The Application of Clinical Genetics

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REVIEW

Genetic Links to Episodic Movement Disorders: Current Insights

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Abstract: Episodic or paroxysmal movement disorders (PxMD) are conditions, which occur episodically, are transient, usually have normal interictal periods, and are characterized by hyperkinetic disorders, including ataxia, chorea, dystonia, and ballism. Broadly, these comprise paroxysmal dyskinesias (paroxysmal kinesigenic and non-kinesigenic dyskinesia [PKD/PNKD], paroxysmal exercise-induced dyskinesias [PED]) and episodic ataxias (EA) types 1–9. Classification of paroxysmal dyskinesias has traditionally been clinical. However, with advancement in genetics and the discovery of the molecular basis of several of these disorders, it is becoming clear that phenotypic pleiotropy exists, that is, the same variant may give rise to a variety of phenotypes, and the classical understanding of these disorders requires a new paradigm. Based on molecular pathogenesis, paroxysmal disorders are now categorized as synaptopathies, transportopathies, channelopathies, second-messenger related disorders, mitochondrial or others. A genetic paradigm also has an advantage of identifying potentially treatable disorders, such as glucose transporter 1 deficiency syndromes, which necessitates a ketogenic diet, and *ADCY5*-related disorders, which may respond to caffeine. Clues for a primary etiology include age at onset below 18 years, presence of family history and fixed triggers and attack duration. Paroxysmal movement disorder is a network disorder, with both the basal ganglia and the cerebellum implicated in pathogenesis. Abnormalities in the striatal cAMP turnover pathway may also be contributory. Although next-generation sequencing has restructured the approach to paroxysmal movement disorders, the genetic underpinnings of several entities remain undiscovered. As more genes and variants continue to be reported, these will lead to enhanced understanding of pathophysiological mechanisms and precise treatment.

Keywords: paroxysmal movement disorders, episodic ataxia, *PRRT2*, *PNKD*, *KCNA1*

Introduction

Episodic or paroxysmal movement disorders (PxMD) are conditions, which occur episodically, are transient, usually have normal interictal periods, and are characterized by hyperkinetic disorders, including ataxia, chorea, dystonia, and ballism.

Broadly, these include two groups: paroxysmal dyskinesias (PxD), which are characterized by the occurrence of transient hyperkinetic movements (Table 1), and episodic ataxias (EA), characterized by recurrent attacks of cerebellar dysfunction (Tables 2 and Table 3).[1] Broad classification schemes have categorized PxMD based on the age of onset, duration of episodes, interictal abnormalities, underlying pathophysiology, genetics and type of movement disorder. The term "dyskinesia" to describe the hyperkinetic movement disorder was proposed by Demirkiran and Jankovic in 1995.[2] Etymologically, the term 'paroxysmal dyskinesias' has been argued to be restrictive in definition by many authors.[3] However, as this term continues to prevail in the literature, we have used it in this article. In PxD, the phenomenology usually consists of chorea, dystonia or ballism. Other movement disorders, including tics, myoclonus, startle syndrome and tremors, are not included in the definition of PxD.

Based on etiology, PxMD may be genetic or acquired. The pattern of inheritance in genetic conditions is usually autosomal dominant, either sporadic or familial.[3,4] The acquired PxMD may arise from structural, metabolic, vascular, immune-mediated, or degenerative etiologies (Table 4).[3] Clues for secondary causes include age at onset above 18 years,

Received: 9 November 2022
Accepted: 24 February 2023
Published: 1 March 2023

Table 1 Summary Table of Genes Associated with Paroxysmal Dyskinesia

Gene	Chromosome	OMIM	Protein	Associated Phenotype	Age at Onset	Other Features	Treatment
PRRT2[25]	16p11.2	614386	Proline-rich transmembrane protein 2	**PKD** PNKD PED PHD	<18 yrs	EA ICCA Epilepsy Hemiplegic migraine Intellectual disability	Carbamazepine and related drugs
PNKD[26]	2q35	609023	PNKD (PNKD-L, PNKD-M, PNKD-S)	**PNKD** PKD PED	<18 yrs	Hemiplegic migraine Episodic migraine Epilepsy	Benzodiazepines
TBC1D24[27–38]	16p13.3	613577	Tre2-Bub2-Cdc16	PED	Childhood	Epilepsy DOORS Non-syndromic hearing loss	
FGF14[39,40]	13q33.1	601515	Fibroblast growth factor 14	PKD PNKD **EA** (fever triggered)	Early childhood to adulthood	SCA27	Carbamazepine/ related drugs Acetazolamide (EA)
GCH1[41]	14q22.2	600225	GTP cyclohydrolase 1	PED	<18 yrs	Dopa responsive dystonia	Levodopa
RHOBTB2[42–47]	8p21.3	607352	Rho-related BTB domain containing protein 2	PKD EA AHC	Childhood to young adulthood	Developmental and epileptic encephalopathy	
Transportopathies							
SLC2A1[47–54]	1p34.2	138140	GLUT1 (Glucose transporter 1)	PED PNKD PKD EA PED with spasticity/ epilepsy	Childhood	Epilepsy Migraine Myoclonus Oculogyric crisis	Ketogenic diet
SLC16A2[55–57]	Xq13.2	300095	MCT8 (monocarboxylate transporter 8)	PKD PNKD PHD	Infancy	Seizures Allan-Herndon-Dudley syndrome Elevated free T3 Microcephaly Developmental delay Microcephaly	Carbamazepine, related druga
ATP7B[58,59]	13q14.3	606882	Copper-transporting ATPase	PKD PNKD	Variable	Wilson's disease	Chelating agents
Second messenger-related							
ADCY5[60,61]	3q21.1	600293	Membrane-bound adenylyl cyclase	PKD PNKD PED PHD	Childhood	Facial chorea Frog-like gait Oculogyric crisis Worsening during sleep	Caffeine Acetazolamide Benzodiazepine
PDE10A[62–64]	6q27	610652	Phosphodiesterase 10A	PNKD	Childhood	Intellectual disability MRI abnormal: striatal signal change	

(*Continued*)

Table 1 (Continued).

