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발작성 운동 이상증 한국인 환자의 임상 및 *PRRT2* 유전자 분석

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Clinical Manifestation and *PRRT2* Analysis of Korean Patients with Paroxysmal Kinesigenic Dyskinesia

Purpose: Paroxysmal kinesigenic dyskinesia (PKD) is a rare paroxysmal movement disorder characterized by recurrent and brief dyskinesia attacks triggered by sudden voluntary movement. The diagnosis of PKD is based on clinical findings, and mutations in the proline-rich transmembrane protein 2 (*PRRT2*) gene have been identified as the cause of PKD. Two Korean cohorts have been reported on *PRRT2* mutation analysis in PKD patients. The purpose of this study was to determine the mutation spectrum of the *PRRT2* gene and to examine the clinical characteristics associated with *PRRT2* mutations.

Methods: We studied 23 members of four families with familial PKD and two families with sporadic PKD which included 9 patients and 2 patients, respectively. Mutation analysis of the *PRRT2* gene was performed using Sanger sequencing. Clinical features of PKD were compared between patients with a *PRRT2* mutation and those with no detectable *PRRT2* mutation.

Results: *PRRT2* mutations were detected in three of four PKD families (75%), and in none of the two sporadic cases (0%). All detected *PRRT2* mutations were c.649dupC (p.Arg217Profs*8). Subjects with detected *PRRT2* mutations had earlier age at onset and longer duration of attacks.

Conclusion: As previously reported in Korean PKD patients, our results confirmed that PRRT2 is a major causative gene for familial PKD, and the c.649dupC is the most frequent mutation. *PRRT2* mutation analysis is required for the molecular diagnosis of familial PKD and for evaluating the clinical manifestations of PKD.

Key Words: Paroxysmal kinesigenic dyskinesia, *PRRT2*, Dystonia

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Introduction

Paroxysmal kinesigenic dyskinesia (PKD) (OMIM #128200) is a rare paroxysmal movement disorder characterized by recurrent and short attacks of purposeless involuntary movement triggered by rapid voluntary motion. These attacks usually have onset during childhood or early adulthood and can involve dystonic postures, chorea, or athetosis. Symptoms become less severe with age and show favorable responses to anticonvulsant medications[1)]. Recently, three different heterozygous truncating mutations in the proline-rich transmembrane protein 2 (*PRRT2*) gene were first reported in eight Han Chinese families with PKD[1)]. Two different mutations in the *PRRT2* gene were simultaneously identified in two lar-

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ge Han Chinese families[2]. Subsequently, many studies have shown that heterozygous mutations in the *PRRT2* gene have been identified in PKD, infantile convulsions and choreoathetosis (ICCA), and benign familial infantile convulsions (BFIC)[3-11]. Although more than 70 *PRRT2* mutations have been reported, the c.649dupC frameshift mutation accounts for nearly 80% of the cases[10]. *PRRT2* mutations are significantly associated with an earlier age at onset of PKD, longer duration of attacks, a more complicated form of PKD, and a tendency toward family history of PKD[12].

To the best of our knowledge, only two Korean cohorts have been previously published on *PRRT2* genetic studies for PKD patients[7,11]. In this study, we aimed to perform a mutation analysis of the *PRRT2* gene in six Korean PKD families and to investigate the clinical manifestations and *PRRT2* mutations in PKD patients.

Materials and Methods

1. Patients

Twenty-three members from four familial and two sporadic families were recruited five families from Samsung Changwon Hospital and one family from Daegu Catholic University Hospital from 2007 to 2015 (Fig. 1). A total of 11 PKD patients were diagnosed according to the diagnostic criteria established by Bruno et al.[13]. The clinical diagnostic criteria of Bruno et al. were as follows: (1) Identified kinesigenic trigger for the attacks; (2) Short duration of attacks (<1 minute); (3) No loss of consciousness or pain during attacks; (4) Exclusion of other organic diseases and normal neurologic examination; (5) Control of attacks with phenytoin or carbamazepine, if tried; and (6) Age at onset between 1 and 20 years, if no family history of PKD.

