Received: 12 June 2022 | Revised: 9 October 2022 | Accepted: 24 October 2022

DOI: 10.1002/jdn.10236

RESEARCH ARTICLE

INTERNATIONAL JOURNAL OF DEVELOPMENTAL NEUROSCIENCE

WILEY

Mild phenotypes of phosphoglycerate dehydrogenase deficiency by a novel mutation of *PHGDH* gene: Case report and literature review

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Funding information
No funding was obtained for this study.

Abstract

Phosphoglycerate dehydrogenase (PHGDH) deficiency is a rare autosomal recessive genetic disease of serine biosynthesis. Its typical features are congenital microcephaly, epileptic seizures, and psychomotor developmental delay. Here, we reported the first Chinese familial cases with genetically confirmed PHGDH deficiency and reviewed several previous reports. Two siblings in this family presented with microcephaly, psychomotor retardation, and epilepsy in early juvenile. Brain magnetic resonance imaging (MRI) showed only a slight change of enlarged ventricle. Biochemical investigations revealed low serum serine and glycine concentrations. The whole-exome sequencing (WES) results identified a missense variant in the *PHGDH* gene (NM_006623.4: exon11: c.1211T>A, p. Val404Asp). Although two patients in this Chinese family carried the same pathogenic mutation in the PHGDH, their symptoms and responses to treatment were not exactly the same. We found a novel variant in the *PHGDH* gene and expanded the genotypic and phenotypic spectrum of serine biosynthesis disorders.

KEYWORDS

developmental delay, microcephaly, *PHGDH* gene, seizures, serine deficiency

1 | INTRODUCTION

L-Serine plays an essential role in the development, growth, structure, and function of the brain at different life stages. Serine biosynthesis disorder is a group of autosomal recessive (AR) metabolic diseases with broad phenotypic variability caused by pathogenic changes in genes encoding enzymes in the L-serine biosynthesis pathway. The three enzymes involved in serine biosynthesis are phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase (PSAT), and phosphoserine phosphatase (PSPH). PHGDH catalyzes the conversion of 3-phosphoglycerate to 3-phosphohydroxypyruvate, which is the first and rate-limiting step in the phosphorylated pathway of serine biosynthesis. Although the deficiency of any enzyme in

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalogram; IUGR, intrauterine growth retardation; MRI, magnetic resonance imaging; NLS, Neu–Laxova syndrome; PHGDH, phosphoglycerate dehydrogenase; WES, whole-exome sequencing.

the pathway has overlapping clinical and biochemical features, PHGDH variations are more predominant in serine deficiency disorders (Abdelfattah et al., 2020; Grant, 2018).

