Received: 17 January 2022 | Revised: 12 July 2022 | Accepted: 19 July 2022

DOI: 10.1002/mgg3.2025

Molecular Genetics & Genomic Medicine Open Access WILEY

ORIGINAL ARTICLE

HPDL mutations identified by exome sequencing are associated with infant neurodevelopmental disorders

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Funding information
National Population Health Data Center Project, Grant/Award Number: SJPT-03-01; National Natural Science Fundation of China, Grant/Award Number: 81701125

Abstract

Background: Recent research found that biallelic *HPDL* variants can cause neurodevelopmental disorder with progressive spasticity and brain white matter abnormalities (NEDSWMA), with only a few reports. Clinical phenotypic information on individuals with damaging *HPDL* variants may also be incomplete. The phenotype of NEDSWMA is characterized by severe neurodevelopmental delay, brain atrophy, and spasticity in infancy.

Methods: Exome sequencing was used in the proband and his parents to identify the underlying genetic cause. Candidate mutations were validated by classic Sanger sequencing. The clinical presentation of the infant who carried *HPDL* variants was summarized.

Results: We identified a novel compound heterozygous variants in *HPDL*, c.995delC (p.T332Mfs) and c.1051C>T (p.Q351*) in the patient a 6-month-old boy presenting with global developmental delay, seizures, hypertonia, and limb spasticity. Brain magnetic resonance imaging (MRI) showed thin corpus callosum, ventriculomegaly, white matter volume reduction, bilateral frontotemporal subarachnoid widening, and sulcus deeping.

Conclusion: Our results provided important information for the associations of variants in *HPDL* with the neurodevelopmental disorder in infants, and broaden the genetic spectrum of *HPDL*-related disease. This is the second report of the *HPDL* mutation causing infant neurodevelopmental disorders in a Chinese population.

KEYWORDS
HPDL gene, infant, neurodevelopmental disorders, spastic movement disorders

1 | INTRODUCTION

Neurodevelopmental disabilities are a group of chronic diseases caused by abnormal development of the central nervous system and have complex pathogenesis of which environmental and genetic are important factors (Duncan & Matthews, 2018; Parenti et al., 2020). Recent research found that biallelic *HPDL* (OMIM:#618994) variants can cause neurodevelopmental disorders (Husain et al., 2020). The gene encodes the 4-hydroxyphenylpyruvate dioxygenase-like protein (HPDL), a critical enzyme in the 4-hydroxymandelate CoQ10 synthesis pathway and widely expressed in most organs with high levels in the central and peripheral nervous system (Banh et al., 2021; Ghosh et al., 2021).

The *HPDL*-related neurodegenerative disorder is clinically characterized by two main phenotypes: a neurodevelopmental disorder with progressive spasticity and brain white matter abnormalities (NEDSWMA), and Spastic paraplegia 83 (SPG83). NEDSWMA presents usually with severe neurodevelopmental delay, brain atrophy, and spasticity in infancy, while SPG83 is characterized by spastic paraplegia in juveniles (Husain et al., 2020; Wiessner et al., 2021).

So far, clinical reports of individuals with damaging *HPDL* variants were limited, and clinical phenotypic information may also be incomplete (Ghosh et al., 2021; Husain et al., 2020; Morgan et al., 2021; Sun et al., 2021; Wiessner et al., 2021). Here, we report one patient from a Chinese family presenting with global developmental delay, hypertonia, and limb spasticity, and summarized the clinical presentation of the infant who carried *HPDL* variants.

2 | MATERIALS AND METHODS

2.1 | Exome sequencing

Samples of the proband and their parents were subjected to the exome sequencing. The detailed methodology has been described previously (Zhao et al., 2020). The variants interpretation rules according to the American College of Medical Genetics and Genomics (ACMG) guidelines for the interpretation of genetics (Richards et al., 2015). Sanger sequencing was performed for validation.

