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MOVEMENT DISORDERS (T. SIMUNI, SECTION EDITOR)

Paroxysmal Movement Disorders: Recent Advances

Zheyu Xu [1] · Che-Kang Lim [2,3] · Louis C. S. Tan [1,4] · Eng-King Tan [1,4]

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Abstract

Purpose of Review Recent advancements in next-generation sequencing (NGS) have enabled techniques such as whole exome sequencing (WES) and whole genome sequencing (WGS) to be used to study paroxysmal movement disorders (PMDs). This review summarizes how the recent genetic advances have altered our understanding of the pathophysiology and treatment of the PMDs. Recently described disease entities are also discussed.

Recent Findings With the recognition of the phenotypic and genotypic heterogeneity that occurs amongst the PMDs, an increasing number of gene mutations are now implicated to cause the disorders. PMDs can also occur as part of a complex phenotype. The increasing complexity of PMDs challenges the way we view and classify them.

Summary The identification of new causative genes and their genotype-phenotype correlation will shed more light on the underlying pathophysiology and will facilitate development of genetic testing guidelines and identification of novel drug targets for PMDs.

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

Introduction

The paroxysmal movement disorders (PMDs) are a group of diverse neurological conditions characterized by the episodic occurrence of involuntary movements with most disorders having a normal interictal examination in between attacks. Historically, the pure PMDs have been subdivided into two groups according to the dominant attack phenomenology: namely the paroxysmal dyskinesias (PxDs) and the episodic ataxias (EAs). Episodic attacks of dyskinesias occur in the PxDs [1] and episodic ataxia in the form of truncal ataxia or limb ataxia occurs in the EAs. Many of the PxDs can be co-morbid with other neurological disorders that are suggestive of an underlying channelopathy, such as epilepsy and migraine. With advancements in next-generation sequencing (NGS) technology, PxDs are also recognized to occur either in isolated forms or as part of a more complex phenotype in a number of rare genetic disorders. Other than the primary forms of PMDs attributable to monogenic gene mutations, PMDs can also occur secondarily to other causes [2]. The primary PMDs may be inherited or have a sporadic occurrence. The inherited forms often have an onset during childhood or adolescence with an autosomal dominant inheritance pattern.

With the increasing genetic and phenotypic variability that is recognized to occur in the PMDs, we have proposed a new way of classifying the PMDs that combines both the genotypic and phenotypic information [3]. This review focuses on how recent genetic developments have influenced the understanding of the pathophysiology and treatment strategies of the PMDs.

This article is part of the Topical Collection on *Movement Disorders*

✉ Eng-King Tan
tan.eng.king@sgh.com.sg

[1] Department of Neurology, National Neuroscience Institute, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore

[2] Department of Clinical Translational Research, Singapore General Hospital, Bukit Merah, Singapore, Singapore

[3] Division of Clinical Immunology and Transfusion Medicine, Department of Laboratory Medicine, Karolinska Institute, Solna, Sweden

[4] Duke-NUS Medical School, 8 College Rd, Singapore 169857, Singapore

Current Nosology of PMDs

Clinical Classification of the PxDs

The currently used classification system of the paroxysmal dyskinesias was first created by Demirkiran and Jankovic in

1996, which was based on attack precipitants and not on phenomenology [1]: That classification system recognizes four entities which include paroxysmal kinesigenic dyskinesia (PKD), paroxysmal non-kinesigenic dyskinesia (PNKD), paroxysmal exercise-induced dyskinesia (PED), and also paroxysmal hypnogenic dyskinesia (PHD). PHD was subsequently reclassified as a frontal lobe epilepsy variant, which is now known as sleep-related hypermotor epilepsies (SHEs). However, with the recent discovery of *PRRT2* mutations in two individuals with PHD [4•], this distinction is blurred and could imply that a subset of what we recognize to be PHD could once again be classified as a PxDs.

Clinical Classification of the Episodic Ataxias

At present, eight EA syndromes are described according to their associated genetic loci. EA1 or EA2 are the most common disorders which are attributable to mutations in *KCNA1* and *CACNA1A* respectively. Other EAs are rare and have only been reported in isolated case reports. Other identified causative genes including mutations in *SLC1A3*, *CACNB4*, and *UBR4* [5]. In addition, association with gene region chromosome 1q42, 19q13 was also observed [6, 7].

