Parkinsonism and Related Disorders 59 (2019) 131–139

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Paroxysmal movement disorders: Recent advances and proposal of a classification system

Xiao-jin Zhang[a,b,c], Zhe-yu Xu[a], Yun-cheng Wu[b], Eng-King Tan[c,d,*]

[a] Department of Neurology, National Neuroscience Institute, Tan Tock Seng Hospital, Singapore
[b] Department of Neurology, Shanghai General Hospital, China
[c] Department of Neurology, National Neuroscience Institute, Singapore General Hospital, Singapore
[d] Duke-NUS Medical School, Singapore

ARTICLE INFO

Keywords:
Paroxysmal kinesigenic dyskinesia (PKD)
Paroxysmal non-kinesigenic dyskinesia(PNKD)
Paroxysmal exercise induced dyskinesia (PED)
Episodic ataxia (EA)
Genetics

ABSTRACT

The increasing recognition of the phenotypic and genotypic heterogeneity that exists amongst the paroxysmal movement disorders (PMDs) is challenging the way these disorders have been traditionally classified. The present review aims to summarize how recent genetic advances have influenced our understanding of the nosology, pathophysiology and treatment strategies of paroxysmal movement disorders. We propose classifying PMDs using a system that would combine both phenotype and genotype information to allow these disorders to be better categorized and studied. In the era of next generation sequencing, the use of a standardized algorithm and employment of selective genetic screening will lead to greater diagnostic certainty and targeted therapeutics for the patients.

1. Introduction

The paroxysmal movement disorders (PMDs) are a group of neurological disorders characterized by intermittent attacks of involuntary movements. These disorders have been traditionally subdivided into two main categories, namely the paroxysmal dyskinesias (PxDs) and the episodic ataxias (EAs), according to their dominant phenomenology with the PxDs defined by the occurrence of episodic attacks of dyskinesia [1] and the EAs defined by transient episodes of ataxia which manifest clinically as incoordination and truncal instability. The aetiology of PMD is diverse, with both primary and secondary causes recognized [2]. The primary PMDs may show a familial inheritance or occur sporadically; with the inherited forms typically showing an autosomal dominant inheritance pattern with onset mostly in childhood or adolescence.

The current clinically based classification of the PMDs is limited by the increasing recognition of the genetic and phenotypic variability that can exist in PMDs. This review focuses on how recent genetic developments have influenced the nosology, pathophysiology and treatment strategies of the PMDs.

2. Current nosology of PMDs

2.1. Clinical classification of PxDs

In 1996, Demirkiran and Jankovic developed the current classification system of the paroxysmal dyskinesias that is widely adopted today. This classifies the disorders according to the precipitants of the attacks, rather than the phenomenology of the attacks as it was recognized that the paroxysmal dyskinesias could manifest as dystonia, chorea, athetosis or a combination of these movements [1]. Four groups of disorders were recognized, which are namely paroxysmal kinesigenic dyskinesia (PKD), paroxysmal nonkinesigenic dyskinesia (PNKD), paroxysmal exercise induced dyskinesia (PED) and paroxysmal hypnogenic dyskinesia (PHD). PHD is no longer regarded as a disorder within the umbrella of the paroxysmal dyskinesias and has instead been reclassified as a familial variant of frontal lobe epilepsy. Recently, *PRRT2* mutations have also been identified in 2 patients with PHD [3], suggesting that the disorder may once again be included amongst the other PxDs.

2.2. "DYT" eponyms of PxDs

With the discovery of monogenic forms of dystonia which included the pure dystonia syndromes, dystonia-plus syndromes and also the

* Corresponding author. Department of Neurology, National Neuroscience Institute, Singapore General Hospital, Outram Road, 169608, Singapore.
E-mail address: tan.eng.king@sgh.com.sg (E.-K. Tan).

https://doi.org/10.1016/j.parkreldis.2019.02.021
Received 19 August 2018; Received in revised form 9 February 2019; Accepted 15 February 2019
1353-8020/

PxDs, these disorders were allocated the acronym *DYT* according to the chronological order in which the corresponding gene locus were discovered. The paroxysmal dyskinesias have thus been assigned the designations of DYT8, DYT9, DYT10, DYT18, DYT19, DYT20 [4]. However, this assignment of PxDs to the DYT loci has become problematic with advances in genetics leading to the discovery of the causative gene, rather than just the gene locus. For example, paroxysmal kinesigenic dyskinesia was first designated as DYT10 and was mapped to chromosome 16p, but subsequently the c.649dupC mutation in the *PRRT2* gene was also found in the family used to define DYT19 that was also mapped to chromosome 16p [5]. It remains uncertain whether DYT10 and DTY19 are genetically distinct disorders or variants of the same condition. Furthermore, as it is now recognized that the as PxDs can clinically manifest with varying combinations of dystonia, chorea and athetosis, dystonia may not be necessarily present hence deigning the designation of DYT even more confusing for this disorder.

2.3. Classification of episodic ataxias (EAs)

Currently eight Episodic Ataxia syndromes are recognized based on their genetic loci, with the majority of cases comprising of either EA1 or EA2, which are caused by mutations in *KCNA1* and *CACNA1A* respectively. The clinical features of the different EA subtypes have considerable overlap, with only EA1 and EA2 recognized to have a distinct clinical phenotype.

EA1 is characterized by episodic ataxia and interictal peri-orbital or limb myokymia that may either be evident clinically or only detectable on electromyography [6]. EA2 is the most common subtype within the family of episodic ataxias, and is characterized by recurrent episodes of ataxia and dysarthria that may last for hours associated with interictal nystagmus [7]. Other EA subtypes are uncommon and have only been reported in one or two families, some with causative genes identified including mutations in *CACNB4*, *SLC1A3* and *UBR4* [8].

3. Genotypic spectrum

3.1. PKD

In 1999, the chromosomal critical region of PKD was mapped to 16p11.2-q12.1 [9], and proline-rich transmembrane protein 2(*PRRT2*) gene was identified as the causative gene for PKD in 2011 [10,11], by utilizing the technique of combining classic linkage analysis with whole-exome sequencing. PRRT2 mutations have been identified as the cause of PKD in 27–65% of patients with PKD, with a reported penetrance of 80–90% in familial cases, and 30–35% in sporadic cases [12].

PRRT2 mutations have also since been identified as the cause of infantile convulsions and choreoathetosis (ICCA) and benign familial infantile epilepsy (BFIE) [13], which suggest that ICCA, BFIE and PKD may lie on the same disease continuum linked by shared molecular/genetic pathology.

The phenotypic pleiotropy of *PRRT2*-associated disease was comprehensively explored in a review of 1444 published cases of subjects bearing mutations in the PRRT2 gene: 41.7% were diagnosed with BFIE, 38.7% with PKD, 14.3% with ICCA with the remaining 76 patients (5%) diagnosed with other disorders including PNKD and PNKD like disorders, PED, epileptic disorders including Dravet syndrome and West syndrome and different headache disorders including hemiplegic migraine and also non-syndromic intellectual disability [5]. Since then, more than 97 different pathogenic *PRRT2* mutations have been identified to date, with the c.649dupC frameshift mutation accounting for than 80.5% of cases for PKD in the earlier mentioned meta-analyses [5]. Biallelic *PPRT2* mutations have been reported in 5 patients who had a more severe disease phenotype including multiple types of paroxysmal movement disorders in the same individual, long duration episodes of ataxia, cognitive disability and cerebellar atrophy [14].

