

# Paroxysmal Kinesigenic Dyskinesia Caused by 16p11.2 Microdeletion and Related Clinical Features

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## Abstract

### Background and Objectives

Isolated paroxysmal kinesigenic dyskinesia (PKD) is mainly caused by *PRRT2* variants and *TMEM151A* variants. Patients with proximal 16p11.2 microdeletion (16p11.2MD) (including *PRRT2*) often have neurodevelopmental phenotypes, whereas a few patients have PKD. Here, we aimed to identify 16p11.2MD in patients with PKD and describe the related phenotypes.

### Methods

Whole-exome sequencing and bioinformatics analysis of copy number variant (CNV) were performed in patients with PKD carrying neither *PRRT2* nor *TMEM151A* variant. Quantitative PCR and low-coverage whole-genome sequencing verified the CNV.

### Results

We identified 9 sporadic patients with PKD and 16p11.2MD (~535 kb), accounting for 9.6% (9/94) of our patients. Together with 9 previously reported patients with PKD and 16p11.2MD, we found that 16p11.2MD was de novo in 11 of 12 tested patients and inherited from a parent in the other patient. And 80% (12/15) of these patients had a mild language delay, 64.3% (9/14) had compromised learning ability, 42.9% (6/14) had a mild motor delay, and 50% (6/12) had abnormal neuroimaging findings. No severe autism disorders were observed.

### Discussion

Mild developmental problems may be overlooked. A detailed inquiry of developmental history and CNV testing are necessary to distinguish patients with 16p11.2MD from isolated PKD.

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Paroxysmal kinesigenic dyskinesia (PKD; MIM #128200) is a rare disorder manifesting as recurrent and brief episodes of choreoathetosis or dystonia triggered by sudden voluntary movements. Variants in the gene *PRRT2* located on chromosome region 16p11.2 were identified to cause PKD in 2011.<sup>1</sup> To date, *PRRT2* variants account for 77%–93% of familial PKD and 21%–45% of sporadic PKD.<sup>2</sup> *TMEM151A* variants were recently identified to cause PKD.<sup>3</sup> The proximal ~600 kb breakpoints 4 and 5 16p11.2 microdeletion (16p11.2MD) (29.6–30.2 Mb–hg19, including *PRRT2*) could be a cause of PKD accompanied by other clinical features.<sup>4</sup> The 16p11.2MD is one of the most common etiologies of neurodevelopmental disorders, including motor/language developmental delay, autism spectrum disorder (ASD), intellectual disability (ID), congenital dysmorphism, and/or obesity, with an incidence of 0.25%–2.9%.<sup>5</sup> To date, more than 400 16p11.2MD carriers have been reported, among which 9 cases have been reported to have PKD.<sup>5,6</sup> Here, we report 9 new patients with PKD and 16p11.2MD.

## Methods

### Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the ethics committee of the Second Affiliated Hospital of Zhejiang University School of Medicine, and all participants provided informed consent.

### Clinical and Genetic Analysis

Patients were enrolled between January 2015 and July 2021. Whole-exome sequencing and bioinformatics analysis of copy number variants (CNVs) were performed in patients who were negative for both *PRRT2* and *TMEM151A* variants. For details, please see eMethods.

### Data Availability

The original data that support the findings are available from the corresponding author on reasonable request.

## Results

Among 94 enrolled patients, 9 sporadic patients (9.6%) were identified with 16p11.2MD (eTable 1, links.lww.com/NXG/A513). Quantitative PCR confirmed deletions in *PRRT2*, which were de novo in 4 patients (P1, P5, P6, and P9), inherited from a father in P8, and could not be tested in parents of the other 4 patients (Figure 1A). Paternity was confirmed by microsatellite analysis (eFigure 1). Low-coverage whole-genome sequencing further confirmed 16p11.2MD in all 9 patients and the father of P8, with a span of ~535 kb (chr.16:29649997-30185157, GRCh 37) containing 30 genes from *SPN* to *MAPK3* (Figure 1B). The father with 16p11.2MD had obesity (body mass index 33.41 kg/m<sup>2</sup>) with a head circumference of 61 cm, but denied PKD and developmental disorders, and neurologic examinations were normal. Variants in other paroxysmal dyskinesia-related genes were not detected in these 9 patients.

The clinical data of the 9 newly identified patients (P1–P9) with PKD and 16p11.2MD and the previously published 9 cases (P10–P18) were summarized in Table 1 (average onset age of PKD, 9.6 years; males/females/unknown, 14/3/1). Features of kinesigenic attacks were typical in all patients except that durations extended to several minutes in 3 patients (P1, P6, and P13).

