Phenotypic variability and genetic characteristics of PRRT2-associated paroxysmal movement disorders in 13 Chinese families

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Abstract

PRRT2-associated paroxysmal movement disorders (*PRRT2*-PxMDs) include paroxysmal kinesigenic dyskinesias (PKD), benign familial infantile epilepsy (BFIE), infantile convulsions and choreoathetosis (ICCA), episodic ataxia (EA), paroxysmal nonkinesiasgenic dyskinesias (PNKD), and, in addition, other childhood-onset movement disorders and different types of seizures may be caused by *PRRT2* mutations, suggesting that the understanding of the spectrum of *PRRT2*-PxMDs is still evolving. We collected and analyzed retrospectively the clinical of children diagnosed with paroxysmal movement disorders by the Department of Neurology of Anhui Provincial Children's Hospital from January 2015 to June 2020. The genetic tests were performed in the probands and their family members. Thirteen children and their family members, 30 in total, were tested. Twenty six patients and 4 (13.34%) carriers from 13 families were identified, 14 (46.67%) were diagnosed with BIE, 7 (23.33%) with PKD, 2 (6.67%) with ICCA, 1 (3.33%) with epilepsy (focal), 1 (3.33%) with infantile spasm (IS), and 1 (3.33%) was diagnosed with PKD and PNKD, Eight different variants were identified in 13 families, and NM_145239.2:c.640-641insC was found in 4 families while recurrent mutation c.649dupC was not found. Three novel mutation, c.884G > C, c.865G > C, and c.-65-1G > C were identified in this study. This study confirmed that there is no clear genotype-phenotype correlation in patients with *PRRT2*-PxMDs, in addition, the clinical findings show variable phenotype within families, including the families affected due to the newly identified pathogenic variants in this study.

1. Introduction

Paroxysmal kinesigenic dyskinesia (PKD) is usually characterized by autosomal dominant inherited dystonia, choreoathetosis, and less commonly ballismus, and is the most common type of paroxysmal movement disorder. In 2011, Chen et al. identified *PRRT2* within a region of 16p11.2 linked to the PKD locus (Chen et al. 2013). In 2013, Wang et al. proposed that the *PRRT2* gene is associated with benign familial infantile epilepsy (BFIE) and infantile convulsions and choreoathetosis (ICCA) (Wang et al. 2013). In recent years, *PRRT2* mutations have been identified in patients with episodic ataxia (EA), paroxysmal nonkinesiasgenic dyskinesias (PNKD), hyperesthetic-induced dyskinesias (PED), familial hemiplegic migraine (FHM), benign scorpion torticollis, etc (Riant et al. 2012; Dale et al. 2012; Gardiner et al. 2012; Marini et al. 2012; Liu et al. 2013; Wood 2012), suggesting that the spectrum of *PRRT2*-associated movement disorders (*PRRT2*-PxMDs), with or without epilepsy, is still evolving.

Most *PRRT2*-PxMDs are caused by heterozygous pathogenic variants in the *PRRT2* gene or, rarely, the 16p11.2, including *PRRT2*, recurrent deletion are inherited in an autosomal dominant manner, and approximately 10% of pathogenic variations are *de novo* and 90% are inherited. However, high phenotypic variability is common in affected family members due to reduced penetrance and variable expressivity. Besides, in some patients typically with a more severe phenotype, *PRRT2*-PxMD is inherited in an autosomal recessive manner.

2. Methods

2.1 Subjects

We collected the data of clinical feature and genetic testing of patients diagnosed with paroxysmal movement disorders in the Department of Neurology of Anhui Provincial Children's Hospital from January 2015 to June 2020.

The diagnostic criteria for BIE were (Vigevano 2005): a) onset age between 3 and 12 months; b) normal development of intelligence and movement before and after the onset of the disease; c) focal attack or focal secondary generalized attack, sometimes as cluster attacks (i.e. more than 2 episodes within 24 hours); d) normal EEG background. Epileptiform discharges were found in EEG during paroxysms, but no epileptiform discharge was found in interictal periods; e) no abnormality in cranial

imaging; and f) exclusion of convulsions caused by metabolic disorders such as hypocalcemia and hypoglycemia.

The diagnostic criteria for PKD were (Bruno et al. 2004): muscular dystonia or choreographic athetosis, induced by sudden movement and lasting for several seconds to 1 minute; no disturbance of consciousness; and exclusion of other organic diseases. This study was approved by the medical ethics committee of Anhui Children's Hospital. All subjects were fully aware of the purpose and content of the study, and written informed consent was obtained from parents and/or guardians of all the subjects before enrolling.