Gene	Chromosome	OMIM	Protein	Associated Phenotype	Age at Onset	Other Features	Treatment
PDE2A[65,66]	11q13.4	602658	Phosphodiesterase 2A	PKD PNKD	Childhood	Epilepsy Intellectual disability	
Channelopathies							
SCN8A[68–73]	12q13.13	614558	Voltage gated sodium channel alfa subunit	PKD/ ICCA	Childhood	Epilepsy Autistic spectrum disorders Intellectual impairment	Carbamazepine, related drugs
KCNA1[74–84]	12p13.32	171260	Voltage gated potassium channel subunit K(v)1.1	PKD PNKD **EA1**	Childhood to adulthood	Epilepsy Migraine Myokymia Neuromyotonia	Acetazolamide Carbamazepine
CACNA1A[85,86]	19p13.13	601011	$Alfa_1$ subunit of the voltage-gated P/Q calcium channel ($Ca_v2.1$)	**EA** PNKD PED Paroxysmal tonic upgaze Paroxysmal torticollis	Childhood	SCA 6 Developmental and epileptic encephalopathy Seizures Familial hemiplegic migraine	Acetazolamide, 4-aminopyridine, levetiracetam
SLC1A3[87]	5p13.2	600111	Solute carrier family 1, member 3, encodes the glutamate transported, excitatory amino acid transporter 1 (EAAT1)	**EA6**	Infancy/ childhood	AHC Intellectual disability Epilepsy Migraine	Acetazolamide
KCNMA1[88–90]	10q22.3	300150	Large conductance voltage and calcium-activated potassium channel, α subunit	PNKD	Childhood	Epilepsy Intellectual disability Axial hypotonia Developmental delay Corticospinal atrophy	
ATP1A3[91–97]	19q13.2	182350	ATPase Na+/K+ transporting subunit	PED PNKD EA	Childhood to adulthood	Rapid-onset dystonia parkinsonism AHC CAPOS syndrome FIPWE RECA	
CLCN2[98]	3q27.1	600570	Chloride channel 2	PKD	Childhood to adulthood	Cognitive impairment Tremor Ataxia Optic atrophy	
CHRNA4[99]	20q13.33	118504	Component of α4.2-nAChR, affects synaptic excitability	PKD	Childhood	GEFS+	Carbamazepine
Mitochondrial							
ECHS1[100–103]	10q26.3	602292	Short-chain enoyl-CoA hydratase	PED	Childhood to adulthood	Leigh's syndrome-like MRI: Abnormal- Signal change in basal ganglia	Ketogenic diet Cocktail of mitochondrial drugs

(*Continued*)

Table 1 (Continued).

Gene	Chromosome	OMIM	Protein	Associated Phenotype	Age at Onset	Other Features	Treatment
PDC *DLAT*[105,106] *PDHA1*[107–109] *PDHX*[104]	 11q23.1 Xp22.12 11p13	 245348 312170 245349	 E2 component of PDC Pyruvate dehydrogenase E1 alpha 1 subunit Pyruvate dehydrogenase complex component X	 PED PNKD PED PNKD EA Paroxysmal dystonia		 Intellectual disability Seizures Episodic ataxia MRI: Abnormal: Signal change in globus pallidus, elevated CSF lactate MRI: Abnormal: Signal change in globus pallidus; elevated CSF lactate Leigh syndrome Lactic acidosis Epilepsy MRI: Abnormal: Signal change in globus pallidus; elevated CSF lactate	 Thiamine Ketogenic diet
Others							
DEPDC5[110] *SACS*[111]	33q12.1-q12.3 13q12.12	614191 604490	GTPase-activating protein subunit Sacsin	PKD PKD	Childhood Variable	Seizures Ataxia, neuropathy	Carbamazepine
BCKD-related							
BCKDHB[112,113]	6q14.1	248611	Branched-chain keto acid dehydrogenase E1 beta polypeptide	PNKD EA	Childhood	Developmental delay Seizures	Isoleucine and valine restriction
DARS2[114]	1q25.1	611105	Mitochondrial aspartyl-tRNA synthetase	PED Exercise-induced ataxia	Childhood to adulthood	Leukoencephalopathy with brainstem and spinal cord involvement	Acetazolamide

Abbreviations: AHC, Alternating hemiplegia of childhood; CSF, Cerebrospinal fluid; DOORS, deafness, onychodystrophy, osteodystrophy, developmental delay and seizures; EA, episodic ataxia; FIPWE, Fever associated paroxysmal weakness and encephalopathy; GEFS+, Generalised epilepsy with febrile seizures plus; PDC, Pyruvate dehydrogenase complex; PED, Paroxysmal exercise-induced dyskinesia; PKD, Paroxysmal kinesigenic dyskinesia; PNKD, Paroxysmal nonkinesigenic dyskinesia; RECA, Relapsing encephalopathy with cerebellar ataxia; ICCA, infantile convulsions with choreoathetosis; SCA, spinocerebellar ataxia.

negative family history, variable duration of symptoms and triggers, or associated clinical features.[5] With the advent of next-generation sequencing, a paradigm shift has emerged in the classification of episodic movement disorders. It is now recognized that variants that cause PxD can also be associated with epilepsy, ataxia, pyramidal signs, developmental delay, and other neurological features. While phenotypic recognition guides treatment, molecular diagnosis may be imperative to streamline therapy in certain disorders. For example, carbamazepine/oxcarbazepine is used to elicit excellent response in paroxysmal kinesigenic dyskinesia (PKD). However, PxD due to glucose transporter 1 (GLUT1)-deficiency syndrome responds to a ketogenic diet.

As these disorders are phenotypically and genotypically complex, episodic movement disorders remain underrecognized by clinicians. In this review, we aim to explore the current genetic links of episodic movement disorders.

Pathophysiology

PxD are considered to be network disorders, with both basal ganglia and cerebellum being implicated in pathophysiology.[5] The aberration may involve either a primary striatal dysfunction or striatal dysfunction secondary to altered outflow from the

Table 2 Summary Table of Genes Associated with Episodic Ataxia

Gene	Chromosome	OMIM	Protein	Associated Phenotype	Other Features
Synaptopathies					
PRRT2[25]	16p11.2	614386	Proline-rich transmembrane protein 2	**PKD** PNKD PED PHD	EA ICCA Epilepsy Hemiplegic migraine Intellectual disability
FGF14[39,40]	13q33.1	601515	Fibroblast growth factor 14	**EA (fever-triggered)** PNKD PKD	SCA27
Transportopathies					
SLC2A1[47–54]	1p34.2	138140	GLUT1 (Glucose transporter 1)	**EA** PED PNKD PKD PED with spasticity/ epilepsy	Epilepsy Migraine Myoclonus Oculogyric crisis
BCKD-related *BCKDHB*[112,113]	6q14.1	248611	Branched-chain keto acid dehydrogenase E1 beta polypeptide	PNKD EA	Developmental delay Seizures
DARS2[114]	1q25.1	611105	Mitochondrial aspartyl-tRNA synthetase	PED Exercise-induced ataxia	Leukoencephalopathy with brainstem and spinal cord involvement
Channelopathies					
ATP1A3[91–97]	19q13.2	182350	ATPase Na+/K+ transporting subunit	PED PNKD	Rapid-onset dystonia parkinsonism AHC CAPOS syndrome FIPWE RECA
CACNA1A[85,86]	19p13.13	601011	Alfa$_1$ subunit of the voltage-gated P/Q calcium channel ($Ca_v2.1$)	**EA2** PNKD PED Paroxysmal tonic upgaze Paroxysmal torticollis	SCA 6 Developmental and epileptic encephalopathy Seizures Familial hemiplegic migraine
CACNB4[68–73]	2q23.3	613855	Voltage dependent calcium channel, beta-4 subunit	**EA5**	Idiopathic generalized epilepsy Juvenile myoclonic epilepsy
KCNA1[74–84]	12p13.32	171260	Voltage gated potassium channel subunit K(v)1.1	PKD PNKD **EA1**	Epilepsy Migraine Myokymia Neuromyotonia

(*Continued*)

Table 2 (Continued).

