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ORIGINAL ARTICLE

De novo variants in *WDR45* underlie beta-propeller protein-associated neurodegeneration in five independent families

Xiaojun Tang[1] | **Xiaoping Lan**[1] | **Xiaozhen Song**[1] | **Wuhen Xu**[1] | **Yuanfeng Zhang**[2] | **Hong Zhang**[3] | **Shengnan Wu**[1]

[1]Molecular Diagnostic Laboratory, Shanghai Children's Hospital, Shanghai Jiaotong University, Shanghai, China

[2]Department of Neurology, Shanghai Children's Hospital, Shanghai Jiaotong University, Shanghai, China

[3]Department of Clinical Laboratory, Shanghai Children's Hospital, Shanghai Jiaotong University, Shanghai, China

Correspondence

Yuanfeng Zhang, Department of Neurology, Shanghai Children's Hospital, Shanghai Jiaotong University, 355, Luding Road, Shanghai 200062, China.
Email: zhangyf1@shchildren.com.cn

Hong Zhang, Department of Clinical Laboratory, Shanghai Children's Hospital, Shanghai Jiaotong University, 355, Luding Road, Shanghai 200062, China.
Email: zhangh@shchildren.com.cn

Shengnan Wu, Molecular Diagnostic Laboratory, Shanghai Children's Hospital, Shanghai Jiaotong University, 355, Luding Road, Shanghai 200062, China.
Email: wushengnan@shchildren.com.cn

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Abstract

Background: Beta-propeller protein-associated neurodegeneration (BPAN) is a rare, X-linked dominant neurodegenerative disease mainly characterized by developmental delay, intellectual disability, epilepsy in childhood and dystonia, parkinsonism, dementia in adulthood. BPAN is caused by variants in *WD repeat domain 45(WDR45)*, which is characterized by iron accumulation in the basal ganglia, however, it may be atypical in early brain MRI.

Methods: Whole exome sequencing was performed for five parents-offspring trios and phenotype-driven data analyses were conducted. All candidate variants were confirmed by Sanger sequencing.

Results: Here, we report five independent children presented variable degree of developmental delay, intellectual disability, and/or epilepsy. Five de novo variants of *WDR45* including four novel truncating variants (one splicing variant, two nonsense variants, and one frameshift variant) were identified. Although their early brain MRI showed no obvious iron accumulation, multifocal spikes, or polyspikes in electroencephalograms (EEG) were observed in four patients.

Conclusion: Our study reports four patients with new variants in *WDR45*, which expands the mutation spectrum of *WDR45*. In addition, our findings provide an early and precise diagnosis basis of BPAN, which is helpful for accurate genetic counseling and prenatal diagnosis.

KEYWORDS

beta-propeller protein-associated neurodegeneration, exome sequencing, variants, *WDR45*

1 | INTRODUCTION

Neurodegeneration with brain iron accumulation (NBIA) is a heterogeneous group of progressive neurological disease characterized by cognitive disability, dystonia, and/or parkinsonism. NBIA5, also known as BPAN, constituted 7% of NBIA caused by variants of *WDR45* (OMIM: 300526). BPAN is mainly characterized by a biphasic clinical progression of global developmental delay, intellectual disability, epilepsy in childhood and dystonia, parkinsonism, and dementia in adulthood (Haack et al., 2012a). Brain magnetic resonance image (MRI) shows low signal on T2 in the globus pallidus and substantia nigra, indicating iron deposition. However, the early brain MRI may be atypical which is especially conspicuous in older individuals, making it difficult to the early diagnosis of BPAN only by MRI (Hayflick et al., 2013).

To our knowledge, BPAN is an X-linked dominant neurodegenerative disease and most reported patients were female. The clinical course of males is more serious or it usually appears in a somatic mosaic manner, indicating that variants in *WDR45* are either fatal or more severe in hemizygous males (Haack et al., 2012a; Zarate et al., 2016). However, since girls with severe phenotypes have also been described, it is suggested that skewing of X-inactivation toward the variants may account for this phenotypic variability (Willoughby et al., 2018).

