Genotype–phenotype correlation of paroxysmal nonkinesigenic dyskinesia

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ABSTRACT Background: Paroxysmal nonkinesigenic dyskinesia (PNKD) is a rare disorder characterized by episodic hyperkinetic movement attacks. We have recently identified mutations in the *MR-1* gene causing familial PNKD. **Methods:** We reviewed the clinical features of 14 kindreds with familial dyskinesia that was not clearly induced by movement or during sleep. Of these 14 kindreds, 8 had *MR-1* mutations and 6 did not. **Results:** Patients with PNKD with *MR-1* mutations had their attack onset in youth (infancy and early childhood). Typical attacks consisted of a mixture of chorea and dystonia in the limbs, face, and trunk, and typical attack duration lasted from 10 minutes to 1 hour. Caffeine, alcohol, and emotional stress were prominent precipitants. Attacks had a favorable response to benzodiazepines, such as clonazepam and diazepam. Attacks in families without *MR-1* mutations were more variable in their age at onset, precipitants, clinical features, and response to medications. Several were induced by persistent exercise. **Conclusions:** Paroxysmal nonkinesigenic dyskinesia (PNKD) should be strictly defined based on age at onset and ability to precipitate attacks with caffeine and alcohol. Patients with this clinical presentation (which is similar to the phenotype initially reported by Mount and Reback) are likely to harbor myofibrillogenesis regulator 1 (*MR-1*) gene mutations. Other "PNKD-like" families exist, but atypical features suggests that these subjects are clinically distinct from PNKD and do not have *MR-1* mutations. Some may represent paroxysmal exertional dyskinesia. **NEUROLOGY 2007;68:1782–1789**

Paroxysmal dyskinesias are a heterogeneous group of movement disorders characterized by intermittent attacks of hyperkinetic involuntary movements without loss of consciousness.[1,2] According to one widely applied classification scheme,[3] paroxysmal dyskinesias can be classified into four subgroups: paroxysmal kinesigenic dyskinesia (PKD), paroxysmal nonkinesigenic dyskinesia (PNKD), paroxysmal exercise-induced dystonia (PED), and paroxysmal hypnogenic dyskinesia (PHD). Each category is further subdivided into idiopathic (familial and sporadic) or secondary, due to a specific etiology such as a stroke, trauma, multiple sclerosis, CNS infections, and other causes.[4] PKD and PNKD compromise a majority of paroxysmal dyskinesia cases; PED and PHD are rare, and PHD is now generally recognized as a form of frontal lobe epilepsy.[5-7] PKD is characterized by brief attacks triggered by sudden movements and have an excellent response to antiepileptic drugs (AEDs) such as carbamazepine or phenytoin.[8] In contrast, PNKD attacks are longer, lasting from minutes to hours. Sudden movements do not trigger attacks, but caffeine, ETOH, stress, sleep deprivation, and exercise can lower the threshold of attacks.[9]

Mount and Reback reported the first family with PNKD in the literature, calling them "familial paroxysmal choreoathetosis."[10] Members of this family had paroxysmal attacks of chorea and athetotic movements and segregated in an autosomal dominant fashion. Reports of families with similar clinical presentations followed.[9,11-13] Various terms were used describ-

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ing this condition, including paroxysmal dystonic choreoathetosis. We favor the term *paroxysmal nonkinesigenic dyskinesia* because it represents the simplest comprehensive phenotypic classification, and we henceforth refer to this disorder as PNKD.[3]

In 1996, we mapped the PNKD gene to the long arm of chromosome 2.[14] Subsequently, numerous investigators have replicated this finding and narrowed the region.[15-18] However, the gene for PNKD was not discovered for many years after the original linkage. Because ion channels are a common cause of mendelian episodic disorders,[19,20] we considered ion channel genes within the chromosome 2 PNKD locus as excellent candidates but were unsuccessful in identifying causative mutations in these genes.

Recently, we have identified mutations in the myofibrillogenesis regulator 1 (*MR-1*) gene on chromosome 2 in eight families with PNKD,[21] and other groups have also reported mutations in *MR-1* gene in PNKD families from different ethnic origins.[22-24] *MR-1* itself is not an ion channel, and its precise function is not yet known, although it is predicted to be an enzyme in a stress response pathway. However, identification of the PNKD gene is a major advance toward better diagnosis, better understanding of disease pathophysiology, and development of more effective treatment options for PNKD. In this article, we performed phenotype–genotype correlations in a large group of paroxysmal dyskinesia families.