However, not all cases of PKD have been attributable to mutations in the *PRRT2* gene with up to 27–65% of PKD cases shown not to harbour *PRRT2* mutations, suggesting that additional yet unidentified pathogenic genes remain to be discovered, or that there is significant phenotypic overlap with the other paroxysmal disorders. A pathogenic heterozygous missense mutation in the sodium channel, voltage gated, type VIII alpha gene (*SCN8A*) was first identified in 3 families with benign familial infantile seizures (BFIS) and infantile convulsions and paroxysmal choreoathetosis (ICCA); which refers to the combination of BFIS and PKD [15]. In a subsequent study in a large cohort of 163 *PRRT2*-negative PKD patients where whole exome sequencing was performed, 3 individuals with PKD were also shown to have a novel, likely pathogenic mutations in the same *SCN8A* gene identified from the earlier BFIS and ICCA families [16]. This same study also identified 2 other novel pathogenic mutations in the potassium calcium-activated channel subfamily M alpha 1 (*KCNMA*1) and solute carrier family 2 member 1 (*SLC2A1*). Other potentially pathogenic genes were also identified in the same study, including the paroxysmal non kinesigenic dyskinesia protein (*PNKD*), potassium voltage-gated channel subfamily A member 1 (*KCNA1*) and Dishevelled, Egl-10 and Pleckstrin domain containing 5 (*DPEDC5*), with mutations in the KCNA1 gene also identified in 2 further PKD families [17]. Other potentially pathogenic genes identified that can cause PKD include *SLC20A2* which can be associated with brain calcification [18] and *CHRNA4* which was identified in a family with both PKD and genetic epilepsy with febrile seizures [19].

3.2. PED

Mutations in the solute carrier family 2, member 1 (*SLC2A1*) gene were first identified in a family with both PED and epilepsy [20]. The *SLC2A1* gene encodes for the glucose transporter type 1 (GLUT1), a membrane protein that mediates glucose transport across the blood-brain barrier. Heterozygous mutations in the *SLC2A1* gene causes the GLUT1-deficiency syndrome, which has a complex phenotype characterized by a variable combination of mental retardation, acquired microcephaly, seizures, epilepsy, paroxysmal movement disorders and complex motor disorder. The GLUT-1 deficiency syndrome is a consequence of a cerebral energy deficit, with the clinical severity ranging from individuals with only mild motor disability, including PED, to others with significant neurological disability [21]. PED is regarded as a non-classical variant of the GLUT 1 deficiency syndrome [22]. In GLUT-1 deficiency syndrome, the type of mutation was shown to be linked to both the degree of mental retardation and also predicted the occurrence of complex movement disorders [23]: mild mental retardation tended to occur in subjects with a missense mutation whereas movement disorders were more commonly observed in subjects with more complex nonsense, frameshift, splice site, translation initiation mutations or multiple exon deletions. While *SLC2A1* mutation have been mostly reported in PED, they have also been described in other PXMDs, including PNKD and EAs [2].

Two other potentially treatable disorders that also result in deficiency brain energy metabolism: Pyruvate dehydrogenase complex-E2 (*PDC-E2*) deficiency and mitochondrial short-chain enoyl-CoA hydratase deficiency (*ECHS1*), have also been reported to present with isolated PED [24,25], thus broadening the genotypic spectrum of PED. More unusually, isolated PED has been reported to be the presenting symptom in carriers of mutations in the parkin RBR E3 ubiquitin protein ligase 2 gene (*PRKN or PARK2*) [2] and GTP cyclohydrolase 1 gene (*GCH1*) [26], which cause early-onset Parkinsonism and Dopa-responsive Dystonia respectively.

3.3. PNKD

Mutations in the myofibrillogenesis regulator 1 (*MR-1*) gene, later renamed as the PNKD gene, was first identified in 2004 to cause PNKD [27]. This is the main pathogenenic gene mediating the pure, isolated forms of PNKD. Compared to the other paroxysmal disorders, *PNKD*

mutation carriers tend to have a much younger age of onset beginning early in infancy or childhood, with attacks typically triggered by coffee and alcohol and comprising of both chorea and dystonia [12]. In patients carrying the *PNKD* mutation, the phenotype is very homogenous and they have a normal interictal examination. To date, 3 different pathogenic *PNKD* mutations have been identified in unrelated families of different ethnicities [2].

As part of a more complex phenotype, PNKD has also been reported in individuals with mutations in several genes including *PRRT2, SLC2A1*, ATPase Na+/K+ transporting subunit alpha 3 gene (*ATP1A3*), adenylate cyclase 5 gene (*ADCY5*) and *KCNMA1*. [2].

3.4. EA1

Potassium voltage-gated channel, shaker-related subfamily, member 1 gene (*KCNA1*) is the only gene found to be associated with EA1 so far [28]. However, individuals with typical EA1 symptoms have been reported not to carry *KCNA1* variations, suggesting that there are other unidentified genes may underlie the disorder.

Following the original descriptions of EA1, the phenotypic spectrum of the disorder has widened considerably. Affected individuals may exhibit additional symptoms during the attacks, such as vertigo, blurred vision, diplopia, nausea, headache, diaphoresis, dysarthria and difficulty in breathing. Other features such as delayed motor development, cognitive disability, epilepsy, choreoathetosis, neuromyotonia and progressive cerebellar ataxia can also be present, with epilepsy being over-represented in EA1 patients [6,29].

No clear genotype-phenotype correlations have been identified in EA1: affected identical twins carrying the same EA1 mutation can show marked variability in the severity of the attacks and associated features, suggesting that non-genetic factors influence the phenotypic expression of EA1 [30]. In individuals with typical EA1 symptoms but do not carry the *KCNA1* mutation, a male preponderance, longer attack duration and tendency to develop progressive disease was observed compared to individuals carrying the *KCNA1* mutation [6].

3.5. EA2

EA2 is the most commonly occurring episodic ataxia, and is caused by heterozygous mutations in calcium channel, voltage-dependent, P/Q type, alpha 1A subunit gene (*CACNA1A*). EA2 has an autosomal dominant inheritance with a penetrance estimated to be between 80 and 90%. Other associated clinical features include migraine, epilepsy, dystonia, fluctuating weakness and cognitive disability. Migraine is reported in up to 50% of cases and may be hemiplegic [8]. The interictal phenotype can be highly variable, ranging from individuals with a normal clinical examination to those with a progressive cerebellar syndrome [31].

3.6. Other EAs

Mutations in the calcium channel, voltage-dependent, beta 4 subunit (*CACNB4*) gene [32], solute carrier family 1, member 3 (*SLC1A3*) gene [33,34] and ubiquitin protein ligase E3 component n-recognin 4(*UBR4*) gene [35] have been reported to cause EA5, EA6 and EA8 respectively. However, these findings have only been reported in one or two families to date. Other reported causes of EAs include mutations in sodium voltage-gated channel alpha subunit 2 (*SCN2A*) gene, fibroblast growth factor 14 (*FGF14)* gene, PRRT2, SLC2A1 and *ATP1A3* [8,12].

The mitochondrial pyruvate dehydrogenase complex (PDC) consists of multiple copies of three subunits: pyruvate dehydrogenase (E1) which is encoded by the pyruvate dehydrogenase E1 alpha 1 unit (*PDHA1)* gene, dihydrolipoamide transacetylase (E2) which is encoded by the dihydrolipoamide S-acetyltransferase (*DLAT)* gene and dihydrolipoamide hydrogenase (E3). The associated E3-binding protein is encoded by the pyruvate complex component X (*PDHX)* gene. PxD, including episodic ataxia, PED and PNKD have been reported in patients with mutations of either *DLAT* or *PDHX* [26].

With the advent of next-generation sequencing (NGS), increased accessibility to genetic testing may uncover novel monogenic forms of PMDs.