In recent years, whole exome sequencing has developed rapidly and it has demonstrated its potential clinical application in identifying the pathogenesis of hereditary diseases. Owing to patients' complex and varied manifestations, achieving an accurate diagnosis is difficult. Therefore, molecular genetic analysis is becoming an effective and necessary tool in the diagnosis of neurodegenerative diseases together with clinical assessment and imaging examination such as MRI.

In this study, five de novo truncating variants in *WDR45* were detected in five unrelated patients, with four of them being novel and one being previously reported. Among them, four new variants comprised a new splicing variant, two novel nonsense variants, and a new frameshift variant. Another variant of c.830+1G>A resulting in a splicing defect has been reported in patients with BPAN before. Our results expand the mutation spectrum of *WDR45* and the phenotypic characteristics of this X-linked dominant neurodegenerative disease. In addition, early diagnosis by trio exome sequencing may prevent the disease from getting worse and it can provide appropriate symptomatic treatment which is beneficial for patients and their families. Furthermore, more case reports were needed to help to elucidate the function of WDR45 which may be important for understanding the genetic etiology, and then, exploring the treatment of this rare and severe heterogeneity disease.

TABLE 1 Genotypes and clinical features of five patients with *WDR45* variants.

Patient ID	1	2	3	4	5
Age	3 years	5 years	16 months	3 years	3 years
Disease-onset age	6 months	1.5 years	8 months	1 year	11 months
Family history	None	None	None	None	None
Sex	Female	Male	Female	Female	Female
Major complain	Febrile seizures at 6 months	Febrile seizures at 1.5 years	Developmental delay at 8 months	Febrile seizuresat 1 years	Seizures at 11 months and developmental delay at 3 years
Variant in	c.976+1G>C	c.830+1G>A	c.10C>T	c.806del	c.726C>G
WDR45	(p.?)	(p.?)	(p.Gln4*)	(p.Asp269Valfs*19)	(p.Tyr242*)
Inheritance	De novo	De novo	De novo	De novo	De novo
Epilepsy	Yes	Yes	No	Yes	Yes
Speech delay	Yes	No	Yes	Yes	Yes
Movement abnormality	Yes	Yes	Yes	No	Yes

1.1 | Clinical description

This study has been approved by the patient's parents and the Ethical Committee of Children's Hospital of Shanghai. Generally, all patients presented variable degree of developmental delay with speech delay and/or motor delay. Clinical features of the five patients are summarized in Table 1.

Patient 1 is a 3-year-old girl born to non-consanguineous and healthy parents via uncomplicated vaginal delivery. At 6 months of age, she first developed a febrile seizure with eye-rolling, cyanotic lips, consciousness lapses, weakness in the limbs, and it attacked five–six times during 1 year. At the age of 3 years, her electroencephalogram (EEG) demonstrated 3–4 Hz spike- and slow-wave bursts on brain especially in sleep (Figure 1a). However, no obvious abnormality was found in the early brain MRI and CT. Subsequently, significant delayed development, poor speech, and gait disturbance were noted. After taken to hospital, she was treated with sodium valproate at 15 months, and then, switched to levetiracetam with oxcarbazepine due to side effects. At present, epileptic has not been well controlled yet and it happened occasionally.

Patient 2 is a 5-year-old boy who was born at full term by cesarean section to healthy non-consanguineous parents. He was first noted to have a febrile seizure with eye-rolling, cyanotic lips, consciousness lapses at 18 months old, and it attacked seven–eight times in 3 years. At the meantime, mild motor delay was occurred. After consultation, he was treated with sodium valproate since July, 2018, but stopped after 2 months by his parents without doctor's permission. After the drug was discontinued, seizure was still occurred sporadically. At the age of 5 years, EEG demonstrated focal spike or polyspike and slow-wave burst on brain in sleep (Figure 1b).

Patient 3 is a 16-month-old girl born to healthy non-consanguineous parents after an uneventful pregnancy. Growth parameters such as height, weight, and head circumference at birth were normal. She was first noted to present signs of motor developmental delay at 8 months. She did not walk independently and had no oral language at 16 months old. Brain MRI revealed bilateral lateral ventricle broadening, while EEG showed no obvious abnormality.

