the catalytic subunit (Lettieri et al., 2019) and together forms a complete CK2 protein kinase structure (Yang et al., 2021). Zhang et al. (2022) and Li et al. (2019) suggested that variants in zinc finger structural domain cause a milder POBINDS phenotype and that epilepsy is more easily controlled. In contrast, Ballardin et al. (2022) suggested that variants in the zinc finger and/or C-terminal structural domains appear to have a more severe phenotype than variants in the N-terminal region in patients with POBINDS. Meanwhile, Li et al. (2019) proposed that the zinc finger structural domain is a hotspot variant region of *CSNK2B*. Therefore, the severity of POBINDS phenotype due to variants located in the region still needs to be further confirmed by counting more variants and cases.

The proband with unexplained first presentation of GTC at 5 months of age reported in this study had clinical manifestations of early onset epilepsy, mild DD, delayed tooth eruption, hypotonia, low cognitive function, and autistic features, along with intermittent furfuraceous rash. EEG, MRI, and cerebrospinal fluid examination showed no significant abnormalities. Incredibly, the patient also developed an intermittent branched rash while on a multidrug combination of DAP, PB, LEV, and VPA. After 4 months of VPA, the seizures were controlled and the rash disappeared. In addition, Ernst et al. (2021) also reported a case of POBINDS with intermittent rash. Consequently, we speculate that the rash may be one of the symptoms of POBINDS, but it is rarely seen in the cases reported so far, and we hope that more cases will confirm this idea.

WES identified a novel variant c.453_c.454insAC (p.H152fs*76) of *CSNK2B* located in the non-zinc finger structural domain. The Mutalyzer 2.0.35 software prediction showed that the amino acid sequence was changed and increased by 11 amino acids from position 152 onwards compared to the normal sequence. The PSIPRED software suggested that *CSNK2B* encodes a significantly different secondary structure of CK2β protein compared to normal. Meanwhile, the ACMG guidelines assessed as pathogenic variants (PVS1+PS2+PM2). The mutant tertiary structure clearly showed an increase in amino acid sequence and a change in protein structure when compared with the wild-type. The variant c.453_c.454insAC (p.H152fs*76) of *CSNK2B* was not included in HGMD, Clinvar and PubMed (https://pubmed.ncbi.nlm.nih.gov/) databases and no case reports of POBINDS were reported.

We reviewed and summarized 81 cases of POBINDS (including the study case, searched in PubMed) and found that approximately 60 variants in *CSNK2B* were reported to be associated with POBINDS. We inductively found that except for exon 1, part of exon 2, and part of exon 7, which are non-coding regions, the most missense

variants (19/60) were detected among the 60 variants, which is consistent with the results obtained by searching the HGMD and Clinvar databases. Moreover, the most variants were located in exon 6 (16/60), and most of the frameshift and missense variants were located in exon 6. The most nonsense variants were located in exon 2 and the most splicing variants were located on IVS5 (Figure 7). With the exception of patients who had not acquired epilepsy age, seizures over 3 years of age, and no seizures, of the 81 case, 66 had seizures under the age of 3 years (inclusive), with GTC seizures being the most common, a result that is consistent with the results of the data analysis by the majority of the authors. Of the 81 cases, 72 showed varying degrees and types of DD; 60/81 showed varying degrees of ID, 30/81 showed hypotonia, 14/81 showed autistic features, 28/81 showed facial deformities, and 8/81 showed LD. Twenty-five cases were treated with a single drug and 32 cases were treated with multiple drugs. LEV with VPA was used most frequently for anti-epileptic treatment, a result consistent with that obtained by Orsini et al. (2022). Detailed genotype, phenotype and treatment information can be found in Table S1.

In addition, we found that POBINDS patients with epilepsy with or without EEG and MRI abnormalities, suggesting that seizures may not be strongly associated with EEG and MRI, or may be related to seizure type, frequency, degree, and seizure mechanism, a result that needs to be confirmed by further studies. Of the 81 patients with POBINDS in this case, 60/81 presented with ID with 35 males and 25 females and males had more moderate to severe ID than females, which is consistent with Ernst et al. (2021), who suggested that males may have more severe ID results than females. Consequently, gender may be a factor affecting ID. Despite the diverse phenotypes of POBINDS, a few patients also exhibit some rare atypical symptoms such as ectodermal abnormalities (Asif et al., 2022; Di Stazio et al., 2023), vascular abnormalities (Di Stazio et al., 2023; Orsini et al., 2022), lymphedema (Orsini et al., 2022), butterfly vertebra (Di Stazio et al., 2023; Orsini et al., 2022), precocious puberty (Nakashima et al., 2019), finger deformities (Di Stazio et al., 2023; Ernst et al., 2021; Orsini et al., 2022; Wilke et al., 2022), and so on. However, epilepsy, DD, ID, facial dysmorphism, hypotonia, and autistic symptoms may be considered as the main typical clinical phenotypes. In this study, although the proband did not show facial dysmorphism, it is presumed that it may be related to the young age, and we will continue to follow-up the proband to see if there are new phenotypes that will enrich the clinical phenotype and expand the POBINDS phenotype spectrum.