The collected clinical data included patient demographics, family histories, results of general and neurologic examinations,

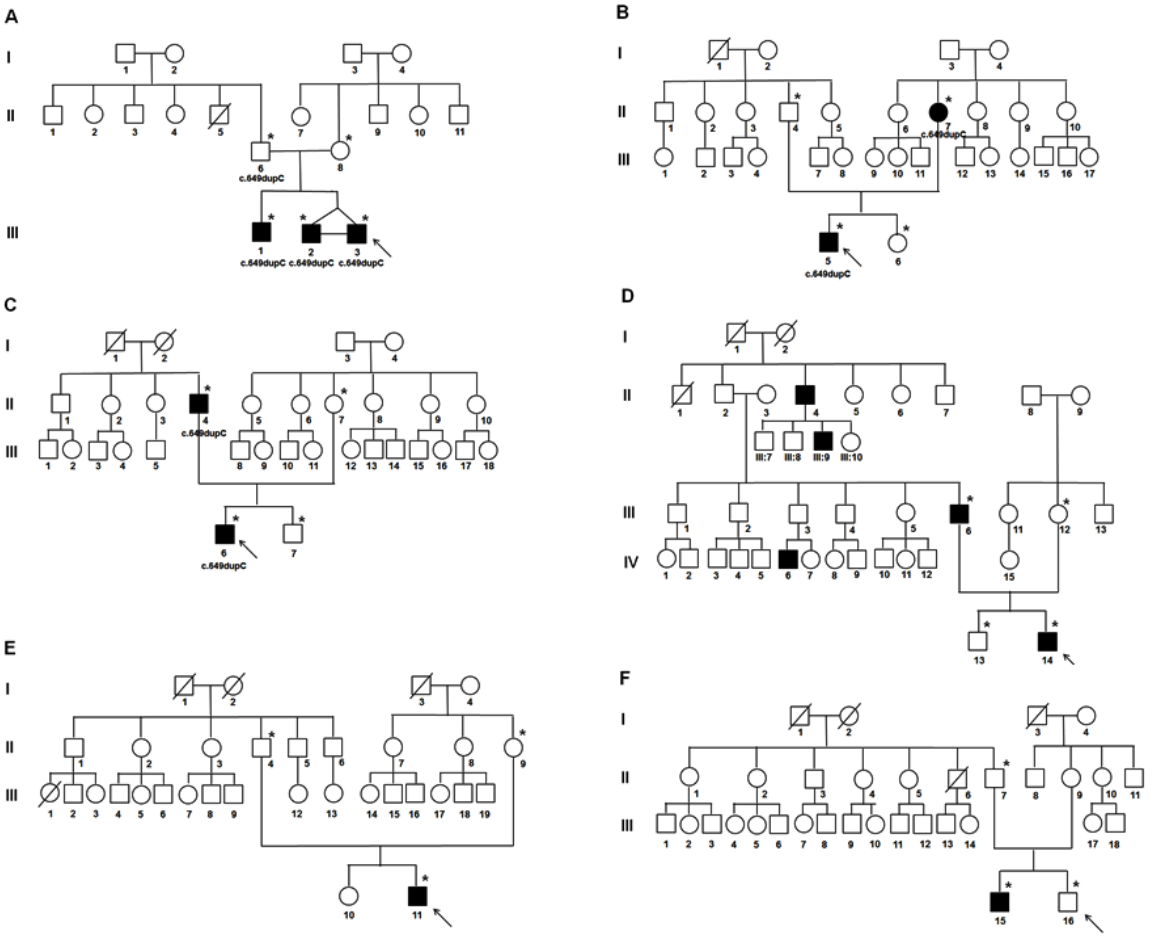

Fig. 1. Pedigrees of six paroxysmal kinesigenic dyskinesia (PKD) families. Pedigrees A, B, C, and D represent familial PKD, and pedigrees D and E are for sporadic PKD. Probands are indicated with arrows. Asterisks (*) depict the subjects who underwent PRRT2 gene mutation analysis, and the PRRT2 genotype is labeled below the symbols. The squares and circles denote males and females, respectively, and the closed and open symbols represent affected and unaffected individuals.

clinical features of the disorder, results of electroencephalography (EEG), 24-hour continuous EEG monitoring, and brain magnetic resonance imaging (MRI). All participants provided written informed consent for the protocols that were approved by the Institutional Review Board of Samsung Changwon Hospital (2013-SCMC-025-00) and Daegu Catholic University Hospital, Republic of Korea (CR-13-083).