Regarding the 16p11.2MD-related phenotype, 80% (12/15) of these patients had mild speech delay, and 4 patients developed a lisp. Learning abilities were compromised in 64.3% (9/14) of patients, among whom 2 received additional educational support, and 7 had a poor academic performance. In addition, mild motor delays were present in 42.9% (6/14) of patients. The average age of walking was 16.50 ± 5.95 months in P1–P9. Uncommonly, ASD, subtle dysmorphism, and obesity were each found in 1 patient. Notably, brain MRI revealed anomalies in 50% (6/12) of patients. The cerebellum was frequently affected, including suspected dermoid cysts (P3, Figure 1C), arachnoid cysts (P7, Figure 1D, P11), and cerebellar atrophy (P10). Neuroimaging findings were usually normal in isolated PKD.

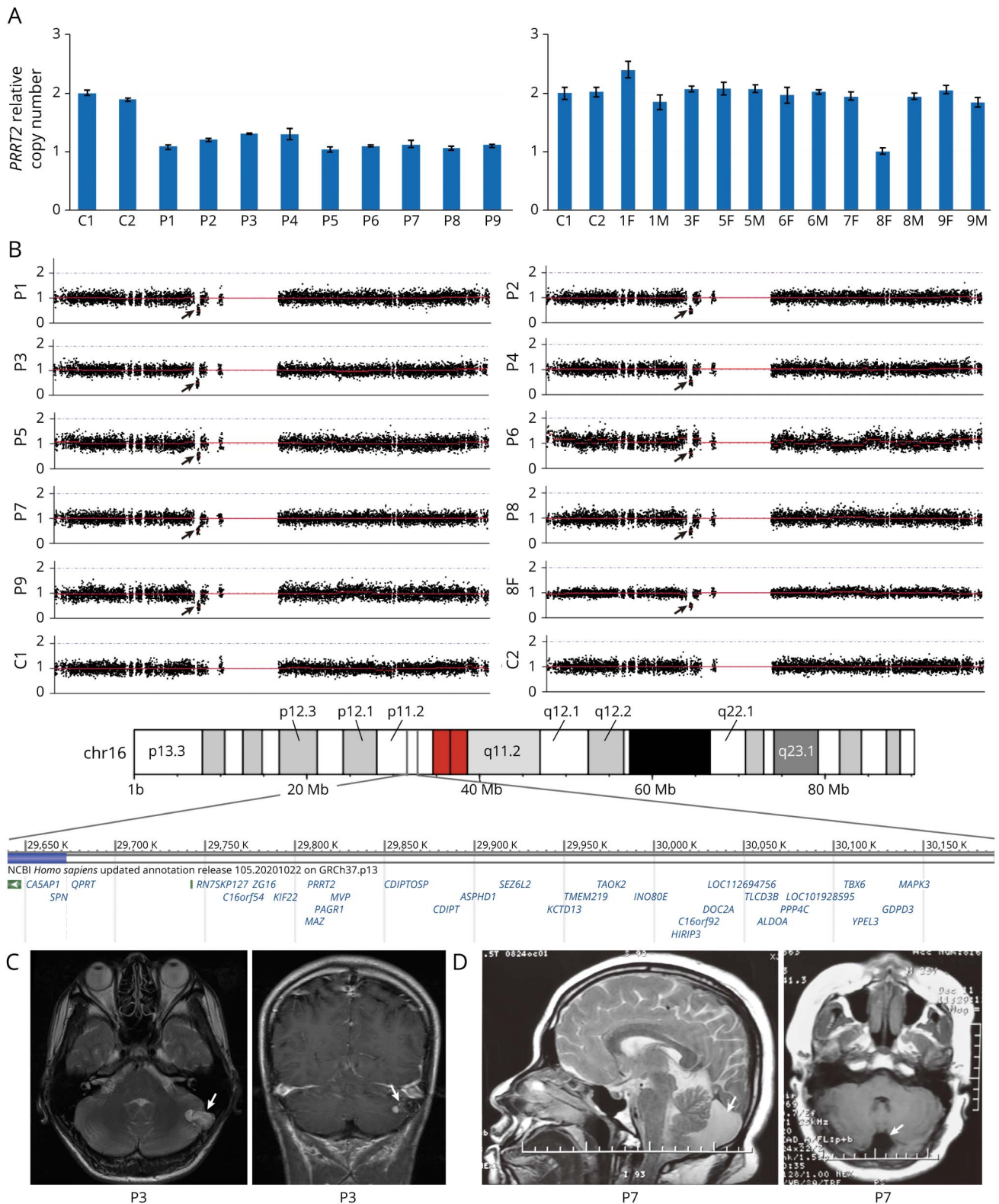
## Discussion

The developmental delay in patients with PKD and 16p11.2MD is similar but milder than that in other 16p11.2MD carriers. In other deletion carriers, language delay was present at high rates (83%), intellectual ability varied with ~30% falling in the normal range and 10.3%–28.1% having ID, and motor delay was common (37.6%–57.1%) with an evaluated mean age of walking of 20.5 ± 8.6 months.<sup>5,7</sup> Brain MRI abnormalities in 16p11.2MD patients mostly are related to posterior fossa and/or craniocervical junction,<sup>7</sup> consistent with our findings.