Gene	Chromosome	OMIM	Protein	Associated Phenotype	Other Features
SLC1A3[87]	5p13.2	600111	Solute carrier family 1, member 3, encodes the glutamate transported, excitatory amino acid transporter 1 (EAAT1)	**EA6**	AHC Intellectual disability Epilepsy Migraine
Mitochondrial					
PDC *DLAT*[105,106] *PDHA1*[107–109] *PDHX*[104]	 11q23.1 Xp22.12 11p13	 245348 312170 245349	 E2 component of PDC Pyruvate dehydrogenase E1 alpha 1 subunit Pyruvate dehydrogenase complex component X	 PED PNKD PED PNKD EA Paroxysmal dystonia	 Intellectual disability Seizures Episodic ataxia MRI: Abnormal: Signal change in globus pallidus, elevated CSF lactate MRI: Abnormal: Signal change in globus pallidus; elevated CSF lactate Leigh syndrome Lactic acidosis Epilepsy MRI: Abnormal: Signal change in globus pallidus; elevated CSF lactate
Others					
UBR4[1]	1p36.13	616055	Ubiquitin protein ligase E3 component N-recognin 4	**EA8**	

Note: Bold text indicates most prominent phenotype associated with gene.
Abbreviations: AHC, Alternating hemiplegia of childhood; CSF, cerebrospinal fluid; EA, episodic ataxia; FIPWE, Fever associated paroxysmal weakness and encephalopathy; GEFS+, Generalised epilepsy with febrile seizures plus; PDC, Pyruvate dehydrogenase complex; PED, Paroxysmal exercise-induced dyskinesia; PKD, Paroxysmal kinesigenic dyskinesia; PNKD, Paroxysmal nonkinesigenic dyskinesia; RECA, Relapsing encephalopathy with cerebellar ataxia; ICCA, infantile convulsions with choreoathetosis; SCA, spinocerebellar ataxia.

cerebellum to the basal ganglia. Striatal cAMP plays a critical role in several hyperkinetic disorders, and it may play a pivotal role in the generation of PxMDs as well.

Evidence for striatal dysfunction emanates from various sources. Patients with stroke in the striatal regions may manifest with PxD. Conditions like *PARKIN*-related genetic Parkinson's disease,[6] characterized by striatal dopaminergic deficiency, may manifest with PED. The globus pallidus interna (Gpi) is a metabolically highly active region and is vulnerable to insults resulting in depletion of cerebral energy, as seen in pyruvate dehydrogenase deficiency and *ECHS1* deficiency, which are associated with PxMD. Deep brain stimulation of the Gpi region is associated with improvement in PxD associated with *GNAO1* and *ADCY5*-related disorders and PNKD.[7,8]

Abnormal cerebellar output has been associated with PKD due to monoallelic *PRRT2* variants. In patients with biallelic *PRRT2* variants, which are considerably rare, episodic ataxia may also be associated. PRRT2, which is highly expressed in cerebellar granule cells, may modulate and alter cerebellar output in patients with *PRRT2*-related PKD. PxD and cerebellar features occur concomitantly in patients with *ATP1A2* and *FGF14*-related disorders. Similarly, PxD can be present in disorders associated with episodic ataxia, as in *CACNA1A* and *KCNA1*-related variants.

Cyclic AMP (cAMP) plays a role in modulating the balance between direct and indirect pathways, which, respectively, facilitate and inhibit execution of movement. cAMP-related pathways may play a role in the pathogenesis of PxD

Table 3 Features of Episodic Ataxia Syndromes

	EA 1	EA 2	EA 3	EA 4	EA 5	EA 6	EA 7	EA 8	EA 9
Gene	*KCNA1*	*CACNA1A*	Not known	Not known	*CACNB4*	*SLC1A3*	Multiple	*UBR4*	*SCN2A*
Chromosome	12p13	19p13	Not known	Not known	2q22-23	5p13.2	Unknown	1p36.12	2q24.3
OMIM	160120	108500	606554	606552	613855	612656	611907	616055	618924
Inheritance	AD	AD	AD	AD	AD	AD/ Sporadic	Variable	AD	AD
Age at onset	Childhood to adolescence	Childhood to adolescence	Variable (1–42 years)	Adulthood	Early adulthood (>20 years)	Childhood to adolescence	Childhood	Childhood	First years of life
Duration of attacks	Seconds to minutes	Hours	Minutes	Minutes to days	Hours	Hours to days	Hours to days	Minutes to hours	Minutes to hours
Associated features	Epilepsy, myokymia, tremor, dysarthria	Seizure, migraine, tonic upgaze, diplopia, hemiplegia	Vertigo, diplopia, tinnitus	Vertigo, tinnitus, diplopia	Vertigo, epilepsy, dysarthria	Epilepsy, hemiplegia, headache	Headache, hemiplegia, vertigo	Headache, vertigo, depression, weakness	Developmental delay, epilepsy
Interictal findings	Myokymia	Nystagmus, ataxia	Myokymia	Nystagmus	Nystagmus, ataxia	Nystagmus, ataxia	No	Nystagmus, ataxia, myokymia	

Abbreviation: AD, autosomal dominant.

related to *ADCY5, PDE10A, PDE2A, GNAO* variants.[5] Overall, the literature favors roles of both the striatum and the cerebellum in the pathogenesis of PxD. The cerebellar nuclei communicate with the striatum via pathway involving the central thalamic nucleus, and this bidirectional influence is likely to play a significant role in PxD.

Table 4 Acquired Paroxysmal Movement Disorders

Etiology	Phenotype	Associated Clinical Features	Evaluation	Treatment
CNS Demyelination				
Multiple sclerosis (MS)[11–13]	PKD	Painful/ painless	Neuroimaging, cerebrospinal fluid oligoclonal bands, serology for anti-aquaporin 4 antibody	Carbamazepine/ oxcarbazepine/ acetazolamide Pregabalin/ gabapentin/ levetiracetam/ clonazepam may also be effective
Neuromyelitis optica spectrum disorders (NMOSD)[14]	PNKD	Multiple daily episodes		
Acute disseminated encephalomyelitis[15]	Paroxysmal dysarthria-ataxia syndrome	Very short (< 1 minute) episodes "Tonic spasms" associated with myelitis more frequent with NMOSD compared to MS		
	PKD	Reported in one patient with pathological laughter		
	PKD			
Vascular				
Transient ischemic attacks (TIA)[21,22]	"Limb shaking" events	May be precipitated by hyperventilation/ hot food consumption	Vascular imaging may show severe stenosis of contralateral internal carotid artery	Revascularisation procedures
Moyamoya disease[23,24]	PKD	Chorea-like episodes	Moyamoya pattern of vessels seen on vascular imaging	
	PNKD			
	PED			
	"Limb shaking" TIA			

(*Continued*)

Table 4 (Continued).