2. Genetic analysis

Genomic deoxyribonucleic acid (DNA) was isolated from peripheral blood leukocytes using the Gentra Puregene Blood kit (Qiagen®, Germantown, MD, USA). The coding region of *PRRT2*, including the flanking sequences, was amplified using primer pairs designed by the authors. Direct sequencing of polymerase chain reaction (PCR) products was performed on the ABI 3130 analyzer (Applied Biosystems®, Foster City, CA, USA) with the BigDye Terminator Cycle Sequencing kit (Applied Biosystems®, Foster City, CA, USA). The sequence variations were analyzed with reference sequence NM_145239.2.

3. Statistical analysis

This study is not suitable for comparative analysis, because the number of subjects is small due to the rarity of the disease[14]. Thus, we show our data descriptively.

Results

1. Clinical manifestations

The demographic data and clinical features of 11 clinically diagnosed PKD patients are shown in Table 1, and the six pedigrees of the 11 cases are shown in Fig. 1. Most patients were male (10/11, 91%), and the median age at the onset of symptoms was 12 years (range: 7-13.5 years). The clinical presentation of the attacks was variable between families and among the affected individuals in the same family. The EEGs and brain MRIs were unremarkable. A good response to carbamazepine was obtained in all patients, and three affected patients who did not receive anticonvulsant drugs showed remission of symptoms with age.

In family A, the proband (III-3) presented with febrile seizures at age three and dyskinetic symptoms at age eight. The symptoms were episodic paroxysmal bilateral dystonic and athetoic movements without aura. His monozygotic twin brother also showed dyskinesia at the same age, but with different manifestations such as unilateral dystonia. His elder brother had similar manifestations of the movement, but at a late age of onset. His father carried the same mutation and did not present any dyskinetic symptoms. The main manifestation in family B was athetosis with abnormal sensation and sensory aura. The proband and his mother B had a greater than 50% reduction of attacks with or without medication. Affected members in family C had similar features such as unilateral dystonia, athetosis, or chorea, while family D showed different manifestations among affected members. Two sporadic cases developed dyskinesia at the ages of 13.5 and 12.5 years and had excellent response to carbamazepine.

2. *PRRT2* mutations

Of the 11 patients with PKD, seven carried the same heterozygous *PRRT2* mutation, c.649dupC (p.Arg217Profs*8) (Fig. 1). All seven patients with *PRRT2* mutation were familial cases from three of four PKD families (75%). The father of three affected children (family A) was an asymptomatic mutation

Table 1. Demographic Data and Clinical Features of 11 Clinically Diagnosed Paroxysmal Kinesigenic Dyskinesia (PKD) Patients

Patient	Sex	Age at present (years)	Age at onset (years)	Family History	Trigger	Involuntary movement	Aura	Duration of attacks(s)	EEG	Brain MRI	Treatment	Remission	*PRRT2* mutation
A III-1	M	25	12.0	Yes	SM	D,A/Bi	Yes	10-29	Normal	Normal	CBZ	CR	+
A III-2	M	23	8.0	Yes	SM	D/Uni	No	30-60	Normal	Normal	CBZ	CR	+
A III-3	M	23	8.0	Yes	SM/IM	D,A/Bi	No	30-60	Normal	Normal	CBZ	CR	+
B II-7	F	51	13.0	Yes	SM	A/Bi	Yes	< 10	ND	Normal	No	> 50	+
B III-5	M	22	7.0	Yes	SM/IM	A/Uni	Yes	10-29	Normal	Normal	CBZ	> 50	+
C II-4	M	43	7.0	Yes	SM	D,A,C/Uni	No	< 10	ND	Normal	No	> 50	+
C III-6	M	21	12.5	Yes	SM/IM	D,A,B,C/Uni	No	10-29	Normal	Normal	CBZ	> 50	+
D III-6	M	45	10.0	Yes	IM	D,A/Bi	Yes	< 10	ND	Normal	No	CR	-
D IV-14	M	15	12.5	Yes	SM/CW	A/Uni	Yes	< 10	Normal	Normal	CBZ	CR	-
E III-11	M	21	13.5	No	IM	D,A/Bi	No	10-29	Normal	Normal	CBZ	CR	-
F III-15	M	18	12.5	No	SM/IM	D/Uni	No	< 10	Normal	Normal	CBZ	CR	-

