INTRODUCTION

Approximately 52.9 million children were reported to have developmental delays in 2016, and 95% of that population resides in low- and middle-income countries (LMICs) (Khan & Leventhal, 2021). According to statistics from the World Health Organization (WHO), approximately 10% of the total population of children suffered disabilities (Dornelas Lde et al., 2015). Global developmental delay was a subgroup of developmental disorders which included more than two developmental disorders: gross/fine motor, speech/language, cognition, social/personal, and activities of daily living. Therefore, the clinical features of global developmental delay exhibited a heterogeneous etiologic profile (Shevell et al., 2003). Notably, Global developmental delay (GDD)
also accounted for 1% to 3% of deaths in children (Khan & Leventhal, 2021).

WDR45B and WDR45 belong to the WIPI or SVP1 family of WD40 repeat-containing proteins. They contain seven WD40 repeats that can fold into beta-propeller structures and mediate protein–protein interactions, as well as a motif in which they interact with phospholipids. Variants in WDR45 and WDR45B had been reported to drive the human neurological diseases beta-propeller protein-associated neurodegeneration (BPAN) (Haack et al., 2012; Saitsu et al., 2013) and intellectual disability (ID) (Anazi et al., 2017), respectively. Knockout (KO) mice of WDR45 and WDR45B demonstrated impaired cognitive function and pathological changes in the central nervous system (CNS) (Ji et al., 2020).

To date, variants in WDR45B are rare, and clinical features are relatively heterogeneous. Only two homozygous nonsense variants (c.799C>T (p. Q267*); c.673C>T (p. R225*)) , three splicing variants (c.619-3A>G; c.427+4A>G; c.67+1G>T), one frameshift variant (c.428-10_435del18), and two missense variants (p. R109Q; p.R225Q) of WDR45B have been identified in 11 families (Almannai et al., 2022; Najmabadi et al., 2011; Suleiman et al., 2018).

In this study, we report another new case with a novel variant and clinical features caused by WDR45B variant.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

Informed consent was obtained from the proband and her family. This study was approved by the Institutional Review Board of The Second Hospital of Hebei Medical University. Clinical features, brain magnetic resonance imaging (MRI), malformations, and other examination results were collected.

2.2 | WES and Sanger sequencing

Genomic DNA was extracted from the whole blood sample. The IDT XGen Exome Research Panel was used to capture libraries, and then, the library was sequenced on the NovaSeq 6000 Sequencing platform. Finally, the paired-end clean reads were compared to the human reference genome (GRCh38/hg38). Variations were annotated through ANNOVAR (Wang et al., 2010), and SNPs with a minor allele frequency of <0.01 in the SNP database were obtained for further analysis. Pathogenic evaluation was performed according to the ACMG (American College of Medical Genetics and Genomics) guidelines (Richards et al., 2015). Sanger sequencing of candidate variants was performed on samples from the proband and her parents to validate the variation identified by WES.

2.3 | Protein 3D structure

DUTE (http://biosig.unimelb.edu.au/duet/stability_prediction) was utilized to predict the stability of mutant proteins. Molecular modeling analysis was performed to show the variations in protein structure. The human WDR45B model was downloaded in the AlphaFold dataset (doi:10.1038/s41586-021-03819-2), and Missense3D software was utilized to simulate mutant structure. UCSF Chimera software was used for 3D protein structure visualization and analysis.

3 | RESULTS

3.1 | Case presentation

An 8-year-old girl was admitted to the hospital due to vomiting, weakness, and poor spirit. She was born at full term, could sit alone at 8 months, crawl at 15 months, walk at 20 months, and only speak overlapping words at two years old; these features suggested global developmental delay. During hospitalization, she could not communicate and walk alone and exhibited spastic quadriplegia, joint contractures, nystagmus, intermittent strabismus, no autonomic movement of limbs, and hypotonia.

Video EEG revealed extensive β-rhythm at 15–20 Hz during the waking and sleeping stages. Cranial MRI showed multiple abnormal signals in the left frontal–parietal lobe and bilateral paraventricular white matter (Figure 1a).

She was firstly treated with ganciclovir (150 mg twice per day) for antiviral, aceglutamide (200 mg/day) for nerve nutrition, and intravenous immunoglobulin (10 g/day). Then, she was treated with mitochondrial treatment cocktail: Vitamin B1 tablets (30 mg tid); Coenzyme Q10 (100 mg tid); Idebenone (30 mg tid); Vitamin E (100 mg qod); Vitamin B2 (25 mg tid); levocarnitine (1 g tid). After that, the vomiting, spirit, and weakness improved, and she was discharged 28 days later.