Genotypic Spectrum of PMDs

PKD

In 1999, the chromosomal region 16p11.2-q12.1 was first identified as the probable location responsible for PKD [8]. Two years later, by combining the techniques of classical linkage analysis with whole exome sequencing, the major causative gene for PKD was found to be the proline-rich transmembrane protein 2 (*PRRT2*) gene [9, 10]. PRRT2 expression is high in the basal ganglia [9] and interacts with synaptosomal associated protein 25 (SNAP25) to influence calcium-induced exocytosis and hence neuronal signaling. In PKD, the PRRT2 is inherited in an autosomal dominant manner but with variable penetrance ranging from 80–90% in familial case to just 30–35% in sporadic cases [11]. PRRT2 mutation carriers have been reported to have an earlier age of onset compared to non-PRRT2 carriers and tend to more commonly report premonitory symptoms [3].

In addition, *PRRT2* mutations have also shown to cause two related disorders: namely infantile convulsions and choreoathetosis (ICCA) and benign familial infantile epilepsy (BFIE) [12], suggesting that both ICCA and BFIE, as well as PKD may represent a spectrum of related disorders and possibly shared the similar molecular or genetic pathogenetic pathways.

In a comprehensive review of 1444 reported PRRT2 mutation carriers: approximately a similar proportion of 40% were diagnosed with either BFIE or PKD, 15% with ICCA and the remaining 5% diagnosed with a range of neurological disorders which included PED, PNKD and PNKD-like disorders, PED, epileptic disorders, different headache syndromes including hemiplegic migraine, and cases of non-syndromic intellectual disabilities [13]. Significant phenotypic pleiotrophy in the PRRT2-related disorders exists with at least 97 distinct pathogenic *PRRT2* mutations identified presently. The c.649dupC frameshift mutation is most commonly reported and accounts for 80.5% of cases for PKD [13]. In cases where biallelic *PPRT2* mutations occur, a more severe disease phenotype has been observed such as co-existence of multiple paroxysmal movement disorders, intellectual or cognitive impairment, and cerebellar atrophy [14].

However, as PRRT2 gene mutations have not been found in all PKD cases, this suggests that additional undiscovered causative genes could be implicated. To add to the complexity, there is considerable phenotypic overlap with the other paroxysmal disorders. Isolated PKDs could also occur as a forme fruste of other more complex inherited neurological disorders.

A pathogenic mutation in the sodium channel, voltage-gated, and type VIII alpha gene (*SCN8A*) was first found in three families with infantile convulsions and paroxysmal choreoathetosis (ICCA) and benign familial infantile seizures (BFIS) [15•]. ICCA refers to the combined presence of both BFIS and PKD. In a subsequent study with 163 PKD patients who were negative for the *PRRT2* mutation, WES was performed and one individual with sporadic PKD was shown to have a novel, likely pathogenic mutation in *SCN8A* [16••]. In two sporadic PKD cases, novel disease-causing mutations were found in the solute carrier family 2 member 1 (*SLC2A1*) and potassium calcium-activated channel subfamily M alpha 1 (*KCNMA*1) genes. Potentially pathogenic genes mutations in the Dishevelled, Egl-10, and Pleckstrin domain containing 5 (*DPEDC5*); paroxysmal non-kinesigenic dyskinesia protein (*PNKD*); and potassium voltage-gated channel subfamily A member 1 (*KCNA1*) genes were found to be to segregating in three families [17]. *PNKD* and *KCNA1* are more frequently associated with other paroxysmal disorders, namely PNKD and EA1 respectively. Potentially pathogenic mutations in *SLC20A2*, which are more frequently associated with familial idiopathic basal ganglia calcification [18], were also found to be causative of PKD. In one family with the co-occurrence of both genetic epilepsy with febrile seizures and PKD, mutations in *CHRNA4* were identified [19], which are more frequently associated with nocturnal frontal lobe epilepsy.