A, athetosis; B, ballismus; Bi, bilateral; C, chorea; CBZ, carbamazepine; CR, complete remission; CW, cold weather; D, dystonia; E, ;EEG, electroencephalogram; F, female; IM, intention to move; M, male; MRI, Magnetic resonance imaging; ND, not done; PRRT2, proline-rich transmembrane protein 2; SM, sudden movement; Uni, unilateral; > 50, greater than 50% remission.

carrier. Two sporadic cases did not have *PRRT2* mutation. The comparison of demographic and clinical data between the PKD patients with and without *PRRT2* mutations is shown in Table 2. Although there was no statistical significance due to a small sample size, the data suggested that subjects with *PRRT2* mutation were younger at onset compared with those without *PRRT2* mutation (median age: 8.0 years vs. 12.5 years). A trend toward longer duration of attacks was seen in patients with *PRRT2* mutation.

Discussion

PKD was first described in a 23-year-old Japanese patient by Shuzo Kure in 1892[10]. Andrew Kertesz called the affliction paroxysmal kinesigenic choreoathetosis, describing his patients with short paroxysms of unilateral or generalized tonic, choreiform, and athetoid movements[15]. Because of familial cases suggesting an autosomal dominant inheritance, a genetic cause of PKD was suspected. Tomita et al. reported 16p11.2-q12.1 as the chromosomal location of the PKD critical region using genome-wide linkage analysis in eight Japanese families with PKD[16], and Bennett et al. implicated the same region in a linkage analysis of an African American family with PKD[17]. By combining next-generation sequencing and linkage analysis, *PRRT2* located on chromosome 16p11.2 was identified as the causative gene of PKD in Chinese PKD families in 2011[1,2]. The *PRRT2* protein was detected in thin axonal processes exiting from the neuron cell bodies and plays an important role in synapse development and function by interacting with SNAP25[18]. The causative role of *PRRT2* mutations has been documented in a variety of additional paroxysmal disorders such as such as benign familial infantile epilepsy, ICCA syndrome, hemiplegic migraine, and episodic ataxia[3-11]. PKD shares some clinical features and common genetic causes with these disorders, which are allelic disorders or *PRRT2*-associated diseases[10].

Table 2. Comparison of Demographic and Clinical Data between Paroxysmal Kinesigenic Dyskinesia (PKD) Patients with and without Proline-Rich Transmembrane Protein 2 (*PRRT2*) Mutations

Variables	Patients with *PRRT2* mutation	Patients without *PRRT2* mutation
No. of patients	7	4
Male (%)	6 (85.7)	4 (100)
Age at onset, median, years, (Range)	8.0 (7-13)	12.5 (10-13.5)
Trigger		
Sudden movement	7	2
Intention to move	3	3
Cold weather	0	1
Involuntary movement		
Dystonia	1	1
Athetosis	2	1
Dystonia+Athetosis	2	2
Dystonia+Athetosis+Chorea	2	0
Laterality		
Unilateral	4	2
Bilateral	3	2
Aura (%)	3 (42.9)	2 (50)
Duration of attacks, seconds		
< 10	2	3
10-29	3	1
30-60	2	0
Attack frequency/day		
<1	1	0
1-5	4	3
6-10	1	0
> 10	1	1
Medication, Carbamazepine	5	3
Outcome, attack status		
Complete remission	3	4
>50% improvement	4	0

PRRT2, proline-rich transmembrane protein 2.

Approximately 70 different *PRRT2* mutations with loss of function have been reported in *PRRT2*-associated diseases, and 78.5% of patients carried the same frameshift mutation, c.649dupC (p.Arg217Profs*8). In PKD, *PRRT2* mutations were detected in 76.3% of familial cases, and c.649dupC was the most common (80.5%), followed by c.649delC (1.8%), c.718C>T (1.8%), and c.649C>T (1.6%)10). Our study showed *PRRT2* mutation in three of the four PKD families (75%) with an autosomal dominant mode; in all of the cases with a detected mutation, it was c.649dupC.

