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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES-REVIEW ARTICLE

Genetic updates on paroxysmal dyskinesias

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Abstract

The paroxysmal dyskinesias are a diverse group of genetic disorders that manifest as episodic movements, with specific triggers, attack frequency, and duration. With recent advances in genetic sequencing, the number of genetic variants associated with paroxysmal dyskinesia has dramatically increased, and it is now evident that there is significant genotype–phenotype overlap, reduced (or incomplete) penetrance, and phenotypic variability. In addition, a variety of genetic conditions can present with paroxysmal dyskinesia as the initial symptom. This review will cover the 34 genes implicated to date and propose a diagnostic workflow featuring judicious use of whole-exome or -genome sequencing. The goal of this review is to provide a common understanding of paroxysmal dyskinesias so basic scientists, geneticists, and clinicians can collaborate effectively to provide diagnoses and treatments for patients.

Keywords Paroxysmal dyskinesia · Dystonia · Genetic kinesigenic · Nonkinesigenic · Exertion-induced · Hypnogenic

Introduction

The neurological syndromes known as paroxysmal dyskinesias involve recurrent episodes of dystonia, chorea, or ballism, with preserved consciousness. By definition, paroxysmal dyskinesias do not include tremor, myoclonus, ataxia, periodic paralysis, neuromyotonia, or epilepsy (Erro and Bhatia 2019), but these conditions can occur in association with paroxysmal dyskinesia.

The paroxysmal dyskinesias have characteristic ages of onset, episode durations, and triggers (Garone et al. 2020). Currently, the most widely accepted classification scheme is based on triggers and duration (Demirkiran and Jankovic 1995): Paroxysmal Kinesigenic Dyskinesia (PKD), Paroxysmal Nonkinesigenic Dyskinesia (PNKD), Paroxysmal Exertion-induced Dyskinesia (PED), and Paroxysmal Hypnogenic Dyskinesia (PHD). These syndromes can be idiopathic, genetic, autoimmune, vascular, metabolic, or due to other causes (Erro and Bhatia 2019). Of the genetic causes, most are autosomal dominant, either de novo or familial (Garone et al. 2020).

While the first description of an individual with paroxysmal dyskinesia may have been as early as 1892 (Kato et al. 2006), the first genetic mutations were not identified until 2004 for PNKD (Rainier et al. 2004), 2008 for PED (Weber et al. 2008), and 2011 for PKD (Chen et al. 2011). As the cost of gene sequencing has fallen dramatically since 2011 (Wetterstrand 2021), the number of genes and specific variants identified have grown and added layers of complexity to the paroxysmal dyskinesias. Variants that cause paroxysmal dyskinesias can also cause ataxia, epilepsy, or other neurological syndromes, in the same individuals. In addition, one variant can manifest as more than one paroxysmal dyskinesia. Finally, although symptomatic therapy can be initiated based on phenotype (e.g., carbamazepine in PKD), treatable conditions such as GLUT1 deficiency or Wilson Disease can present as paroxysmal dyskinesias. To avoid

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missing a treatable cause, it is critical to identify the variant in suspected genetic paroxysmal dyskinesia.

There are several recent reviews of this topic (Sethi et al. 2021; Manso-Calderón 2019; Zhang et al. 2019; Ahn and Ko 2020; Erro and Bhatia 2019; Garone et al. 2020). This review will update the rapidly expanding list of genes associated with paroxysmal dyskinesias and discuss diagnostic implications.

Overview of main phenotypes and associated syndromes

As the PKD, PNKD, PED, and PHD classes (Demirkiran and Jankovic 1995) are heterogeneous entities, it is more accurate to discuss the gene-specific phenotypes separately (see next section). Nevertheless, the original descriptions, largely based on phenotypes of the main underlying genes, still provide a useful framework.