The *PHGDH* gene is located on chromosome 1q12 and encodes a protein composed of 533 amino acids with a molecular mass of 56.8 kDa (Cho et al., 2000). In situ hybridization studies of mice and rats have shown that PHGDH is highly expressed during early development, especially in the ventricle and subventricular regions, and it is particularly involved in cell proliferation (Tabatabaie et al., 2010). *PHGDH* gene mutations are associated with two kinds of disease phenotypes: classical PHGDH deficiency (OMIM: 601815) and Neu–Laxova syndrome (NLS, OMIM: 256520). Since first reported by Jaeken et al. (1996), a total of 43 patients with the *PHGDH* gene variants were identified in 23 articles (Abdelfattah et al., 2020; Acuna-Hidalgo et al., 2014; Benke et al., 2017; Brassier et al., 2016; Cavole et al., 2020; de Koning et al., 1998; el-Hattab et al., 2016; Glinton et al., 2018; Häusler et al., 2001; Jaeken et al., 1996; Klomp et al., 2000; Kraoua et al., 2013; Mattos et al., 2015; Méneret et al., 2012; Ni et al., 2019; Pind et al., 2002; Pineda et al., 2000; Poli et al., 2017; Shaheen et al., 2014; Tabatabaie et al., 2009, 2011; Takeichi et al., 2018; Tao & Lu, 2021). An overview of clinical characteristics in patients who were reported with clear genetic etiology of *PHGDH* gene mutations is summarized in Data S1. In previous reports, the non-lethal form of PHGDH deficiency was divided into three phenotypes based on severity: infantile, juvenile, and adult phenotypes, resulting in a similar and overlapping clinical phenotypic spectrum (van der Crabben et al., 2013). Symptoms of infantile PHGDH deficiency were microcephaly, early-onset seizures, and severe psychomotor retardation. Infantile patients appeared with seizures within a few months to 1 year after birth and then probably developed different types of intractable seizures including infantile spasms (Klomp et al., 2000; Kraoua et al., 2013; Pineda et al., 2000), generalized tonic–clonic seizures (Benke et al., 2017; de Koning et al., 1998), atonic seizures (Brassier et al., 2016; de Koning et al., 1998; Häusler et al., 2001), and myoclonic seizure (Brassier et al., 2016). The majority of infantile patients developed hyperexcitability and feeding difficulties during the first months of life and subsequently developed severe psychomotor delay. Neuroimaging showed brain atrophy with enlarged ventricles and hypomyelination. Electroencephalogram (EEG) revealed multifocal epileptiform discharges with slow background activity. Juvenile PHGDH deficiency showed much milder symptoms; two teenaged siblings with a milder phenotype presented with intellectual deficiency, absence seizures, and behavior problems. Magnetic resonance imaging (MRI) manifested with no special findings (Tabatabaie et al., 2011). Currently, the oldest patient comes from Méneret et al. (2012) who reported a 31-year-old male patient with congenital cataracts, mild walking difficulties, and mild mental disability in childhood but developed a progressive polyneuropathy in adulthood. NLS represents the most severe form of phenotypic spectrum in serine biosynthesis defect, which is characterized by multiple congenital anomalies including severe intrauterine growth retardation (IUGR), microcephaly, ichthyosis, and distinctive craniofacial features including sloping forehead, prominent eyes, depressed nasal bridge, hypertelorism, and short neck (Shaheen et al., 2014). Overlapping symptoms between the NLS, infantile, juvenile, and adult phenotypes can be found, demonstrating that the serine biosynthesis defects spectrum is a continuum of phenotypes.

In this study, we reported the clinical features and genetic results of two Chinese siblings with PHGDH deficiency. Our study expanded the clinical spectrum of PHGDH-related serine deficiency.

2 | MATERIALS AND METHODS

2.1 | Subjects

We studied a Chinese family of two affected individuals presenting the features of PHGDH deficiency. Two members were physically examined, and their medical history was evaluated. Further diagnostic tests included blood tests, EEG, brain MRI, and genetic analysis. This study was conducted according to the Declaration of Helsinki human studies research. The study was approved by the Ethical Review Board of Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology. Informed consent was obtained from the patients and their parents.

2.2 | Whole-exome sequencing (WES) and Sanger sequencing

Genomic DNA was extracted from the peripheral blood of patients and their parents. The genomic DNA library was captured using IDT XGen Exome Research Panel. Then WES was performed based on the NovaSeq 6000 Sequencing platform using paired-end reads. BCL2FASTQ, Burrows–Wheeler Aligner (BWA) (Li & Durbin, 2009), ANNOVAR (Wang et al., 2010), Genome Analysis Toolkit (GATK) software (McKenna et al., 2010), SIFT (Sim et al., 2012), POLYPHEN2 (Adzhubei et al., 2010), LRT,

MUTATIONTASTER (Schwarz et al., 2014), and FATHMM (Shihab et al., 2014) were used for data processing and analysis. The detected variants were analyzed using the dbSNP, OMIM, HGMD, and ClinVar databases. All the detected variants were filtered by clinical features, inherent pattern, type, frequency, and databases included. Subsequently, Sanger sequencing was performed to validate the variants identified by WES.