PED

The first gene identified to cause PED was the solute carrier family 2, member 1 (*SLC2A1*) gene: pathogenic mutation of this gene was discovered in a family with the phenotype of

both epilepsy and PED [20]. *SLC2A1* encodes the glucose transporter type 1 (GLUT1), a membrane-bound protein that facilitates glucose transfer across the blood-brain barrier. Heterozygous *SLC2A1* results in the GLUT1 deficiency syndrome: which is a complex disorder with a varying combination of intellectual impairment, epilepsy, microcephaly, complex movement disorders, and/or paroxysmal movement disorders. The GLUT-1 deficiency syndrome could have a clinical severity that would range from subjects with evidence of only mild motor abnormalities including only isolated PED to subjects with more severe neurological impairments [21]. The type of gene mutation present in GLUT-1 deficiency syndrome determines both the level of intellectual impairment and also the occurrence of complex movement disorders [22]. Subjects carrying a missense mutation typically only exhibit mild mental retardation whereas subjects carrying the more complex gene mutations such as the frameshift, nonsense, splice site, translation initiation mutations, or multiple exon deletions tend to also manifest complex movement disorders as part of their disease. Most cases of PED associated with mutations in *SLC2A1* are inherited in an autosomal dominant manner. Rare cases of GLUT1 deficiency inherited recessively have also been reported in literature [23]. Additionally, *SLC2A1* mutations have also been reported in the other PMDs [2].

Pyruvate dehydrogenase complex-E2 (*PDC-E2*) deficiency and mitochondrial short-chain enoyl-CoA hydratase deficiency (*ECHS1*) are two treatable neurological disorders which result from abnormalities in brain energy metabolism. These disorders have infrequently been reported to have an initial presentation with only isolated PED [24, 25]. In mutations carriers of the GTP cyclohydrolase 1 (*GCH1*) [26••] or parkin RBR E3 ubiquitin protein ligase 2 (*PARK2* or *PRKN*) [2] genes, isolated PED has also been described as the sole presenting symptom. The aforementioned genes are more commonly associated with dopa-responsive dystonia and early-onset parkinsonism respectively. In two siblings with succinic semialdehyde dehydrogenase deficiency, the occurrence of PED as part of a more complex phenotype has been described [27].

PNKD

In 2004, mutations of the myofibrillogenesis regulator 1(*MR-1*) gene were found to be causative of PNKD [28]. The *MR-1* gene was subsequently renamed as the *PNKD* gene. This is the major pathogenic gene that is seen in families with isolated PNKD, with near complete penetrance reported. In contrast to the other paroxysmal disorders, individuals carrying mutations in *PNKD* commonly have an earlier age of onset beginning from infancy or early childhood [11]. The attacks of PNKD can have both dystonic and choreic features with alcohol and caffeine described as typical attack triggers. Proven *PNKD* mutation carriers have a homogenous phenotype with normal neurological examination when examined in between attacks. PNKD attributable to *PNKD* gene mutations are not associated with epilepsy. At present, three different pathogenic *PNKD* mutations have been described in unrelated families with different ethnic origin [2]. PNKD can also occur as part of a complex phenotype in patients carrying mutations in other genes, including adenylate cyclase 5 gene (*ADCY5*), ATPase Na^+/K^+ transporting subunit alpha 3 gene (*ATP1A3*), *SLC2A1*, *PRRT2*, and *KCNMA1* [11].

In the ADCY5-related dyskinesias, no precise triggers have been identified and the duration of the paroxysmal movement disorders could range from minutes to hours and up to days during periods of intercurrent illness. Unlike the other movement disorders, a striking feature is the exacerbation of movements during drowsiness and sleep [29]. A range of different paroxysmal movement disorders have also been reported in this disorder [30] and paroxysmal movement disorders can precede the onset of chronic movement disorders that subsequently dominate the patient's clinical picture [31].

EA1

At present, only mutations in the potassium voltage-gated channel, shaker-related subfamily, and member 1 (*KCNA1*) gene have been linked to EA1 [32]. However, *KCNA1* non-mutation carriers exist who have been described to manifest symptoms that are virtually identical to *KCNA1* carriers. This suggests that there could be other yet undiscovered genes that could also be responsible for EA1.

Currently, EA1 is recognized to have a much wider phenotype than what was originally described. Other than ataxia, other symptoms that could occur during the attacks include visual blurring, diplopia, headaches, dyspnea, dysarthria, and also nausea. Epilepsy is also a common co-morbidity in EA1. Other neurological findings in EA1 have also included intellectual disability, delayed motor milestones, progressive ataxia, neuromyotonia, and also choreoathetosis [33, 34].

In EA1, no distinct associations between genotype and phenotype have been observed. Genetically identical EA1 twins who harbor the same mutation have been reported to exhibit marked variability in both attack severity and other associated features. This observation is suggestive that the phenotype of EA1 manifest by the individual could also be influenced by other environmental or epigenetic factors at play [35]. In *KNCA1* non-mutation carriers who manifest features that typify EA1, they are more often male, have longer attack durations, and are at greater risk of developing progressive disease compared to *KCNA1* mutation carriers [33].