Etiology	Phenotype	Associated Clinical Features	Evaluation	Treatment
Immune-mediated				
Systemic lupus erythematosus/ Anti-phospholipid antibody syndrome[16]	PKD	Described as painful "tonic spasms"	Positive antibodies for SLE/ beta-2 microglobulin, lupus anticoagulant, anti-cardiolipin antibody	Carbamazepine
Metabolic				
Hypocalcemia	PKD PNKD	Seizures, psychiatric issues, cognitive impairment	Reduced blood Calcium/ Phosphorus, low or normal PTH Basal ganglia calcification	Correction of calcium/ phosphorus level
Hypoglycemia[17,18]	PKD PNKD PED	Precipitated by fasting or in the latter part of the night/ early morning	Insulinoma is the most common etiology	Removal of tumor
Hyperglycemia[17,18]	PKD/ PNKD	Confusion, seizures		Achieve euglycemia
Hyperthyroidism[20]	PKD-Chorea-athetosis/ dystonia	Tremor	Abnormal thyroid hormone level	Treatment to achieve euthyroid status

Abbreviations: PKD, paroxysmal kinesigenic dyskinesia, PNKD, paroxysmal non-kinesigenic dyskinesia, PED, paroxysmal exercise-induced dyskinesia, SLE, systemic lupus erythematosus.

Classification of Paroxysmal Disorders

In 1977, Lance classified kinesigenic PxD clinically into familial and sporadic forms.[9] Demirkiran and Jankovic, in 1995, suggested a classification scheme based on triggering factors, independent of the duration of attacks. This scheme classified PxD into paroxysmal kinesigenic dyskinesia (PKD), paroxysmal non-kinesigenic dyskinesia (PNKD), paroxysmal exercise-induced dyskinesia (PED), and paroxysmal hypnogenic dyskinesia (PHD). PKD was triggered by sudden movements, PED by sustained exercise, and triggers in PNKD were heterogeneous but it was neither precipitated by sudden movement or sustained exercise. PHD was later determined to be a form of autosomal dominant frontal lobe epilepsy (ADFLE). This classification scheme continues to remain popularly used in the literature.

With the recognition of genetic underpinnings of PxMDs, certain classical notions have been challenged. For example, *PRRT2* variants, which are the most frequent cause of primary PKD, are characterized by very brief episodes triggered by sudden movements. Hence, both the triggering factor and the duration of attacks are important in phenotypic understanding, bolstered by the molecular variant involved.

Another paradigm is to consider these disorders as either "isolated" or associated with other forms of neurological dysfunction. Yet another paradigm is to consider that these disorders are either primary ("familial") or secondary ("acquired"), as proposed by Goodenough et al[10] "Primary" disorders generally indicate an underlying genetic cause, whereas "secondary" disorders indicate an acquired disorder. Acquired disorders, largely considered to be "treatable", affect the same circuitry, and manifest as paroxysmal movements. Some of these disorders include demyelination (multiple sclerosis,[11–13] neuromyelitis optica spectrum disorder,[14] acute disseminated encephalomyelitis[15]), immune-mediated (systemic lupus erythematosus/antiphospholipid antibody syndrome[16]), metabolic (hypoglycemia/ hyperglycemia,[17,18] calcium abnormalities, hyperthyroidism[19,20]), and limb-shaking transient ischemic attacks (internal carotid artery stenosis[21,22]/ Moyamoya disease[23,24]) (Table 4). Clues that point towards a primary etiology include age at onset below 18 years, presence of family history and fixed triggers and attack duration. Secondary disorders, on the other hand, may have age at onset above 18 years, absence of family history and variable triggers and duration of attacks. The term "primary" is controversial as it suggests absence of etiology, when, in fact, these disorders are "secondary" to specific genetic abnormalities. Another connotation was that primary disorders should lack interictal abnormalities,

which may be prevalent in secondary disorders. It is now well-established that this may not be used as a discerning feature, as interictal abnormalities may be seen in several so-called primary disorders, as in *SLC2A1* variants.

The other large group of PxMD is episodic ataxia. So far, nine subtypes of EA have been described (EA 1 to 9), of which EA1 and EA2 are the most frequent (Table 2). EAs are characterized by brief episodes of sudden-onset ataxia, which last seconds to minutes. Patients may also demonstrate interictal myokymia and/or neuromyotonia (Table 3).

Paroxysmal Dyskinesias

PxD are movement disorders that involve recurrent episodes of dystonia, chorea, athetosis or ballism without loss of consciousness. PKD is the most frequently occurring PxMD, with an incidence of 1 per 150,000. It is characterized by attacks of chorea/dystonia, which are less than 1 min in duration, and are triggered by sudden motion. Chen et al identified that variants in the proline-rich transmembrane protein 2 (*PRRT2*) gene were associated with most cases of PKD and related disorders.[25] Since then, several other mutations have been identified to cause PKD, and include *SCN8A, ADCY5* and *SLC16A2* mutations (Table 2).

PNKD is rare, with a prevalence of 1 per 100,000. It is inherited in an autosomal dominant pattern. The responsible gene is *PNKD*, earlier known as myofibrillator regulator-1 (MR-1) gene. The disease usually originates in childhood, and the usual triggers are alcohol, coffee, stress and fatigue. The usual duration is minutes to hours. The condition may regress with age. Compared to PKD, PNKD episodes are rather less frequent. Individuals with variants in the PNKD gene have usual age at onset in infancy or early childhood, nearly universal precipitation by caffeine and alcohol, and respond to sleep and benzodiazepines, which abort attacks.

PED differs from PKD and PNKD in that attacks are triggered by sustained exercise and usually consist of episodes of dystonia lasting from minutes to hours. *SLC2A1* variants account for 30–40% of patients with PED. Other important genes include *GCH1, ECHS1*, pyruvate dehydrogenase complex-related, and genetic Parkinson's disease.

Genetic PxMD may be pathophysiologically categorized into synaptopathies, transportopathies, channelopathies, second-messenger related disorders and mitochondrial disorders (Figure 1).