2.3 | Copy number variant (CNV)

Genomic DNA was fragmented, and sequencing libraries were prepared using the TruSeq Library Construction Kit. Libraries were sequenced using a high-throughput sequencing platform (Illumina, San Diego, USA). All the sequences were aligned to the human reference genome hg38 using the Burrows–Wheeler algorithm. CNVs were detected through tools containing CNVkit and CNVnator (Abyzov et al., 2011; Talevich et al., 2016) and annotated subsequently. The reference database for screening the pathogenicity of the CNVs includes OMIM, DECIPHER, DGV, Orphanet, and other databases.

3 | RESULTS

3.1 | Case report

The proband was an 8-year-old boy born to consanguineous parents. He is the younger brother of the family. The pregnancy and the delivery were normal. At the age of 1 year, his physical examination revealed a height of 73 cm (10th–25th centile), a weight of 9.4 kg (10th–25th centile), and a head circumference of 42 cm (below the 3rd centile). The seizures occurred at the age of 4 years, presenting with the head backward and losing consciousness. Oral levetiracetam was then administered at that time, but the attacks were not controlled completely; shortly after that, he experienced atonic seizures and myoclonic seizures that were difficult to control with multi-antiepileptic medications. At the age of 8 years, his parents noticed that he had cognitive decline, so they came to our hospital for consultation. Physical examination showed that his weight was 26 kg (25th–50th centile) and his head circumference was 50 cm (10th–25th centile). Nervous system examination was performed during the interictal period, and there were no positive ataxia signs. The Child Development Assessment Scale indicated that his development was lagging behind severely. He could not write his name and perform. Poor coordination and balance of movements were manifested as being unable to stand on one leg and being prone to wrestling. The EEG showed multifocal epileptiform discharges with slow background activity during wake and sleep (Figure 1a). Brain MRI demonstrated mild widened cerebellar sulci (Figure 1b). Routine biological tests including blood count cells and blood chemistry were normal. High-performance liquid chromatography (HPLC) revealed that the fasting plasma serine concentration was significantly decreased (56.2 μmol/L, normal 120–196 μmol/L) and the value of glycine was normal (302.4 μmol/L, normal 194–365 μmol/L). Valproic acid was added to his therapeutic regimen, and the frequency of seizures was decreased by 90% during the follow-up. But he still suffered from irritability and growth retardation.

Patient 2 was the older brother of the proband, and he was 14 years old. He was born at term with an uncomplicated perinatal course. Milestones of motor development were generally normal (sit at 6–7 months, stand alone at 10–11 months, and walk at 1.5 years). Similar to his sibling, he developed seizures at the age of 4 years. Before coming to our hospital, he had received a variety of anti-seizure medications (levetiracetam, valproic acid, and topiramate) with uncontrollable seizures. At age 14, a physical examination revealed a 32 kg weight and a 50.5 cm head circumference (both below the 3rd centile). There were large patches of melanin on the right face and ichthyosis on his leg's skin. In addition, he was presented with irritability and obvious mental retardation. EEG results showed severe multifocal epileptic abnormalities (Figure 1c). MRI showed a slightly enlarged ventricle (Figure 1d). Levetiracetam was replaced with lamotrigine, and the other two anti-seizure medications were kept. During the follow-up, his epilepsy had been partially controlled with multiple anti-seizure medications.

3.2 | Genetic analysis

To further analyze the potential cause, CNVs and WES of two patients and their parents were performed. CNV analysis did not reveal any deletions or duplications assumed to be causative (Table S2). WES criteria for variant filtering were as follows: minor allele frequency (MAF) <0.05 for gnomAD_exome_popmax, gnomAD_genome_popmax, and gnomAD3_genome_AF_Popmax; the rare variants that meet this condition are listed in Table S3. De novo, AR, and X-linked inheritance were identified by genotypes of proband and parents. Variants were evaluated by referencing dbSNP, OMIM, HGMD, ClinVar, and other databases. SIFT, POLYPHEN2, LRT, MUTATIONTASTER, FATHMM, REVEL, and other software programs were used to predict protein function caused by gene

variation. Finally, we demonstrated a homozygous variant NM_006623.4: exon11: c.1211T>A (p. Val404Asp) of PHGDH, which had not been reported previously. Two siblings have a homozygous variant on the *PHGDH* gene, which was inherited from their parents and was confirmed through Sanger sequencing (Figure 2). The variant we found was not exhibited in gnomAD and Exome Aggregation Consortium (ExAc), and it was predicted to be probably damaging in silico analyses (deleterious by SIFT, probably damaging by POLYPHEN2 _HDIV, disease caused by MUTATIONTASTER, REVEL score of 0.749). The c.1211T>A mutation was classified as likely pathogenic according to the practical statement released by the American College of Medical Genetics and Genomics.

