Clinical/Scientific Notes

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PRRT2 MUTATION CORRELATED WITH PHENOTYPE OF PAROXYSMAL KINESIGENIC DYSKINESIA AND DRUG RESPONSE

The Bruno et al.[1] criteria are commonly used to diagnose paroxysmal kinesigenic dyskinesia (PKD), listed as follows:

- Identified kinesigenic trigger for the attacks
- Short duration of attacks (1 minute)
- No loss of consciousness or pain during attacks
- Exclusion of other organic diseases and normal neurologic examination
- Control of attacks with phenytoin or carbamazepine, if tried
- Age at onset between 1 and 20 years, if no family history of PKD

Our previous study has identified *PRRT2* as a causative gene for PKD,[2] which was supported by several independent groups.[3–5] To date, many *PRRT2* mutations in PKD have been reported, but the genotype–phenotype relationship of PKD has not been well-studied. Our objective was to investigate correlations of *PRRT2* mutations with phenotypes of PKD and responses to carbamazepine in a cohort of patients with PKD.

Classification of evidence. This study provides Class IV evidence of a correlation between phenotype and genotype in patients with PKD, the *PRRT2* mutation, and response to carbamazepine.

Methods. We recruited 81 patients with PKD, including 44 familial cases from 14 pedigrees and 37 possibly sporadic cases, from Huashan Hospital and First Affiliated Hospital during 2 periods, December 2005 to March 2011 (stage 1) and April 2011 to April 2012 (stage 2), prior to or after the discovery of *PRRT2* mutations, respectively. All cases met Bruno et al. criteria. The study followed standard protocol approvals, registrations, and patient consents.

Clinical evaluations were performed and patients were followed up. Sanger sequencing was performed to identify *PRRT2* mutations. Differences in clinical characteristics between patients with PKD with and without *PRRT2* mutations were tested using the 2-sample *t* test or the χ^2 test. A generalized estimating equation (GEE) model was used to account for familial correlation. SAS version 9.2 (SAS Inc., Cary, NC) was used for statistical analyses.

Results. Phenotypes of patients with PKD in this study were classified into 2 subtypes, choreoathetosis or dystonia, according to their main symptoms (detailed classifications seen in appendix e-1 on the *Neurology*® Web site at www.neurology.org). Three cases had a positive history of infantile convulsions, and one had viral encephalitis before onset of PKD attacks. All others had no significant medical history. Available EEG and brain MRI showed unremarkable results.

Four documented *PRRT2* mutations,[2,6] including c.649dupC, c.514_517delTCTG, c.972delA, and c.649delC, were detected in 100% of familial cases and 11% of possibly sporadic cases (table e-1 and table e-2). The c.649dupC mutation was also detected in the asymptomatic parents of family 34 and 47, suggesting the incomplete penetrance of this mutation. Interestingly, we found a de novo mutation of c.649dupC in the patient with PKD of Mongolian ancestry.[7]

Associations between *PRRT2* mutations and the clinical presentation of PKD are shown in table 1. The mean age at onset in *PRRT2* mutation carriers was significantly lower than that in non-*PRRT2* mutation carriers. All 48 *PRRT2* mutation carriers expressed the choreoathetosis phenotype, while 33 non-*PRRT2* mutation carriers presented with dystonia or choreoathetosis phenotype. PKD attacks were bilateral in 100% of the *PRRT2* mutation carriers but in only 42% of the non-*PRRT2* mutation carriers. Compared to the non-*PRRT2* mutation carriers, *PRRT2* mutation carriers had longer duration of PKD attacks. These differences remained statistically significant between 2 groups even when familial correlations among several patients with PKD were considered using the GEE model.