Two months later, the child still exhibited hypotonia and could not sit or stand alone. The nystagmus was improved. Brain MRI showed a reduced range of multiple...
FIGURE 1  Clinical and genetic features of the proband. (a) Characteristic change of the proband MRI. MRI images showed patchy abnormal signals in the left frontal–parietal lobe and bilateral paraventricles, and high-density signals in T2 and FLAIR. MRI: magnetic resonance imaging. (b) Pedigree chart and genotype information of the proband. +, wild-type; Black arrow, proband. (c) Genotype validated by Sanger sequencing. Homozygous variants were inherited from the father and mother. −, variant type; +, wild type. (d) Evolutionary conservation analysis of the 226th amino acid residue. Red highlighted amino acid residue: the wild-type amino acid residue among multiple species. Blue highlighted amino acid residue: the variant amino acid residue. (e) Variants reported summary. Red square: Reported truncated variants. Red circle: Reported missense variants. Yellow circle: Variants discovered in our case. WD1 ~7: WD repeats 1–7.
abnormal signals in the left frontal–parietal lobe and bilateral paraventricular lobe.

3.2 Whole-exome sequencing, data interpretation, and literature review

To further identify the cause of disease, whole-exome sequencing (WES) was performed. A homozygous variant in \textit{WDR45B} [NM_019613.4: c.677G>C (p. Arg226Thr)] was found in our patient (Figure 1b). It was a nonsynonymous variant that resulted in an amino acid change from arginine to threonine at the 226th residue of \textit{WDR45B}. The variant was absent in published databases such as gnomAD and Exome Aggregation Consortium (ExAC). The variant was predicted to be damaging to proteins (SIFT: Damaging, Polyphen2_HDIV: Damaging, Mutation Taster: Disease-causing) and classified as VUS according to ACMG guidelines. The homozygous variant was confirmed by Sanger sequencing (Figure 1c). Further conservation analysis among multiple species showed that the amino acid was highly conserved (Figure 1d). We reviewed all reported variants of \textit{WDR45B} and found all variants (including our case) located within the repeat WD domains (Figure 1e).

3.3 3D protein structure changing

Protein structural analysis was performed to further explore the effect of variant on protein function. DUET software predicted that the variant R226T destabilizes protein structure with $-2.059 \text{ Kcal/mol}$. R226T variant obviously changed the hydrogen bond connection of the 226th amino acid. The hydrogen bond between the 226th amino acid and the original 207, 229th amino acid is broken, and the hydrogen bond is formed with the 208th amino acid (Figure 2). These changes of the structure may tend to be protein unstable.

4 DISCUSSION

WD40 repeat was defined as around 40 amino acids which terminated in a tryptophan–aspartic acid (W-D) dipeptide. WD40 repeat proteins contained four or more WD40 repeat units, which were crucial for forming the circular solenoid domain (WD40 domain) (Smith, 2008). Previously, studies demonstrated WD40 repeat proteins involved in a variety of functions from signal transduction and transcription regulation to cell cycle control, autophagy, and apoptosis (Stirnimann et al., 2010). Notably, some WD40 repeat proteins were reported to be associated with rare disorders, for example, \textit{WDR45} with psychomotor development delay (Saitsu et al., 2013), \textit{WDR35} with cranioectodermal dysplasia (Gilissen et al., 2010), and \textit{WDR56} with short-rib thoracic dysplasia (Cavalcanti et al., 2011), etc. (Li & Roberts, 2001).

As \textit{WDR45} and \textit{WDR45B} were also reported associated with development delay, for example, J Suleiman et al. described a homozygous pathogenic variant (c.673C>T, p.R225*) in two families. The probands exhibited profound development delay, early-onset refractory epilepsy, progressive spastic quadriplegia, contractures, and brain malformations (Suleiman et al., 2018); Najmabadi et al. reported a homozygous missense variant (R109Q) from three members of a closely related family with intellectual disability and microcephaly (Najmabadi et al., 2011); Almannai et al. presented 12 individuals from seven unrelated families with microcephaly, global developmental delay, seizures, and spastic quadriplegia (Almannai et al., 2022). These studies demonstrated the role of \textit{WDR45B} in neurodevelopmental diseases.