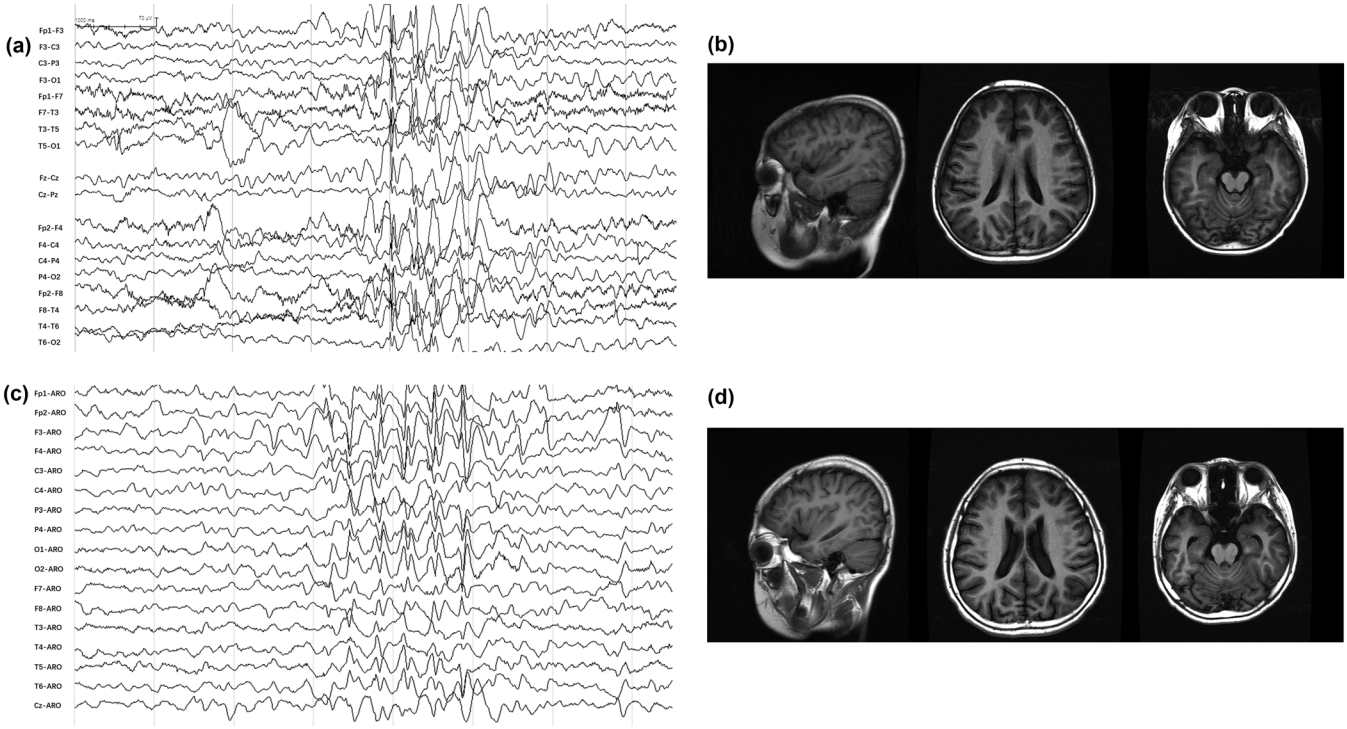

FIGURE 1 The patients' clinical examination of electroencephalogram (EEG) and brain magnetic resonance imaging (MRI). (a) The younger brother's EEG at 8 years old. (b) The brain magnetic resonance imaging for the younger brother at the age of 8 years showed mild widened cerebellar sulci. (c) The older brother's EEG at 14 years old. (d) The older brother's MRI at 8 years old demonstrated a slightly enlarged ventricle.