To the best of our knowledge, two Korean cohorts have been previously described in *PRRT2* mutation analyses in PKD patients. Youn et al. reported on *PRRT2* mutations in three of five PKD families (60%) and two of 19 sporadic cases (10.5%)[7]. Seong et al. reported *PRRT2* mutation in seven patients: three from six familial cases (50%) and four from 23 sporadic cases (17%)[11]. From three Korean cohorts including our study, *PRRT2* mutation was found in 65.2% (15/23) of familial PKD cases and 13.6% (6/44) of sporadic cases (Table 3). Among 15 *PRRT2* mutation-positive cases, 12 had c.649dupC, and the other three had 649delC, c.629dupC, and c.323_324delCA. Interestingly, male patients were predominant in Korean PKD (male:female ratio = 62:5, 92.5%:7.5%), compared with the non-Korean PKD cohorts of 62.8% males versus 37.2% females[10].

Our study revealed that the *PRRT2* mutation carriers had an earlier age at onset compared with those without *PRRT2* mutation (8.0 years vs. 12.5 years). This result was similar to two Korean reports by Youn et al. (12.0 years vs. 14.0 years)[7] and Seong et al. (10.0 years vs. 13.8 years)[11]. Huang et al. reported that *PRRT2* mutation carriers were younger at onset, experienced longer

Table 3. The Results of *PRRT2* Gene Mutation Analysis of Korean Patients with PKD (including review of two literatures)

	Familial PKD			Sporadic PKD		
	Total No of patients* (families)	*PRRT2* mutation-positive		*PRRT2* mutation-positive		
		No of patients (families)	No of male	Total No of patients*	No of patients	No of male
JY Youn et al.[7]	8 (5)	5 (3)	5	19	2	2
MW Seong et al.[11]	6 (6)	3 (3)	3	23	4	3
This study	9 (4)	7 (3)	6	2	0	0
Total	23 (15)	15 (9)	14	44	6	5

*Total number of PKD patients who underwent *PRRT2* gene mutation analysis; PKD, paroxysmal kinesigenic dyskinesia; *PRRT2*, proline-rich transmembrane protein 2

attacks, and tended to present with complicated PKD and combined phenotypes of dystonia and chorea[12]. Our patients with *PRRT2* mutation tended to have longer duration of attacks but did not show significant correlation with other phenotypes due to the limited number of patients.

It is thus unclear if all patients with *PRRT2* mutation develop paroxysmal symptoms. A study by van Vliet et al. suggested that the estimated penetrance of the *PRRT2* mutation was 61%; however, when both PKD phenotype and infantile convulsions were considered, the penetrance was 90%[6]. The present study included an unaffected individual with a *PRRT2* mutation who is the father of three children with PKD. Even among *PRRT2* mutation carriers, there are remarkable phenotypic variabilities. Family members carrying identical *PRRT2* mutations often exhibit variable phenotypes or different diseases. The phenotype can vary even at different ages of the same patient[19]. In this study, affected family members showed variable clinical manifestations within the same family. The proband of family A also had a history of febrile seizures, presenting with different phenotypes at different ages. This remarkable phenotypic variability in *PRRT2* mutations might imply genetic buffering and/or environmental factors. Age-dependent expression can also play a role in pleiotropic effects. For example, BFIC occurs in early infancy and then remits, whereas PKD is more typical of late childhood or adolescence. However, the molecular mechanisms underlying the remarkable pleiotropy associated with *PRRT2* mutations remain unclear[20-22].

To date, the *PRRT2* mutation has not been found in one-quarter of familial PKD or in most sporadic cases, suggesting the involvement of additional genetic mutations or possible misdiagnoses due to clinical overlap. Recently, *SCN8A* has been reported as a novel gene in which a recurrent mutation causes BFIC/ICCA according to whole exome sequencing[23]. In addition, mutations in *SLC2A1* and *CLCN1*, which are the causative genes of paroxysmal nonkinesigenic dyskinesia and myotonia congenita, were detected in clinically diagnosed and *PRRT2*-negative PKD cases[23]. Therefore, further comprehensive genetic studies in PKD patients without *PRRT2* mutation need to be investigated.