Currently, POBINDS is treated with symptomatic support without specific treatment. VPA or LEV is often used as a single drug or in combination with other AEDs (Yang et al., 2021). Nevertheless, despite AED treatment to control epilepsy, Yang et al. (2021) and Li et al. (2019) suggested that ID, DD persisted. Yang et al. (2021) also suggested that the lack of significant improvement in dyslexia and dyspraxia may be related to the fact that CK2 is an important regulator of neurodevelopment (Blanquet, 2000). Rehabilitation exercises can be performed to improve ID, LD, motor, and language impairments, which remains a challenge for the treatment of POBINDS disease. Vascular, skeletal, cardiac, and other malformed can be treated surgically. Selvam et al. (2021) suggested that abnormal growth and height stagnation may be a phenotype of POBINDS. Yang et al. (2022) and Selvam et al. (2021) reported that growth hormone (GH) treatment was effective in patients with POBINDS who presented with short stature, providing evidence for the use of GH treatment for short stature due to *CSNK2B* variation (Yang et al., 2022). Ernst et al. (2021) also reported a case of POBINDS with partial GH deficiency. Therefore, we hypothesized that GH is good for improving and treating patients with growth retardation of POBINDS, especially GH deficiency type, but this result

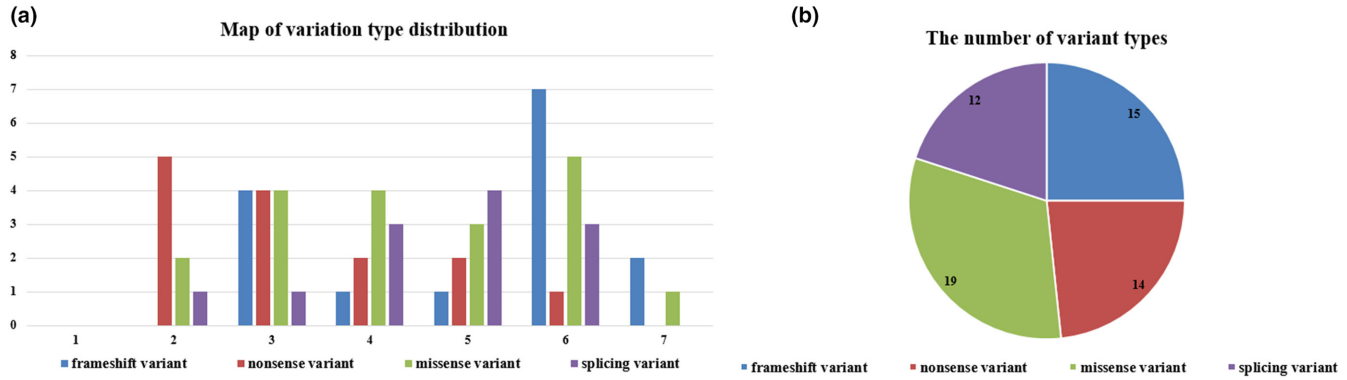

FIGURE 7 Characterization of the distribution of *CSNK2B* variants. (a) Map of variation type distribution. (b) The number of variant types.

needs to be confirmed by more cases studies to facilitate the detection of GH-related indicators to guide clinical use.

5 | CONCLUSION

The study reports a novel variant c.453_c.454insAC (p.H152fs*76) of *CSNK2B*. Eighty-one cases of POBINDS were studied to summarize *CSNK2B* variant types, phenotypes and treatment, elucidating the relationship between genotype and phenotype as well as ID and sex, and broadening the genetic and phenotypic spectrum. We hope to collect more cases to further study the relationship between genotype and phenotype, which will be beneficial for genetic counseling, early diagnosis, and early treatment of POBINDS patients and lay the foundation for effective reduction of neurodevelopmental disorders.

AUTHOR CONTRIBUTIONS

Danyang Li, Chuan Zhang, and Ling Hui designed the research; Danyang Li, Bingbo Zhou, Xinyuan Tian, Yupei Wang, Shengju Hao, Chuan Zhang and Ling Hui analyzed the data; Danyang Li, Chuan Zhang and Ling Hui wrote the paper; and all the authors read, critically revised, and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have nothing to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This research was approved by the Review Board of the Institutional Review Committee of Gansu Provincial Maternity and Child Health Hospital and conducted according to the tenets of the Declaration of Helsinki. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual (s) and the minor (s)' legal guardian of kin for the publication of any potentially identifiable images or data included in this article.

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SUPPORTING INFORMATION

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

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