METHODS We analyzed the clinical information of 49 patients from eight kindreds harboring *MR-1* mutations. Mutation analysis included direct sequencing of all exons including approximately 50 base pairs of flanking intronic DNA. (In the mutation analysis, 52 subjects were found to be harboring the mutation; of these, we did not have detailed clinical information of 2 patients, and one was an asymptomatic infant at the time of evaluation.[21]) We also reviewed information of 22 patients from six kindreds with the clinical diagnosis of PNKD, referred for genetic testing, who did not have the *MR-1* mutation. PNKD was clinically diagnosed when patients had "attacks of involuntary movements occurring spontaneously."[3] Patients with PKD (attacks occurring abruptly after sudden voluntary movements) and PED (attacks of involuntary movements precipitated by prolonged physical exertion) were excluded. All sporadic cases were excluded.

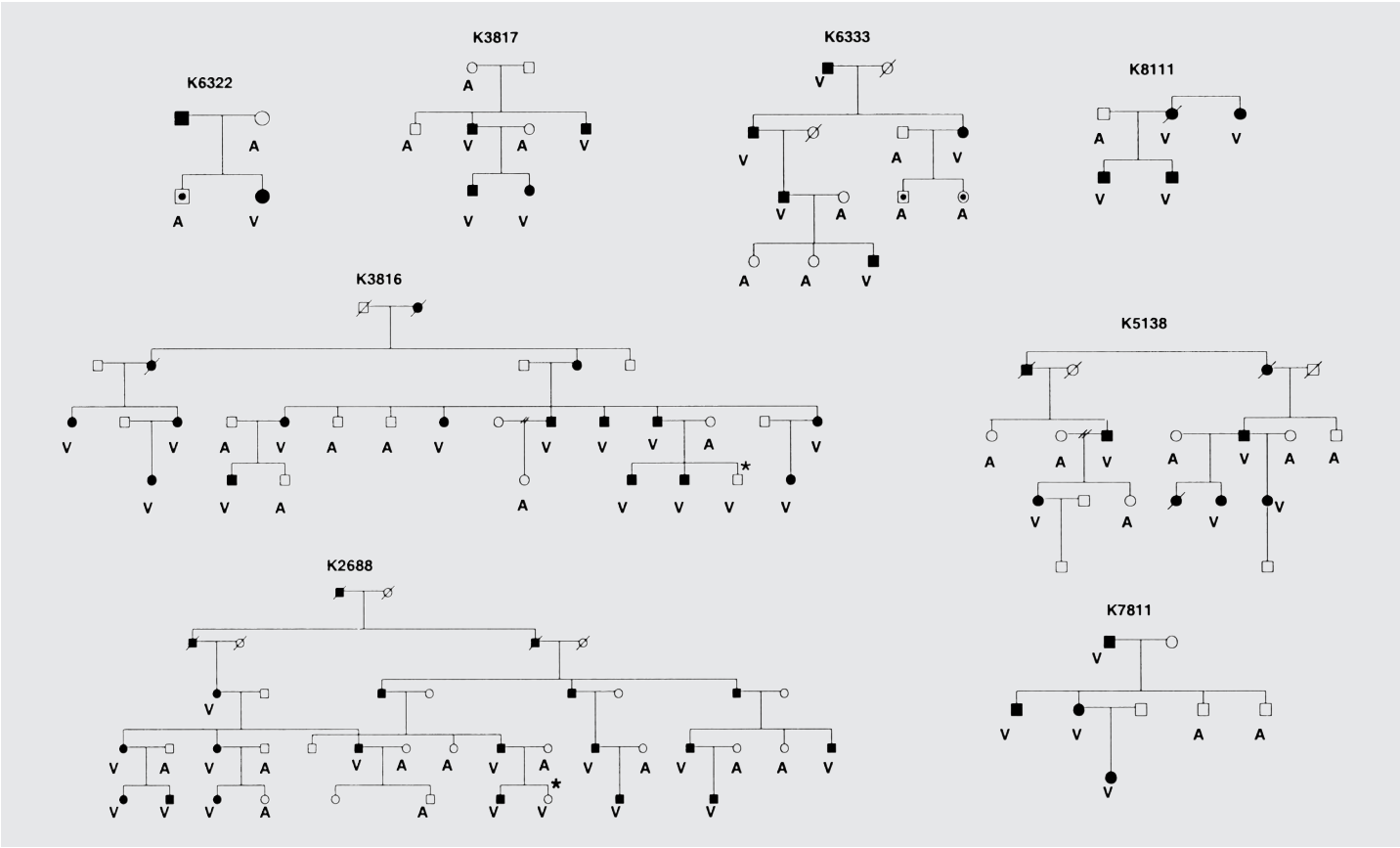
We collected the following information: age at onset, precipitant of attacks, presence and description of aura, duration and phenomenology of attack, pain during attacks, alteration of consciousness, frequency of attacks, course of illness, medications tried and response, any other associated neurologic disorders, and family history. All English-speaking patients were interviewed by one neurologist (M.B.) based on a structured protocol. All non–English-speaking patients filled out the same questionnaire with the help of native-speaking neurologist. The clinical team involved in clinical data collecting was blinded to the results of *MR-1* mutation when the information was collected. One kindred (Kindred 6,322) was lost to follow-up and thus, only the original medical records were analyzed in this family.