The diagnosis of other types of *PRRT2*-PxMDs was depended on the results of genetic testing.

2.2 Molecular genetic analysis

This study was performed with the Anhui Provincial Children's Hospital. Peripheral blood samples were obtained from the patient upon receiving written informed consent from the parents or guardians, and whole-exome sequencing (WES), as described previously (Tong et al. 2018), were performed by Chigene (Beijing, China) in the patients and their family members. xGen Exome Research Panel v1.0 (IDT, Iowa, USA) was used to construct whole exome library and Next-generation sequencing (NGS) was performed on Illumina Novaseq 6000 platform (Illumina, Santiago, USA). Quantitative PCR or Sanger sequencing were used to confirm the candidate variation.

2.3 Variants analysis

Raw data cleaning was following the standard instruction recommended by Illumina, followed by paired-end alignment using Burrows-Wheeler Aligner (BWA) and variants calling by using software package GATK, and SNPs and short, < 50bp, indels were screened. Using the online analysis platform provided by Chigene (<https://chigene.org>), variation were annotated by using multiple databases including the 1000 genomes project database, dbSNP, ESP, ExAC, OMIM, Orphanet, and etc., and the significance of the pathogenicity of variations was predicted using tools SIFT (<http://sift.jcvi.org/>), PolyPhen-2

(<http://genetics.bwh.harvard.edu/pph2/>) and MutationTaster (<http://www.mutationtaster.org/>). The pathogenicity of variations was evaluated according to the American College of Medical Genetics and Genomics (ACMG) (Richards et al. 2015).

3. Results

3.1 Clinical features

Patients and their family members, 30 sample in total, from 13 unrelated families were analyzed, and 26 patients were diagnosed with *PRRT2*-PxMDs (Table 1), and the pedigrees were showed in Figure 1.

Patient 12, from family 6, was a boy diagnosed at age 6 months and 10 days, the only child of an unrelated couple. He was born in a natural childbirth after 36 weeks plus 5 days of labor without history of asphyxia. His father had a history of BIE and PKD, and his aunt had a history of PKD. He was found having nodding and embracing seizures in clusters, 6-8 times/cluster, lasting 1-2 minutes, and 3-5 clusters/day, at age 5 months and 26 days, most of which occurred when he was just awake or sleepy. The patient had normal head MRI, genetic metabolic blood screening and urine screening, electrocardiogram and heart color ultrasound tests. Video electroencephalogram (VEEG) showed extensive medium-high amplitude slow wave bursts for about 1 second, accompanied by an electromyography (EMG) burst during the attacks of nodding and hug movements (Figure 2A), concurrent with. After treatment with ACTH (2.0 IU/kg/d, two weeks) and sodium valproate (VPA) for (20 mg/kg/d, one month), his seizure stopped at the age of 8 months and the EEG returned to normal (Figure 2B). At one year of follow-up, the patient had no seizures or neuromotor developmental delay.

The summarization and distribution of 26 patients with *PRRT2*-PxMDs were showed in Table 2.

3.2 Genetic analyses

Eight *PRRT2* variations were found in 30 of the 49 tested members, including 4 carriers without phenotype, and the recurrent variant c.640-641insC was identified in 10 patients from 5 families, which was previously reported correlating with PKD or BFIS (PMID:22623405;22744660). Two of 3 novel variants, c.884G>C, c.865G>C, except c.-65-1 G>C, are VUS (variation of uncertain significance). (Table 3). All variations were confirmed by using quantitative PCR or Sanger sequencing.

4. Discussion

Precisely describing *PRRT2*-associated paroxysmal movement disorders (*PRRT2*-PxMDs) is still a challenge (Ebrahimi-Fakhari et al. 2015). Apart from the core phenotypes, kinesigenic dyskinesia (PKD), benign familial infantile epilepsy (BFIE), paroxysmal kinesigenic dyskinesia with infantile spasm (PKD/IS), and infantile convulsions and choreoathetosis (ICCA) of *PRRT2*-PxMDs, *PRRT2* pathogenic variants have been identified in patients diagnosed with several childhood-onset movement disorders and seizures, including paroxysmal nonkinesigenic dyskinesia (PNKD) (Delcourt et al. 2015; Wang et al. 2013), paroxysmal exertion-induced dyskinesia (Liu et al. 2012), and episodic ataxia (Delcourt et al. 2015). Patients diagnosed with PKD who have heterozygous *PRRT2* deletion (16p11.2 deletion) tend to have additional disorders including developmental delay (DD), intellectual disability (ID), and/or autism spectrum disorder (ASD) (Termsarasab et al. 2014; Weber et al. 2013; Silveira-Moriyama et al. 2013), and individuals with biallelic *PRRT2* mutations usually have a more severe phenotype including ID, and seizures. (Delcourt et al. 2015) However, there is no comprehensive evidence for genotype-phenotype correlations in core phenotypes of *PRRT2*-PxMDs and phenotypic variation is common within or between families affected due to the same *PRRT2* mutation. In our study, BIE and PKD are usually diagnosed in the same family, in siblings (in family 1), actually, indicating reduced penetrance.