Patient 4 is a 3-year-old girl who was born at term after an uneventful pregnancy to healthy non-consanguineous parents. The first febrile seizure occurred at 1-year old presenting with eye-rolling, cyanotic lips, no response, upper limb jitter, and it attacked five times during the last and a half year. At the meantime, she had poor language and the brain MRI showed slightly less white matter. At the age of 3 years, her EEG demonstrated 3–4 Hz spike- and slow-wave bursts on brain in sleep and more than 10 episodes of absence were observed during the waking period (Figure 1c).

Patient 5 is a 3-year-old girl with profound developmental delay who was delivered with a history of asphyxiation and her parents were healthy and non-consanguineous. Her first seizure was observed at 11 months. She was able to walk but

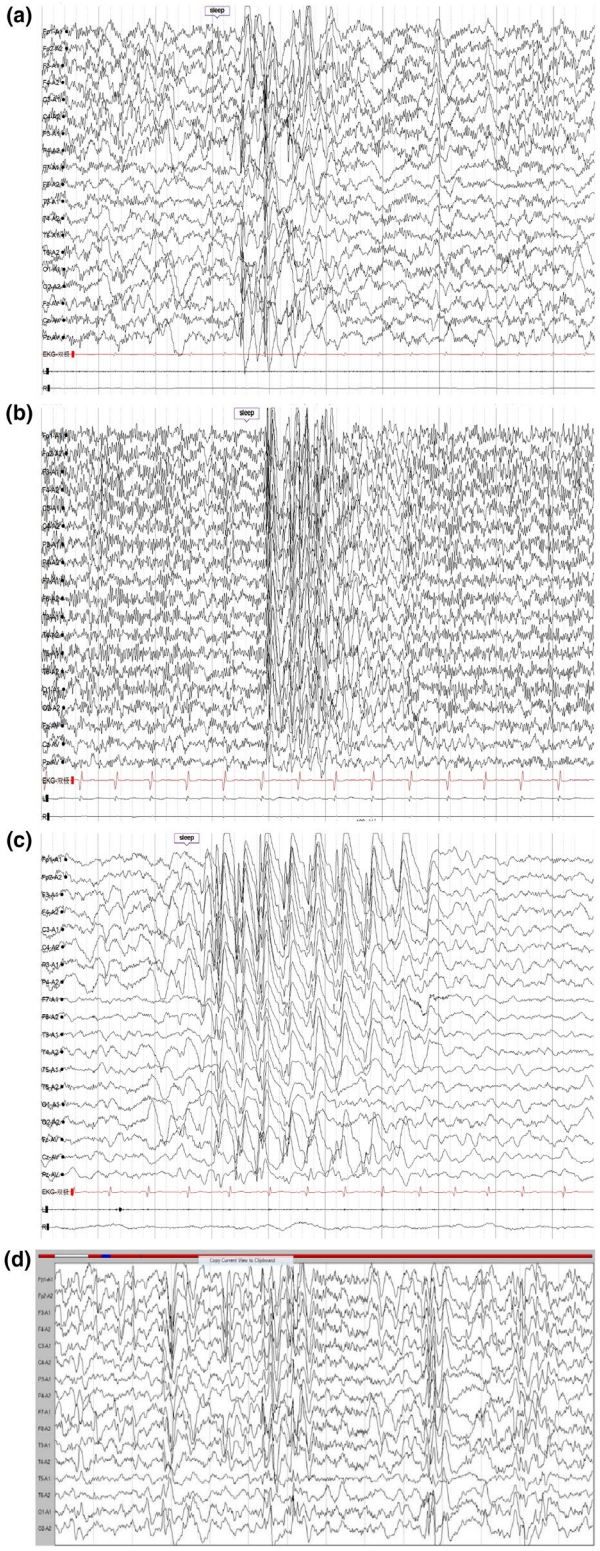

FIGURE 1 Electroencephalogram (EEG) in four patients. EEG at the age of 3 years in patient 1 (a), age of 5 years in patient 2 (b), age of 3 years in patient 4 (c), and age of 3 years in patient 5 (d). Multifocal spikes or polyspikes were observed in the four patients.