To our knowledge, neurodevelopmental disorders have been rarely reported in patients with PKD carrying heterozygous *PRRT2* frameshift/missense variants. A few patients with biallelic *PRRT2* variants were reported to have cognitive problems.<sup>4</sup> Neurodevelopmental phenotypes in 16p11.2MD are related to other genes in this region. For example, *MAPK3* is a key component of MAPK/ERK pathway associated with ASD-related features in mice models.<sup>5</sup> Deficiency of the *KCTD13* ortholog in zebrafish resulted in macrocephaly.<sup>5</sup> And both *Kctd13*-deficient and *Taok2*-deficient mice displayed cognitive problems.<sup>5</sup>

The 16p11.2MD is characterized by a broad spectrum of neurodevelopmental phenotypes with varying penetrance.<sup>5</sup> Here, 16p11.2MD accounted for 9.6% of patients with PKD carrying neither *PRRT2* nor *TMEM151A* variant. Developmental features of 16p11.2MD may be mild; therefore, a detailed inquiry of developmental history and CNV testing are necessary to distinguish these patients from isolated PKD. The WES-based CNV testing is cost-effective while has limitation in detecting small CNVs (<100 kb). High-resolution chromosomal microarray could be a precise tool.

**Figure 1** Genetic Findings and Brain Images



(A) The copy number of *PRRT2* detected by qPCR in 9 patients with PKD and available parents. C1 and C2 are controls, P1–P9 represent patients, 1 F/M is the father/mother of patient 1, and so on. The relative copy number of *PRRT2* was calculated with CopyCaller software v2.1, and subject C1 was selected as the calibrator sample with a copy number of 2. (B) Black arrows indicate the 16p11.2 microdeletions detected with low-coverage whole-genome sequencing. The associated genes were generated with the NCBI Genome Browser (GRCh37.p13) and displayed under the graphic structure of chromosome 16. (C) MRI of patient 3 showing a lesion at the left edge of the cerebellum (white arrows, left: T2 weighted, right: T1 FLAIR). (D) MRI of patient 7 showing an arachnoid cyst at the cerebellar vermis (white arrows, left: T2 weighted, right: T1 FLAIR). FLAIR = fluid-attenuated inversion recovery; PKD = paroxysmal kinesigenic dyskinesia.