The *PRRT2* gene is located in 16p11.2, containing 4 exons with a total length of 3794 bp and encodes 340 amino acids. Protein PRRT2 is mainly expressed in cerebral cortex, basal ganglia and cerebellum, and it is functioning transferred from cortex to basal ganglia and cerebellum during the development of nervous system. Age-dependent decreasing levels of PRRT2 in the nervous system may explain the age-dependence of BFIE and PKD. We identified no c.649dupC, the recurrent mutation reported previously in most of patients (Ono et al. 2012; Méneret et al. 2012; Lee et al. 2012), but the truncating mutation c.640-c.641insC (c.640dupC) in 4 families (family 1, 4, 5, and 7) instead, however, the diagnosis ranges from nonsyndromic BFIE to relatively severe PKD in these families, not to mention PKD due to the novel mutation p.A289P we identified in family 8, for example, which was supposed to cause a milder phenotype.

Infantile spasm (IS) is usually considered a serious epileptic encephalopathy, most of the seizures are refractory, and patients with IS are at the high risk of having ID. In this study, patient 12, from family 6, was diagnosed with IS without history of hypoxia, as previously reported, who had normal development until the last follow-up, while his father was diagnosed with ICCA. After taking anti-epilepsy treatment and one year of follow-up, the seizures ceased and his mental motor development was normal.

5. Conclusion

PRRT2-PxMDs include PKD, BFIE, ICCA, EA, PNKD, FHM, PED, benign spasmodic torticollis, and other diseases, and genotype-phenotype correlation is still unclear, which was proved in this study. We found that c.640_c.641insC occurred in most of our patients, instead of the recurrent insertion at c.649, and, in addition, we identified novel variants c.884G>C, c.865G>C, and c.-65-1G>C that cause variable phenotype within the families. In short, our research expanded the spectrum of pathogenic variation of *PRRT2*, however, the clinical findings strengthened the point that *PRRT2*-PxMDs, in the context of dominant inherited disease, have no genotype-phenotype correlation.

Declarations

6.Ethics approval and consent to participate

This study was approved by the medical ethics committee of Anhui Provincial Children's Hospital. The guardians of all subjects fully understand the purpose and content of the study, and obtain written informed consent from the guardians of all subjects before participating in the study.

7.Consent for publication

The manuscript has been approved by all authors for publication.

8.Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

9.Conflicts of interest

None of the authors has any conflict of interest to disclose.

10.Fund

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11.Authors' contributions

Lulu Wu: Data collection and article writing; Xinyu Yang: Data collection and article writing; Xiaocui Wang: Guiding clinical data collection; Shuang Yu: Participating in data collection; Bin Yang: Guiding research process and modifying articles

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Tables

Table 1 The clinical features of the patients diagnosed with <i>PRRT2</i> -PxMDs. None of patients was found having mental retardation or abnormal brain MRI							
Patient	Family/ member	Gender	Phenotype	Onset age of epilepsy	Type of seizures	Seizures in cluster	Onset age of PKD
1	1/I-2	M	PKD	N	N	N	15Y
2	1/II-1	F	BFIE	7M	GTCS	Y	N
3	1/II-2	M	BFIE	6M	GTCS	Y	N
4	2/I-1	M	PKD	N	N	N	10Y
5	2/II-1	M	BIE	4M	Focal	Y	N
6	3/II-2	M	BFIE	4M	Focal	Y	N
7	4/I-1	M	BFIE	4M	Focal	Y	N
8	4/II-1	M	PKD	N	N	N	16Y
9	4/II-2	F	BFIE	12M	GTCS	Y	N
10	5/I-1	F	PKD	N	N	N	14Y
11	5/II-1	M	ICCA	7M	GTCS	Y	15Y
12	6/I-2	M	IS	6M	IS	Y	N
13	6/II-1	F	BFIE	7M	Focal	Y	N
14	6/II-2	F	BFIE	6M	Focal	Y	N
15	6/III-1	M	PKD	N	N	N	14Y
16	7/I-1	F	PKD	N	N	N	13Y
17	7/II-1	M	ICCA	8M	GTCS	Y	14Y
18	7/II-2	M	BFIE	5M	GTCS	Y	N
19	8/II-1	M	EP	1M28D	Focal	Y	N
20	8/II-2	M	BFIE	5M	GTCS	N	N
21	8/III-1	F	BFIE	6M	Focal	Y	N
22	9/I-1	M	PKD/PNKD	N	N	N	14Y
23	9/II-1	F	BFIE	4M	Focal	Y	N
24	10/I-1	F	BFIE	6M	Focal	Y	N
25	10/II-1	M	BFIE	3M17D	Focal	Y	N
26	11/I-1	M	PKD	N	N	N	4Y