3 | RESULT

3.1 | Clinical case report

The proband II-1, a 6-month boy with a head circumference of 41 cm, was born after cesarean section at 39 weeks of gestational age. The parents had a non-consanguineous marriage without a family history of genetic diseases. The patient was not capable of controlling his head, gaze fixation or visual tracking, recognizing his parents, and unable to roll, crawl or sit independently. Physical examination detected nystagmus, insensitive to light reflection, hands clenched, lower limbs hypertonia, and forward sitting position. The levels of lactate was 3.15 mmol/L (normal range: 0.5–2.0) and pyruvate was 21.7 μmol/L (normal range: 20–100) (Table 1). Brain magnetic resonance imaging (MRI) showed thin corpus callosum, ventriculomegaly, white matter volume reduction, bilateral frontotemporal subarachnoid widening, and sulcus deepening (Figure 1a). The electroencephalogram (EEG) shows epileptic waves. The patient was initially diagnosed with cerebral palsy (CP) and developmental delay.

3.2 | Genetic results

By exome sequencing, in the proand: II-1, the compound heterozygous variants c.995delC (p.T332Mfs) and c.1051C>T (p.Q351*) in *HPDL* gene were revealed, of which the mutation c.1051C>T (p.Q351*) has not been reported previously. The father and mother of the proband carry the variant c.1051C>T (p.Q351*) and c.995delC (p.T332Mfs) respectively (Figure 1B,C).

4 | DISCUSSION

The *HPDL* gene, consisting of a single exon, encodes the 4-hydroxyphenylpyruvate dioxygenase-like protein (HPDL) belonging to the vicinal oxygen chelate (VOC) superfamily of metalloenzymes. It is located in mitochondrial intermembrane space with the predicted N-terminal mitochondrial localization signal and 2 predicted VOC domains, which are related to mitochondrial respiratory function (Sun et al., 2021).

Biallelic *HPDL* variants are associated with infant neurodevelopmental disorders, and the affected individuals usually show cognitive impairment and motor disability, with variable features including seizures, ocular disturbances, and respiratory failure. The first patients with this disease were reported by Husain in 2020, and a number of cases have been reported at present. The clinical presentations in these patients are summarized in Table 1.

Bi-allelic *HPDL* variants are related to a broad range of human phenotypes. The most common symptom is global developmental delay (GDD) and hypertonia, which are present after birth or in the first months of life. The available MRI suggested that all patients are abnormal, with a reduction of white matter volume, thin corpus callosum,

TABLE 1 Summary of the clinical presentation of the previously reported infants with *HPDL* variants