In conclusion, PKD is a rare disorder in Korea and has shown clinical heterogeneity including phenotypic variability and incomplete penetrance. The *PRRT2* mutation was strongly related to familial PKD and trended to a younger age at onset and longer duration of attacks. The *PRRT2* mutation analysis is required for the molecular diagnosis of familial PKD and to evaluate the clinical manifestations of PKD.

요약

목적: 발작성 운동 이상증(PKD)은 갑작스런 자발적인 운동에 의해 유발되는 짧고 반복적인 운동 장애를 특징으로 하는 드문 발작성 운동 장애이다. PKD의 진단은 증상 진단에 근거하며, 유전자적 검사가 진단에 보조적으로 도움을 줄 수 있다. 본 연구의 목적은 *PRRT2* 유전자의 돌연변이 스펙트럼을 측정하고, *PRRT2* 돌연변이와 관련된 임상 특징을 알아보기 위함이다.

방법: 우리는 가족성 PKD 4가족 및 산발성 PKD 2가족에게서 PKD 환자 11명을 포함하여 전체 23명을 대상으로 연구하였다. Sanger sequencing을 이용하여 *PRRT2* 유전자의 돌연변이 분석을 수행 하였다. *PRRT2* 변이가 PKD 환자와 *PRRT2* 변이가 없는 PKD 환자의 임상 양상을 비교하였다.

결과: *PRRT2* 돌연변이는 가족력이 있는 PKD군에서는 4가족 중 3가족(75%), 9명의 PKD 환자 중 7명(77.8%)에게서 발견되었다. 그러나 가족력이 없는 산발적인 2명의 PKD 환자에서는 *PRRT2* 변이가 발견되지 않았다. 발견된 모든 *PRRT2* 돌연변이는 c.649dupC (p.Arg217Profs * 8)이었다. *PRRT2* 돌연변이를 가진 PKD 환자는 발병이 좀 더 어린 나이에 발생하고 발병 기간도 더 길었다.

결론: 본 연구결과는 이전의 한국인 PKD 환자의 보고와 동일하게 *PRRT2*가 가족 PKD의 주요 원인 유전자이고, c.649dupC가 가장 흔한 돌연변이임을 확인하였다. *PRRT2* 돌연변이 분석은 가족력이 있는 PKD 환자의 분자 진단 및 PKD의 임상 증상을 평가하는 데 필요하다.