We reviewed all published cases of \textit{WDR45B} and summarized the clinical features, physical examinations, genetic variants (Table 1), and brain MRI results (Table 2). Compared with the other reported cases, our case showed specific features including multiple abnormal signals around the bilateral paraventricular white matter. No
| Family | No. | Age         | Gender | Developmental delay (19/20) | Spastic quadriplegia (15/20) | Epilepsy (17/20) | variants                      | Variant type | Reference        |
|--------|-----|-------------|--------|-----------------------------|-------------------------------|------------------|--------------------------------|--------------|------------------|
| Family 1 | 1   | 16 years    | Female | +                           | +                             | +                | c.799C>T, p.Q267*               | Homozygous   | PMID: 28,503,735 |
|        | 2   | 8 years     | Male   | +                           | +                             | +                |                                |              |                  |
|        | 3   | 9 months    | Female | +                           | +                             |                  |                                |              |                  |
| Family 2 | 4   | 20 years    | Male   | +                           | +                             | +                | c.673C>T, p.R225*               | Homozygous   |                  |
|        | 5   | 14 years    | Female | +                           | +                             | +                |                                |              |                  |
| Family 3 | 6   | 8 years     | Female | +                           | +                             |                  |                                |              |                  |
| Family 4 | 7   | NA          | NA     | NA                          | NA                            | NA               | Homozygous                     | PMID: 21937992 |                  |
| Family 5 | 8   | 4 years     | Female | +                           | −                             | +                | c.674G>A, p.R225Q              | Homozygous   | PMID: 35322404  |
|        | 9   | 14 years    | Male   | +                           | −                             | −                |                                |              |                  |
| Family 6 | 10  | 21 months   | Male   | +                           | +                             | +                | c.619-3A>G                     | Homozygous   |                  |
| Family 7 | 11  | 6 years     | Male   | +                           | +                             | +                | c.619-3A>G                     | Homozygous   |                  |
|        | 12  | 22 months   | Male   | +                           | +                             |                  |                                |              |                  |
| Family 8 | 13  | 7 months    | Male   | +                           | +                             | +                | c.673C>T, p.R225*              | Homozygous   |                  |
| Family 9 | 14  | 8 years     | Female | +                           | +                             | +                | c.427+4A>G                     | Homozygous   |                  |
|        | 15  | 10 years    | Female | +                           | +                             |                  |                                |              |                  |
|        | 16  | 11 years    | Male   | +                           | +                             |                  |                                |              |                  |
| Family 10 | 17 | 15 years    | Female | +                           | +                             |                  | c.67+1G>T                     | Homozygous   |                  |
|        | 18  | 3 years     | Male   | +                           | +                             |                  |                                |              |                  |
| Family 11 | 19 | 3 years     | Female | +                           | NA                            | +                | c.677C>T, p.R226T              | Homozygous   |                  |
| Our case | 20  | 8 years     | Female | +                           | −                             | +                | c.677C>T, p.R226T              | Homozygous   | Our case        |
| Family | No. | Age   | Gender | Microcephaly (15/20) | Ventriculomegaly (14/20) | Reduced cerebral white matter volume with thin corpus callosum (14/20) | Thinning of cerebral gray matter (15/20) | Reference |
|--------|-----|-------|--------|----------------------|--------------------------|------------------------------------------------------------------------|------------------------------------------|-----------|
| Family 1 | 1   | 16 years | Female | −                    | +                       | +                                                                      | +                                         | PMID:28503735 |
|        | 2   | 8 years  | Male   | −                    | +                       | +                                                                      | +                                         |           |
|        | 3   | 9 months | female | −                    | +                       | +                                                                      | +                                         |           |
| Family 2 | 4   | 20 years | Male   | +                    | NA                      | NA                                                                    | NA                                        |           |
|        | 5   | 14 years | Female | +                    | +                       | +                                                                      | +                                         |           |
| Family 3 | 6   | 8 years  | Female | +                    | +                       | +                                                                      | +                                         |           |
| Family 4 | 7   | NA     | NA     | NA                   | NA                      | NA                                                                    | NA                                        | PMID: 21937992 |
| Family 5 | 8   | 4 years  | Female | +                    | +                       | +                                                                      | +                                         | PMID: 35322404 |
|        | 9   | 14 years | Male   | +                    | −                       | −                                                                      | −                                         |           |
| Family 6 | 10  | 21 months | Male   | +                    | NA                      | NA                                                                    | NA                                        |           |
| Family 7 | 11  | 6 years  | Male   | +                    | +                       | +                                                                      | +                                         |           |
|        | 12  | 22 months | Male   | +                    | +                       | +                                                                      | +                                         |           |
| Family 8 | 13  | 7 months | Male   | +                    | +                       | +                                                                      | +                                         |           |
| Family 9 | 14  | 8 years  | Female | +                    | +                       | +                                                                      | +                                         |           |
|        | 15  | 10 years | Female | +                    | +                       | +                                                                      | +                                         |           |
|        | 16  | 11 years | Male   | +                    | +                       | +                                                                      | +                                         |           |
| Family 10 | 17  | 15 years | Female | +                    | NA                      | NA                                                                    | NA                                        |           |
|        | 18  | 3 years  | Male   | +                    | +                       | +                                                                      | +                                         |           |
| Family 11 | 19  | 3 years  | Female | +                    | +                       | +                                                                      | +                                         |           |
| Our case | 20  | 8 years  | Female | −                    | −                       | −                                                                      | −                                         | Our case  |
spastic quadriplegia, microcephaly, ventriculomegaly, reduced cerebral white matter volume in the corpus callosum, or thinning of cerebral gray matter was observed in our case.