4. Nosology challenge

It remains a considerable challenge for the clinician to diagnose, and correctly classify the different paroxysmal movement disorders according to the clinical characteristics of the disorder. The paroxysmal nature of the disorder requires the clinician to make a clinical diagnosis based on descriptions or videos provided by the patient, as these events are rarely captured in the clinical setting. In a single attack, multiple hyperkinetic movement disorders or can be observed in the individual, often with considerable overlap. Positive genetic findings are difficult to interpret when the clinical diagnosis of the disorder remains uncertain. Further verification will be necessary to confirm whether all existing reported mutations of PMD-associated genes are pathogenic, as some reported mutations could represent non-pathogenic variants, and are not disease causing.

Although genetic and phenotypic pleiotropy is present in the paroxysmal movement disorders, the current system of classification based on the clinical features of the attacks is still helpful to guide initial limited genetic screening. This is as each clinically recognized category of the paroxysmal movement disorder tends to be more commonly associated with specific genetic mutations Table 1.

In 2014, Erro et al. reviewed 500 genetically proven cases of the primary paroxysmal dyskinesias (PKD, PED and PNKD) and proposed that these disorders should be classified according to a two axis system. Axis 1 classification was based on the clinical characteristics and triggers of the paroxysmal dyskinesias. Axis 2 classification was based on the presence or absence of any of the four causative genes for paroxysmal movement disorders (PRRT2, MR-1, KCNMA1 and SLC2A1) that were recognized then. A suggested algorithm was proposed to guide genetic testing based on the four recognized genes [36]. However, this proposed classification system did not actually integrate genotypic and phenotypic information to guide the classification of the paroxysmal disorders. Since the publication of this proposed classification scheme, further genetic causes of the different paroxysmal movement disorders have been identified.

One potential classification system for the paroxysmal movement disorders, similar to what has been proposed for dystonia, is to combine both phenotype and the genotype features to allow the disorders to be further subdivided based on genetic findings [37]. The main clinical categories of PKD, PED, PNKD and EA can be retained, and combined with the genetic findings. The earlier classifications of DYT and EA based on the presumed genetic locus should be abandoned. For example, PKD associated with the *PRRT2* and *SCN8A* mutations should be named as PKD-*PRRT2* and PKD-*SCN8A* respectively. PED should be subclassified as PED-*SCL2A1* PED-*DLAT*, PED-*ECHS1*, PED-*PRKN2*, PED-*CGH1* according to the mutation found, and likewise PNKD can be subclassified into PNKD-*ATP1A3* and PNKD-*ADCY5*. This proposed classification scheme incorporating both the clinical and molecular diagnosis would allow better subtyping in this field and facilitate identification of similarities and the differences in the various disorders. With the expected future discovery of new pathogenic mutations, ongoing confirmation and verification of existing genetic mutations, this classification system will need to be updated to reflect the evolving landscape and updated as new information is obtained.

5. Pathophysiology

The exact pathophysiological mechanisms underlying the PMDs remains to be fully understood. Prior to recent genetic discoveries, PMDs were hypothesized to be channelopathies as mutations in genes

Table 1
Clinical criteria/typical characteristics and causative genes of PMDs. All criteria require exclusion of secondary or psychogenic causes of paroxysmal movement disorders, and no loss of consciousness during attacks. Bold font is the main causative gene.

Paroxysmal dyskinesias: Attacks of dystonia and/or chorea		
PKD	• Age at onset between 1 and 20 years, if no family history of PKD	*PRRT-2*
	• Identified kinesigenic trigger for the attacks	*ADCY5/SCN8A/DEPDC5*
	• Short duration of attacks (< 1 min)	*SLC16A2/KCNMA1/KCNA1*
	• Good response to antiepileptics	
PED	• Onset of attack from childhood to adulthood	*SLC2A1*
	• Triggered by exercise (at least minutes of exercise)	*GCH1//PARKIN/ADCY5/PRRT2/ATP1A3/PARK2*
	• Duration of attacks between 5 and 30min	*PDHA1/PDHX/DLAT*
	• Response to treatment varies	
PNKD	• Onset in infancy or early childhood	*MR-1(PNKD)*
	• No clear triggering factor, but coffee, alcohol and stress are precipitating factors	*PRRT2/ADCY5/SLC2A1/ATP1A3/KCNMA1/BCKD*
	• Duration of attacks: from 10 min to 4 h	*complex*
	• No clear response to antiepileptics other than benzodiazepines	
Episodic Ataxias: Attacks of cerebellar ataxia		
EA1	• Triggered by sudden movement or emotional and physical stress	*KCNA1*
	• Onset in early childhood, between 2 and 15 years old	*PRRT-2*
	• Short duration of attacks: seconds to minutes	
	• Interictal myokymia	
EA2	• Triggered by alcohol, caffeine, fatigue, stress and exercise	*CACNA1A*
	• Onset age between 5 and 20 years old	
	• Duration of attacks varies: minutes to days	
	• Interictal nystagmus	
EA3-EA8	• Other EA subtypes have only been reported in one or two families.	*CACNB4(EA5)*
	• The presence of vertigo and tinnitus and the absence of interictal nystagmus and shorter episodes distinguish EA3 from EA1 and EA2.	*SLC1A3(EA6)*
		UBR4(EA8)
	• EA4 characterized by brief ataxia, vertigo, gaze-evoked nystagmus (GEN), and defective smooth pursuit. does not respond to acetazolamide.	*SCN2A/PRRT2/SLC2A1*
		FGF14/PDHA1/PDHX/ATP1A3/BCKD complex
	• The clinical features of EA5 were similar to those of EA2. Its onset is later than that of EA2.	
	• Clinical phenotypes of EA6 were different from each other.	
	• Clinical features of EA7 were similar to those of EA2, except without interictal findings.	
	• The attacks of EA8 characterized by unsteadiness, general weakness, and slurred speech, response to clonazepam, instead of acetazolamide.	

encoding for ion channels were found to be frequently associated with other episodic neurological disorders including epilepsy, migraine and also paroxysmal dyskinesias. The recent discovery of mutations in genes encoding for ion channels such as *SCN8A, KCNMA1* and *ATP1A3* in patients with paroxysmal movement disorders, lends further credence to the channelopathy hypothesis. In the case of the episodic ataxias, mutations have been identified in the genes encoding membrane ion channels or transmembrane transporters which play a role in excitatory neurotransmission. Furthermore, some PxMDs exhibit exquisite sensitivity to anti-epileptics, which act by modulating ion channels [38]. However, none of the three major PxDs-associated genes (*PRRT2, MR1 and SLC2A1*) encode ion channels, which casts some doubt on the channelopathy hypothesis as the sole pathological explanation for the PMDs [39].

As listed out in Table 2, the PMDs can mostly be grouped into three categories according to their presumed pathogenic mechanisms derived from their associated genetic mutations: neurotransmission synaptopathies (*PRRT2*, *PNKD*, *SLC16A2*, *ADCY5*), brain energy transportopathies (*SLC2A1, DLAT, PDHA1, PDHX, SLC1A3*), and channelopathies (*SCN8A, KCNMA1, ATP1A3, KCNA1, CACNA1A, CACNB4, SCN2A*). This suggests that alterations in synaptic neurotransmission, brain energy metabolism and ion channel function can all be involved in the pathogenesis of PMDs. Potentially, the PMDs can be classified according to their underlying pathophysiology, such as PMD-channelopathies, PMD – neurotransmission synaptopathies and PxD-glucose transportopathies.