References

1) Chen WJ, Lin Y, Xiong ZQ, Wei W, Ni W, Tan GH, et al. Exome sequencing identifies truncating mutations in PRRT2 that cause paroxysmal kinesigenic dyskinesia. Nat Genet 2011;43: 1252-5.
2) Wang JL, Cao L, Li XH, Hu ZM, Li JD, Zhang JG, et al. Identification of PRRT2 as the causative gene of paroxysmal kinesigenic dyskinesias. Brain 2011;134: 3493-501.
3) Liu Q, Qi Z, Wan XH, Li JY, Shi L, Lu Q, et al. Mutations in PRRT2 result in paroxysmal dyskinesias with marked variability in clinical expression. J Med Genet 2012;49: 79-82.
4) Liu XR, Wu M, He N, Meng H, Wen L, Wang JL, et al. Novel PRRT2 mutations in paroxysmal dyskinesia patients with variant inheritance and phenotypes. Genes Brain Behav 2013;12: 234-40.
5) Méneret A, Grabli D, Depienne C, Gaudebout C, Picard F, Dürr A, et al. PRRT2 mutations: a major cause of paroxysmal kinesigenic dyskinesia in the European population. Neurology 2012;79: 170-4.
6) van Vliet R, Breedveld G, de Rijk-van Andel J, Brilstra E, Verbeek N, Verschuuren-Bemelmans C, et al. PRRT2 phenotypes and penetrance of paroxysmal kinesigenic dyskinesia and infantile convulsions. Neurology 2012;79: 777-84.
7) Youn J, Kim JS, Lee M, Lee J, Roh H, Ki CS, et al. Clinical manifestations in paroxysmal kinesigenic dyskinesia patients with proline-rich transmembrane protein 2 gene mutation. J Clin Neurol 2014;10: 50-4.
8) Ono S, Yoshiura K, Kinoshita A, Kikuchi T, Nakane Y, Kato N, et al. Mutations in PRRT2 responsible for paroxysmal kinesigenic dyskinesias also cause benign familial infantile convulsions. J Hum Genet 2012;57: 338-41.
9) Heron SE, Grinton BE, Kivity S, Afawi Z, Zuberi SM, Hughes JN, et al. PRRT2 mutations cause benign familial infantile epilepsy and infantile convulsions with choreoathetosis syndrome. Am J Hum Genet 2012;90: 152-60.
10) Ebrahimi-Fakhari D, Saffari A, Westenberger A, Klein C. The evolving spectrum of PRRT2-associated paroxysmal diseases. Brain 2015;138: 3476-95.
11) Seong MW, Kim HJ, Jeon BS, Ehm GH, Yang HJ, Kim YE, et al. PRRT2 mutation in Korean patients with paroxysmal kinesigenic dyskinesia: a clinico-genetic analysis. Neurol Asia 2014;19: 357-62.
12) Huang XJ, Wang T, Wang JL, Liu XL, Che XQ, Li J, et al. Paroxysmal kinesigenic dyskinesia: clinical and genetic analyses of 110 patients. Neurology 2015;85: 1546-53.
13) Bruno MK, Hallett M, Gwinn-Hardy K, Sorensen B, Considine E, Tucker S, et al. Clinical evaluation of idiopathic paroxysmal kinesigenic dyskinesia: new diagnostic criteria. Neurology 2004;63: 2280-7.
14) Hackshaw A. Small studies: strengths and limitations. Eur Respir J 2008;32:1141-3.
15) Kertesz A. Paroxysmal kinesigenic choreoathetosis. An entity within the paroxysmal choreoathetosis syndrome. Description of 10 cases, including 1 autopsied. Neurology 1967;17: 680-90.
16) Tomita H, Nagamitsu S, Wakui K, Fukushima Y, Yamada K, Sadamatsu M, et al. Paroxysmal kinesigenic choreoathetosis locus maps to chromosome 16p11.2-q12.1. Am J Hum Genet 1999;65: 1688-97.
17) Bennett LB, Roach ES, Bowcock AM. A locus for paroxysmal kinesigenic dyskinesia maps to human chromosome 16. Neurology 2000;54: 125-30.
18) Lee HY, Huang Y, Bruneau N, Roll P, Roberson ED, Hermann M, et al. Mutations in the gene PRRT2 cause paroxysmal kinesigenic dyskinesia with infantile convulsions. Cell Rep 2012;1: 2-12.
19) Valtorta F, Benfenati F, Zara F, Meldolesi J. PRRT2: from paroxysmal disorders to regulation of synaptic function. Trends Neurosci 2016;39: 668-79.
20) Gardiner AR, Bhatia KP, Stamelou M, Dale RC, Kurian MA, Schneider SA, et al. PRRT2 gene mutations: from paroxysmal dyskinesia to episodic ataxia and hemiplegic migraine. Neurology 2012;79: 2115-21.
21) Heron SE, Dibbens LM. Role of PRRT2 in common paroxysmal neurological disorders: a gene with remarkable pleiotropy. J Med Genet 2013;50: 133-9.
22) Stelzl U, Worm U, Lalowski M, Haenig C, Brembeck FH, Goehler H, et al. A human protein-protein interaction network: a resource for annotating the proteome. Cell 2005;122: 957-68.
23) Gardella E, Becker F, Møller RS, Schubert J, Lemke JR, Larsen LH, et al. Benign infantile seizures and paroxysmal dyskinesia caused by an SCN8A mutation. Ann Neurol 2016;79: 428-36.
24) Wang HX, Li HF, Liu GL, Wen XD, Wu ZY. Mutation analysis of MR-1, SLC2A1, and CLCN1 in 28 PRRT2-negative paroxysmal kinesigenic dyskinesia patients. Chin Med J (Engl) 2016;129: 1017-21.