			Clinical presentation									
Patient	Age of onset/ current age	Family history	GDD/ ID	Hypertonia	Seizures/ epilepsy	Ocular	Facial	MRI	Lactate; pyruvate (mmol/L)	cDNA variant(s)	Protein variant(s)	Reference
P1/M	Birth/8 years	+	+	+	+	+	N/D	White matter and corpus callosum volume reduction; myelination was deficient	2.7; N/D	c.342_343ins TGCC (hom.)	p.A115C fs*82(hom.)	Husain et al. (2020)
P2/M	6 months/34 years	+	+	+	+	−	N/D	N/D	N/D	c.779G>A (hom.)	p.G260E (hom.)	Husain et al. (2020)
P3/M	6 months/11 years	+	+	+	+	+	N/D	Brain stem involvement	5.2; N/D	c.721C>T (hom.)	p.Q241* (hom.)	Husain et al. (2020)
P4/M	1 week/22 years	−	+	+	+	+	N/D	N/D	4.3; N/D	c.650T>C/c.797T>C	p.L217P/p.I266T	Husain et al. (2020)
P5/M	3 weeks/5 years	+	+	+	+	+	N/D	N/D	4.0; N/D	c.503G>A/c.537G>C	p.C168Y/p.W179C	Husain et al. (2020)
P6/M	6 weeks/5 years	−	+	+	+	−	N/D	N/D	N/D	c.701T>C/c.743T>C	p.L234P/p.L248P	Husain et al. (2020)
P7/M	5 months/2 years	−	+	+	−	+	N/D	White matter and corpus callosum volume reduction	4.3; N/D	c.469T>C/c.753C>A	p.W157D/p.H251Q	Husain et al. (2020)
P8/M	Birth/13 years*	+	+	+	+	+	+	Cortical atrophy; corpus callosum hypoplasia; cerebellar vermis hypoplasia/atrophy; ventriculomegaly; white matter defects	N/D	c.232G>A (hom.)	p.A78T (hom.)	Ghosh et al. (2021)
P9/M	3 months/4.5 years	−	+	+	+	+	+	Cortical atrophy; ventriculomegaly	N/D	c.376G>A (hom.)	p.G126S (hom.)	Ghosh et al. (2021)
P10/M	6 months/8 years	+	+	+	+	+	+	Cortical atrophy; corpus callosum hypoplasia; cerebellar vermis hypoplasia/atrophy; ventriculomegaly; white matter defects; brainstem hypoplasia	N/D	c.491T>C (hom.)	p.L164P (hom.)	Ghosh et al. (2021)
P11/F	4 months/11 years*	+	+	+	+	+	+	Cortical atrophy; corpus callosum hypoplasia; cerebellar vermis hypoplasia/atrophy; ventriculomegaly; white matter defects; brainstem hypoplasia	N/D	c.954dup (hom.)	p.G319R fs*15 (hom.)	Ghosh et al. (2021)
P12/M	8 months/2.5 years	−	+	+	+	+	−	Cortical atrophy; corpus callosum hypoplasia; ventriculomegaly; white matter defects	N/D	c.94C>T (hom.)	p.Q32* (hom.)	Ghosh et al. (2021)
P13/F	4 months/4 years	−	+	+	+	+	N/D	Mild supratentorial atrophy and hypomyelination	n; N/D	c.1013T>C/c.769_771 delinsTC	p.L338P/p.Q257fs	Wiessner et al. (2021)
P14/F	10 months/11 months	−	+	+	+	N/D	N/D	Leigh syndrome, bilateral frontal white matter hypoattenuation	N/D	c.27C>A/c.569C>T	p.C9*/p.P190L	Wiessner et al. (2021)
P15/F	12 months/N/A	−	+	+	−	+	N/D	Corpus callosum agenesis; abnormal cortical gyration; periventricular leukomalacia	n; N/D	c.256del (hom.)	p.A86fs (hom.)	Wiessner et al. (2021)