PKD is the most common phenotype of paroxysmal dyskinesia, with an estimated prevalence of 1/150,000 (Van Rootselaar et al. 2009). An estimated 40–90% of cases of PKD are due to *PRRT2* variants (Tian et al. 2018; Erro et al. 2017). Nearly all have a kinesigenic voluntary movement trigger, but half also have non-kinesigenic triggers including anxiety, startle, intention-to-move, coffee, sleep deprivation (Erro, Sheerin, and Bhatia 2014a), or fatigue. These triggers cause dystonia, chorea (Erro, Sheerin, and Bhatia 2014a), athetosis (Ebrahimi-Fakhari et al. 2015), or ballism (Fusco et al. 2014). Attacks tend to be less than 1 min long and occur > 10 times per day (up to hundreds per day) (Erro, Sheerin, and Bhatia 2014a). They can be unilateral, bilateral (Ebrahimi-Fakhari et al. 2015), alternating (Huang et al. 2015), focal, or generalized (Erro, Sheerin, and Bhatia 2014a), do not affect consciousness (Van Rootselaar et al. 2009), and do not cause pain (Ebrahimi-Fakhari et al. 2015). In half of the individuals, attacks are preceded by sensory auras that can be used to avoid subsequent motor attack, by halting the triggering movement (Erro, Sheerin, and Bhatia 2014a). Symptoms tend to begin in youth, mean age of onset is ~ 10 years, there is a 2:1 M:F predominance, and attack frequency decreases with age (Erro, Sheerin, and Bhatia 2014a). PKD responds well to antiepileptics, with carbamazapine as the first choice (Sethi, Erro, and Bhatia 2021).

PNKD is the second most common phenotype of paroxysmal dyskinesia, with an estimated prevalence of 1/1,000,000 (Van Rootselaar et al. 2009). Up to 71% have variants in the *MR-1* gene (Bruno et al. 2007), now renamed *PNKD* (Sethi, Erro, and Bhatia 2021). PNKD is characterized by attacks of dystonia, chorea, ballism (Erro, Sheerin, and Bhatia 2014a), or athetosis (Sethi, Erro, and Bhatia 2021), that can be unilateral, alternating (Sethi, Erro, and Bhatia 2021), bilateral, focal, or generalized (Erro, Sheerin, and Bhatia 2014a). Attack duration ranges from minutes to hours (Erro, Sheerin, and Bhatia 2014a) and are *triggered by caffeine or alcohol in nearly all individuals* (Bruno et al. 2007). Additional triggers include heat or cold, stress, excitement, laughter, fever, menstruation, and tiredness (Erro, Sheerin, and Bhatia 2014a). Of note, almost 7% report prolonged exercise as a trigger, and rarely, as the main trigger (Erro, Sheerin, and Bhatia 2014a). Approximately 40–60% (Erro, Sheerin, and Bhatia 2014a, b; Bruno et al. 2007) experience an aura consisting of weakness, shortness of breath, or migraine. The average age of onset is 4–5 years (Erro, Sheerin, and Bhatia 2014a; Bruno et al. 2007), and there is an approximately 1.3:1 M:F predominance (Erro, Sheerin, and Bhatia 2014a). Unlike PKD, PNKD attacks tend to happen less frequently (weekly) (Erro, Sheerin, and Bhatia 2014a), and decreases with age (Bruno et al. 2007). Treatment involves avoiding triggers and a trial of clonazepam or other anticonvulsants, even though response is not consistent (Sethi, Erro, and Bhatia 2021). DBS of bilateral internal globus pallidus has also been successful in treating PNKD symptoms (Van Coller et al. 2014).

PED is the third most common phenotype of paroxysmal dyskinesia (Van Rootselaar et al. 2009). The first PED gene identified is *SLC2A1*, which encodes glucose transporter 1 (GLUT1) (Weber et al. 2008). However, *SLC2A1* only causes < 30% of PED (Schneider et al. 2009; Erro, Sheerin, and Bhatia 2014a; Baschieri et al. 2014). PED attacks combine chorea and dystonia in > 95% (Erro, Sheerin, and Bhatia 2014a) with focal or unilateral involvement being most common (Erro, Sheerin, and Bhatia 2014a). Attacks can also include migraine, oculogyric crises, gait disturbance, clumsiness, and weakness (Erro, Sheerin, and Bhatia 2014a). Most attacks range from 15 to 45 min, and occur several times per week (Erro, Sheerin, and Bhatia 2014a) with no sensory aura (Erro, Sheerin, and Bhatia 2014a). Up to 65% also report epilepsy, learning difficulties, ataxia, pyramidal signs, or hemolytic anemia (Erro, Sheerin, and Bhatia 2014a). Treatment is via ketogenic or Adkins diet, or triheptanoin (Mochel et al. 2016). Acetazolamide (Anheim et al. 2011) or levodopa (Baschieri et al. 2014) are possibly beneficial.