RESULTS Eight pedigrees segregating *MR-1* mutations are shown in figure 1, and their clinical characteristics are summarized in table E-1 on the *Neurology* Web site at www.neurology.org. There were 49 patients (27 male and 22 female) in this group (table). The penetrance of *MR-1* mutation was extremely high: there was one asymptomatic carrier (marked with an asterisk in the figure), but this patient was too young to be considered unaffected. Penetrance was calculated as 98%. There were no phenotype differences between five kindreds (K2688, K3816, K5138, K3817, and K8111) with the alanine to valine mutation at amino acid 7 (A7V) and three kindreds (K6333, K6322, and K7811) with alanine to valine mutation at amino acid 9 (A9V).

The onset of attacks ranged from age 3 months to 12 years (average: 4.0 ± 4.6 years). Sixteen (33%) patients had attacks starting before age 1 year. Interictal neurologic examinations were normal in all patients, except for one with cerebral palsy according to the local neurologist involved in the patients' care.

Forty-one percent of mutation positive patients reported premonitory sensations preceding an attack. Of those who described the premonitory sensation, 80% described this as a focal limb sensation (stiffening or numb sensation), whereas 20% described this as more generalized internal feeling resembling anxiety. The attacks manifest with a variable combination of dystonia and chorea; 88% reported some combination of chorea and dystonia, whereas 12% reported dystonia only. Even when combination of dystonia and chorea were reported, phenomenology was less variable within the same kindred; e.g., in Kindred 2,688, episodes were more dystonic in the first months of life, but as they grew older, more choreic components were observed after the initial phase of dystonia. Speech involvement was reported in 45% of the patients. Less common phenomenology reported include blepharospasm, risus sardonicus, and diplopia at the height of an attack. The attack duration ranged from several minutes to 12 hours, but typical attacks were 10 minutes to 1 hour. Attack frequency varied, even

Figure 1 Pedigree of eight paroxysmal nonkinesigenic dyskinesia kindreds with *MR-1* mutation



■ Affected male, ● affected female, □ unaffected male, ○ unaffected female; a dot in an unfilled square or circle denotes "unknown" phenotype. * Asymptomatic carrier, although too young at the time of evaluation to be consider unaffected. A = normal (homozygous alanine); V = mutation (heterozygous alanine/valine). This figure is reproduced (with modifications) from Hum Mol Genet 2004;13: 3161–3170.

within the families. Eighty-six percent of patients reported at least 1/week attacks at some point of life, but 6% reported only several attacks in their life, including one patient who reported only one attack in his life. Natural history varied, but there was a general tendency to decreasing attack frequency with aging. There was no gender difference.

Eighty-two percent of patients reported emotional stress as lowering attack threshold. In addition to negative stress, two patients reported that positive stress (excitement, such as playing computer games, or joyous conversation) could lower the attack threshold. Two patients reported that attacks occurred more frequently during let down periods (relaxation after stress, vacation, weekend, etc.). Caffeine and alcohol were frequent precipitants, reported in nearly 100% of patients who had ingested these compounds. There was only one patient who confidently stated that he could drink coffee without any problem, but this was the patient who had only one attack in his life, after witnessing the defeat of his favorite soccer team. In contrast, no patients reported nicotine as a precipitant. Menstruation (6%), heat (22%), exercise (12%), hunger (6%), and fatigue (12%) were less common but strong precipitants in some subjects. Sleep benefit was common (70%) but variable, even within a family.