P16/F	1 month/1 year	−	+	+	+	+	N/D	Corpus callosum hypoplasia; cerebral atrophy; global delay of myelination	n; N/D	c.788C>T (hom.)	p.T263M (hom.)	Wiessner et al. (2021)
P17/M	7 days/6 years	−	+	+	+	+	N/D	Global cerebral atrophy; reduced white matter volume	n; N/D	c.342_345dup (hom.)	p.A116fs (hom.)	Wiessner et al. (2021)
P18/M	7 months/19 months	+	+	+	+	−	N/D	Corpus callosum agenesis; global cerebral atrophy; reduced white matter volume; ventriculomegaly	N/D	c.3G>C (hom.)	p.M1? (hom.)	Wiessner et al. (2021)

(Continues)

TABLE 1 (Continued)

Patient	Age of onset/ current age	Family history	Clinical presentation					MRI	Lactate; pyruvate (mmol/L)	cDNA variant(s)	Protein variant(s)	Reference
			GDD/ ID	Hypertonia	Seizures/ epilepsy	Ocular	Facial					
P19/M	1 month/5 years	−	+	+	−	−	N/D	Corpus callosum hypoplasia; reduced white matter volume	N/D	c.995del/c.650T>C	p.T332fs/p.L217P	Wiessner et al. (2021)
P20/F	Infancy/7 years	+	+	+	+	−	N/D	Corpus callosum hypoplasia; hypomyelination	N/D	c.1072T>G (hom.)	p.W358G (hom.)	Wiessner et al. (2021)
P21/F	11 months/3.5 years	−	+	+	−	−	N/D	corpus callosum hypoplasia	N/D	c.110G>C (hom.)	p.R37P (hom.)	Wiessner et al. (2021)
P22/M	Infancy/N/A	−	+	N/D	+	−	N/D	corpus callosum agenesis; global cerebral atrophy; ventriculomegaly	N/D	c.788C>G (hom.)	p.T263M (hom.)	Wiessner et al. (2021)
P23/F	12 months/11 years	−	+	N/D	−	−	N/D	Corpus callosum agenesis; widening of occipital horns of lateral ventricles	N/D	c.256del (hom.)	p.A86fs (hom.)	Wiessner et al. (2021)
P24/M	6 months/12 years	+	+	+	−	+	N/D	N/D	N/D	c.149_151del/ c.537G>A	p.G50del/p.W179*	Morgan et al. (2021)
P25/M	6 months/18 months	−	+	+	N/D	+	N/D	Cerebral white matter abnormalities; diffuse brain atrophy; ventriculomegaly	Slightly high; slightly high	c.232G>A (hom.)	p.A78T (hom.)	Numata-Uematsu et al. (2021)
P26/M	2 days/8 years	+	+	+	+	+	N/D	Thin cortical layer; small brain volume; thin corpus callosum; wide sulci and extra-encephalic spaces	n; N/D	c.596_599del; insCAGGTC; AGGAT/ c.215_226del; InsTGTACG; GCCTGGAT	p.L199P; fs*15/; p.R72L; fs*60	Sun et al. (2021)
P27/M	2 months/N/A	−	+	+	+	+	N/D	Delayed myelin sheath formation in the white matter; thinning of the parietal, frontal, and temporal cortices	Elevated; N/D	c.1067_1071del/ c.131A>T	p.A356V fs*45/p. Q44L	Sun et al. (2021)
P28/M	Birth/6 months	−	+	+	+	+	−	Thin corpus callosum; ventriculomegaly; white matter volume reduction; bilateral frontotemporal subarachnoid widening; sulcus deeping	3.15; n	c.995del/c.1051C>T	p.T332Mfs/p.Q351*	This study