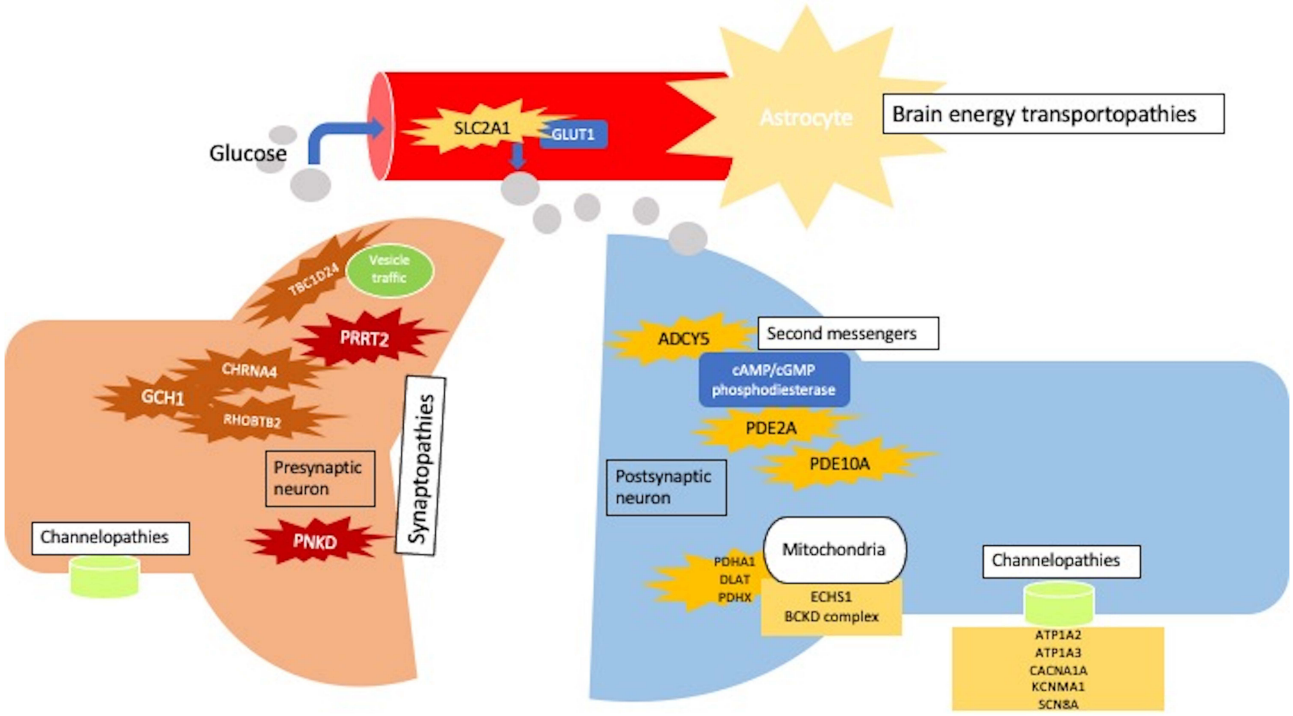

Figure 1 Pathophysiology and classification of paroxysmal dyskinesia.

Synaptopathies

PRRT2 (OMIM 614386)

Proline-rich transmembrane protein 2 (PRRT2) modulates neurotransmitter release by its interaction with presynaptic proteins, SNAP25 and synaptotagmin. Additionally, it influences Nav1.2/Nav1.6 channels and modulates neural transmission.

In patients with PKD, there may be an autosomal dominant family history of PKD or a form of epilepsy called benign familial infantile seizure (BFIS). Both PKD and BFIS may co-exist, termed infantile convulsions with choreoathetosis (ICCA) syndrome. The term ICCA has been replaced with PKD/infantile convulsions (PKD/IC). Patients with PKD/IC develop epilepsy within the first 2 years of life and subsequently develop PKD. These attacks have a kinesigenic trigger but may also be precipitated by exercise and emotions. These attacks are very brief (<1 min) and occur several times a day. While between 70% and 90% of patients with PKD have autosomal dominant inheritance, the remaining have de novo mutations. Penetrance is incomplete (60–90%). Other phenotypes include PNKD, PED, PHD, paroxysmal torticollis, episodic ataxia, hemiplegic migraine, childhood absence epilepsy and intellectual disability. Nearly 30% of *PRRT2*-related patients with PKD have PKD/IC. Truncating mutations in *PPRT2* as a cause of PKD were first identified in 2011.[25] Loss-of-function (LOF) variants are mostly observed in PKD. The most frequent is the frameshift mutation, c.649dupC (p.Arg217ProfsTer8), which leads to a premature stop codon. Treatment is by carbamazepine and oxcarbazepine. Attacks tend to decrease with advancing age.

PNKD (OMIM 609023)

PNKD was earlier known as the myofibrillogenesis regulator-1 (*MR-1*) gene. It accounts for nearly 70% of PNKD.[3] The PNKD encodes three alternate splice proteins of 385, 361 and 142 amino acids. The long isoform, PNKD-L, is enriched in the central nervous system, while the intermediate (PNKD-M) and short (PNKD-S) isoforms are more widespread. The PNKD-L and PNKD-M forms are homologous to hydroxyacylglutathione hydrolase (HAGH), which detoxifies methylglyoxal, a compound present in coffee and ethanol. This may explain why coffee and alcohol precipitate attacks in PNKD. PNKD also interacts with RAB-interacting molecule (RIM1) AND RIM2 and affects nigrostriatal release of dopamine. PNKD-L has also been associated with Tourette syndrome.[26] Attacks in PNKD may be triggered by alcohol, coffee, stress and emotions. These usually last from 10 min to an hour but may continue up to 12 h and are infrequent. Treatment of PNKD comprises benzodiazepines, levetiracetam and valproic acid.

TBC1D24 (OMIM 613577)

TBC1 domain family member 24 (TBC1D24) is a member of the GTPase activating proteins. It is needed for normal brain development due to its role in synaptic function and vesicle traffic. Variants in *TBC1D24* gene have been associated with diverse phenotypes, of which epilepsy is predominant. Epilepsy types usually include pharmaco-resistant myoclonic, focal, multifocal[27] and early-onset epileptic encephalopathy, epilepsia partialis continua (EPC) and familial infantile myoclonic epilepsy (FIME).[28–31] Other syndromes include DOORS (deafness, onychodystrophy, osteodystrophy, developmental delay and seizures)[32] and non-syndromic hearing loss.[33] Missense and loss-of-function variants are spread throughout the protein. Rolandic epilepsy - exercise induced dystonia phenotype - has been reported in one family. In this family, epilepsy was self-limited but dystonia persisted into adulthood.[34] Exercise-induced paroxysmal dystonia was reported in two patients.[35] Other phenotypes associated with *TBC1D24* variants include alternating hemiplegia of childhood (AHC),[36] AHC and EPC combination,[37] and paroxysmal facial and limb myoclonus in infancy.[38] Treatment includes carbamazepine, benzodiazepine and acetazolamide.

FGF14 (OMIM 601515)

Fibroblast growth factor 14 (FGF 14) is a regulator of Cav2.1 presynaptic channel and modulates vesicular transport and synaptic transmission. Mutations in FGF14 are associated with EA.[39] EA episodes present in childhood, are triggered by fever, and may be associated with vomiting and headache. These may last for several days. It is inherited in an autosomal

dominant fashion. PKD and PNKD in isolation or in association with EA have also been reported.[40] It is also a cause of the rare autosomal dominant spinocerebellar ataxia type 27 (SCA 27). Treatment is with acetazolamide.

GCH1 (OMIM 600225)

GTP cyclohydrolase 1, a catalyst in the formation of tetrahydropterin, is encoded by *GCH1*. Tetrahydropterin is required for the manufacture of dopamine, phenylalanine and serotonin. The characteristic phenotype associated with *GCH1* variants is dopa-responsive dystonia. However, these may manifest with PED. Autosomal dominant familial PED, with exercise-induced foot posturing, has been reported in a family, with heterozygous stop codon variant in exon 1, c.411G>T.[41] Other features in this family included restless leg syndrome, depression, migraine and atypical parkinsonism. PED responded to low-dose levodopa.