**AUTHOR CONTRIBUTIONS**
Jinhong Zhang: Conceptualization, Methodology, Data mining; Yan Lu, Xiaoyu Tian: Clinical data collection; Xinyi Men, Yange Zhang, Huifang Yan: Writing- Original draft preparation; Zuozen Yang, Fan Yang: Software, Data interpretation; Xiuxia Wang: Supervision, Writing- Reviewing and Editing.

**ACKNOWLEDGMENT**
We thank the proband and her family for their kind cooperation. We also thank the family for allowing these data to be submitted to the public database [ClinVar: SUB11631086].

**FUNDING INFORMATION**
This work was supported by the Medical Science Research Project Plan of Hebei Province (No. 2019078).

**CONFLICT OF INTEREST**
All authors declare no conflicts of interest.

**ETHICS STATEMENT**
All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional review board of The Second Hospital of Hebei Medical University. Informed consent was obtained from the proband and her family.

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**REFERENCES**
Almannai, M., Marafi, D., Abdel-Salam, G. M. H., Zaki, M. S., Duan, R., Calame, D., Herman, I., Levesque, F., Elbendary, H. M., Hegazy, I., Chung, W. K., Kavus, H., Saeidi, K., Maroofian, R., AlHashim, A., Al-Otaib, A., Al Madhi, A., Abou al-Seood, H. M., Alasmari, A., … El-Hattab, A. W. (2022). El-Hattab-Alkuraya syndrome caused by biallelic WDR45B pathogenic variants: Further delineation of the phenotype and genotype. Clinical Genetics, 101(5–6), 530–540.

Anazi, S., Maddirevula, S., Faqieh, E., Alsedairi, H., Alzahrani, F., Shamseldin, H. E., Patel, N., Hashem, M., Ibrahim, N., Abdulwahab, F., Ewida, N., Alsaih, H. S., Al sharif, H., Alamoudi, W., Kentab, A., Bashiri, F. A., Alnaser, M., AlWedel, A. H., Alfadhel, M., … Alkuraya, F. S. (2017). Clinical genomics expands the morbid genome of intellectual disability and offers a high diagnostic yield. Molecular Psychiatry, 22(4), 615–624.

Cavalcanti, D. P., Huber, C., Le Quan Sang, K. H., Bautjat, G., Collins, F., Delezoide, A. L., Dagoneau, N., Le Merrer, M., Martinovic, J., Mello, M. F. S., Vekemans, M., Munnich, A., & Cormier-Daire, V. (2011). Mutation in IFT80 in a fetus with the phenotype of Verma-Naumoff provides molecular evidence for Jeune-Verma-Naumoff dysplasia spectrum. Journal of Medical Genetics, 48(2), 88–92.

Dornelas Lde, F., Duarte, N. M., & Magalhaes Lde, C. (2015). Neuropsychomotor developmental delay: conceptual map, term definitions, uses and limitations. Revista Paulista de Pediatria, 33(1), 88–103.