Table 2.Clinical features of 30 cases of *PRRT2*-PxMDs

Clinical features	Value
BFIE	N=14
Age of onset	5.5(3-12) months
Focal	9(64.3%)
GTCS	5(35.7%)
Remission age	7(4-14) months
PKD	N=7
Age of onset	14(4-16)years
Triggers	Sudden movement
ICCA	N=2
Age of onset of epilepsy	7 months and 8 months
Age of onset of PKD	14 years and 15 years
PKD remission age	16 years and 18 years
Epilepsy (focal)	N=1
Age of onset	1 month 28 days
Remission age	3 months
EEG	Normal
IS	N=1
Age of onset	6M
Seizure form	Clusters of nodding hugs
EEG	Video-EEG during seizure detected spastic seizures
Remission age	8 months
PKD and PNKD	N=1
Age of onset	14 years
Triggers	Sudden movement, emotional agitation, or drinking
Remission age	28 years
Carriers	N=4

Table 3 Interpretation of <i>PRRT2</i> variations identified in 13 families										
Family	Nucleic acid changes	Amino acid changes (NM_145239.2)	Position	Mutation type	Inherit	SIFT	Polyphen-2	Mutation Taster	ACMG Classification	ACMG Interpretation
1	c.640-c.641insC	p.Ala214Alafs*11	Exon2	frameshift	Mother	-	-	-	Pathogenic	PVS1+PP1
2	c.884G>C	p.Ser295Thr	Exon2	point	Father	Damaging	Possibly damaging	Disease causing	Uncertain significance	PM2+PP3
3	loss1(all)	901bp	Exon2	deletion	De novo	-	-	-	Pathogenic	PVS1+PS2 +PM2
4	c.640-c.641insC	p.Ala214Alafs*11	Exon2	frameshift	Father	-	-	-	Pathogenic	PVS1+PP1
5	c.640-c.641insC	p.Ala214Alafs*11	Exon2	frameshift	Father	-	-	-	Pathogenic	PVS1+PP1
6	c.641delC	p.Ala214Alafs*15	Exon2	frameshift	Father	-	-	-	Pathogenic	PVS1+ PM1 PP1
7	c.640-c.641insC	p.Ala214Alafs*11	Exon2	frameshift	Father	-	-	-	Pathogenic	PVS1+PP1
8	c.865G>C	p.A289P	Exon2	point	Mother	Damaging	Possibly damaging	Polymorphism	Uncertain significance	PM2+PP3
9	c.640G>C	p.A214P	Exon2	point	Father	Damaging	Probably damaging	Polymorphism	Uncertain significance	PM1+PP3
10	c.718C>T	p.R240X	Exon2	point	Father	-	-	Disease causing	Pathogenic	PVS1+PM2
11	c.640-c.641insC	p.Ala214Alafs*11	Exon2	frameshift	Father	-	-	-	Pathogenic	PVS1+PP1
12	deletion	deletion	Exon2	deletion	Mother	-	-	-	Likely Pathogenic	PVS1+ PM2
13	c.-65-1G>C	-	lvs1	point	De novo	-	-	-	Pathogenic	PVS1+ PS2 +PM2

N, no; Y, yes

* According to interpretation of S Richards et al.(PMID: 25741868)

Figures

Figure 1

Pedigrees of patients with PRRT2-PxMDs.

Figure 2

The EEG of patient 12 from family 6 (A) Ictal EEG and EMG tracing A series of nodding and hug movements were detected. During the same period, EEG's extensive medium-high amplitude slow wave bursts for about 1 second, accompanied by EMG bursts. EMG and EEG changes have a trivial relationship (B) EEG after 2 months of treatment: Normal infant EEG.