Recent genetic functional studies have emphasized the role of the cerebellum, in the pathophysiology of PKD where ion channel mutations or synaptic protein mutations act by inducing Purkinje cell firing abnormalities, which was shown to lead to cerebellar dysfunction and generation of the PMD phenotype in mice [40,41]. Using a *CACNA1*A knock-in-mouse with delayed Purkinje cell expression, Mark et al. was able to show that the delayed expression of abnormal P/Q type calcium channel in the Purkinje cells in adult mice was able to induce the same neurological phenotype as CACNA1A knock-out mice, thus highlighting the key role of the Purkinje cells in the pathophysiology of PKD. Xiong et al. studied *PRRT2*-loss-of-function mutant mice and showed that optogenetic stimulation of the cerebellar granule cells was able to result in transient increase followed by suppression of Purkinje cell firing and expression of PKD-like behaviours in mice.

6. Treatment

The treatments for paroxysmal movement disorders have largely been unchanged with the exception of the recent development of novel therapies. Deep genetic phenotyping of the disorder in the future may allow for better disease definition and may influence treatment choice.

6.1. PKD

The PKDs are characterized by their exquisite sensitivity to anti-epileptics, in particular, phenytoin and carbamazepine which are anti-epileptics that modulate the voltage-gated sodium channels [42]. An enhanced treatment response to low dose carbamazepine (50 mg/day) has also been reported in PRRT2 mutation carriers [43]. This characteristic has been suggested as a clinical feature that could distinguish between PRRT2 and non-PRRT2 mutation carriers in PKD. However, in patients with a homozygous or compound heterozygous PRRT2 mutations, treatment resistance to anti-epileptics has been reported [14,44]. Other interventions that have been explored for the treatment of PKD include low-dose lamotrigine, which was shown to result in attack remission in more than 90% of cases [45] and thalamotomy was also shown to be effective in one family [46].

Table 2
Genetic characteristics and related phenotypes.
SNAP25: synaptosomal-associated protein 25 kDa. Others see text for abbreviation.

gene	locus	protein	Function/pathogenesis*	PMDs	Other paroxysmal disorders/ symptoms
PRRT2	16p11.2-q12.1	Proline-rich transmembrane protein	presynaptic protein modulates SNARE complex formation, involved in glutamate exocytosis. Mutations may induce neuronal hyperexcitability	PKD ICCA BFIS PED EA	Hemiplegic Migraine Febrile seizures Childhood absence Epilepsy
SCN8A	12q13.13	sodium voltage-gated channel alpha subunit	Essential for the rapid membrane depolarization that occurs during the formation of the action potential in excitable neurons. Mutation pathogenesis is unknown.	PKD	Infantile epileptic
PNKD	2q33-35	PNKD	Synaptic protein that modulates neuro-transmitter release. Mutation may lead to neuronal hyperexcitability.	PNKD	
KCNMA1	10q22.3	Large-conductance voltage,Ca (2 +)_activated K+ channel, alpha subunit, subfamily M	Fundamental to the control of smooth muscle tone and neuronal excitability. Mutation pathogenesis is unknown.	PNKD	Epilepsy
SLC2A1	1p34.2	Glucose transporter	Membrane protein mediate glucose transport across the blood- brain barrier. Mutations cause GLUT1 deficiency, resulting cerebral energy deficit.	PED PNKD EA	GLUT-DS Epilepsy Migraine Episodic choreoathetosis/Spasticity syndrome
ATP1A3	19q13.2	ATPase Na + /K + transporting subunit	The Na/K-ATPase pump is a major determinant of resting membrane potentials, exclusively expressed in neurons, particularly GABAergic neurons of the basal ganglia and cerebellum Mutation pathogenesis is unknown.	PNKD PED EA	Hemiplegic attacks Epilepsy Paroxysmal eye movements Paroxysmal dysautonomia Migraine
ADCY5	3q21.1	membrane-bound adenylyl cyclase enzymes	ADCY5 strongly expressed in striatum integrates signals from multiple adenosine and dopamine receptors. Mutation increases adenylate cyclase activity, affecting signal transduction within the striatum.	PKD PNKD PED	Oculogyric crises Restless legs syndrome Facial myokymia
GCH1	14q22.2	GTP cyclohydrolase	Enzyme catalyzes the first step in the synthesis of tetrahydrobiopterin, essential for dopamine synthesis. Mutations result in haplo-insufficiency with reduced striatal dopamine levels.	PED	Dopa-responsive Dystonia
DLAT	11q23.1	Dihydrolipoamide S-acetyltransferase	encodes component E2 of the multi-enzyme pyruvate dehydrogenase complex (PDC). Mutations cause pyruvate dehydrogenase E2 deficiency.	PED	
PDHA1	Xp22.12	pyruvate dehydrogenase E1 alpha 1 subunit	A mitochondrial multienzyme complex link between glycolysis and the tricarboxylic acid cycle. Mutation cause pyruvate dehydrogenase E1-alpha deficiency.	PED EA	Epilepsy
PDHX	11p13	pyruvate dehydrogenase complex component X	Catalyzes the conversion of pyruvate to acetyl coA, a minor antigen for anti-mitochondrial antibodies. Mutations cause pyruvate dehydrogenase deficiency.	EA PED	Episodic weakness
KCNA1	12q13	K(V)1.1 Voltage-gated potassium channel subunit	Voltage-gated potassium channel strongly expressed in the cerebellum, hippocampus and motor axons. Mutations impair channel dynamics, causing increased neuronal excitability.	EA1	Epilepsy Paroxysmal dyspnea Cataplexy
CACNA1A	19p13	Ca(V) 2.1 Voltage-gated calcium channel subunit	Voltage-dependent calcium channel strongly expressed in the cerebellum. Mutations impair synaptic transmission.	EA2 Paroxysmal torticollis Paroxysmal tonic upgaze	Migraine Absence Epilepsy Fluctuating hemiplegic weakness
CACNB4	2q22–q23	Ca(V)2.1 Voltage-gated calcium channel subunit	Biased expression in cerebellum adult and cortex adult. Mutation pathogenesis is unknown.	EA5	Juvenile myoclonic epilepsy
SLC1A3	5p13.2	EAAT1 glucose transporter	Biased expression in cerebellum adult and cortex adult. Mutation pathogenesis is unknown.	EA6	Epilepsy Migraine hemiplegic attacks

(*continued on next page*)

Table 2 (*continued*)

gene	locus	protein	Function/pathogenesis*	PMDs	Other paroxysmal disorders/ symptoms
SCN2A	2q24.3	sodium voltage-gated channel alpha subunit 2	Transmembrane glycoprotein comp-lexes, function in the generation and propagation of action potentials in neurons and muscle. Mutation pathogenesis is unknown.	EA	Neonatal epilepsy Paroxysmal pain
FGF14	13q33.1	fibroblast growth factor 14	Biased expression in cerebellum adult and cortex adult. Mutation pathogenesis is unknown.	EA	Paroxysmal dystonia Headaches
UBR4	1p36.13	ubiquitin protein ligase E3 compon-ent n-recognin 4	Interacts with the retinoblastoma associated protein in the nucleus and with calcium bound calmodulin in the cytoplasm. Mutation pathogenesis is unknown.	EA8	

6.2. PED

Unlike PKD, medical treatment of PED with anti-epileptics has been largely ineffective and avoidance of triggers such as prolonged exercise remains the cornerstone of therapy. Treatable causes of PED such as young-onset Parkinson's Disease [47] and inherited mutations of the GTP-cyclohydrolase 1 (GCH-1) [48] should be identified as these disorders are responsive to levodopa therapy. Other scattered case reports have reported partial success or success with acetazolamide [49], levodopa, trihexyphenidyl, benzodiazepine and also pallidotomy [1,42]. The ketogenic diet has been shown to reduce attack frequency in PED in GLUT1 mutation [50], SLC2A1 mutation and Pyruvate dehydrogenase complex-E2-deficiency (PDC-E2) carriers [51,52]. The modified Atkins diet has also been shown to reduce attack frequency and severity in four patients with GLUT-1 deficiency syndrome [53]. More recently, Triheptanoin, an odd-chain triglyceride which acts by replenishing metabolic intermediates in the Krebs cycle, has been shown to be able to reduce 90% of the attacks in PED with the added benefits of being better tolerated than the Atkins diet [54]. Recently, one patient with PED attributable to ECHS1 gene mutation was reported to have reductions in attack severity and frequency following treatment with a mitochondrial cocktail [55].

