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Clinical Manifestations in Paroxysmal Kinesigenic Dyskinesia Patients with Proline-Rich Transmembrane Protein 2 Gene Mutation

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Background and Purpose Given the diverse phenotypes including combined non-dyskinetic symptoms in patients harboring mutations of the gene encoding proline-rich transmembrane protein 2 (*PRRT2*), the clinical significance of these mutations in paroxysmal kinesigenic dyskinesia (PKD) is questionable. In this study, we investigated the clinical characteristics of PKD patients with *PRRT2* mutations.

Methods Familial and sporadic PKD patients were enrolled and *PRRT2* gene sequencing was performed. Demographic and clinical data were compared between PKD patients with and without a *PRRT2* mutation.

Results Among the enrolled PKD patients (8 patients from 5 PKD families and 19 sporadic patients), *PRRT2* mutations were detected in 3 PKD families (60%) and 2 sporadic cases (10.5%). All familial patients with a *PRRT2* gene mutation had the c.649dupC mutation, which is the most commonly reported mutation. Two uncommon mutations (c.649delC and c.629dupC) were detected only in the sporadic cases. PKD patients with *PRRT2* mutation were younger at symptom onset and had more non-dyskinetic symptoms than those without *PRRT2* mutation. However, the characteristics of dyskinetic movement did not differ between the two groups.

Conclusions This is the first study of *PRRT2* mutations in Korea. The presence of a *PRRT2* mutation was more strongly related to familial PKD, and was clinically related with earlier age of onset and common non-dyskinetic symptoms in PKD patients. **J Clin Neurol 2014;10:50-54**

Key Words paroxysmal dyskinesia, paroxysmal, dyskinesia, chorea, dystonia, *PRRT2*.

Introduction

Paroxysmal kinesigenic dyskinesia (PKD) is the most common paroxysmal movement disorder and is characterized by brief, unilateral or bilateral involuntary movements that are precipitated by sudden movements.¹⁻³ Recently, the gene encoding proline-rich transmembrane protein 2 (*PRRT2*) mutations are identified as the causative gene for PKD.^{4,5} In familial PKD patients, *PRRT2* gene mutations, most commonly c.649dupC, were present in the majority of patients.^{4,6-8} How-

ever, in sporadic cases, the prevalence of *PRRT2* gene mutations have been variously reported as 20–45%,^{7,9,10} and diverse *PRRT2* gene mutations have been identified.^{5-7,9,11} In addition, many non-dyskinetic symptoms, such as migraine, dystonia, and seizure, can be combined in PKD patients.¹² Even in PKD families, *PRRT2* gene mutations can be inherited with only non-dyskinetic symptoms.⁶⁻⁹

Interestingly, *PRRT2* gene mutations can manifest as a broad spectrum of phenotypes, and have been reported in patients with infantile convulsions with paroxysmal choreoathetosis or benign familial infantile epilepsy,^{8,10,13} and even in patients with migraine and episodic ataxia.^{14,15} Based on the diverse prevalence of *PRRT2* mutations and the various phenotypes associated with these mutations, the meaning of the *PRRT2* gene mutation in PKD remains a matter of debate.

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This study investigated the clinical significance and genetic characteristics of *PRRT2* gene mutations in PKD by comparing the clinical manifestations of Korean PKD patients with and without *PRRT2* gene mutations.

Methods

Subjects

Patients with PKD at a movement disorders and pediatric outpatient clinic in Samsung Medical Center, and Soonchunhyang University Hospital, Seoul, Korea, were enrolled between July 2011 and November 2012. All subjects met the diagnostic criteria for PKD.¹² The genealogical, clinical, and genetic data of the enrolled patients were investigated and analyzed. We compared the data of PKD patients with and without *PRRT2* gene mutations. Seizure, writer's cramp, and migraine were assessed as non-dyskinetic symptoms.^{6-9,12} All subjects were briefed in detail concerning the study and provided written informed consent to participate. The study was approved by the Institutional Review Board of Samsung Medical Center.