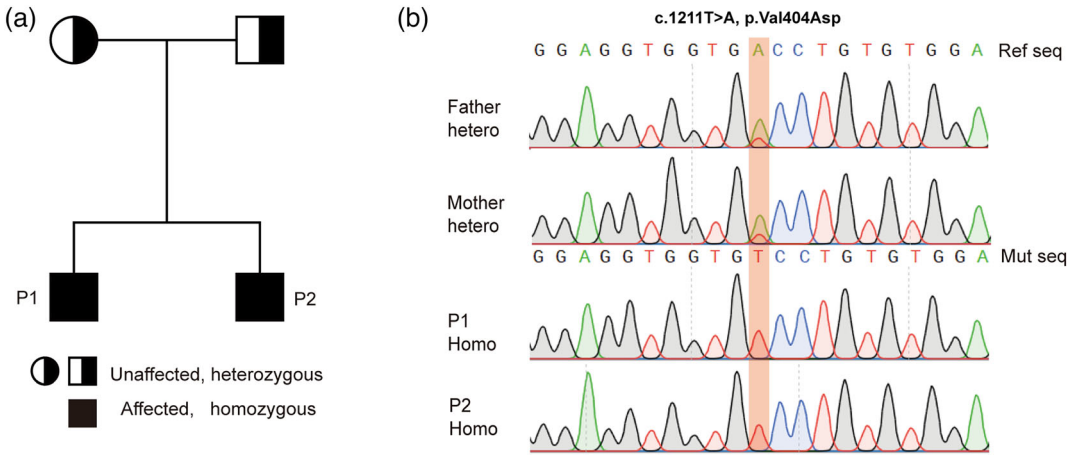

FIGURE 2 Identification of the variant in phosphoglycerate dehydrogenase (PHGDH). (a) Pedigree of the affected family. The filled symbol identifies individuals with PHGDH deficiency. The parents were represented by half-shaded squares and circles. (b) Sanger sequencing results

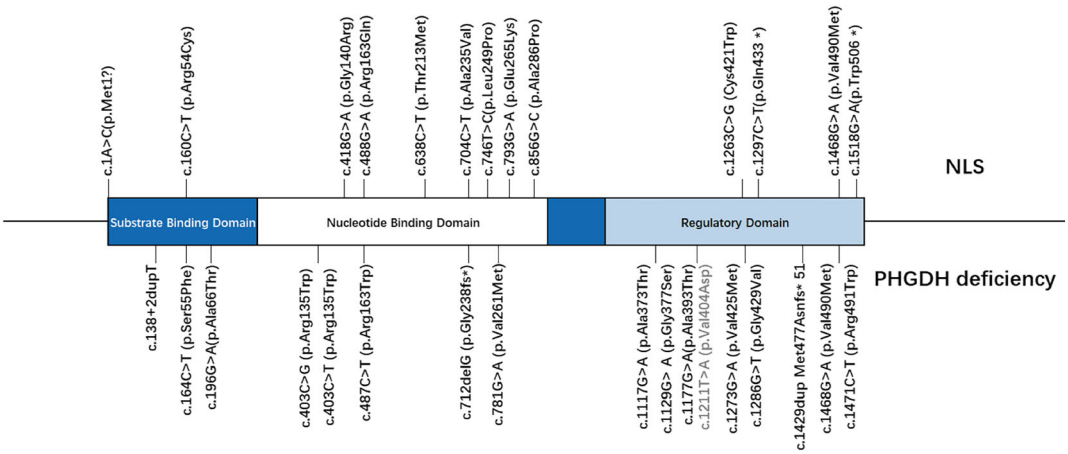

FIGURE 3 Protein structure and modeling of phosphoglycerate dehydrogenase (PHGDH) variants with Neu–Laxova syndrome (NLS) (upper panel) and PHGDH deficiency (lower panel) in previous studies. The variant of our case was highlighted in red font.