Clonazepam and diazepam were the most effective medications, taken both as a prophylactic and as an abortive agent. Thirty-four of 35 patients (97%) who tried clonazepam, clorazepate, diazepam, or oxazepam had favorable responses. One patient resumed his coffee and alcohol drinking after starting the clonazepam, and another takes clonazepam once a month, before he goes out to parties. In contrast, 4 patients who tried phenobarbital and 1 who tried primidone reported no benefit with these agents. Many patients tried various AEDs as prophylactic agents. Out of the 6 who tried valproate, 4 reported initial response, but loss of response over the years, 1 reported no effect, and 1 still takes it, although this patient continues to have attacks and takes diazepam for acute attacks. Similarly, patients who tried phenytoin and carbamazepine reported complete lack of response. One patient still currently takes lamotrigine, but her attack frequency has increased over the course of years. Of the 4 patients reported to have tried haloperidol, either as prophylactic or abortive agent, 3 could not tolerate the side effects and immediately stopped the medication. One patient is still taking prophylactic haloperidol, but takes diazepam abortively for attacks. Other medications tried prophylactically include anticholinergics and lithium

Table Summary of clinical characteristics for *MR-1* mutation–positive and –negative patients

	MR-1 mutation positive	*MR-1* mutation negative
Number of patients	49	22
Male	27	14
Female	22	8
Age at onset*	4.0 ± 4.6	12.3 ± 10.8
Premonitory sensation	41%	63%
Precipitants		
Alcohol*	98% (n = 44)	0% (n = 6)
Caffeine*	98%	38%
Exercise*	12%	68%
Fatigue	12%	32%
Emotional stress*	82%	27%
Sleep benefit*	70%	36%
Attack phenomenology*		
Dystonia	12%	36%
Chorea	—	18%
Combination of dystonia and chorea*	88%	27%
Ballism	—	18%
Typical attack duration (minimum and maximum)	10 minutes to 1 hour (2 minutes to 12 hours)	10 minutes to few hours (2 minutes to 11 hours)
Attack frequency*		
At least once a week at some point in life*	86%	32%
Attack response to medication*		
Clonazepam, other benzodiazepine	97% (n = 34)	Initially 90%, effect worn off in 60% (n = 10)
Antiepileptics	10% (n = 10)	50% (n = 6)
Natural history		
Better	61%	38%
Same	21%	38%
Worse	18%	23%
Associated neurologic disease		
Migraine headaches*	47%	5%
Seizure/epilepsy*	0%	23%
Other	Prenatal asphyxia	Basal ganglia calcification
	Mental retardation	Ataxia
		Attention deficit hyperactivity disorder
		Learning disability
		Cluster headache

* $p < 0.05$ by χ^2 test.

(without any effect), acetazolamide (1 patient reporting some reduction in the pain during attack), and L-dopa (effective taken with clonazepam in 2 patients).

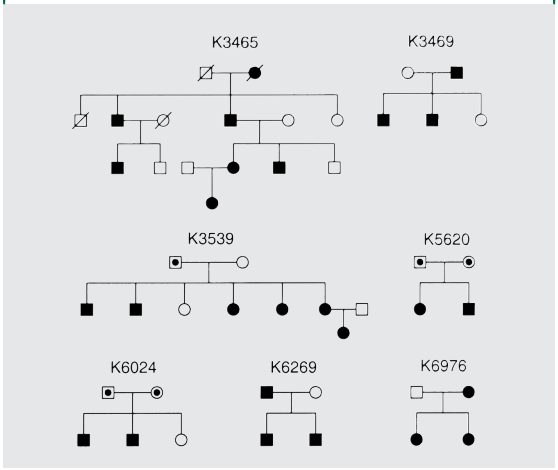
Headache, including migraine, was a common associated neurologic disease reported by the patients. Among 30 patients providing an adequate history for headache diagnosis, 14 patients (47%) met the International Headache Society criteria for migraine headache.[25] Other associated neurologic disease included 1 patient with prenatal asphyxia and 1 patient with mental retardation. Otherwise, we did not find any patients or family members with epilepsy or infantile convulsion, commonly associated with PKD.[8]

Among 7 women who were able to comment on their experience during pregnancy, 5 (71%) reported that they had no attacks or notably fewer attacks during pregnancy (especially during the first and third trimesters).

Six pedigrees without *MR-1* mutations are

■ Affected male, ● affected female, □ unaffected male, ○ unaffected female; a dot in an unfilled square or circle denotes "unknown" phenotype.