EA2

Amongst the eight different episodic ataxias recognized, EA2 is by far the most common. This disorder is due to pathogenic

mutations in calcium channel, voltage-dependent, P/Q type, and alpha 1A subunit gene (*CACNA1A*) and shows an autosomal dominant inheritance pattern. This gene has a reported penetrance estimated in the range of between 80 and 90%. Similar to EA1, other clinical features are also present in EA2: dystonia, epilepsy, intellectual impairment, variable degrees of weakness, and migraine have all been reported. Migraine, which includes hemiplegic migraines, is extremely common and is seen in up to half of all EA2 cases [5]. The interictal phenotype can range from subjects with an entirely normal examination to those who develop a progressive cerebellar disorder [36].

Other EAs

Mutations in other genes including the calcium channel, voltage-dependent, beta 4 subunit (*CACNB4*) [37], solute carrier family 1, member 3 (*SLC1A3*) gene [38, 39], and ubiquitin protein ligase E3 component n-recognin 4 (*UBR4*) [40] genes have been shown to result in EA5, EA6, and EA8 respectively. However, these have mostly been only found in one or two families. Mutations in the fibroblast growth factor 14 (*FGF14*) gene have been described to be associated with EA in four different families and one sporadic case [41, 42]. The FGF14 gene encodes for the FGF homologous factor which acts by modulating voltage-gated sodium channels and potassium channels at the axonal initial segment [43, 44•]. Mutations in other genes, such as *PRRT2*, sodium voltage-gated channel alpha subunit 2 (*SCN2A*), *ATP1A3*, and *SLC2A1* have also been described to be associated with EA [5, 11].

Three distinct subunits together constitute the mitochondrial pyruvate dehydrogenase complex (PDC); these include pyruvate dehydrogenase (E1), dihydrolipoamide transacetylase (E2), and dihydrolipoamide hydrogenase(E3). The pyruvate dehydrogenase E1 alpha 1 unit (*PDHA1*) and dihydrolipoamide S-acetyltransferase (*DLAT*) genes encode for E1 and E2 respectively. The pyruvate complex component X (*PDHX*) gene codes for the E3-binding protein. Mutations of either *DLAT* or *PDHX* have been reported to be associated with other PxD, which include PED, PNKD, and EA [26••].

The main genetic mutations linked to the different PxMDs and their associated neurological disorders are summarized in Tables 1 and 2.

Other Genetic Paroxysmal Movements Disorders

PHD was previously classified as one of the paroxysmal dyskinesias but since has been regarded as a form of the autosomal dominant nocturnal frontal lobe epilepsies (ADNFLE)s [82], which are now termed as the sleep-related hypermotor epilepsies (SHEs) [83]. PHD is characterized by the occurrence of short duration attacks of paroxysmal dystonic, choreoathetoid, and ballistic attacks during sleep [1] and exhibits treatment

Table 1 The main genes reported with the paroxysmal movement disorders of PKD, PED, and PNKD and the other associated clinical phenotypes

Causative gene	Gene function	Other associated phenotypes
Paroxysmal kinesigenic dyskinesias (PKD)		
PRRT2	Interacts with synaptotagmin and the SNARE complex presynpatically. AMPA receptors postsynaptically and is a negative modulator of membrane-bound voltage-gated Na^+ channels	*Infantile convulsions and choreoathetosis* (ICCA) [12] *Benign familial infantile epilepsy* (BFIE) [12] *Hemiplegic and other types of migraine* [45, 46] Paroxysmal torticollis [45, 46] Also reported with PED, PNKD, and EA
ADCY5	Adenyl cyclases	*ADCY5-associated disease* [29, 47]: Benign hereditary chorea [48] Generalized dystonia and myoclonus [49] Familial myoclonus dystonia [50] Spastic paraparesis [51] Also reported in PED and PNKD
SCN8A	Voltage-gated sodium channel	*Early infantile epileptic encephalopathy type 13* [52, 53] Familial isolated myoclonus [54]
DEPDC5	Negative regulator of the target of the rapamycin complex 1 (mTORC1)	*The DEPDC5-related epilepsies including familial and sporadic epilepsies* [55]
SLC16A2/MT8	Thyroid hormone transporter	*Allan-Herndon-Dudley syndrome* (X-linked) [56]
SLC20A2	Phosphate transporter	*Familial idiopathic basal ganglia calcification* (IBGC) [57]
KCNMA1	Voltage and calcium-activated potassium channel	Syndrome of generalized epilepsy paroxysmal dyskinesias and developmental delay [58] Also reported in PNKD
CHRNA4	Nicotinic acetylcholine receptor alpha 4 subunit gene	*Nocturnal frontal lobe epilepsy* [59]
Paroxysmal exercise-induced dyskinesia (PED)		
SCL2A1/GLUT1	Glucose transporter	*GLUT-1 deficiency syndrome* [60] Also reported in PKD, PNKD, and EA
GCH1	GTH cyclohydroxylase 1	*DOPA-responsive dystonia* (DRD) [61]