RHOBTB2 (OMIM 607352)

RHOBTB2 encodes an atypical Rho-related BTB-containing protein 2, a GTPase. Heterozygous variants have been reported to lead to developmental and epileptic encephalopathies,[42,43] postnatal microcephaly, intellectual impairment and Rett-like phenotype.[44] Paroxysmal movement disorders, including chorea, dystonia and dyskinesias, were reported in a series of 13 patients.[42] Stereotypies were observed in three patients. Another patient with developmental delay had status epilepticus at 3 months of age, followed by paroxysmal dystonia at the age of one year due to a de novo missense variant in the *RHOBTB2* gene, c.1532G>A [p.Arg511Gln].[45] The paroxysmal movements responded to carbamazepine. Severe paroxysmal choreodystonia, along with aplasia cutis congenita, without epilepsy, was reported in another patient with a heterozygous missense variant, c.1448G>A [p.Arg483His].[46]

In 2021, *TMEM151A* variants were also recognized as a cause of PKD.[47]

Transportopathies

SLC2A1 (OMIM 138140)

SLC2A1 gene encodes the glucose transporter type 1 (GLUT1) on the blood–brain barrier, responsible for transport of glucose across the barrier and astrocytic membrane. Mutations lead to a wide spectrum of neurological disorders, including GLUT1 deficiency syndrome (GLUT1-DS), PED, progressive spastic paraparesis combined with PED[48,49] and epilepsy. PKD and PNKD with *SLC2A1* variants have also been described.[50] Familial PED due to *SLC2A1* mutation is an autosomal dominant condition.[51] Most of the GLUT1-DS cases with PED are due to missense variants in *SLC2A1*. On the other hand, splice site, nonsense, insertion and deletion mutations are associated with severe phenotypes, including epilepsy, developmental delay and spasticity.

PED, induced by fasting or exercise, may be a main feature of GLUT1 deficiency.[52] The movement disorder may include chorea-athetosis, dystonia, or ataxia. Often the lower limbs are involved. The movement disorder is provoked by sustained exercise.[53] Paroxysmal ocular movements, described as "aberrant gaze saccades", have also been reported with GLUT1-DS.[54]

CSF glucose below the 10th percentile, CSF: serum glucose below the 25th percentile, and CSF lactate levels below the ninetieth percentile are highly suggestive of GLUT1-DS.[55]

Recognition is imperative, as the institution of the ketogenic diet is beneficial in this condition.

SLC16A2 (OMIM 300095)

SLC16A2 encodes the monocarboxylate transporter type 8 (MCT8), a thyroid hormone transporter in the brain. Variants in *SLC16A2* gene lead to Allan-Herndon-Dudley (AHD) syndrome, characterized by severe developmental delay and peripheral thyrotoxicosis. It is an X-linked recessive disorder. Thyroid hormone abnormalities include raised free T3, low reverse T3, low total/free T4 and normal or slightly elevated TSH level.

Axial hypotonia is a central feature.[56] Eventually, spasticity may develop. Other features include muscle weakness, torsional nystagmus, contractures, skeletal abnormalities and central nervous system hypomyelination. p.R271H and p. G564R variants may result in a severe clinical phenotype. P.G564E variant has been associated with a relatively mild

phenotype.[57] PKD in association with AHD syndrome has been reported with a missense variant (c.1535T>C [p. Leu512Pro]) and a frameshift stop codon.[58] It can be evoked by passive movement.

ATP7B (OMIM 606882)

Wilson's disease (WD), due to mutations in *ATP7B* gene, is an uncommon cause of PxMD. PKD was reported in a 22-year-old male with WD, which was completely remitted with oxcarbazepine.[59] PNKD has also been reported in a patient with WD, which responded to trientine, whose attacks lasted for seconds, and were ameliorated by smoking.[60]

Second-Messenger Related

ADCY5 (OMIM 600293)

Adenylyl cyclase 5 (*ADCY5*)-related disorders comprise a spectrum of hyperkinetic and often paroxysmal disorders that include chorea, dystonia, and myoclonus.[61] Adenylyl cyclase is required for the conversion of ATP to cyclic adenosine-3',5'-monophosphate (cAMP), which is an important second messenger in several intracellular processes. ADCY5 is the most common isoform of adenylyl cyclase, which is present in the striatum, and through the cAMP signaling pathways, prevents involuntary movements. ADCY5 comprises 1261 amino acids and is encoded by a gene located on chromosome 3p21.1. It has two transmembrane helical domains (M1 and M2) which bind to two intracellular catalytic domains (C1 and C2).

The p.A726T variant seems to harbor a milder phenotype. Somatic mosaicism, which may be seen in nearly 43% of de novo cases, may lead to milder phenotypes.[62] Autosomal dominant inheritance prevails, although autosomal recessive inheritance has also been reported. Intercurrent illness, fatigue and stress may trigger these attacks. It was originally described as "Essential" or "benign" chorea or "familial dyskinesia and facial myokymia."

Prominent facial dyskinesia is a hallmark feature and includes a combination of chorea and myoclonus. Upper limb involvement is also observed. Axial hypotonia, with frog-like adaptive gait are other features. Bouts last minutes to hours and worsen in the third decade of life. Thereafter, they either plateau or resolve. "Ballistic bouts" are frequently painful, truncal dystonia flexion-extension movements, which occur during drowsiness or sleep. Other phenotypes associated with *ADCY5* mutations include familial myoclonus-dystonia, childhood-onset chorea, and alternating hemiplegia of childhood.

ADCY-related have been observed to respond to caffeine. Other drugs include benzodiazepine such as clonazepam and acetazolamide.

PDE10A (OMIM 610652)

Phosphodiesterase 10A (PDE10A) is richly present in the striatum.[63] While striatal cAMP is synthesized by ADCY5, it is degraded by PDE10A. Biallelic variants in the *PDE10A* gene lead to loss of striatal cAMP, and hyperkinetic movement disorders.[64] De novo mutations may lead to chorea in childhood. Bilateral T2-weighted symmetrical and bilateral striatal hyperintensities may be seen.[65]

PDE2A (OMIM 602658)

PDE2A is enriched in the striatal medium spiny neurons. It encodes phosphodiesterase 2A that catalyzes cAMP and cyclic guanosine monophosphate (cGMP). Loss-of-function homozygous mutations in *PDE2A* gene have been associated with early onset chorea.[66] In these patients, PxD preceded development of chorea. Additionally, the child had intellectual impairment and EEG abnormalities. Biallelic *PDE2A* mutations were reported in three patients (two were siblings).[67] Two patients presented with refractory paroxysmal dyskinesia, which was misdiagnosed as epilepsy. One patient had epilepsy at the age of 4 months. All patients also had cognitive impairment or developmental delay.

Channelopathies

SCN8A (OMIM 614558)

SCN8A encodes the alpha subunit of the $Na_v1.6$ voltage-gated sodium channel, which is abundant in the brain and is pivotal in generation and propagation of action potentials. Heterozygous missense variant c.5302A>G [p.Asn1768Asp] was reported in epileptic encephalopathy, characterized by early onset seizures, autism and SUDEP.[68] Heterozygous missense variant c.4423G>A [p.Gly1475Arg] has been reported to lead to early onset epileptic encephalopathy[69] Missense variants lead to increased channel activity. De novo heterozygous missense mutation in c.4408C>A [p.Gln1470Lys] reported in a patient with possible antenatal onset of severe episodic tremulousness associated with hyperekplexia-like startle response, drug-refractory seizures and developmental regression, acquired microcephaly and gastroparesis.[70]

SCN8A mutation has been recognized as a cause of infantile convulsions and paroxysmal choreoathetosis (ICCA), which is a combination of benign familial infantile seizures (BFIS) and paroxysmal kinesigenic dyskinesia (PKD).[71] Gain-of-function mutations have been associated with epileptic encephalopathy.[68] Loss-of-function mutations have been associated with cognitive dysfunction.[72]

SCN8A missense mutation (c.4447G>A; p.E1483K) was reported in three families with infantile seizures and development of PKD in puberty, in the form of dystonia.[71] However, some doubt was raised regarding the true PKD nature as one of the patients demonstrated cortical discharges on EEG during the PKD episode. Paroxysmal tonic upgaze (PTU) has also been described in one child associated with the *SCN8A* variant.[73]

KCNA1 (OMIM 171260)

KCNA1 encodes a voltage gated shaker-related family submember 1 potassium channel, Kv1.1 alpha subunit, which plays a role in presynaptic repolarization and modulation of inhibitory input to the cerebellum. Pathogenic variants are LOF and lead to reduced inhibitory input to the cerebellum. Inheritance is autosomal dominant, with reduced penetrance.