Figure 2 Pedigree of seven paroxysmal nonkinesigenic dyskinesia kindreds without *MR-1* mutation



shown in figure 2, and their clinical characteristics are summarized in table E-2. There were 22 patients (14 males and 8 females). The average age at onset was 12.3 ± 10.8 years. Neurologic examination results were unremarkable interictally, except for 2 patients in Kindred 6,976, who had baseline mild ataxia.

Aura was reported in 63% of the patients. Attack phenomenology was dystonia in 36%, chorea in 18%, a combination of dystonia and chorea in 27%, and ballism in 18% of the patients. Attack duration was between a few minutes up to 12 hours, but typical attacks were 10 minutes to a few hours. Frequency varied: 32% reported attacks at least once a week, and the rest reported attacks to be between couple of times per month to several times a year. Exercise was the most common trigger, reported in 68% of the patients, followed by caffeine (38%), fatigue (32%), emotional stress (27%), heat (23%), and hunger (14%). Menstruation, alcohol, and nicotine were not reported as triggers in any of the patients. Sleep benefit was reported in 36% of the patients.

The medication most commonly tried was benzodiazepines (both as prophylactic and abortive agent. All of the 8 patients reported some response, but 4 members of Kindred 3,465 reported that the effect of benzodiazepine has worn off over the course of years. Various AEDs were tried as prophylactic agents with mixed results; partial response was reported with valproate, carbamazepine, topiramate, and gabapentin, but other patients reported no response with carbamazepine, and worsening with phenytoin or carbamazepine. Two patients tried acetazolamide; both reported mild to moderate improvement. Two patients tried L-dopa; one reported no response, and other reported worsening of attacks.

Associated neurologic illness included epilepsy/seizures in 5 patients (23%). Of these, 2 patients from Kindred 3,469 also had basal ganglia calcification on their brain CT scan. Baseline mild ataxia on neurologic examination was reported in 2 patients from Kindred 6,976.[26] Migraine without aura, cluster headache, attention deficit hyperactivity disorder with autism, and learning disability were each reported in 1 patient (5%).

DISCUSSION The clinical characteristics of PNKD with *MR-1* mutations were uniform, in contrasted to the group of clinically diagnosed PNKD in whom no *MR-1* mutations were found. The age at onset was young; most of the patients with *MR-1* mutations in our series had onset in infancy or childhood. The oldest age at onset in the *MR-1* mutation group was 21 years, but this patient had only a single attack in his life. The young onset of attacks is in keeping with the original report of Mount and Reback and subsequent families that were linked to chromosome 2. However, since then, many patients with PNKD have been reported in the literature, under the definition of "attacks of involuntary movements occurring spontaneously."[3] This has resulted in a more heterogeneous view of PNKD. A review of large number of patients with PNKD in the literature reported average age at onset to be 12 years.[27] This age onset is similar to our familial paroxysmal dyskinesia patients with spontaneous attacks and without *MR-1* mutations. In sporadic cases, onset age tends to be even higher; many of the sporadic PNKD patients have psychogenic movement disorders.[28] Our data suggest that individuals with *MR-1* mutations have a younger average age at onset. This is an important distinction between paroxysmal dyskinesia families with and without *MR-1* mutations. However, Kindred 3,469 had onset in infancy, and both Kindred 5,620 and 6,269 had early childhood onset. Thus, early onset is not an exclusive feature of *MR-1* gene mutations.

Another uniform feature of *MR-1*–mutated families was the precipitation of the attacks by caffeine and alcohol. This was reported in nearly 100% of patients, among those who tried caffeine and alcohol (some patients were too young, and others never tried alcohol, knowing already from other family members that the alcohol would be a precipitant to their attacks). In patients without the mutation, caffeine was still a precipitant in some patients (reported overall approximately 40%), but none

reported alcohol as a precipitant. In the literature, families with PNKD are described as ". . . hereditary disorder characterized by attacks of muscle contractions, induced by alcohol among other factors"[11] and ". . . spread across 100 years and four countries, is the provocative effect of alcohol."[29] Although we do not know the exact function of *MR-1*, it is homologous to the hydroxyacylglutathione hydrolase (HAGH) of the glyoxalase system.[21] HAGH catalyzes the final step in conversion of methylglyoxal (a compound produced as a by-product of glycolysis, but also found in considerable amount in coffee and alcohol beverages) to lactic acid and reduced glutathione.[30,31] The precipitation of PNKD attacks by coffee and alcohol is a nearly uniform and clinically defining feature of PNKD due to *MR-1* mutations. Emotional stress was another very common precipitant, but in patients both with and without *MR-1* mutations.