Table 1 (continued)

Causative gene	Gene function	Other associated phenotypes
		Parkinson's disease [62]
PARKIN/PARK2	E3 ubiquitin ligases	Parkinson's disease (juvenile type 2)
ATP1A3	Alpha 3 subunit of the Na^+/K^+ ATPase pump	*Alternating hemiplegia of childhood* (AHC) [63, 64] *Cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss syndrome* (CAPOS) [65] *Rapid onset dystonia--parkinsonism* (RDP) [66] Relapsing encephalopathy with cerebellar ataxia (RECA) [67] Rapid onset ataxia [68] Early-onset epileptic encephalopathy with late hemiplegic attacks [69] Also reported in PNKD and EA
PDHA1	Pyruvate dehydrogenase E1 alpha 1 subunit	*Pyruvate dehydrogenase E1 alpha deficiency* Neonatal encephalopathy with lactic acidosis Also reported in episodic ataxia [70]
PDHX	Pyruvate dehydrogenase E3 binding protein	*Lacticacidemia due to PDX1 deficiency/Leigh-like disease* [71]
DLAT	Pyruvate dehydrogenase E2 subunit dihydrolipoamide acetyltransferase (E2)	*Pyruvate dehydrogenase E2 deficiency* [72]
Paroxysmal non-kinesigenic dyskinesias (PNKD)		
MR-1/PNKD	Myofibrillogenesis regulator-1	NA
BCKD complex	Mitochondrial branched chain alpha ketoacid dehydrogenase kinase	*Maple syrup disease* Also reported in EA

The main genes are highlighted in bold while the main clinical phenotypes associated with the particular gene are highlighted in italic

Table 2 The main genes associated with the episodic ataxias and the main phenotype associated mutations of the named gene

Episodic ataxias			
EA type	Main gene	Gene function	Other associated phenotypes
EA1	***KCNA1***	Potassium gated channel subfamily member 1	Also reported in PKD [17] and PNKD [73]
EA2	***CACNA1A***	Calcium voltage-gated channel subunit alpha1 A	*Familial hemiplegic migraine 1* [74] *Spinocerebellar ataxia 6* [75] Paroxysmal torticollis of infancy (BPTI) [76] Autism with childhood onset epileptic encephalopathy [77] Autosomal recessive progressive myoclonic epilepsy [78]
EA5	***CACNB4***	Voltage-gated calcium channel beta 4 subunit	*Familial epilepsy* [37]
EA6	***SLC1A3/EEAT1***	Solute Carrier Family 1 Member 3 gene/astrocytic excitatory amino acid transporter 1 (EAAT1)	Episodic ataxia, hemiplegic migraine and seizures [79] Migraine with aura including hemiplegia [80]
EA8	***UBR4***	Ubiquitin ligase protein (interacts with calmodulin)	
Others: E-A3--8	*FGF14*	Fibroblast growth factor 14 (interacts with the voltage-gated sodium channels 1.2 and 1.6)	*Spinocerebellar ataxia 27* (SCA 27) [81]

The main genes are highlighted in bold while the main clinical phenotypes associated with the particular gene are highlighted in italic

sensitivity to sodium channel blockers. Clinically, the attacks of PHD and ADNFLE are difficult to distinguish. PRRT2 mutations were recently identified in two patients with PHD [4•]: in one family, PHD was diagnosed in the index case and the father was diagnosed with PKD, suggesting that PHD have wide spectrum of phenotypes and might be included as a subtype of the PxDs.