Abbreviations: F, female; M, male; n, normal; N/D, not described; +, present; −, absent; MRI, magnetic resonance imaging.

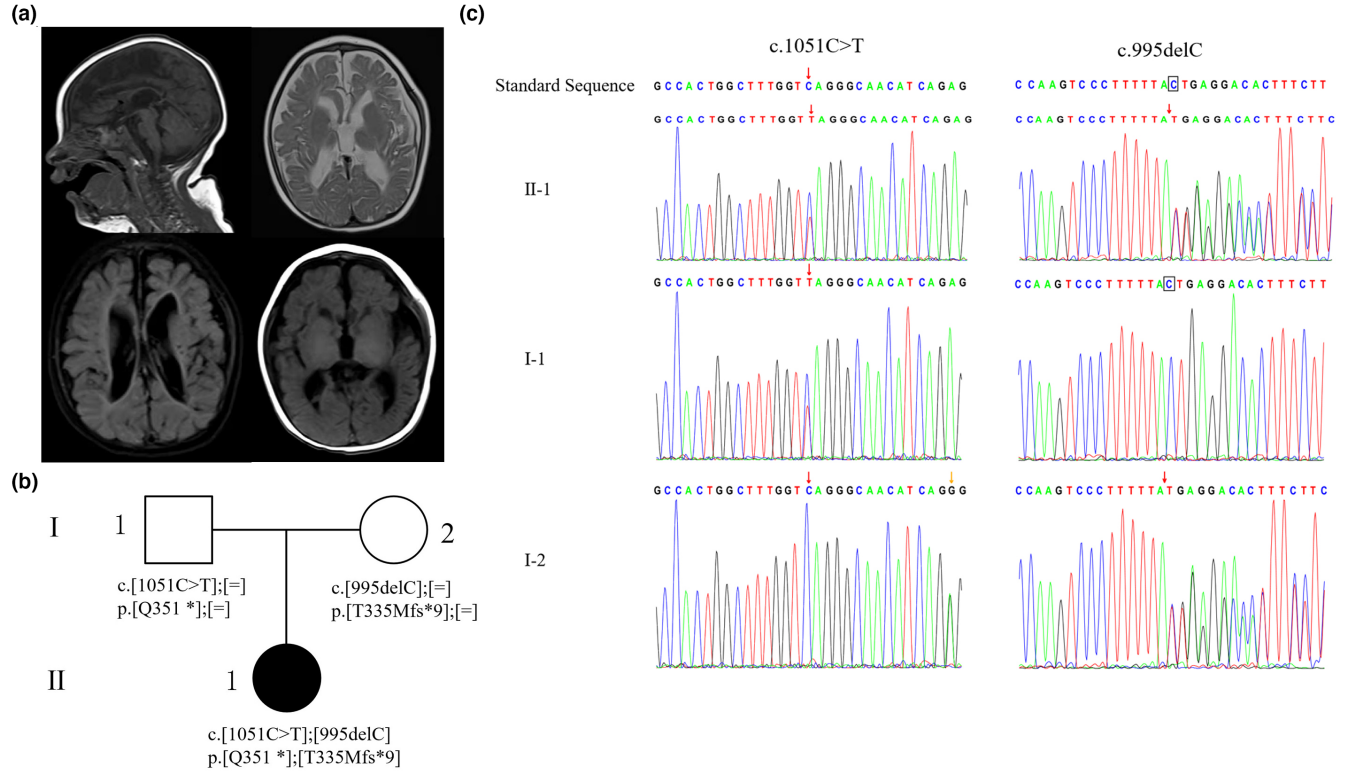

FIGURE 1 (a) Brain magnetic resonance imaging (MRI) of the patient. MRI showed thin corpus callosum, ventriculomegaly, white matter volume reduction, bilateral frontotemporal subarachnoid widening, sulcus deeping. (b) Pedigree of the family with neurodevelopmental disorders. Dark colors indicate patients with the compound heterozygous variants, c.995delC (p.T332Mfs) and c.1051C>T (p.Q351*) in *HPDL* gene (NM_032756.4). An open square or circle denotes an unaffected member who carried a single heterozygous mutation. (c) Sequencing chromatograms of *HPDL* variants.

deficient myelination, and other abnormalities. Most patients had seizures or epilepsy (21/27), and ocular disturbances were found in more than one-third of patients (19/27), which included nystagmus, cortical blindness, poor tracking, and strabismus. Ghosh et al. noticed few patients had nonspecific facial dysmorphic features. The patient, in this case, showed cognitive impairment, motor disability, epilepsy symptoms, and no facial dysmorphic features. In addition to the thin corpus callosum, ventriculomegaly, and white matter volume reduction, MRI also showed bilateral frontotemporal subarachnoid widening and sulcus deeping.

We identified novel compound heterozygous variants, c.995delC (p.T332Mfs) and c.1051C>T (p.Q351*) in the *HPDL* gene in the patient with global developmental delay, hypertonia, and limb spasticity. The c.995delC (p.T332Mfs) variant was a frameshift variant and had been reported previously (Duncan & Matthews, 2018). The variant c.1051C>T (p.Q351*) has not been reported which is predicted to lead to truncating protein. According to the ACMG guidelines, the variant c.995delC (p.T332Mfs) is classified as pathogenic (PVS1+PM2+PP5), and variant c.1051C>T (p.Q351*) is likely pathogenic.

Clinical phenotypic information on individuals with damaging *HPDL* variants may also be incomplete. The proband was initially diagnosed with cerebral palsy (CP) and developmental delay in our hospital and eventfully was diagnosed with NEDSWMA after genetic sequencing. The study provides important clinical phenotypic information for the NEDSWMA in infants and enriches our knowledge of *HPDL* mutations.

AUTHOR CONTRIBUTIONS

Yanhong Wang and Shiyue Mei designed the study, Xuan Zheng and Chao Feng undertook the molecular work, Xiaoge Fan and Lei Liu collected and analyzed the data, Yanhong Wang, Pengbo Guo, and Zhi Lei wrote the manuscript. All authors discussed the results and contributed to the final manuscript.

ACKNOWLEDGMENTS

The authors wish to thank the subjects and families for participating in the study. This work was supported by the National Natural Science Foundation of China [grant number 81701125] and the National Population Health Data Center Project (sub-project: SJPT-03-01).

CONFLICT OF INTEREST

The authors report no relevant conflicts of interests related to the manuscript.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

All subjects provided signed informed consent forms for participation in the present study. The present study was approved by the Institutional Review Board of Children's hospital affiliated with Zhengzhou University (Zhengzhou, China).

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How to cite this article: Wang, Y., Zheng, X., Feng, C., Fan, X., Liu, L., Guo, P., Lei, Z., & Mei, S. (2022). *HPDL* mutations identified by exome sequencing are associated with infant neurodevelopmental disorders. *Molecular Genetics & Genomic Medicine*, *10*, e2025. https://doi.org/10.1002/mgg3.2025