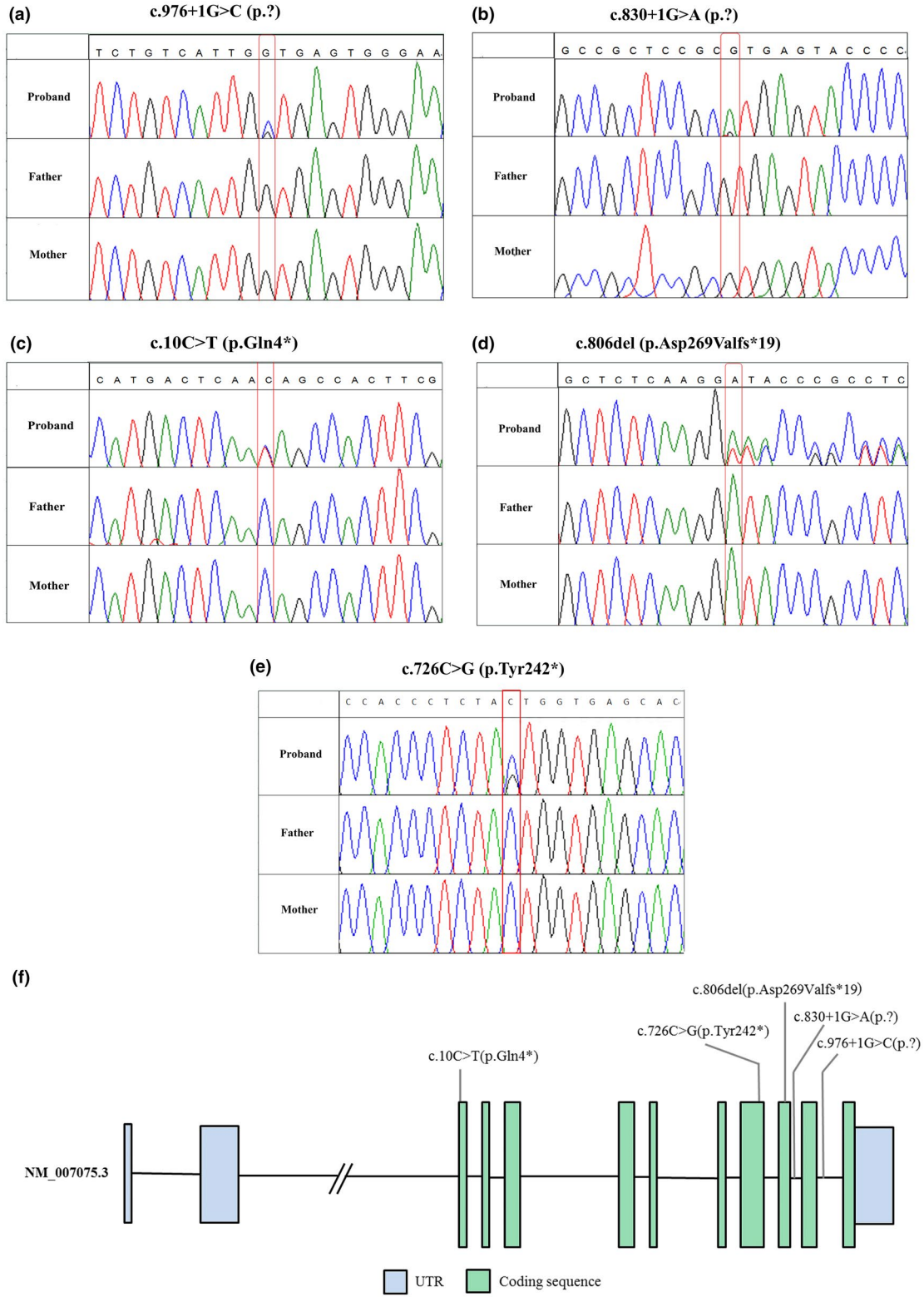

FIGURE 2 Diagram of *WDR45* gene variants. (a-e) The de novo variants of *WDR45* identified in five independent patients with intellectual disability, delayed development, and/or epilepsy. (f) Summary of *WDR45* variants identified in our study.

no speech was developed at 2-year old. At the age of 3 years, brain MRI showed abnormal white matter myelination and EEG demonstrated 3–5 Hz polyspike and slow-wave burst on brain (Figure 1d).