Gilissen, C., Arts, H. H., Hoischen, A., Spruijt, L., Mans, D. A., Arts, P., vanLier, B., Steehouwer, M., vanReeuwijk, J., Kant, S. G., Roepman, R., Knoers, N. V. A. M., Veltman, J. A., & Brunner, H. G. (2010). Exome sequencing identifies WDR35 variants involved in Sensenbrenner syndrome. American Journal of Human Genetics, 87(3), 418–423.

Haack, T. B., Hogarth, P., Kruer, M. C., Gregory, A., Wieland, T., Schwarzmayr, T., Graf, E., Sanford, L., Meyer, E., Kara, E., Cuno, S. M., Harik, S. I., Dandu, V. H., Nardocci, N., Zorzi, G., Dunaway, T., Tarnopolsky, M., Skinner, S., Frucht, S., … Hayflick, S. J. (2012). Exome sequencing reveals de novo WDR45 mutations causing a phenotypically distinct, X-linked dominant form of NBIA. American Journal of Human Genetics, 91(6), 1144–1149.

Ji, C., Zhao, H., Li, D., Sun, H., Hao, J., Chen, R., Wang, X., Zhang, H., & Zhao, Y. G. (2020). Role of Wdr45b in maintaining neural autophagy and cognitive function. Autophagy, 16(4), 615–625.

Khan, I., & Leventhal, B. L. (2021). Developmental delay. StatPearls. Li, D., & Roberts, R.(2001). WD-repeat proteins: Structure characteristics, biological function, and their involvement in human diseases. Cellular and Molecular Life Sciences, 58(14), 2085–2097.

Najmabadi, H., Hu, H., Garshasbi, M., Zemojtel, T., Abedini, S. S., Chen, W., Hosseini, M., Behjati, F., Haas, S., Jamali, P., Zecha, A., Mohseni, M., Püttrmann, L., Vahid, L. N., Jensen, C., Moheb, L. A., Bieneck, M., Larti, F., Mueller, I., … Ropers, H. H. (2011). Deep sequencing reveals 50 novel genes for recessive cognitive disorders. Nature, 478(7367), 57–63.

Richards, S., Aziz, N., Bale, S., Bick, D., das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., Rehm, H. L., & ACMG Laboratory Quality Assurance Committee. (2015). Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine, 17(5), 405–424.

Saitsu, H., Nishimura, T., Muramatsu, K., Kodera, H., Kumada, S., Sugai, K., Kasai-Yoshida, E., Sawaura, N., Nishida, H., Hoshino, A., Ryujin, F., Yoshioka, S., Nishiyama, K., Kondo, Y., Tsurusaki, Y., Nakashima, M., Miyake, N., Arakawa, H., Kato, M., … Matsumoto, N. (2013). De novo mutations in the autophagy gene WDR45 cause static encephalopathy of childhood with neurodegeneration in adulthood. Nature Genetics, 45(4), 445–449.

Shevell, M., Ashwal, S., Donley, D., Flint, J., Gingold, M., Hirtz, D., Majnemer, A., Noetzel, M., Sheth, R. D., & Quality Standards Subcommittee of the American Academy of Neurology & Practice Committee of the Child Neurology Society. (2003). Practice
parameter: Evaluation of the child with global developmental delay: Report of the Quality Standards Subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society. Neurology, 60(3), 367–380.
Smith, T. F. (2008). Diversity of WD-repeat proteins. Sub-Cellular Biochemistry, 48, 20–30.
Stirnimann, C. U., Petsalaki, E., Russell, R. B., & Müller, C. W. (2010). WD40 proteins propel cellular networks. Trends in Biochemical Sciences, 35(10), 565–574.
Suleiman, J., Allingham-Hawkins, D., Hashem, M., Shamseldin, H. E., Alkuraya, F. S., & el-Hattab, A. W. (2018). WDR45B-related intellectual disability, spastic quadriplegia, epilepsy, and cerebral hypoplasia: A consistent neurodevelopmental syndrome. Clinical Genetics, 93(2), 360–364.
Wang, K., Li, M., & Hakonarson, H. (2010). ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. Nucleic Acids Research, 38(16), e164.

How to cite this article: Zhang, J., Lu, Y., Tian, X., Men, X., Zhang, Y., Yan, H., Yang, F., Yang, Z., & Wang, X. (2022). A homozygous variant of WDR45B results in global developmental delay: Additional case and literature review. Molecular Genetics & Genomic Medicine, 10, e2036. https://doi.org/10.1002/mgg3.2036