6.3. PNKD

The PNKD attacks differ from PKD in that they do not exhibit a good treatment response to conventional anticonvulsants, but may respond to benzodiazepines. Oxcarbazepine has been recently reported to be effective treatment for PNKD attacks [56]. Avoidance of triggers such as caffeine, alcohol and stress remains the cornerstone of the management of the disorder, particularly when symptoms are mild. A variety of other drugs such as haloperidol, anticholinergics, gabapentin, levetiracetam, nitric oxide synthetase inhibitors, adenosine agonists/antagonists, acetazolamide, piracetam and levodopa have all been tried, but generally have only shown partial treatment success [57–59]. It remains uncertain whether genotype in PNKD could influence medication efficacy, and further genotypic stratification of the disorder is necessary.

6.4. EAs

The attacks of EA1 are responsive to both acetazolamide and AEDs, in particular carbamazepine and valproate. EA2 can show a dramatic response to acetazolamide, however the side effect profile of acetazolamide can limit the use of this drug in clinical practice. Alternatively, 4-aminopyridine (4-AP), a nonselective potassium channel has been demonstrated to reduce attack frequency and improve quality of life [12]. In the tottering mouse, the animal model of EA2, 4-AP and 3,4- diaminopyridine have been demonstrated to prevent attacks [60]. Patients with EA3, EA5 and EA6 have been reported to respond to acetazolamide. Interestingly, unlike the other episodic ataxias, acetazolamide is not effective in EA8 patients and the attacks instead respond to clonazepam [35].

7. Diagnostic work-up

To evaluate paroxysmal movement disorders, the most important step in the diagnostic process is to obtain a detailed clinical history. This would include: the phenomenology of the attacks and interictal symptoms, triggering factors, duration of attacks, family history, previous history of intracranial injury and current level of neurological function. Videotapes, when possible, would allow for proper characterization of the attacks. The neurological examination should be performed where feasible both during the attack and also interictal periods.

Neuroimaging and blood tests (including a blood glucose level, serum calcium and thyroid function tests) are useful investigations to

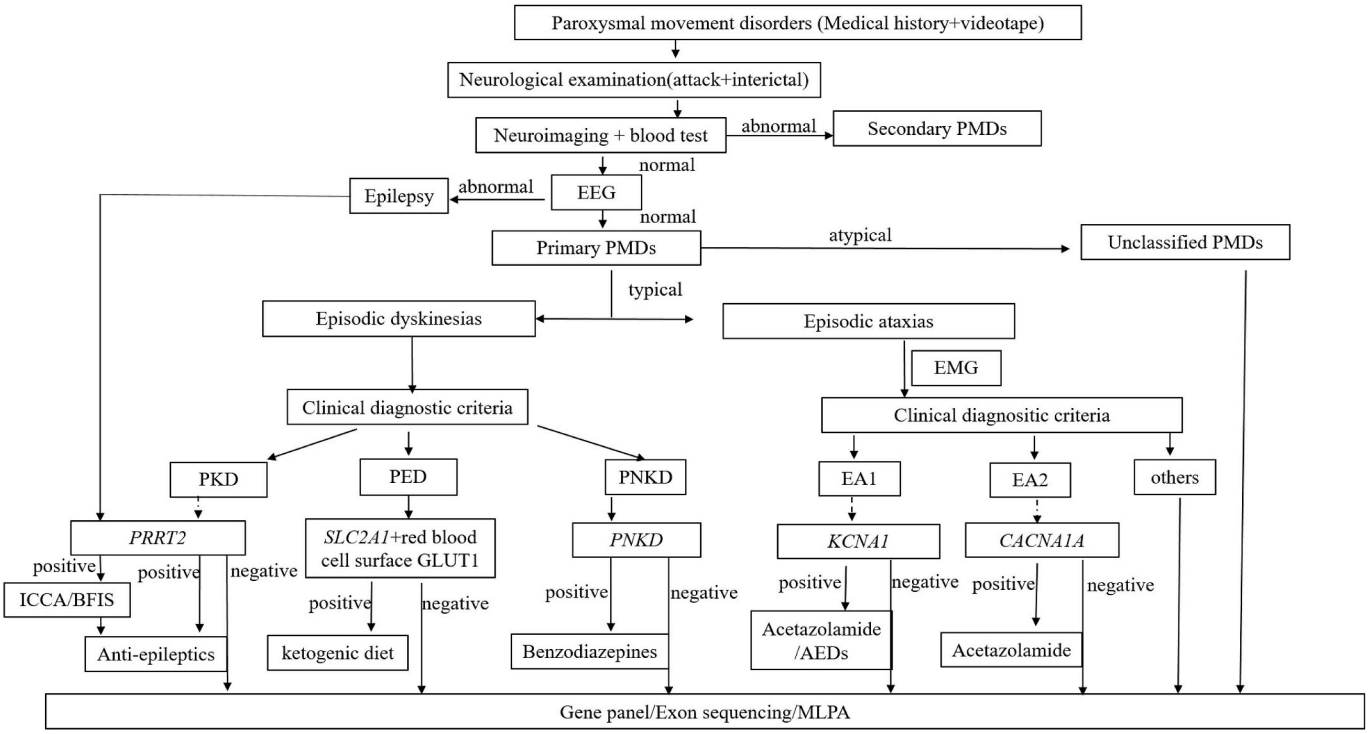

Fig. 1. Diagnostic workflow for paroxysmal movement disorders.

rule out secondary causes of PMD. The electroencephalogram (EEG) can be useful to detect previously unrecognized epileptic activity and electromyography (EMG) can be employed to identify myokymia.

Careful consent should be undertaken prior to genetic testing. As phenotype-genotype correlations are not well defined in the PMDs, pre-test and post-test counselling will be necessary. Although genetic testing is now readily available commercially, problems with Direct to Consumer (DTC) genetic testing remain [61]. The choice of gene sequencing method is dependent on costs and the yield of testing. If clinical findings do not point towards a particular candidate gene, use of a gene panel or exome sequencing may be preferable as sequential testing for multiple genes is usually more expensive [62]. If necessary, multiplex ligation-dependent probe amplification (MLPA) can be applied to allow the detection of longer deletions, duplications, intronic variants. A suggested diagnostic algorithm is presented in Fig. 1.

8. Limitations and challenges

There is currently no widely accepted classification system of PMD that can effectively combine genotype and phenotype features to replace the existing classical nosology of the PMDs. Causative genetic mutations have yet to be identified in a proportion of patients presenting with PMDs, which would limit the application of any proposed classification since this needs to be constantly modified as new information arise. The high costs of genetic testing remain a challenge in the clinical care of these patients.

9. Conclusions

Recent advances in the genetics of the PMDs are shedding further light in our understanding of the pathophysiological and treatment approaches of these disorders. Although the current clinical classification of the different PMDs still has utility, revisions of the existing classification system is necessary to allow more detailed and accurate subtyping of the different disorders. Standardized workflow and selective genetic screening will lead to greater diagnostic certainty and may allow for targeted therapy in the future.