Sleep benefit (attack resolving if the patients went to sleep during their attacks) was a characteristic for PNKD previously reported[32] and was found in patients both with and without the *MR-1* mutations. Not all of the patients in our data reported sleep benefit, but when present, it was dramatic. One subject stated, "the only thing that will help is sleep, so I just try to go to sleep." This resembles the sleep benefit described by migraine patients. The prevalence of migraine was high in *MR-1* mutation carriers, reported in 47% of the patients. Because migraine is a highly prevalent intermittent neurologic disorder,[33] we cannot be certain whether this is a coincidental occurrence or related to the *MR-1* mutation.

The third distinguishing feature of patients with *MR-1* mutations was attack response to clonazepam or diazepam. Traditionally, PNKD attacks were thought to be difficult to treat, in contrast to its counterpart, PKD, which almost always responds to AEDs.[8] Although some did report that the effect wore off over the course of years, patients with *MR-1* mutations were highly responsive to benzodiazepines. AEDs, or antidopaminergic agents such as haloperidol, which were previously reported to be successful, were not as effective.[34] Patients without *MR-1* mutation also had a relatively favorable response to benzodiazepines when tried. Our study is limited in that these data are retrospective. The identification of the *MR-1* gene may enable us to perform more successful therapeutic trials by enrolling groups of patients with more homogeneous pathophysiology. The paroxysmal dyskinesia kindreds reported here without *MR-1* mutations had more intrafamily and interfamily heterogeneity compared with the kindreds with *MR-1* mutations. Kindred 3,465, previously reported in the literature,[35] and thought somewhat clinically atypical for PNKD, did not have a *MR-1* mutation. Members of this kindred had exercise-induced painful dystonia. Some of the members did not have dystonic attacks but had exercise-induced painful cramps. The association of the attacks and the exercise raises the possibility that they may have PED. Kindreds 3,539 and 6,024 also had exercise as a trigger, but they had spontaneous attacks not triggered by exercise as well, and some of the patients with *MR-1* mutations did report exercise as precipitants of the attacks, complicating this issue. The gene for PED has not been discovered yet. A family with PED, rolandic epilepsy, and writer's cramp mapping to chromosome 16, near the PKD locus, was reported.[36] However, linkage of one family with typical PED presentation excluded a mutation in *MR-1* and linkage to chromosome 16 pericentric PKD locus.[37] Exercise-induced cramps were once thought to be a forme fruste of PNKD, but none of our *MR-1* mutation carriers reported exercise-induced cramps. Recently, a Canadian family of European decent with PNKD was reported to have their gene locus linked to the 2q31 region, raising the possibility of a second locus for PNKD.[38] However, the clinical presentation of this family was quite different from our analysis of *MR-1*–mutated patients. Age at onset ranged from childhood to 50s, and alcohol as well as caffeine were not reported as triggers. The attacks in this family were reported not to respond to clonazepam. Attacks were characterized as "symmetric dystonia of hands and feet." This report is in keeping with our data, that clinical presentations of *MR-1*–mutated families are relatively homogenous, compared with patients without *MR-1* mutations.

Based on our data, we propose clinical criteria for PNKD with *MR-1* mutation:

1. Hyperkinetic involuntary movement attacks, with dystonia, chorea, or combination of these, typically lasting 10 minutes to 1 hour, but up to 4 hours
2. Normal neurologic examination results between attacks, and exclusion of secondary causes
3. Onset of attack in infancy or early childhood
4. Precipitation of attacks by caffeine and alcohol consumption
5. Family history of movement disorder meeting Criteria 1 through 4

Some of the families clinically diagnosed with PNKD who did not have *MR-1* mutations are more similar to PED. Using our criteria, PNKD with *MR-1* mutation is clinically and genetically quite

homogeneous. There are clearly patients and families with atypical dyskinesias that are similar but distinct from PNKD. In our experience, none of these have *MR-1* mutations. We favor classifying these as "atypical paroxysmal dyskinesia." Among these, additional distinct phenotypes may ultimately be recognized.

Further delineation of *MR-1* protein function will lead to understanding of PNKD pathophysiology. Discovery of additional paroxysmal dyskinesia loci will lead to further refinement of molecular classification and enable further genotype–phenotype correlations.

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