More recently, paroxysmal dyskinesias triggered by fever and hot weather have been described in two sisters as part of a complex phenotype including mild developmental delay, absence epilepsy, and non-progressive ataxia associated with the gamma-aminobutyric acid transaminase (GABA-T) deficiency as a result of recessive mutations in the 4-aminobutyrate

aminotransferase (*ABAT*) gene [84••]. These paroxysmal episodes of chorea alongside drowsiness have a duration ranging from 1 to 10 min, triggered by fever and hot weather. GABA-T deficiency results in increased GABA levels in the brain [85]. However, it remains unclear how enhanced GABA neurotransmission can result in the occurrence of hyperkinetic movement disorders.

Further novel genetic mutation(s) of the PMDs will likely be discovered with more widespread use of next-generation sequencing (NGS).

Challenges in PMD Nosology

Accurate clinical recognition and diagnosis of the different PMDs can be very difficult. The clinical attacks are rarely witnessed by the clinician, requiring the diagnostic process to be heavily reliant on videos or history provided rather than careful observation in the clinical setting. Multiple phenomenologies can occur in a clinical attack and can also be observed at different time points in the same individual. Even when genetic mutations are found, the significance of the findings could be difficult to establish when no firm clinical diagnosis has been made. Furthermore, some of the reported mutations could be non-pathogenic and require further verification studies.

Although the currently adopted clinically based classification system has limitations, it is still useful and can inform on first-line limited genetic screening as since each broad grouping of the different PMDs are more likely to be linked to particular gene mutations.

Pathophysiology

Much remains uncertain regarding the pathophysiology of the different PMDs. The prevailing hypothesis is that the PMDs are channelopathies. This inference has been made as ion channels gene mutations have been shown to be causative in other episodic neurological disorders such as epilepsy and migraine, which can be found co-morbid with the PMDs. The more recent discovery of *SCN8A*, *KCNMA1*, and *ATP1A3* gene mutations in patients with PMDs provides further support for the channelopathy hypothesis. In addition, mutations in the genes encoding ion channels and transmembrane transporters have been found to be responsible for the EAs. Some of the PMDs are highly responsive to treatment with low-dose anti-epileptics, targeting ion channels [86].

However, the channelopathy hypothesis itself remains insufficient to fully explain the pathophysiology of all the PMDs. The major genes that are associated with PMDs (*PRRT2*, *MR1*, and *SLC2A1*) do not encode ion channels [87••] and further work is required to elucidate the gene function of these key pathogenic genes.

However, a recent breakthrough in the molecular physiology of PRRT2 mutation has once again given greater credence to the channelopathy hypothesis, with PRRT2 acting by modulating the function of voltage-gated Na^+ channels which are located at the axon initial segment [88••]. PRRT2 has been largely believed to act on the synapse by interacting with the fast Ca^{2+} sensor synaptotagmin and components of the SNARE complex which mediate the fusion of synaptic vesicles and also the postsynaptically with the AMPA receptors [89, 90]. Using neurones derived from induced pluripotent stem cells of both heterozygous and homozygous siblings carrying the most common PRRT2 mutation C649dupC to study PRRT2 at a molecular level, Fruscione et al. showed that PRRT2 acts as a negative modulator of membrane-bound voltage-gated Na^+ channels $Na_v1.2$ and $Na_V1.6$ to decrease their membrane exposure and hence decrease Na^+ current. PRRT2 mutations thus result in increased voltage-dependent Na^+ current and increased intrinsic excitability [88••]. SCN8A encodes for $Na_V1.6$ and pathogenic gain-of-functions mutations in SCN8A affecting the $Na_V1.6$ alpha subunit inactivation gate have been found to be the causative gene in three families with BFIS and PKD [15•]. This discovery of the negative modulatory role of PRRT2 on the $Na_v1.6$ explains why PRRT2 mutations and gain-of-function mutations in SCN8A can cause a similar disease phenotype that also responds to treatment with Na^+ channel blockers.

In a similar fashion, FGF14, for which mutations have been reported in EA, acts by modulating the voltage-gated sodium channels and potassium channels, including those present at the axon initial segment [43, 44•] and also voltage-gated calcium channels at the presynaptic membrane [91]. Thus genes mediating the PMDs may not directly encode for ion channels, but may encode modulator proteins that regulate ion channel function to cause the similar phenotype of PMDs that are caused by ion channel gene mutations, hence accounting for the wide genetic and phenotypic pleiotrophy observed in these disorders.