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding sources

This work was supported by National Medical Research Council, Singapore, Shanghai Jiaotong University Medical and Industrial Cross Project [YG2014QN10]; Shanghai Health Bureau Youth Research Project [20124Y120].

References

[1] M. Demirkiran, J. Jankovic, Paroxysmal dyskinesias: clinical features and classification, Ann. Neurol. 38 (1995) 571–579.
[2] A. Meneret, E. Roze, Paroxysmal movement disorders: an update, Revue. neurol. 172 (2016) 433–445.
[3] X.R. Liu, D. Huang, J. Wang, Y.F. Wang, H. Sun, B. Tang, W. Li, J.X. Lai, N. He, M. Wu, T. Su, H. Meng, Y.W. Shi, B.M. Li, B.S. Tang, W.P. Liao, Paroxysmal hypnogenic dyskinesia is associated with mutations in the PRRT2 gene, Neurol. Genet. 2 (2016) e66.
[4] N. Bruggemann, C. Klein, Genetics of primary torsion dystonia, Curr. Neurol. Neurosci. Rep. 10 (2010) 199–206.
[5] D. Ebrahimi-Fakhari, A. Saffari, A. Westenberger, C. Klein, The evolving spectrum of PRRT2-associated paroxysmal diseases, Brain. J. Neurol. 138 (2015) 3476–3495.
[6] T.D. Graves, Y.H. Cha, A.F. Hahn, R. Barohn, M.K. Salajegheh, R.C. Griggs, B.N. Bundy, J.C. Jen, R.W. Baloh, M.G. Hanna, C. Investigators, Episodic ataxia type 1: clinical characterization, quality of life and genotype-phenotype correlation, Brain 137 (2014) 1009–1018.
[7] J. Jen, G.W. Kim, R.W. Baloh, Clinical spectrum of episodic ataxia type 2, Neurology 62 (2004) 17–22.
[8] K.D. Choi, J.H. Choi, Episodic ataxias: clinical and genetic features, J. Mov. Disord. 9 (2016) 129–135.
[9] H. Tomita, S. Nagamitsu, K. Wakui, Y. Fukushima, K. Yamada, M. Sadamatsu, A. Masui, T. Konishi, T. Matsuishi, M. Aihara, K. Shimizu, K. Hashimoto, M. Mineta, M. Matsushima, T. Tsujita, M. Saito, H. Tanaka, S. Tsuji, T. Takagi, Y. Nakamura, S. Nanko, N. Kato, Y. Nakane, N. Niikawa, Paroxysmal kinesigenic choreoathetosis locus maps to chromosome 16p11.2-q12.1, Am. J. Hum. Genet. 65 (1999) 1688–1697.
[10] J.L. Wang, L. Cao, X.H. Li, Z.M. Hu, J.D. Li, J.G. Zhang, Y. Liang, A. San, N. Li, S.Q. Chen, J.F. Guo, H. Jiang, L. Shen, L. Zheng, X. Mao, W.Q. Yan, Y. Zhou, Y.T. Shi, S.X. Ai, M.Z. Dai, P. Zhang, K. Xia, S.D. Chen, B.S. Tang, Identification of PRRT2 as the causative gene of paroxysmal kinesigenic dyskinesias, Brain 134 (2011) 3493–3501.