Genetic analysis

Genomic DNA was isolated from peripheral blood leukocytes using the Wizard Genomic DNA Purification kit according to the manufacturer's instructions (Promega, Madison, WI, USA). We performed polymerase chain reaction (PCR) and direct sequencing of all coding exons and their flanking sequences for the *PRRT2* gene using primer pairs designed by the authors (available upon request). PCR was performed in a Veriti® thermal cycler (Applied Biosystems, Foster City, CA, USA) and cycle sequencing was performed using an ABI Prism 3100×1 Genetic Analyzer with the BigDye Terminator

Cycle Sequencing Ready Reaction kit (Applied Biosystems). Sequence variations were analyzed with reference to the wild-type sequence (RefSeq No. NM_145239.2) using the Sequencher program (Gene Codes, Ann Arbor, MI, USA).

Statistical analyses

All demographic and clinical data are presented as mean, SD, and median values. Differences between the PKD patients with and without *PRRT2* gene mutations were evaluated using unpaired Student's *t*-test or Mann-Whitney U test for continuous and ordinary variables, while Pearson's chi-square test or Fisher's exact test was used for categorical variables. The level of statistical significance was set at $p < 0.05$. All statistical analyses were conducted using PASW for Windows, version 18.0 (SPSS, Chicago, IL, USA).

Results

Clinical characteristics of the enrolled PKD patients

Eight familial PKD patients from 5 families and 19 sporadic PKD patients were enrolled (Fig. 1). In all enrolled subjects the paroxysmal movement was typically induced by sudden movements, and lasted for less than 1 min. Premonitory sensation or aura was reported in 15 patients (55.6%) and facial involvement was evident in 6 (22.2%). Dyskinetic movement usually involved the limbs (92.6%). In 55.6% of enrolled patients, the dyskinesia was shown unilaterally. The results of a physical examination, electroencephalography, and magnetic resonance imaging of the brain were normal in all subjects. Of the 27 patients, 5 did not need medication either because of remission or because they experienced only mild disturbance in their daily life; 18 of the 22 medically treated pa-

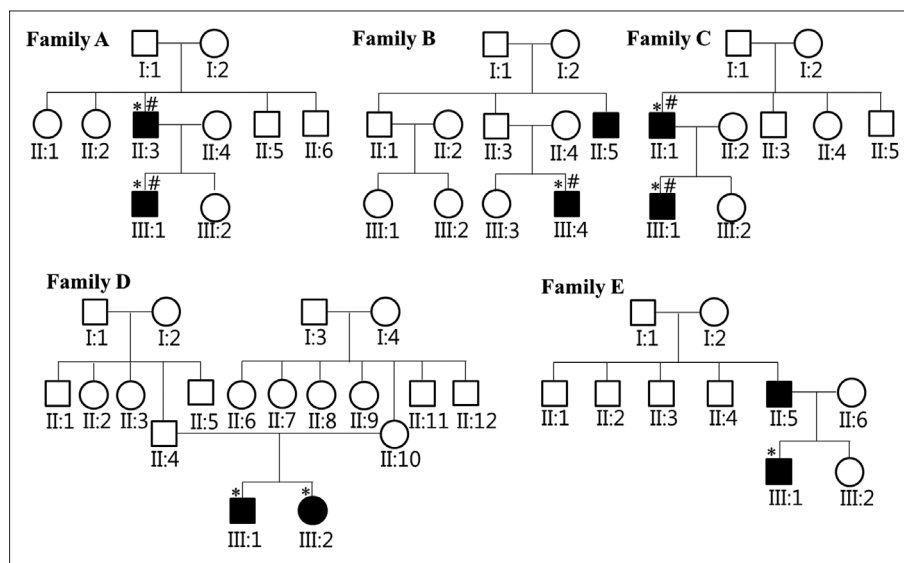


Fig. 1. The pedigrees of five Korean PKD families. Filled and open symbols indicate relatives with and without PKD, respectively. *Subjects who underwent *PRRT2* gene mutation analysis, #Subjects with *PRRT2* gene mutation. PKD: Paroxysmal kinesigenic dyskinesia, *PRRT2*: proline-rich transmembrane protein 2.

tients (18.8%) were in complete remission after medication.