PHD is the least common phenotype of paroxysmal dyskinesia. The attacks occur during NREM sleep, and include dystonic posturing, ballistic or choreic movements, without ictal EEG abnormalities (Meierkord et al. 1992). In most cases, attacks are less than 1 min and are indistinguishable from frontal lobe epilepsy (Provini, Plazzi, and Lugaresi 2000; Meierkord et al. 1992). In many reviews, PHD is considered epileptic rather than a movement disorder (Sethi, Erro, and Bhatia 2021). However, *ADCY5* (Friedman et al. 2016) and *PRRT2* (Liu et al. 2016) can present with PHD. Finally, Lugaresi reported 2 cases of PHD with longer attack

durations of 2–50 min (Lugaresi, Cirignotta, and Montagna 1986), one who was eventually diagnosed with Huntington disease (Provini, Plazzi, and Lugaresi 2000).

Pathophysiology/genes

According to their underlying disease mechanisms, genetic paroxysmal dyskinesias can be grouped into the synaptopathies, second-messenger related disorders, transportopathies, channelopathies, mitochondrial, or dyskinesias of miscellaneous causes that affect neuronal function. For an overview, see Fig. 1.

Synaptopathies

As a group, these diseases involve alterations to the normal functions of cellular processes at the presynaptic terminals that affect neurotransmitter release.

PRRT2

PRRT2 (OMIM 614386) on 16p11.2 encodes proline-rich transmembrane protein 2, a transmembrane protein in presynaptic terminals that modulates SNAP25 and synaptotagmin 1/2 (Valtorta et al. 2016), affecting vesicle fusion and neurotransmitter release (Zhao et al. 2020). *PRRT2* also modulates Nav1.2/Nav1.6 channels, influencing neuronal excitability (Fruscione et al. 2018). The pathophysiology of *PRRT2* variants in PKD may be related to abnormal