1.2 | Genetic analysis

Genomic DNA for WES and Sanger sequencing from patients and their parents was isolated from whole blood collected

with kit (QIAGEN, Germany) following the manufacturer's instruction. Whole exome sequencing was performed for five parents-offspring trios and data analysis were conducted as described elsewhere (Feng et al., 2020) with evaluating single nucleotide variants, small insertion/deletions, and copy number variations. Sanger sequencing was performed to confirm all candidate variants from WES (*WDR45* for NM_007075.3). The primers used to amplify the variant sequence were *WDR45*-E11-F(5′ ACTGACCCTGCCACCCTCTAC 3′) and *WDR45*-E11-R(5′ TTGTGGAAGGTCCCATCTACG 3′), *WDR45*-E3-F(5′ TACAGGCATAAGCCACCACGC 3′) and *WDR45*-E3-R(5′ TACAGGCATAAGCCACCACGC 3′), *WDR45*-E10-F(5′ ACTGACCCTGCCACCCTCTAC 3′) and *WDR45*-E10-R(5′ GGCTGTTCCCACTCACCAAT 3′), *WDR45*-E6-9-F(5′ GTTGAAGTCTGGTCCTCATCC 3′) and WDR45-E6-9-R(5′ CAGTGCTGTCCCCCTTACTG 3′). The clinical significance of variants was interpreted according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) recommendations (Richards et al., 2015). Alamut Visual was used to predict the pathogenicity of variants and the protein region function and structure were obtained from UniProt and SWISS-MODEL, respectively.

2 | RESULTS

Written informed consent for using the clinical information and genetic findings were obtained from the patients' parents. The coverage of targeted regions with depths greater than 50× reads is more than 91%. In this study, five different de novo variants of *WDR45* including four novel variants were discovered by trio-based whole exome analysis. Sanger sequencing confirmed that these variants were heterozygous in the patients and were absent in their unaffected parents (Figure 2).

Whole exome sequencing identified a total of five distinct truncating variants in *WDR45* gene, including four novel variants (c.976+1G>C, c.10C>T, c.806del, and c.726C>G) and one recurrent variant (c.830+1G>A). Trio-based analysis revealed all variants occurred de novo with confirmation by Sanger sequencing. The five *WDR45* variants detected in our cohort, comprising one frameshift variant, two nonsense variants, and two canonical splicing variants, are absent from the gnomAD database (http://gnomad-old.broadinstitute.org/).

Two canonical variants, c.976+1G>C adjacent to exon 11 and c.830+1G>A adjacent to exon 10, were detected in patient 1 (Figure 1a) and patient 2 (Figure 1b), respectively. Both variants were predicted to disrupt the canonical splicing donor site and result in potential exons skipping. These variants are expected to result in altered function of *WDR45* gene product. A different nucleotide change at the same position of c.976+1G>A has been previously reported in patients of BPAN with severe intellectual disability and developmental delay, strengthening the pathogenicity of c.976+1G>C variant. Notably, another canonical splicing variant c.830+1G>A, previously reported in multiple patients with BPAN, was detected in a mosaic manner with an allele fraction of 53% at 100x coverage in the patient 2. Sanger sequencing confirmed this finding.

Two nonsense variants, c.10C>T and c.726C>G were detected in patient 3 (Figure 1c) and patient 5 (Figure 1e), respectively. Besides, another frameshift variant, c.806del, was detected in patient 4 (Figure 1d). These three variants were predicted to introduce a premature stop codon and were expected to result in the loss of function of the protein of the *WDR45* gene. Although these variants have not been reported before, some software predicted these variants were deleterious and they were classified into pathogenic according to the guideline of ACMG.

3 | DISCUSSION

Beta-propeller protein-associated neurodegeneration (BPAN) is a form of neurodegeneration with brain iron accumulation caused by variant of *WDR45* with highly clinical and genetic heterogeneity (Haack et al., 2012b). It is mainly divided into two periods. The first stage is characterized by global delayed development, intellectual disability, and/or epilepsy in childhood which remains stable until early adulthood. In the second stage, dyskinesia such as progressive dystonia, parkinsonism, and dementia were occurred in adulthood (Haack, Hogarth, Gregory, Prokisch, & Hayflick, 2013; Haack et al., 2012a; Hayflick et al., 2013). In the early stage, clinical phenotypes may be nonspecific and whole exome sequencing will enable early detection of BPAN in children so that patients can be diagnosed before getting worse (Gregory, Kurian, Haack, Hayflick, & Hogarth, 1993).