[11] W.J. Chen, Y. Lin, Z.Q. Xiong, W. Wei, W. Ni, G.H. Tan, S.L. Guo, J. He, Y.F. Chen, Q.J. Zhang, H.F. Li, Y. Lin, S.X. Murong, J. Xu, N. Wang, Z.Y. Wu, Exome sequencing identifies truncating mutations in PRRT2 that cause paroxysmal kinesigenic dyskinesia, Nat. Genet. 43 (2011) 1252–1255.
[12] E.M. McGovern, E. Roze, T.J. Counihan, The expanding spectrum of paroxysmal movement disorders: update from clinical features to therapeutics, Curr. Opin. Neurol. 31 (2018) 491–497.
[13] S.E. Heron, B.E. Grinton, S. Kivity, Z. Afawi, S.M. Zuberi, J.N. Hughes, C. Pridmore, B.L. Hodgson, X. Iona, L.G. Sadleir, J. Pelekanos, E. Herlenius, H. Goldberg-Stern, H. Bassan, E. Haan, A.D. Korczyn, A.E. Gardner, M.A. Corbett, J. Gecz, P.Q. Thomas, J.C. Mulley, S.F. Berkovic, I.E. Scheffer, L.M. Dibbens, PRRT2 mutations cause benign familial infantile epilepsy and infantile convulsions with choreoathetosis syndrome, Am. J. Hum. Genet. 90 (2012) 152–160.
[14] M. Delcourt, F. Riant, J. Mancini, M. Milh, V. Navarro, E. Roze, V. Humbertclaude, C. Korff, V. Des Portes, P. Szepetowski, D. Doummar, B. Echenne, S. Quintin, N. Leboucq, R. Singh Amrathlal, J. Rochette, A. Roubertie, Severe phenotypic spectrum of biallelic mutations in PRRT2 gene, J. Neurol. Neurosurg. Psychiatr. 86 (2015) 782–785.
[15] E. Gardella, F. Becker, R.S. Moller, J. Schubert, J.R. Lemke, L.H. Larsen, H. Eiberg, M. Nothnagel, H. Thiele, J. Altmuller, S. Syrbe, A. Merkenschlager, T. Bast, B. Steinhoff, P. Nurnberg, Y. Mang, L. Bakke Moller, P. Gellert, S.E. Heron, L.M. Dibbens, S. Weckhuysen, H.A. Dahl, S. Biskup, N. Tommerup, H. Hjalgrim, H. Lerche, S. Beniczky, Y.G. Weber, Benign infantile seizures and paroxysmal dyskinesia caused by an SCN8A mutation, Ann. Neurol. 79 (2016) 428–436.
[16] W.T. Tian, X.J. Huang, X. Mao, Q. Liu, X.L. Liu, S. Zeng, X.N. Guo, J.Y. Shen, Y.Q. Xu, H.D. Tang, X.M. Yin, M. Zhang, W.G. Tang, X.R. Liu, B.S. Tang, S.D. Chen, L. Cao, Proline-rich transmembrane protein 2-negative paroxysmal kinesigenic dyskinesia: clinical and genetic analyses of 163 patients, Mov. Disord. 33 (2018) 459–467.
[17] X.M. Yin, J.H. Lin, L. Cao, T.M. Zhang, S. Zeng, K.L. Zhang, W.T. Tian, Z.M. Hu, N. Li, J.L. Wang, J.F. Guo, R.X. Wang, K. Xia, Z.H. Zhang, F. Yin, J. Peng, W.P. Liao, Y.H. Yi, J.Y. Liu, Z.X. Yang, Z. Chen, X. Mao, X.X. Yan, H. Jiang, L. Shen, S.D. Chen, L.M. Zhang, B.S. Tang, Familial paroxysmal kinesigenic dyskinesia is associated with mutations in the KCNA1 gene, Hum. Mol. Genet. 27 (2018) 625–637.
[18] V.S. Kostic, I.N. Petrovic, Brain calcification and movement disorders, Curr. Neurol. Neurosci. Rep. 17 (2017) 2.
[19] Y.L. Jiang, F. Yuan, Y. Yang, X.L. Sun, L. Song, W. Jiang, CHRNA4 variant causes paroxysmal kinesigenic dyskinesia and genetic epilepsy with febrile seizures plus? Seizure 56 (2018) 88–91.
[20] Y.G. Weber, A. Storch, T.V. Wuttke, K. Brockmann, J. Kempfle, S. Maljevic, L. Margari, C. Kamm, S.A. Schneider, S.M. Huber, A. Pekrun, R. Roebling, G. Seebohm, S. Koka, C. Lang, E. Kraft, D. Blazevic, A. Salvo-Vargas, M. Fauler, F.M. Mottaghy, A. Munchau, M.J. Edwards, A. Presicci, F. Margari, T. Gasser, F. Lang, K.P. Bhatia, F. Lehmann-Horn, H. Lerche, GLUT1 mutations are a cause of paroxysmal exertion-induced dyskinesias and induce hemolytic anemia by a cation leak, J. Clin. Invest. 118 (2008) 2157–2168.
[21] D. Gras, E. Roze, S. Caillet, A. Meneret, D. Doummar, T. Billette de Villemeur, M. Vidailhet, F. Mochel, GLUT1 deficiency syndrome: an update, Rev. Neurol. 170 (2014) 91–99.
[22] A. Suls, P. Dedeken, K. Goffin, H. Van Esch, P. Dupont, D. Cassiman, J. Kempfle, T.V. Wuttke, Y. Weber, H. Lerche, Z. Afawi, W. Vandenberghe, A.D. Korczyn, S.F. Berkovic, D. Ekstein, S. Kivity, P. Ryvlin, L.R. Claes, L. Deprez, S. Maljevic, A. Vargas, T. Van Dyck, D. Goossens, J. Del-Favero, K. Van Laere, P. De Jonghe, W. Van Paesschen, Paroxysmal exercise-induced dyskinesia and epilepsy is due to mutations in SLC2A1, encoding the glucose transporter GLUT1, Brain. J. Neurol. 131 (2008) 1831–1844.
[23] W.G. Leen, J. Klepper, M.M. Verbeek, M. Leferink, T. Hofste, B.G. van Engelen, R.A. Wevers, T. Arthur, N. Bahi-Buisson, D. Ballhausen, J. Bekhof, P. van Bogaert, I. Carrilho, B. Chabrol, M.P. Champion, J. Coldwell, P. Clayton, E. Donner, A. Evangeliou, F. Ebinger, K. Farrell, R.J. Forsyth, C.G. de Goede, S. Gross, S. Grunewald, H. Holthausen, S. Jayawant, K. Lachlan, V. Laugel, K. Leppig, M.J. Lim, G. Mancini, A.D. Marina, L. Martorell, J. McMenamin, M.E. Meuwissen, H. Mundy, N.O. Nilsson, A. Panzer, B.T. Poll-The, C. Rauscher, C.M. Rouselle, I. Sandvig, T. Scheffner, E. Sheridan, N. Simpson, P. Sykora, R. Tomlinson, J. Trounce, D. Webb, B. Weschke, H. Scheffer, M.A. Willemsen, Glucose transporter-1 deficiency syndrome: the expanding clinical and genetic spectrum of a treatable disorder, Brain. J. Neurol. 133 (2010) 655–670.
[24] J. Friedman, A. Feigenbaum, N. Chuang, J. Silhavy, J.G. Gleeson, Pyruvate dehydrogenase complex-E2 deficiency causes paroxysmal exercise-induced dyskinesia, Neurology 89 (2017) 2297–2298.
[25] S. Olgiati, M. Skorvanek, M. Quadri, M. Minneboo, J. Graafland, G.J. Breedveld, R. Bonte, Z. Ozgur, M.C. van den Hout, K. Schoonderwoerd, F.W. Verheijen, I.W.F. van, H.F. Chien, E.R. Barbosa, H.C. Chang, S.C. Lai, T.H. Yeh, C.S. Lu, Y.H. Wu-Chou, A.J. Kievit, V. Han, Z. Gdovinova, R. Jech, R.M. Hofstra, G.J. Ruijter, W. Mandemakers, V. Bonifati, Paroxysmal exercise-induced dystonia within the phenotypic spectrum of ECHS1 deficiency, Movement disorders, Off. J. Mov. Disord. Soc. 31 (2016) 1041–1048.
[26] R. Erro, K.P. Bhatia, Unravelling of the paroxysmal dyskinesias, J. Neurol. Neurosurg. Psychiatry. 90 (2) (2019 Feb) 227–234, https://doi.org/10.1136/jnnp-2018-318932 Epub 2018 Sep 21. PMID: 30242089.
[27] S. Rainier, D. Thomas, D. Tokarz, L. Ming, M. Bui, E. Plein, X. Zhao, R. Lemons, R. Albin, C. Delaney, D. Alvarado, J.K. Fink, Myofibrillogenesis regulator 1 gene mutations cause paroxysmal dystonic choreoathetosis, Arch. Neurol. 61 (2004) 1025–1029.
[28] D.L. Browne, S.T. Gancher, J.G. Nutt, E.R. Brunt, E.A. Smith, P. Kramer, M. Litt, Episodic ataxia/myokymia syndrome is associated with point mutations in the human potassium channel gene, KCNA1, Nat. Genet. 8 (1994) 136–140.
[29] M.C. D'Adamo, S. Hasan, L. Guglielmi, I. Servettini, M. Cenciarini, L. Catacuzzeno, F. Franciolini, New insights into the pathogenesis and therapeutics of episodic ataxia type 1, Front. Cell. Neurosci. 9 (2015) 317.
[30] T.D. Graves, S. Rajakulendran, S.M. Zuberi, H.R. Morris, S. Schorge, M.G. Hanna, D.M. Kullmann, Nongenetic factors influence severity of episodic ataxia type 1 in monozygotic twins, Neurology 75 (2010) 367–372.
[31] W. Nachbauer, M. Nocker, E. Karner, I. Stankovic, I. Unterberger, A. Eigentler, R. Schneider, W. Poewe, M. Delazer, S. Boesch, Episodic ataxia type 2: phenotype characteristics of a novel CACNA1A mutation and review of the literature, J. Neurol. 261 (2014) 983–991.
[32] A. Escayg, M. De Waard, D.D. Lee, D. Bichet, P. Wolf, T. Mayer, J. Johnston, R. Baloh, T. Sander, M.H. Meisler, Coding and noncoding variation of the human calcium-channel beta4-subunit gene CACNB4 in patients with idiopathic generalized epilepsy and episodic ataxia, Am. J. Hum. Genet. 66 (2000) 1531–1539.
[33] J.C. Jen, J. Wan, T.P. Palos, B.D. Howard, R.W. Baloh, Mutation in the glutamate transporter EAAT1 causes episodic ataxia, hemiplegia, and seizures, Neurology 65 (2005) 529–534.
[34] B. de Vries, H. Mamsa, A.H. Stam, J. Wan, S.L. Bakker, K.R. Vanmolkot, J. Haan, G.M. Terwindt, E.M. Boon, B.D. Howard, R.R. Frants, R.W. Baloh, M.D. Ferrari, J.C. Jen, A.M. van den Maagdenberg, Episodic ataxia associated with EAAT1 mutation C186S affecting glutamate reuptake, Arch. Neurol. 66 (2009) 97–101.
[35] J. Conroy, P. McGettigan, R. Murphy, D. Webb, S.M. Murphy, B. McCoy, C. Albertyn, D. McCreary, C. McDonagh, O. Walsh, S. Lynch, S. Ennis, A novel locus for episodic ataxia:UBR4 the likely candidate, Eur. J. Hum. Genet. 22 (2014) 505–510.
[36] R. Erro, U.M. Sheerin, K.P. Bhatia, Paroxysmal dyskinesias revisited: a review of 500 genetically proven cases and a new classification, Movement disorders, Off. J. Mov. Disord. Soc. 29 (2014) 1108–1116.
[37] A. Albanese, K. Bhatia, S.B. Bressman, M.R. Delong, S. Fahn, V.S. Fung, M. Hallett, J. Jankovic, H.A. Jinnah, C. Klein, A.E. Lang, J.W. Mink, J.K. Teller, Phenomenology and classification of dystonia: a consensus update, Mov. Disord. 28 (2013) 863–873.
[38] O. Waln, J. Jankovic, Paroxysmal movement disorders, Neurol. Clin. 33 (2015) 137–152.
[39] R. Erro, K.P. Bhatia, A.J. Espay, P. Striano, The epileptic and nonepileptic spectrum of paroxysmal dyskinesias: channelopathies, synaptopathies, and transportopathies, Movement disorders, Off. J. Mov. Disord. Soc. 32 (2017) 310–318.
[40] G.H. Tan, Y.Y. Liu, L. Wang, K. Li, Z.Q. Zhang, H.F. Li, Z.F. Yang, Y. Li, D. Li, M.Y. Wu, C.L. Yu, J.J. Long, R.C. Chen, L.X. Li, L.P. Yin, J.W. Liu, X.W. Cheng, Q. Shen, Y.S. Shu, K. Sakimura, L.J. Liao, Z.Y. Wu, Z.Q. Xiong, PRRT2 deficiency induces paroxysmal kinesigenic dyskinesia by regulating synaptic transmission in cerebellum, Cell Res. 28 (2018) 90–110.
[41] M.D. Mark, T. Maejima, D. Kuckelsberg, J.W. Yoo, R.A. Hyde, V. Shah, D. Gutierrez, R.L. Moreno, W. Kruse, J.L. Noebels, S. Herlitze, Delayed postnatal loss of P/Q-type calcium channels recapitulates the absence epilepsy, dyskinesia, and ataxia phenotypes of genomic Cacna1a mutations, J. Neurosci. Off. J. Soc. NeuroscI. 31 (2011) 4311–4326.
[42] K.P. Bhatia, Paroxysmal dyskinesias, Mov. Disord. 26 (2011) 1157–1165.
[43] H.F. Li, W.J. Chen, W. Ni, K.Y. Wang, G.L. Liu, N. Wang, Z.Q. Xiong, J. Xu, Z.Y. Wu, PRRT2 mutation correlated with phenotype of paroxysmal kinesigenic dyskinesia and drug response, Neurology 80 (2013) 1534–1535.
[44] A. Labate, P. Tarantino, M. Viri, L. Mumoli, M. Gagliardi, A. Romeo, F. Zara, G. Annesi, A. Gambardella, Homozygous c.649dupC mutation in PRRT2 worsens the BFIS/PKD phenotype with mental retardation, episodic ataxia, and absences, Epilepsia 53 (2012) e196–199.
[45] F. Li, Z.D. Lin, Y. Hu, W. Li, C.C. Xue, N.D. Poonit, Lamotrigine monotherapy for paroxysmal kinesigenic dyskinesia in children, Seizure 37 (2016) 41–44.
[46] S. Horisawa, M. Sumi, H. Akagawa, T. Kawamata, T. Taira, Thalamotomy for paroxysmal kinesigenic dyskinesias in a multiplex family, Eur. J. Neurol. 24 (2017) e71–e72.
[47] M. Bozi, K.P. Bhatia, Paroxysmal exercise-induced dystonia as a presenting feature of young-onset Parkinson's disease, Mov. Disord. 18 (2003) 1545–1547.
[48] R.C. Dale, A. Melchers, V.S. Fung, P. Grattan-Smith, H. Houlden, J. Earl, Familial paroxysmal exercise-induced dystonia: atypical presentation of autosomal dominant GTP-cyclohydrolase 1 deficiency, Dev. Med. Child Neurol. 52 (2010) 583–586.
[49] M. Synofzik, J. Schicks, T. Lindig, S. Biskup, T. Schmidt, J. Hansel, F. Lehmann-Horn, L. Schols, Acetazolamide-responsive exercise-induced episodic ataxia associated with a novel homozygous DARS2 mutation, J. Med. Genet. 48 (2011) 713–715.
[50] A.S. Alter, K. Engelstad, V.J. Hinton, J. Montes, T.S. Pearson, C.I. Akman, D.C. De Vivo, Long-term clinical course of Glut1 deficiency syndrome, J. Child Neurol. 30 (2015) 160–169.
[51] R.A. Head, R.M. Brown, Z. Zolkipli, R. Shahdadpuri, M.D. King, P.T. Clayton, G.K. Brown, Clinical and genetic spectrum of pyruvate dehydrogenase deficiency: dihydrolipoamide acetyltransferase (E2) deficiency, Ann. Neurol. 58 (2005) 234–241.
[52] C.A. McWilliam, C.K. Ridout, R.M. Brown, R.C. McWilliam, J. Tolmie, G.K. Brown, Pyruvate dehydrogenase E2 deficiency: a potentially treatable cause of episodic dystonia, Eur. J. Paediatr. Neurol. 14 (2010) 349–353.
[53] W.G. Leen, L. Mewasingh, M.M. Verbeek, E.J. Kamsteeg, B.P. van de Warrenburg, M.A. Willemsen, Movement disorders in GLUT1 deficiency syndrome respond to the modified Atkins diet, Mov. Disord. 28 (2013) 1439–1442.
[54] F. Mochel, E. Hainque, D. Gras, I.M. Adanyeguh, S. Caillet, B. Heron, A. Roubertie, E. Kaphan, R. Valabregue, D. Rinaldi, S. Vuillaumier, R. Schiffmann, C. Ottolenghi, J.Y. Hogrel, L. Servais, E. Roze, Triheptanoin dramatically reduces paroxysmal