KCNA1 mutations have been primarily associated with episodic ataxia type 1 (EA1), with or without myokymia,[74] epilepsy and severe dyskinesias with neonatal epilepsy.[75] A heterozygous c.257G>A R86Q variant was reported with PNKD.[76] Familial PKD is reported with c.956 T>G (p.319 L>R) and c.765 C>A (p.255 N>K) variants.[77] In two patients, classical PKD was associated with p.Gly396Val and p.Gly396Arg variants.[78] Among non-neurological manifestations, hypomagnesemia is also caused by mutations in *KCNA1*.[79,80] Seizure-related variants cluster in S1/S2 domains of the transmembrane region and pore region of Kv1.1.[81] Variants associated with EA1 occur along the entire length of the protein. Most mutations are missense, although frameshift mutations have also been reported.[82]

It has also been observed that individuals with *KCNA1* variants at the C-terminus are more likely to suffer from seizures and developmental delay than those with variants at the N-terminus.[83,84]

CACNA1A (OMIM 601011)

CACNA1A encodes the $alfa_1$ subunit of the voltage-gated P/Q calcium channel ($Ca_v2.1$). LoF variants in the *CACNA1A* gene disrupt calcium entry into the cerebellar Purkinje and granule cells, where these channels are richly present.[85] The disease is autosomal dominant, with 80–90% penetrance.

Whereas GoF variants are associated with developmental and epileptic encephalopathy, epilepsy and familial hemiplegic migraine, LoF variants occur in PxMD, including EA2, PKD and PED.

EA2 is the most frequently occurring EA syndrome. The episodes are longer in comparison to EA1, and patients may also have vertigo, vomiting and dysarthria. Nearly 50% of patients may have migraine (hemiplegic), epilepsy or dystonia. These patients may also develop a progressive ataxia syndrome. Downbeat nystagmus may be observed. Paroxysmal tonic upgaze has also been reported in childhood, preceding the development of EA.[86] EA2 is allelic with familial hemiplegic migraine type 1 (FHM1), CAG repeats in the *CACNA1A* gene may result in spinocerebellar ataxia type 6.

SLC1A3 (OMIM 600111)

The solute carrier family 1, member 3, encodes the glutamate transported, excitatory amino acid transporter 1 (EAAT1). Heterozygous variants in SLC1A3 are observed in EA type 6, which is inherited in an autosomal dominant pattern.[87]

Episodes of ataxia and epilepsy occur and are longer than CACNA1A-related disorder, lasting up to hours to days. Myokymia, nystagmus and tinnitus are not observed. Migraine may be associated additionally.

KCNMA1 (OMIM 300150)

KCNMA1 gene encodes the alfa subunit of "Big K+ (BK)" large conductance calcium and voltage-gated potassium channel (KCa1.1). This channel is enriched in the brain and modulates action potential and neurotransmitter release. Pathogenic GoF variants are associated with autosomal dominant PxD and epilepsy. LoF variants present with developmental delay/intellectual impairment, ataxia, axial hypotonia, and speech abnormalities.[88] The p.Asp434Gly variant was associated with PNKD, epilepsy or both. P.Glu884Lys and p.Asn1053Ser variants were associated with early onset PNKD with developmental delay.[89] Another variant, p.Arg458Ter, was associated with PNKD, epilepsy, developmental delay and cerebellar and corticospinal atrophy.[90]

ATP1A3 (OMIM 182350)

ATP1A3 is the alfa-three isoform of the Na+/K+ ATPase pump. Pathogenic variants may manifest with many neurological and non-neurological syndromes, including rapid-onset dystonia parkinsonism, alternating hemiplegia of childhood, cerebellar ataxia,[91] optic atrophy and sensorineural hearing loss syndrome (CAPOS).[92–94] *ATP1A3* variants have been recognized as an important cause of AHC.[95] The p.Asp923Asn variant has also been recognized as a cause of PED. In this case, AHC manifested first, followed by PED. R756H and R756L have been associated with fever-associated encephalopathy and generalized weakness, progressing to develop ataxia.[96] This entity was termed "fever associated paroxysmal weakness and encephalopathy (FIPWE)" and "relapsing encephalopathy with cerebellar ataxia (RECA)."[97]

CLCN2 (OMIM 600570)

CLCN2 variants result in loss of function of chloride channel 2 and have been associated with leukoencephalopathy. Usually, these patients present with cognitive impairment, tremor, ataxia, and optic atrophy. A homozygous variant, p.Ser375CysTer6 in the *CLCN2* gene, was associated with onset of paroxysmal kinesigenic dyskinesia since the age of 21 years.[98] MRI brain showed characteristic signal change in the posterior limb of the internal capsule, cerebral peduncles, cerebellar peduncles, and cerebellar white matter. PKD was completely abolished with carbamazepine.

CHRNA4 (OMIM 118504)

Mutations in *CHRNA4* have been associated with PKD or generalized epilepsy with febrile seizures plus (GEFS+). It is inherited in an autosomal dominant manner. It was identified in a family in which one individual had GEFS+ and two had PKD. A fully co-segregated mutation (NM_000744: c.979G>A) was identified.[99]

Mitochondrial

ECHS1 (OMIM 602292)

ECHS1 gene encodes for short-chain enoyl-CoA hydratase, which is a mitochondrial enzyme involved in valine and isoleucine pathways.[100] Four main phenotypes have been described - a neonatal form with rapid progression, a severe infantile form with basal ganglia degeneration, a slowly progressive infantile form and paroxysmal exercise-induced dystonia, with a normal interictal period. It is also associated with Leigh's syndrome.[101] In a family of two siblings, the older sibling had a Leigh-like syndrome, with generalized dystonia and severe pallidal changes on MRI. The younger sibling developed only paroxysmal exercise-induced dystonia, with mild pallidal signal changes on MRI. Both siblings had compound heterozygous *ECHS1* variants (c.232G>T [p.Glu78Ter] and c.518C>T [p.Ala173Val].[102] Valine-restricted diet may be of potential benefit.[103]

Pyruvate Dehydrogenase Complex (PDC)

PDC deficiency necessitates prompt recognition so that a ketogenic diet may be initiated. It leads to ATP production deficits, and a host of neurological disorders, including microcephaly, epilepsy, hypotonia, developmental delay, and Leigh syndrome. Acute energy failure in infancy may lead to abnormalities in basal ganglia and PxMD.[104]

Homozygous missense variant (c.470T>G; p.Val157Gly) in the *DLAT* gene has been associated with PED.[105] This patient presented with PED at the age of 3 years, which would last for 5–15 min. He had intellectual disability, dysconjugate gaze and pyramidal features. *DLAT* gene encodes for dihydrolipoamide acetyltransferase, the E2 component of the PDC. A ketogenic diet may be of benefit, as may thiamine replacement. Signal change in bilateral globus pallidus may be seen on T2-weighted MRI. *DLAT* gene variants may also lead to episodic dystonia and developmental delay.[106]

PDHA1 variants have also been associated with PED.[107] One patient with a c.647T>C (p.Leu216Ser) was associated with reduced penetrance.[107] This patient had abnormal MRI findings with pallidal signal change and was treated with thiamine. PED was reported in another patient with heat-associated dystonia, which was ameliorated with levodopa.[108] PNKD has also been reported.[109] Paroxysmal dystonia and episodic ataxia[104] have also been reported in association with *PDHA1* variants.