As BPAN is an X-linked dominant disease, the majority of diagnosed patients were female and most of male patients were chimera, suggesting that lethality might be saved by the mosaicism (Haack et al., 2012a; Willoughby et al., 2018; Zarate et al., 2016). As patient 2 in a mosaic manner reported in this study showed milder phenotypes. His main symptom was febrile seizure lasting for a few seconds, after tic, he was in good condition. Besides, brain MRI in early childhood is always reported normal (Hayflick et al., 2013) and it becomes obvious in adulthood with hyperintense signal in T1 in substantia nigra when nervous system worsens (Kruer et al., 2012; Willoughby et al., 2018).

WDR45 (WIPI4) is an important member of the WD repeat protein interacting with phosphoinositides (WIPI) family taking part in many vital biological processes such as cell cycle, signal transduction, gene regulation, apoptosis together

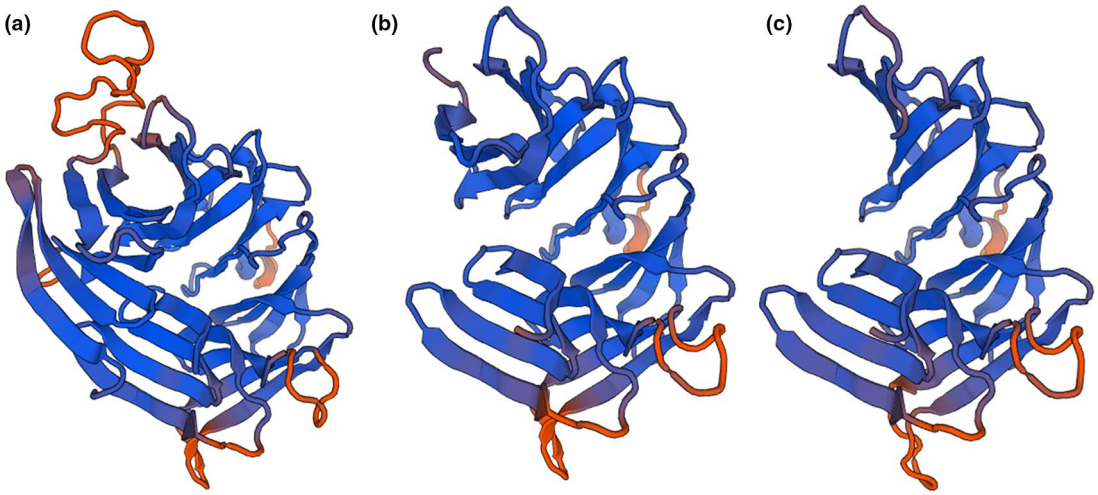

FIGURE 3 The three-dimensional structure of WDR45. (a) 3D-structure of the wild-type WDR45; (b) 3D-structure of the variant of c.806del (p.Asp269Valfs*19). (c) 3D-structure of the variant of c.726C>G (p.Tyr242*).