However, mutations in other genes that do not encode for ion channels or ion channel modulators have also been implicated in the PMDs, suggesting that the channelopathy hypothesis cannot be the sole explanation for the pathophysiology of the PMDs and our understanding of the pathophysiology of the PMDs remains far from complete. In 2017, Erro et al. proposed that the different PMDs can be mostly categorized into three groups according to their presumed pathophysiological mechanisms that have been inferred from their associated gene mutations [87]: the neurotransmission synaptopathies in which synapse formation and/or function is impaired, the channelopathies in which ion channel and neuronal excitability is altered, and the transportopathies in which glucose transport or brain energy metabolism is affected. Since the original proposal of Erro et al., further causative gene mutations for the

PMDs have been described which involve the aforementioned described pathways: the neurotransmission synaptopathies (*PRRT2*, *PNKD*, *SLC16A2*, *ADCY5*), channelopathies (*SCN8A*, *KCNMA1*, *ATP1A3*, *KCNA1*, *CACNA1A*, *CACNB4*, *SCN2A*), and brain energy transportopathies (*SLC2A1*, *DLAT*, *PDHA1*, *PDHX*, *SLC1A3*). Thus, perturbations in any of these three pathways can all be responsible for the pathogenesis of PMDs. Other recently described genes associated with the PMDs such as *DEPDC5* which encodes for the negative regulator of the target of the rapamycin complex 1, *SLC16A2*, whose chief function is as a thyroid hormone transporter and the occurrence of PMDs in GABA transaminase deficiency do not readily explain the occurrence of the paroxysmal movement disorders.

The basal ganglia/corticothalamic circuits play an important role in the control of voluntary movements with the thalamus as the key nexus [92]. The role of the thalamocortical networks in the pathophysiology of the PKDs has been recently explored using functional magnetic resonance imaging and diffusion tensor imaging. Long et al. was able to show that PKD patients exhibited altered connectivity between the thalamus and the motor cortex: increased functional and structural connectivity was observed between the ventral lateral/anterior thalamic nuclei and a lateral motor area [93]. Additionally, PRRT2 mutation carriers demonstrated thalamo-prefrontal hypoconnectivity. As such, PKD can be regarded as a circuit disorder [94]. More recent genetic functional studies emphasized the central role of the cerebellum.

Recent genetic functional studies have also highlighted the central role of the cerebellum in the pathophysiology of PKD. In the mouse model either ion channel or synaptic protein mutations could both lead to abnormal firing patterns in the Purkinje cells and the appearance of both the PMD phenotype and ataxia in mice [89, 95].

Diagnosis and Investigation of the PMDs

To evaluate paroxysmal movement disorders, obtaining a detailed clinical history is the first and vital step of the diagnostic process. Important features that should be taken note of include attack phenomenology, triggers, and duration. Clinical features during the interictal period should also be noted. To properly characterize the attacks, videotapes when feasible should be used. However, dyskinetic attacks could also cause incoordination and gait disturbances and can be difficult to distinguish clinically from ataxia [91]. Where possible, the neurological examination should be performed both during the attack and also between the attacks to identify interictal examination findings that may allow for diagnostic possibilities to be narrowed. However, in situations where paroxysmal movement disorders exist alongside other movement disorders as part of a complex phenotype, for which there could be a varying combination of different movement disorders, identifying the predominant movement disorder or clinical syndrome may be difficult.

Neuroimaging and blood tests are useful to exclude secondary causes of PMD and to look for the presence of basal ganglia calcifications. The electroencephalogram (EEG) can detect previously unrecognized epileptic activity. Rarely, electromyography (EMG) can be useful to detect subclinical myokymia. However, these investigations are rarely helpful in narrowing down the diagnostic possibilities and genetic testing using NGS techniques of either WES or WGS is necessary particularly in light of the marked genetic pleiotrophy observed in these disorders. The use of WES has also been advocated for the diagnosis of mitochondrial disorders such as the pyruvate dehydrogenase complex deficiency disorders [70].

The initial selection of gene sequencing method to be used depends on the desired yield and costs of testing. In cases where clinical findings do not implicate a specific gene to test first, the preferred initial approach could be via a gene panel, or more detailed testing such as WES or WGS [96].