Non-dyskinetic symptoms were reported in three of the eight familial PKD patients (37.5%) and one (5.3%) sporadic

patient. Among the four PKD patients with non-dyskinetic symptoms, non-febrile benign infantile seizure was noted in two subjects (family A II:3 and one sporadic patient). Mi-

Table 1. Comparison of demographic and clinical data between the PKD patients with and without PRRT2 gene mutations

	PKD patients with a PRRT2 mutations	PKD patients without a PRRT2 mutations	p
No. of subjects	7	20	
Age, years			0.925
Mean (SD)	26.6 (15.5)	20.6 (4.3)	
Median	19.0	20.0	
Male, n (%)	7 (100)	19 (95)	1.000
Age at onset, years			0.007*
Mean (SD)	11.0 (2.8)	13.8 (1.8)	
Median	12.0	14.0	
Paroxysmal kinesigenic dyskinesia			
Main phenotype, n (%)			0.726
Choreoathetosis	2 (28.6)	8 (40)	
Dystonia	3 (42.9)	9 (45)	
Mixed	2 (28.6)	3 (15)	
Frequency/day, n (%)			0.828
<5	1 (14.3)	6 (30)	
5–10	1 (14.3)	3 (15)	
>10	5 (71.4)	11 (55)	
Duration in seconds, n (%)			0.072
<10	5 (71.4)	18 (90)	
10–30	2 (28.6)	0 (0)	
30–60	0 (0)	2 (10)	
Laterality of paroxysmal movement			0.678
Unilateral	4 (57.1)	11 (55)	
Bilateral	3 (42.9)	9 (45)	
Face involvement	0 (0)	6 (30)	0.155
Involved limb			1.000
Upper limb only	0 (0)	2 (10)	
Lower limb only	0 (0)	0 (0)	
Both	7 (100)	18 (90)	
Premonitory sensation	5 (71.5)	10 (50)	0.408
Combined non-dyskinetic symptoms, n (%)	4 (57.1)	0 (0)	0.002*
Seizure	2 (28.6)	0 (0)	
Migraine	1 (14.3)	0 (0)	
Writer's cramp	1 (14.3)	0 (0)	
Medication			0.895
Phenytoin	0 (0)	2 (10)	
Carbamazepine	5 (71.4)	13 (65)	
Oxcarbazepine	0 (0)	2 (10)	
No medication treatment	2 (28.6)	3 (15)	
Response to medication			1.000
Medically treated patients	5	17	
Complete remission	4 (80)	14 (82.4)	
Incomplete remission	1 (20)	3 (17.6)	

*p<0.05.

PKD: paroxysmal kinesigenic dyskinesia, PRRT2: proline-rich transmembrane protein 2.

graine without aura was also seen in one subject (family C II:1). The remaining PKD patient had typical writer's cramp (family C III:1).

Identification of the *PRRT2* gene mutation

Genetic analysis identified 3 *PRRT2* gene mutations in 3 of the 5 PKD families (60%) and in 2 of the 19 sporadic cases (10.5%). The c.649dupC mutation, which is a known as hot-spot mutation, was detected in three PKD families, but not in the sporadic cases. Two uncommon mutations (c.649delC and c.629dupC) that have mostly been reported in sporadic cases^{7,10,11} were also identified in two of the sporadic subjects in this study.

Clinical characteristics: PKD patients with and without *PRRT2* mutations

Comparison of demographic data revealed that PKD patients with *PRRT2* gene mutations reported being younger at symptom onset than those without gene mutations (Table 1). The clinical manifestation of paroxysmal dyskinesia did not differ between PKD patients with and without *PRRT2* gene mutations. Although premonitory sensation was appeared to be more common in patients with *PRRT2* gene mutations, the difference was not statistically significant. Comparison of non-dyskinetic symptoms revealed that PKD patients with *PRRT2* gene mutations had more non-dyskinetic symptoms than those without. Assessment of the medications for treatment and the responses to medication revealed no significant difference between the PKD patients with and without *PRRT2* gene mutations.

