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

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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 deepening.

**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 deeping (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 proband: 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,
| Patient | Age of onset/current age | Family history | Clinical presentation | cDNA variant(s) | Protein variant(s) | Reference |
|---------|--------------------------|----------------|----------------------|----------------|--------------------|-----------|
| P1/M    | Birth/5 years            | −              | + + + + +             | c.324-343insTGC | p.A115fsX82(bom.)  | Husain et al. (2020) |
| P2/M    | 6 months/34 years        | +              | + + + + −             | c.779G>A (hom.) | p.G260E (hom.)     | Husain et al. (2020) |
| P3/M    | 6 months/11 years        | +              | + + + + +             | c.720C>T (hom.) | p.Q241* (hom.)     | Husain et al. (2020) |
| P4/M    | 1 week/22 years          | −              | + + + + +             | N/D            | N/D                | Husain et al. (2020) |
| P5/M    | 3 weeks/5 years          | +              | + + + + +             | c.503G>A (hom.) | p.L164P (hom.)     | Husain et al. (2020) |
| P6/M    | 6 weeks/5 years          | −              | + + + + +             | c.469T>C (hom.) | p.W157D (hom.)     | Husain et al. (2020) |
| P7/M    | 5 months/2 years         | +              | + + + + +             | c.233G>A (hom.) | p.A78T (hom.)      | Ghosh et al. (2021)  |
| P8/M    | Birth/13 years*          | +              | + + + + +             | c.1013T>C (hom.)| p.G319RfsX15(bom.)| Ghosh et al. (2021)  |
| P9/M    | 4 months/11 years*       | +              | + + + + +             | c.954dup (hom.)| p.L338P/p.Q257fs   | Ghosh et al. (2021)  |
| P10/M   | 6 months/8 years         | +              | + + + + +             | c.491T>C (hom.)| p.L164P (hom.)     | Ghosh et al. (2021)  |
| P11/F   | 4 months/4 years         | +              | + + + + +             | c.1013T>C (hom.)| p.G319RfsX15(bom.)| Ghosh et al. (2021)  |
| P12/M   | 8 months/11 months       | +              | + + + + +             | c.491T>C (hom.)| p.L164P (hom.)     | Ghosh et al. (2021)  |
| P13/F   | 4 months/4 years         | +              | + + + + +             | c.954dup (hom.)| p.L338P/p.Q257fs   | Ghosh et al. (2021)  |
| P14/F   | 10 months/11 months      | +              | + + + + +             | c.954dup (hom.)| p.L338P/p.Q257fs   | Ghosh et al. (2021)  |
| P15/F   | 12 months/1 months       | +              | + + + + +             | c.954dup (hom.)| p.L338P/p.Q257fs   | Ghosh et al. (2021)  |
| P17/M   | 1 year                   | −              | + + + + +             | c.954dup (hom.)| p.L338P/p.Q257fs   | Ghosh et al. (2021)  |
| P18/M   | 7 months/19 months       | +              | + + + + +             | c.954dup (hom.)| p.L338P/p.Q257fs   | Ghosh et al. (2021)  |
| Patient | Age of onset/ current age | Family History | Seizures/ epilepsy | Hypertonia | Ocular Facial | MRI | cDNA variant(s) | Protein variant(s) | Reference |
|---------|--------------------------|----------------|-------------------|-----------|---------------|-----|----------------|-------------------|-----------|
| P21/M   | 11 months/ 3 years       | −              | −                 | +         | +             | −   | N/D            | N/D               | Wiessner et al. (2021) |
| P22/M   | 6 months/ 12 months      | −              | +                 | +         | +             | +   | N/D c.788C    | p.T263M (hom.)     | Wiessner et al. (2021) |
| P23/F   | 12 months/ 11 months     | −              | +                 | +         | +             | +   | N/D c.537A    | p.L199P fs*15/ p.R72L fs*60 | Numata-Uematsu et al. (2021) |
| P24/M   | 6 months/ 12 months      | +              | +                 | +         | N/D           | N/D | N/D c.995del/c.1051C | p.T332Mfs/p.Q351* | This study |
| P25/M   | 6 months/ 12 months      | +              | +                 | +         | −             | N/D | N/D c.232G    | p.A356V fs*45/ p.Q44L | Sun et al. (2021) |
| P26/M   | Birth/ 6 months          | −              | +                 | +         | +             | −   | N/D c.995del/c.1051C | p.T332Mfs/p.Q351* | This study |

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

We identified novel compound heterozygous variants, c.995delC (p.T332Mfs) and c.1051C>T (p.Q351*) in the 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.

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 eventually 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.

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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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