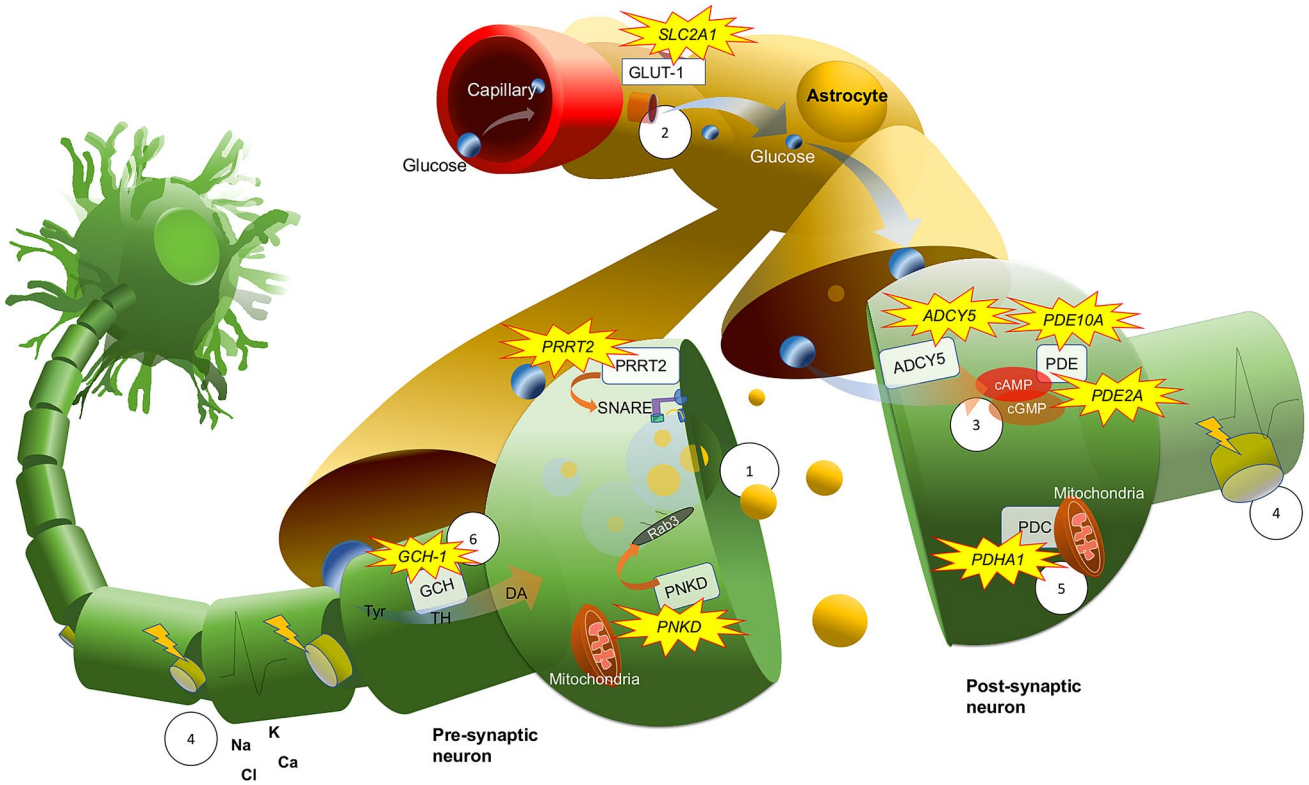

Fig. 1 Genetic paroxysmal dyskinesias grouped by pathophysiology. A hypothetical pre- and post-synaptic neuron (green) is shown with an astrocyte (yellow) and a capillary (red). Defects of synaptic function (1), transporters (2), second messengers (3), ion channels (4), mitochondria (5), or other enzymatic or cellular processes (6) can cause paroxysmal dyskinesias. The synapse (1) is at the center-right of the image, and is the site of action for *PRRT2* and PNKD, which act on SNARE complex and Rab3-interacting molecules, respectively, to modulate neurotransmitter release. The activity of various transporters, including GLUT1 (2) encoded by *SLC2A1,* affect energy or metabolite availability. Other transporters include *ATP7B* (not pictured) where defects lead to toxic accumulation of substances. Variants of *ADCY5*, *PDE10A*, and *PDE2A* affect the second messengers (3) cAMP and cGMP. Various ion channels (4) maintain resting membrane potential or affect action potential generation. Mitochondria (5) are critical for energy homeostasis and house enzymes like pyruvate hydrogenase (PDH), partially encoded by *PDHA1*. A variety of other genes (6) are involved in neurotransmitter synthesis, ion balance, or regulating cell life cycle. GTP Cyclohydrolase (GCH) is shown catalyzing tetrahydrobiopterin (TH) synthesis, necessary for dopamine (DA) production. For a comprehensive list, see Table 3. Legend: GLUT1 (Glucose Transporter 1), Tyr (Tyrosine), PDE (Phosphodiesterase)

transmission at cerebellar parallel fiber-Purkinje cell synapses (Tan et al. 2018).

PRRT2 causes a spectrum of symptoms including PKD, benign familial infantile seizures (BFIS), or infantile convulsions with choreoathetosis (ICCA) (a combination of PKD and BFIS), which is also called PKD with infantile convulsions or PKD/IC (Valtorta et al. 2016; Szepetowski et al. 1997; Bruno et al. 2004). These represent > 94% of *PRRT2* cases (Ebrahimi-Fakhari et al. 2015). *PRRT2* is also implicated in PNKD, PED (Erro, Sheerin, and Bhatia 2014a), PHD (Liu et al. 2016), paroxysmal torticollis, migraine, hemiplegic migraine, episodic ataxia, febrile seizures, childhood-absence epilepsy, and intellectual disability (Valtorta et al. 2016; Méneret et al. 2013).