The utility of using a targeted gene panel to provide a genetic diagnosis was recently studied in a prospective multicenter study involving 27 tertiary movement disorders centers in Luxembourg, Algeria, and France [97••]: 378 subjects who had developed one or more movement disorders, with an age of onset before the age of 40 and/or a positive family history underwent genetic testing using a targeted gene panel which tested for 127 genes associated with movement disorders, of which a more limited selection of 11 genes known to be associated with paroxysmal movement disorders including hyperekplexia were also included. This mixed cohort included 20 patients with PMDs gave a fairly high diagnostic yield of 35%, suggesting that targeted gene sequencing could be a cost-effective first step diagnostic tool for the PMDs. If the results are negative, consideration should be given to WES or WGS.

However, the NGS techniques are not be able to detect large deletions, chromosomal rearrangements, and trinucleotide expansions. Another problem common to all WGS techniques is the identification of gene variants of unknown significance and further confirmatory testing using functional testing may be required. Although a number of genetic databases are currently available to deposit genotype-phenotype information, this is a rapidly evolving field with marked genetic and phenotype pleiotrophy seen.

Treatment of the PMDs

Anti-convulsants remain the key therapy in the treatment of the PMDs. Recent genetic and also imaging advances in the PMDs has allowed novel therapies to be developed that target the particular biochemical or brain circuit pathway implicated in the PMDs. It is expected that in the future, genetic

phenotyping of the PMDs would guide the use of targeted therapies for the treatment of the PMDs.

PKD

The PKDs are readily treated by anti-epileptics, particularly phenytoin and carbamazepine which act on the voltage-gated sodium channels modulators [98]. However, treatment failure to anti-epileptics has been reported in homozygous or compound heterozygous PRRT2 mutation carriers [14, 99]. Lamotrigine, another sodium channel blocker with additional functions of suppressing glutamate and aspartate release, has been demonstrated to be very effective in the treatment of PKD [100]. More recently, thalamotomy of the ventro-oral nucleus was also shown to be an effective treatment for PKD in four members of one family, with complete or near complete remission of attacks achieved without the use of pharmacotherapy [101].

PED

Unlike the other PMDs, treatment of PED largely relies on the avoidance of attack triggers. Isolated case reports have reported partial to complete success using trihexyphenidyl, benzodiazepines, acetazolamide [102], and pallidotomy [1, 98].

Advances in the understanding of the genetics and underlying pathophysiological mechanisms of PED resulted in the targeted drug development of PED linked to particular disease mutations, including new therapies for PED linked to genetic defects in cerebral energy metabolism. In GLUT1 mutation [103], SLC2A1 mutation and pyruvate dehydrogenase complex-E2 deficiency (PDC-E2) carriers [72, 104], attack frequency could be reduced with consumption of the ketogenic diet. Likewise, the modified Atkins diet is helpful in the GLUT-1 deficiency syndrome [105]. Triheptanoin, a triglyceride that replenishes metabolic intermediates in the Krebs cycle resulted in almost complete remission of PED attacks [106]. The mitochondrial cocktail reduced attack severity and frequency in PED with a causative mutations in ECHS1 [107]. Levodopa is an effective treatment for PED associated with the GTP cyclohydrolase 1 (GCH-1) mutations [108].

PNKD

In PNKD, the attacks may respond to benzodiazepines but generally not anti-epileptics with the exception of oxcarbazepine [109]. Control of the disorder still relies on the avoidance of attack. A long list of drugs including acetazolamide, adenosine agonists/antagonists, anticholinergics, gabapentin, haloperidol, levetiracetam, levodopa, nitric oxide synthetase inhibitors, and piracetam and levodopa have been used with varying degrees of success, with most only showing partial effectiveness [110–112].

EAs

The attacks of EA1 can respond to acetazolamide and anti-epileptics. In EA2, acetazolamide is typically effective but the side effects of acetazolamide can be a rate limiting step in clinical practice. The non-selective potassium channel blocker, 4-aminopyridine(4-AP), has been useful in reducing attack frequency [11]. Individuals with EA3, EA5, and EA6 can also be acetazolamide responsive. EA8 differs from the other episodic ataxias in that treatment response to acetazolamide is not seen with the attacks instead responding to clonazepam [40].

Conclusions

Genetic advances have provided new insights in the pathophysiological mechanisms underpinning PMDs and have led to the introduction of novel targeted treatments for the disorders. Improvements to the current classification system of the PMDs will be necessary to reflect the increasing genetic and phenotypic complexity of these conditions.

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Compliance with Ethical Standards

Conflict of Interest Eng-King Tan received honorarium for editorial duties for European Journal of Neurology and Parkinsonism related disorders. Zheyu Xu, Che-Kang Lim, and Louis CS Tan each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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