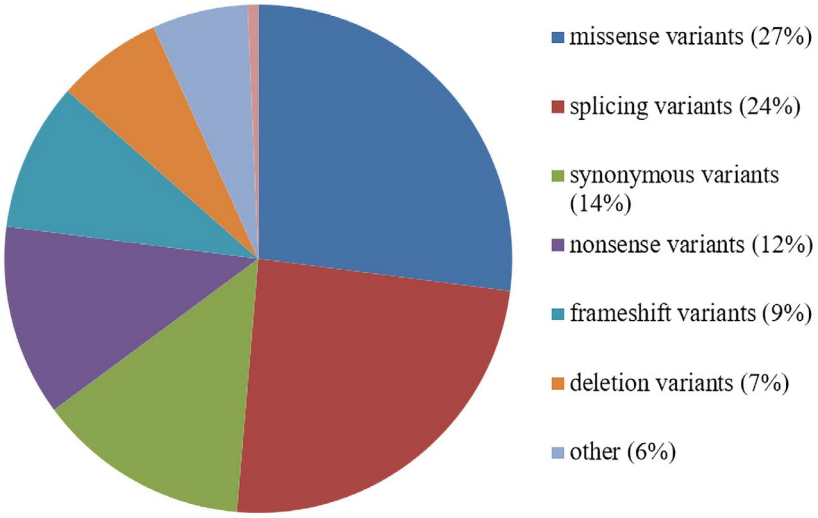

FIGURE 4 A classification map of all reported variants of the *WDR45* gene. One hundred and forty-eight variants of *WDR45* have been reported yet. The spectrum of variant types comprised 27% (40/148) missense variants, 24% (36/148) splicing variants, 14% (20/148) synonymous variants, 12% (18/148) nonsense variants, 9% (14/148) frameshift variants, 7% (10/148) deletion variants, 1% (1/148) insertion variants, and 6% (9/148) other variants.

with other WIPI members (Li & Roberts, 2001; Tsuyuki et al., 2014). And WIPI4 itself is involved in the pathway of autophagy, iron storage, ferritin metabolism, and so on (Zhao et al., 2015). In 2013, WDR45 was first been reported associated with autophagy dysfunction, providing a strong evidence that autophagy defect is closely related to neurodegenerative disorders (Doorn & Kruer, 2013). However, the pathogenesis of BPAN still remains unclear and whether activation of autophagy is a beneficial treatment needs more researches.

WDR45 is made up of a seven-bladed propeller structure containing a conserved motif to interact with phospholipids (Figure 3a) and the variants of c.10C>T, c.806del (Figure 3b) and c.726C>G (Figure 3c) in WDR45 identified in this study will destroy the structure. Our results supplement the variants of WDR45 in mutation database and provide some new information on the molecular basis and the phenotypic characteristics of BPAN. Besides, the evidence of iron deposition in the basal ganglia in early brain MRI may be atypical (Russo et al., 2019). Therefore, BPAN should not be excluded if patient accompanied with developmental delay or epilepsy in childhood regardless of whether he showed normal imageological examination.

In recent years, the rapid development of whole exome sequencing and its application in the detection of genetic diseases have brought hope for the clinical diagnosis of a large number of hereditary diseases (Alfares et al., 2018).

Until now, one hundred and forty-eight variants of the *WDR45* gene have been reported already (Figure 4). More cases were needed to be reported to expand the spectrum of *WDR45* germline variants and deep understand this disease.

In this study, five de novo variants of *WDR45* were identified by parent-offspring trio exome sequencing, indicating that the detection of variants using WES can provide a more reliable basis for the final diagnosis. Considering the serious clinical manifestation of patients with BPAN, early diagnosis and regular clinical follow-up may be of great significance for patients to improve their quality of life. In addition, providing some appropriate genetic counseling for patients can help to prevent the disease from worsening and it may provide appropriate symptomatic treatment.

4 | CONCLUSION

In conclusion, our study reports five de novo variants with BPAN including four new variants in five independent non-consanguineous Chinese families, which expands the mutation spectrum of *WDR45*. These five children showed typical development delay, intellectual disability, and/or epilepsy. Although their early brain MRI showed no significant iron accumulation, multifocal spikes, or polyspikes were observed in the EEG. The application of trio exome sequencing contributes to the early detection of BPAN, which can help patients get timely genetic counseling preventing the disease from worsening and open the way for preimplantation genetic diagnosis and future prenatal checkups. However, there is no effective treatment for this disease at present, so it is necessary to further explore the pathogenic gene and its function in order to better understand the disease, and then, find out the effective treatment.

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CONFLICT OF INTEREST

The authors have no conflicts of interests to declare.

AUTHORS CONTRIBUTIONS

XT, HZ, and SW designed the study. XS and WX performed the experiments. XL and YZ analyzed clinical and genetic data. XT and SW wrote the manuscript.

DATA AVAILABILITY STATEMENT

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

ORCID

Xiaojun Tang https://orcid.org/0000-0003-0560-7314
Xiaozhen Song https://orcid.org/0000-0002-8767-8732
Shengnan Wu https://orcid.org/0000-0002-2245-2273

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