Therefore, considering the symptoms, biochemical characteristics, and genetic analysis, we established the PHGDH deficiency diagnosis.

4 | DISCUSSION AND CONCLUSIONS

L-Serine is a key intermediate in cellular metabolism. Besides its role in protein synthesis, serine is a precursor of several essential compounds, including cysteine, phosphatidylserine, sphingomyelin, and the neuromodulators D-serine and glycine. It is also a main source of N^5,N^{10}-methylenetetrahydrofolate, a major one-carbon donor that is required for the synthesis of purines and thymidine (El-Hattab, 2016; Tabatabaie et al., 2010). L-Serine can be used as a potent survival-promoting factor for the central nervous system.

Serine deficiency disorders mainly manifest with a neurological phenotype, and the damage to the brain occurs before birth. However, the clinical phenotype was extremely variable. PHGDH deficiency represents a broad spectrum of disease severity ranging from a severe lethal type of NLS to adult-onset polyneuropathy. In this study, the two patients had microcephaly, psychomotor retardation, and seizures. Brain MRI showed only a slight change. The molecular investigation identified a homozygous variant in the *PHGDH* gene. Plasma amino acid measurements confirmed the specific serine synthesis. Indeed, when we compared our patients to previously reported cases, we found it difficult to classify them as infantile or juvenile type. In previous studies, infantile PHGDH deficiency patients can typically present with IUGR, microcephaly, intractable early-onset seizures, severe psychomotor retardation, and brain atrophy with hypomyelination on neuroimaging. Additionally, visual problems such as cataracts and nystagmus were frequently reported (de Koning et al., 1998; Jaeken et al., 1996; Klomp et al., 2000; Kraoua et al., 2013; Pineda et al., 2000; Poli et al., 2017). In Tabatabaie et al.'s (2011) study, a juvenile phenotype was reported in two children with much milder symptoms. Two patients were diagnosed in their teens. They showed normal early developmental milestones and subsequently experienced a moderate developmental delay, developing absence seizures at school age. Our patients had a normal history of pregnancy and delivery, and no obvious symptoms occurred during the period after birth. Both siblings developed epileptic seizures at 4 years old, but different clinical seizure patterns were documented. Their brain MRI did not show evidence of corpus callosum atrophy and hypomyelination in the infantile form. Remarkably, three patients had been reported to lose the ability to walk independently (Benke et al., 2017). We speculated that regression could also be a feature of this disease. Although there was no regression in the two siblings in our study, they can only receive school education in special schools. Ichthyosiform scaling was prominent in our patient's leg. According to literature data, more than 50% of patients with serine deficiency developed ichthyosis, which might be caused by a deficiency of stratum corneum ceramides (Takeichi et al., 2018). Anemia may be due to insufficient activated tetrahydrofolate synthesis secondary to serine deficiency, and it can also affect epidermal cell division leading to skin pathology (el-Hattab et al., 2016).

The previously reported plasma serine concentrations of patients with PHGDH deficiency range between 19 and 69 μmol/L, glycine between 63 and 120 μmol/L, serine concentrations in cerebrospinal fluid (CSF) between 3 and 9 μmol/L, and glycine concentrations between 1 and 24 μmol/L. Plasma and CSF serine values in severe phenotype patients were in the same range as

those in the mild form of PHGDH deficiency patients (Tabatabaie et al., 2011). In fact, it is not possible to predict the clinical phenotype from the amino acid concentrations. A recently published study by Abdelfattah et al. (2020) postulated that the individual residual enzyme activity of mutant proteins is the major determinant of the phenotypic variability, but further structural and functional studies are needed.