In stage 1, 25 patients were prescribed 100 mg bid carbamazepine. The remaining 19 patients whose attacks had vanished were not prescribed any medication. After carbamazepine interventions, 12 cases achieved complete resolution of symptoms even if the dose was decreased to 50 mg/d, 5 patients required carbamazepine 100 mg tid to control their attacks, and 8 patients still experienced occasional

Supplemental data at www.neurology.org

Table 1 Correlation of *PRRT2* mutations with PKD phenotypes and drug responses

	PRRT2 mutations			
Phenotype	**Carriers**	**Noncarriers**	***p* Value**	**P-GEE**
Presentation				
Choreoathetosis	48	7		
Dystonia	0	26	3.8×10^{-15}	NA
Laterality				
Bilateral	48	14		
Unilateral	0	19	5.4×10^{-10}	NA
Response to carbamazepine				
Stage 1				
Complete	12	0		
Incomplete	0	13		
Not treated	19	0	1.9×10^{-16}	NA
Stage 2				
Complete	13	2		
Incomplete	0	18		
Not treated	4	0	1.6×10^{-8}	NA
Stage 1 + stage 2				
Complete	25	2		
Incomplete	0	31		
Not treated	23	0	1.1×10^{-20}	NA
Age at onset, y, mean ± SD	7.63 ± 3.72	13.52 ± 2.69	2.2×10^{-11}	1.4×10^{-7}
Duration of episode, s				
<5	5	15		
≥5	43	18	2.2×10^{-4}	8.1×10^{-4}

Abbreviations: NA = not applicable; P-GEE = *p* value of generalized estimating equation; PKD = paroxysmal kinesigenic dyskinesia.

PKD attacks. The 12 cases who responded completely to carbamazepine were later confirmed to carry *PRRT2* mutations. However, the 13 patients who did not completely respond to carbamazepine did not harbor *PRRT2* mutations.

In stage 2, a different dose of carbamazepine was prescribed after screening for *PRRT2* mutations: 50 mg/d for mutation carriers and 100 mg bid for non-mutation carriers. Four mutation-carrying patients whose symptoms vanished were not treated. PKD attacks were completely resolved in 13 mutation carriers after administrating the aforementioned dose of carbamazepine. However, of the 20 non-*PRRT2* mutation carriers, only 2 achieved complete resolution, 16 achieved incomplete control of dyskinesias, and 2 others had only slight relief of their attacks.

Combining the results of 2 stages, all *PRRT2* mutation carriers responded completely to low-dose carbamazepine, while 94% of the non-*PRRT2* mutation carriers did not have a full response to carbamazepine, even after the dose was increased.

Discussion. Our study revealed a strong correlation of *PRRT2* mutations with PKD phenotypes and drug response. Therefore, we propose that *PRRT2* mutations be incorporated into the Bruno et al. criteria. Also, we propose that low-dose (50 mg/d) carbamazepine can completely resolve the attacks in cases with *PRRT2* mutations. Further studies are required to identify other causative genes for those cases without *PRRT2* mutations.

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Author contributions: Dr. Li: data acquisition, analysis and interpretation of data, statistical analysis, drafting the manuscript. Dr. Chen: data acquisition, analysis and interpretation of data. Dr. Ni: data acquisition. Dr. K Wang: data acquisition. Dr. Liu: data acquisition. Prof. N Wang: data acquisition, analysis and interpretation of data. Prof. Xiong: analysis and interpretation of data. Prof. Xu: statistical analysis, manuscript revision. Prof. Wu: funding, study design and conceptualization, data acquisition, analysis and interpretation of data, technical and material support, drafting and critical revision of the manuscript.

Acknowledgment: The authors thank the participants for taking part in this study.

Study funding: Supported by a grant from the National Natural Science Foundation of China to Zhi-Ying Wu (81125009, Beijing), the Program for Outstanding Academic Leader of Shanghai (12XD1406000), and a grant from State Key Laboratory of Neuroscience (SKLN–201205).

Disclosure: The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received July 16, 2012. Accepted in final form December 20, 2012.

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Neurology 2013;80;1534-1535 Published Online before print March 27, 2013
DOI 10.1212/WNL.0b013e31828cf7e1