Discussion

We investigated the clinical meaning of *PRRT2* gene mutations in Korean PKD patients. This is the first study on the *PRRT2* mutation in Korean population. Despite many reports of *PRRT2* mutations in patients with PKD and other diseases, their clinical role in PKD remains unclear and debatable. Only a few studies have compared the clinical characteristics of PKD patients with and without *PRRT2* gene mutations, and their results have been equivocal.^{16,17} PKD patients with *PRRT2* gene mutations typically report an earlier age of symptom onset and are more likely to have non-dyskinetic symptoms than those without gene mutations.

Echoing previous studies,^{16,17} PKD patients with *PRRT2* gene mutations were younger at disease onset in the present study. Assessment of the clinical data revealed that the clinical features of paroxysmal movement were highly typical and homogeneous, similar to previous studies.^{12,18} Although premonitory sensation appeared to be more commonly observed

in the PKD patients with *PRRT2* gene mutations than those without, as reported previously,¹⁶ the difference was not statistically significant. These findings correspond well with a previous study that found no difference between these two groups, with the exception of premonitory sensation.¹⁶ However, another study found a higher prevalence of the choreo-athetotic phenotype and longer duration of paroxysmal dyskinesia in PKD patients with *PRRT2* gene mutations.¹⁷ In the present study, there was no significant difference between the two groups, even when the duration of episodes was dichotomized into <5 s and >5 s ($p=0.580$) just like the previous study.

Of great interest, PKD patients with *PRRT2* mutations had more non-dyskinetic symptoms than those without gene mutations. This contrasts with a previous study that found no evidence of a relationship between the presence of a gene mutation and non-dyskinetic symptoms.¹⁶ This discrepancy may be attributable to the particular non-dyskinetic symptoms assessed in each study; while in the present study, seizure, migraine, and writer's cramp were assessed, that previous study assessed only seizure as non-dyskinetic symptoms.¹⁶ Comparison of the percentage of patients with seizure revealed no statistically significant difference between patients with and without *PRRT2* gene mutations ($p=0.060$), in accordance with previous observations.¹⁶ The evaluation of various non-dyskinetic symptoms in PKD patients could be important because many previous studies already have found various non-dyskinetic symptoms in PKD patients^{6-9,12} and *PRRT2* gene mutations in other diseases.^{14,15} Furthermore, *PRRT2* gene mutations can be inherited with only non-dyskinetic symptoms.^{6,8,9}

Presently, *PRRT2* gene mutations were found in three of the five PKD families (60%); all of the detected *PRRT2* gene mutation in the familial cases was c.649dupC. This finding corresponds well with previous studies identifying *PRRT2* gene mutations as the cause in familial PKD.^{4,6-11} Although *PRRT2* gene mutations have been detected in up to 90% of Chinese familial PKD patients,⁶ in other studies, the prevalence rates were 58–75% of familial PKD patients in Asian countries.^{4,10,16}

In addition, among the *PRRT2* gene mutations, c.649dupC is the most commonly reported in familial PKD patients.^{4-8,10} Interestingly, in the present study the prevalence of *PRRT2* mutations in sporadic PKD patients was lower than those in previous studies,^{5-7,9,11} and the c.649dupC mutation was not found in sporadic patients. Similarly various mutations other than c.649dupC have been detected in sporadic PKD patients.^{8,9,11}

The present study was subject to some limitations. Since only a small number of patients was enrolled, there is a possibility of selection bias. The differences between the results of the our study and those of previous studies could be attributable to this limitation. However, despite the small sample it

was still possible to elucidate statistically the clinical features of PKD patients with *PRRT2* gene mutation. In addition, since exon analysis of the *PRRT2* was conducted using Sanger sequencing, large deletions, duplications or intron mutations may have been overlooked.

In conclusion, the prevalence of *PRRT2* gene mutations was strongly related with familial PKD, and partially with sporadic PKD. Clinically, PKD patients with *PRRT2* gene mutations may be associated with earlier onset and non-dyskinetic symptoms. Further studies involving larger patient populations and evaluations of diverse non-dyskinetic symptoms are needed.

Conflicts of Interest

The authors have no financial conflicts of interest.

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