To date, 17 PHGDH mutations have been identified with classical PHGDH deficiency, and 13 variants are related to NLS. Moreover, missense variants in this gene are considered a common variant type. Homozygous nonsense variation of PHGDH caused the most severe NLS phenotypes (Bourque et al., 2019; Mattos et al., 2015). A homozygous mutation c.1211T>A (p. Val404Asp) in PHGDH was detected in our parents. The V404D mutation in PHGDH was predicted to be destabilizing in three software: MCSM ($\Delta\Delta G$): −1.266 kcal/mol; SDM ($\Delta\Delta G$): −1.81 kcal/mol; and DUET ($\Delta\Delta G$): −1.248 kcal/mol (Pandurangan et al., 2017; Pires et al., 2014, 2020).

Although patients in different families carried the same pathogenic mutation in the *PHGDH* gene, their symptoms and responses to treatment were not the same. Based on the literature review and our data, most variants associated with nonlethal PHGDH deficiency disorder are located in the regulatory domain. The missense variant in our patients is in the regulatory domain. In contrast, the majority of NLS-associated variants are located in the nucleotide-binding domain (Figure 3).

Treatment with serine and glycine has been implemented in serine biosynthesis defects since the first reports by Jaeken et al. (1996). Oral L-serine has been reported to reduce seizure frequency occurring significantly (de Koning, 2017; de Koning et al., 2002). The epileptic abnormalities gradually resolved, and improved background activity of EEG was shown after several months of the oral L-serine treatment (de Koning et al., 1998). Follow-up EEGs showed free epileptic activity, and antiepileptic drugs were successfully discontinued (de Koning et al., 2002). de Koning et al. (2004) confirmed that when L-serine treatment was initiated before birth, the prognosis appeared to be very good, and normal psychomotor development could be observed. Regrettably, some patients could not receive L-serine medical treatment due to a lack of L-serine purchase channel, just like our patients. Control of seizures could greatly improve the life quality of patients, so we adjusted anti-seizure medications. During the 2 years of treatment, the frequency of seizures in our patients was reduced. However, long-term effects needed follow-up. Of course, we are still helping patients to inquire about L-serine.

PHGDH deficiency is a severe but potentially treatable congenital disorder of amino metabolism. The diagnosis of serine deficiency disorders is often delayed by atypical clinical phenotypes. Despite its various and evolving phenotypes, the diagnosis of serine biosynthesis defects is based on clinical features, biochemical profile, enzyme assay, and molecular testing. Currently, molecular genetic testing is the best approach for diagnosis. As exome sequencing is becoming more readily available, the phenotypic spectrum of the clinical spectrum of serine deficiency disorders will continue to expand.

Here, we reported a novel pathogenic mutation in the *PHGDH* gene of serine biosynthesis disorders; in our case, consistent with previous reports, patients had microcephaly, psychomotor retardation, seizures, and low serine concentrations, but brain MRI showed only a slight change. To our knowledge, only one study reported two cases of MRI with normal results in juvenile cases (Tabatabaie et al., 2011). Meanwhile, we analyzed and summarized the clinical and genetic characteristics of patients with PHGDH variants in previous reports, thereby expanding and further elucidating the genotype–phenotype spectrum and reinforcing the importance of molecular diagnosis for genetic counseling in serine deficiency diseases. Especially in children with global developmental delay and seizure, genetic testing is helpful.

ACKNOWLEDGMENTS

The authors would like to thank the family for participating and supporting this study.

CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest.

ETHICS APPROVAL STATEMENT

This study was in compliance with the Declaration of Helsinki and was approved by the Ethical Review Board of Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology.

PATIENT CONSENT STATEMENT

Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consents were obtained from the parents of the patients for the publication of this study.

AUTHOR CONTRIBUTIONS

YL and SX designed and organized the study. YL, LC, and TS acquired the clinical data, prepared the samples from the family members, and interpreted the genetic analyses. JF did the literature searching. JF and YL wrote the manuscript that was edited by all other authors. TS reviewed and edited the final manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

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

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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: Fu, J., Chen, L., Su, T., Xu, S., & Liu, Y. (2023). Mild phenotypes of phosphoglycerate dehydrogenase deficiency by a novel mutation of *PHGDH* gene: Case report and literature review. *International Journal of Developmental Neuroscience*, *83*(1), 44–52. https://doi.org/10.1002/jdn.10236