**Table 1** Clinical and Genetic Features of Patients With PKD And 16p11.2 Microdeletion

Patient	Age, AAO/sex	Trigger of attacks	Duration of attacks	Type of attacks	Response to medication	Comorbidity/age	Interictal EEG	Brain MRI	BMI (kg/m <sup>2</sup> )/age	Motor/language development and learning ability	CNV
P1	22y, 11y/M	SM, R	20–40 s (occasionally lasts minutes)	C	Complete control on CBZ 50 mg/d	FS/3 y	Mild changes	N	17.5/15 y	Walking and speaking first words at 16 mo; attending normal schools with poor performance	535 kb De novo
P2	29y, 10y/M	SM, S	NA	M	NA	NA	NA	NA	NA	NA	535 kb NA
P3	17y, 10y/M	SM, S	10–30 s	D	Incomplete control on OXC 150 mg/d (occasional attacks)	NO	NA	A lesion at the left edge of the cerebellum may be a dermoid cyst or a teratoma.	18.4/17 y	Walking at 13 mo; speaking relatively clearly at 24 mo; slurred speech; attending regular schools with poor performance.	535 kb NA
P4	21 y, 15y/M	SM	10–30 s	C	Complete control on CBZ 100 mg/d	IC/<1 y	N	N	18.6/17 y	Walking at 14 mo; speaking relatively clearly at 3 y; slurred speech that cannot be corrected by surgery; attending normal schools with poor performance.	535 kb NA
P5	21 y, 13y/M	SM, S, R	5–20 s	D	Incomplete control on CBZ 100 mg/d (occasional attacks)	NO	N	A benign nodule containing lipids at the left parietal skull	20.3/17 y	Walking at 12 mo; speaking relatively clearly at 24 mo; attending regular schools with poor performance.	535 kb De novo
P6	12 y, 4 y/F	SM	30–40 s (occasionally lasts minutes)	C	Incomplete control on CBZ 100 mg/d (occasional attacks)	IC/6 mo, 10 mo	N	A lesion at the right frontal lobe, may be glial hyperplasia or ischemia	15.6/12 y	Walking and speaking first words at 16 mo; attending regular schools with average performance.	535 kb De novo
P7	25y, 12y/M	SM, S	10–30 s	M	Incomplete control on CBZ 50 mg/d (occasional attacks)	IC/6 mo–4 y	N	Arachnoid cyst at the cerebellar vermis	NA	Walking and speaking at around 30 mo; slurred speech; attending normal schools with poor sports and academic performance.	535 kb NA
P8	13 y, 9 y/F	SM, S	5–6 s	D	Complete control on CBZ 50 mg/d	IC/4 mo	N	NA	19.4/12 y	Walking at 19 mo; speaking relatively clearly at 24 mo; slurred speech; poor expressive language; attending normal schools with average performance.	535 kb Paternally
P9	25y, 13y/M	SM	10–30 s	M	Incomplete control on OXC 150 mg/d (occasional attacks)	NO	N	N	22.0/24 y	Walking and speaking at around 12 mo; attending a regular school with poor performance	535 kb De novo
P10 <sup>8</sup>	NA/M	SM	NA	C	CBZ responsive	IC/NA, parkinsonism/17 y	N	Cerebellar atrophy	NA	Motor development was normal. First words were spoken at 18–20 mo; verbal learning disabilities; received educational support.	544 kb De novo
P11 <sup>9</sup>	NA, 7 y/M	SM	<10 s	M	Complete control on CBZ 400 mg/d	IC/11 mo	N	Arachnoid cyst in the cerebellopontine angle	NA	Walking at 18 mo; slightly slow language development; struggling at school, but never requiring additional school support.	660 kb De novo
P12 <sup>10</sup>	NA, 6 y/NA	SM	NA	PKD	CBZ responsive	NO	NA	NA	NA	Speech delay; mild orobuccal dyspraxia	430 kb De novo
P13 <sup>11</sup>	NA, 5 y/M	SM, R	<30 s (occasionally lasts minutes)	M	Complete control on CBZ 400 mg/d	Tics and subtle dysmorphism	NA	NA	NA	NA	525 kb NA
P14 <sup>12</sup>	NA, 5 y/M	SM	<60 s	D	NA	IC/infancy–3.5 y	NA	NA	NA	Fine motor skills and balance compromised; speech delay; attending a special school; limited vocabulary and learning disabilities.	895 kb NA

Continued

**Table 1** Clinical and Genetic Features of Patients With PKD And 16p11.2 Microdeletion (continued)

Patient	Age, AAO/sex	Trigger of attacks	Duration of attacks	Type of attacks	Response to medication	Comorbidity/age	Interictal EEG	Brain MRI	BMI (kg/m <sup>2</sup> )/age	Motor/language development and learning ability	CNV
P15 <sup>13</sup>	NA, 10.5 y/M	SM	5–10 s	D	Good control on CBZ 250 mg/d	Spondyloilisthesis, Asperger syndrome/4–5 y	N	NA	NA	Normal motor development; mild language delay; attending regular schools.	533.9 kb De novo
P16 <sup>14</sup>	NA, 8.5 y/M	SM, S	10–30 s	D	Good control on CBZ 8 mg/kg/d	NA	N	N	NA	NA	550 kb De novo
P17 <sup>15</sup>	NA, 11 y/M	SM	>10 s	D	Good control on CBZ 300 mg/d	NO	N	N	NA	No language disability and autistic features; normal intelligence;	591 kb De novo
P18 <sup>15</sup>	NA, 13 y/F	SM	2–3 s	C	Good control on OXC 450 mg/d	IC/8 mo	Mild changes	N	19.5/12 y 29.3/22 y	No speech abnormalities or autistic features; normal intelligence.	832 kb De novo

Abbreviations: AAO = age at onset; BMI = body mass index; C = choreoathetosis; CBZ = carbamazepine; CNV = copy number variant; D = dystonia; IC = infantile convulsion; M = mixed type; N = normal; NA = not available; OXC = oxcarbazepine; PKD = paroxysmal kinesigenic dyskinesia; R = rest; S = stress, startle; SM = sudden movement. P1–P9 were patients identified in our center, and P10–P18 were patients from the literature.

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Yu-Lan Chen, MD	Second Affiliated Hospital of Zhejiang University, Hangzhou, China	Acquisition and analysis of data and drafting of the manuscript
Dian-Fu Chen, PhD	Second Affiliated Hospital of Zhejiang University, Hangzhou, China	Acquisition and analysis of data
Hua-Zhen Ke, MD	Second Affiliated Hospital of Zhejiang University, Hangzhou, China	Acquisition and analysis of data
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Hong-Fu Li, MD, PhD	Second Affiliated Hospital of Zhejiang University, Hangzhou, China	Acquisition and analysis of data and review of the manuscript
Zhi-Ying Wu, MD, PhD	Second Affiliated Hospital of Zhejiang University, Hangzhou, China	Study design and supervision, acquisition and analysis of data, and review of the manuscript

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