Variants in the *PDHX* gene have been associated with non-progressive encephalopathy (five cases).[104] One patient had paroxysmal dystonia.

Others

DEPDC5 (OMIM 614191)

One patient with PKD associated with *DEPDC5* variant was identified. The patient started having episodic bilateral limb posturing at the age of 13 years, with up to 30–40 attacks occurring per day. A variant c.3311C>T (p.S1104L) was identified in the patient and his mother, who also had similar attacks between 9 and 31 years of age.[110]

SACS (OMIM 604490)

Two patients with autosomal recessive spastic ataxia of Charlevoix-Saguenay have been reported to have PKD. In one patient, compound heterozygous mutations in the *SACS* gene were identified (p.P3007S and p.H3392fs). In the second patient, a homozygous truncating mutation (p.W1376X) was identified.[111]

BCKD Complex

Maple syrup urine disease (MSUD) is an autosomal recessive condition, due to mutations in the branched-chain alfa-ketoacid dehydrogenase (BCKD) complex.

PNKD, involving curvature of the trunk to alternating sides, was reported in a 22-month child, diagnosed to have chronic intermediate MSUD, based on abnormal levels of branched chain amino acids and elevated alloisoleucine level.[112] Paroxysmal spasticity was reported in two siblings with MSUD. These siblings exhibited compound heterozygous mutations (c.1076G>A [p.Arg359Lys] and c.705delT [p.Cys235Ter]) in the *BCKDHB* gene (OMIM 248611).[113]

DARS2 (OMIM 611105)

Variants in *DARS2*, which encodes a mitochondrial aspartyl-tRNA synthetase, are associated with leukoencephalopathy with brainstem and spinal cord involvement and brain lactate elevation (LBSL). One patient with paroxysmal exercise-induced ataxia and areflexia has been reported, who responded well to acetazolamide therapy.[114]

Genetic Approach to Paroxysmal Movement Disorders

Although the genetic understanding of PxMD has vastly expanded, clinical history and examination remain the cornerstone of initial evaluation. Presence of certain features may inform a secondary etiology of PxMD. These features include age at onset above 18 years, variable triggers, variable duration of attacks, absence of a family history, abnormal interictal examination, and abnormal neuroimaging. Family history of PxMD or associated conditions, such as epilepsy or migraine, may be obtained. However, an entirely clinical approach is insufficient due to low penetrance, phenotypic and genotypic pleiotropy.

Functional movement disorders (FMD) should be excluded, based on clinical features of entrainment, distractibility, and inconsistency. Other supportive features which may suggest FMD, but are not invariably present, include poor response to medication, onset in adult age, sudden onset, presence of a precipitating factor, stable or waxing/waning

course, presence of other non-neurological functional symptoms, and improvement with placebo.[115] Features related to the attack include poor responsiveness during the attack, uncommon triggering factors, variable attack duration and frequency, paroxysmal tremor, combination of multiple movement disorders during an attack, "huffing and puffing" vocalizations, specific motor patterns such as opisthotonos, rhythmic pelvic activity, side-to-side movement, isolated facial involvement, and very long duration of attacks.[5] Treatable acquired conditions which can lead to PxMD such as hypocalcemia, hypoglycemia, demyelinating and vascular disorders etc. must be excluded. In patients in whom the suspicion for an acquired or secondary cause does not occur, one should proceed directly to genetic testing.

Genetic Evaluation

In children with associated developmental delay, dysmorphism, autism spectrum disorder or epilepsy, chromosomal microarray should be a first-tier diagnostic test.[116] Pathogenic copy number variants (CNV), detected by microarray techniques, may not be picked up by next-generation sequencing (NGS) gene panels or whole-exome sequencing (WES).

Gene-panel testing is a second-tier investigation, in which multiple genes are sequences in parallel. The advantage of gene panels over WES or whole-genome sequencing (WGS) is that the former offers high-resolution coverage for exon deletions or duplications at exons, which may not be detected by the latter. Moreover, the possibility of detection of variants of unknown significance, which are unrelated to the phenotype, is reduced with gene panels, compared to WES/WGS.[4]

In patients where deep phenotyping is complex, WES/WGS is preferable as a second-tier investigation. WES/WGS should be performed if gene panel is negative. WGS has certain advantages over WES, including continuous coverage, intronic coverage, noncoding and intergenic variants, and ability to detect expanded repeats, and smaller CNVs. However, the technique to detect repeat expansions by WGS is available on only research basis. Hence, trinucleotide repeats need additional testing. The disadvantages of NGS techniques are their inability to detect CNVs and balanced translocations.

Mosaicism is reported in several PxMDs, including those related to *ADCY5, ATP1A3, PDHA1* and *SLC2A1*. These require additional techniques for detection.

Future Directions

Underlying genetic diagnosis is present in only 50% of patients with PxMDs. A deeper understanding of the genetic basis of PxMD may guide future research and therapeutics. Targeting cerebellar outflows may be used in certain conditions, which demonstrate poor response to drugs, such as ATP1A3-related PxMD.[5] Modulation of the cAMP signalling pathway may also be a promising therapeutic avenue and has already been harnessed in ADCY5-related PMD, which may respond to caffeine via effects on the adenosine A2A receptors. Whether genotype has a major impact on treatment remains to be seen, and there is a shift towards precision-based medicine in the treatment of PxMD. Examples include bypassing glucose transport defect in GLUT1-DS via the ketogenic diet and supplementing levodopa in *GCH*-1 related PMD. Advances in understanding of molecular mechanisms will help to guide future development of genetic and molecular therapies.

Conclusions

PxMD are a network disorder, with both the basal ganglia and the cerebellum implicated in its pathogenesis. Abnormalities in the striatal cAMP turnover pathway may also be implicated in PxMD. PxMD demonstrate great phenotypic pleiotropy, making molecular diagnosis challenging.

Although NGS has restructured its approach to PxMDs by uncovering the genetic architecture of many PxMDs, genetic underpinnings of several remain undiscovered. As more genes and variants continue to be reported in relation to PxMD, these will lead to enhanced understanding of pathophysiological mechanisms and precise treatment.

Acknowledgments

The authors thank their institutes for their support.

Disclosure

None of the authors report any conflict of interest.

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