motor disorder in patients with GLUT1 deficiency, J. Neurol. Neurosurg. Psychiatry 87 (2016) 550–553.
[55] A. Mahajan, J. Constantinou, C. Sidiropoulos, ECHS1 deficiency-associated paroxysmal exercise-induced dyskinesias: case presentation and initial benefit of intervention, J. Neurol. 264 (2017) 185–187.
[56] A. Kumar, A. Szekely, B. Jabbari, Effective treatment of paroxysmal nonkinesigenic dyskinesia with Oxcarbazepine, Clin. Neuropharmacol. 39 (2016) 201–205.
[57] M. Alemdar, P. Iseri, M. Selekler, S.S. Komsuoglu, Levetiracetam-responding paroxysmal nonkinesigenic dyskinesia, Clin. Neuropharmacol. 30 (2007) 241–244.
[58] D.L. Coulter, P. Donofrio, Haloperidol for nonkinesiogenic paroxysmal dyskinesia, Arch. Neurol. 37 (1980) 325–326.
[59] W. Loscher, A. Richter, Piracetam and levetiracetam, two pyrrolidone derivatives, exert antidystonic activity in a hamster model of paroxysmal dystonia, Eur. J. Pharmacol. 391 (2000) 251–254.
[60] M. Strupp, J. Teufel, A. Zwergal, R. Schniepp, K. Khodakhah, K. Feil, Aminopyridines for the treatment of neurologic disorders, Neurol. Clin. Pract. 7 (2017) 65–76.
[61] D.M. Buhat, E.K. Tan, Genetic testing of LRRK2 in Parkinson's disease: is there a clinical role? Park. Relat. Disord. 20 (Suppl 1) (2014) S54–S56.
[62] L. Silveira-Moriyama, S. Kovac, M.A. Kurian, H. Houlden, A.J. Lees, M.C. Walker, E. Roze, A.R. Paciorkowski, J.W. Mink, T.T. Warner, Phenotypes, genotypes, and the management of paroxysmal movement disorders, Dev. Med. Child Neurol. 60 (2018) 559–565.