PRRT2-related neurological disorders share autosomal dominant inheritance, incomplete penetrance, and variable expressivity (Ebrahimi-Fakhari et al. 2015). Nearly 90% are familial, and > 75% have the same frameshift variant c.649dupC (p.Arg217ProfsTer8) resulting in a premature stop codon (Ebrahimi-Fakhari et al. 2015) and haploinsufficiency. Missense variants also tend to localize to transmembrane and loop domains of the C-terminal (Zhao et al. 2020). These are consistent with a loss-of-function mechanism in *PRRT2*-associated diseases. Finally, not all variants are associated with normal interictal neurological examination (Labate et al. 2012).

PNKD

PNKD (OMIM 609023) on 2q35, formerly known as myofibrillogenesis regulator-1 (*MR-1* gene), encodes at least three alternatively spliced proteins: long (PNKD-L, only expressed in CNS), medium (PNKD-M) and short (PNKD-S) (Lee et al. 2004; Ghezzi et al. 2009). *PNKD* is homologous to hydroxyacylglutathione hydrolase (*HAGH*), whose product is involved in metabolism of methylglyoxal, a compound contained in coffee, alcoholic beverages, and produced by oxidative stress (Lee et al. 2004). *PNKD* also modulates neurotransmitter release via Rab3-interacting molecules (Shen et al. 2015), affecting nigrostriatal dopamine release in a caffeine and ethanol-dependent manner (Lee et al. 2012).

Three heterozygous variants affecting PNKD-L and PNKD-S are implicated in PNKD. These include missense heterozygous variants in exon 1 at c.66C > T (p.Ala7Val) and c.72C > T (p.Ala9Val) (Rainier et al. 2004) and a c.97G > C (p.Ala33Pro) variant in exon 2 (Ghezzi et al. 2009). The latter manifests as PNKD + episodic ataxia.

PNKD variants affecting PNKD-L and PNKD-M can cause non-PNKD presentations as well, including PKD + seizures (Tian et al. 2018) with a frameshift c.956dupA (p.Arg320AlafsTer45), episodic ataxia-with a predicted deleterious missense variant p.Gly89Arg (Boles, Sheldon, and Trifiletti 2013), familial hemiplegic migraine with a c.1022delC (p.Pro341fsTer2) variant (Gardiner et al. 2015). Finally, heterozygous *PNKD* p.Ala33Pro can cause non-paroxysmal chorea, myoclonus, and dystonia (Pandey, Tomar, and Mahadevan 2019), and PNKD-L nonsense variant (chr2: 219204814 C/T) is implicated in Tourette Syndrome (Sun et al. 2018) as well.

TBC1D24

TBC1D24 (OMIM 613577) on 16p13.3 encodes a TBC (Tre2-Bub2-Cdc16) and TLDc (TBC Lysin-motif Domain Catalytic) domain-containing protein. This protein coordinates the Ras superfamily, including Rab proteins and GTPases, thus regulating vesicle trafficking at synapses (Mucha et al. 1993). Most affected individuals are biallelic variants at TBC domain, or compound heterozygous for both the TBC and TLDc domains. Pathogenic variants cause synaptic defects (Lüthy et al. 2019).

TBC1D24 can cause a spectrum of neurological disorders including epilepsy (familial infantile myoclonic epilepsy, progressive myoclonus epilepsy, early-infantile epileptic encephalopathy 16), chronic encephalopathy, DOORS (deafness, onychodystrophy, osteodystrophy, intellectual disability, and seizures), autosomal dominant or recessive nonsyndromic hearing loss (Mucha et al. 1993), and movement disorders including paroxysmal dyskinesias (Lüthy et al. 2019; Steel et al. 2020), tremors, and episodic ataxia (Zimmern et al. 2019).

PED was reported in two cases both starting in infancy, with dystonic posturing or full body stiffening triggered by exercise. The first patient had heterozygous p.Gln301Ter (predicted to cause nonsense-mediated decay) and p.Ser202Leu variants (Steel et al. 2020) and also developed orofacial dyskinesia episodes after singing or tongue protrusion. There were three GTCs that resolved with carbamazepine. Interictally, there was mild ataxia, dysarthria, intention tremor, myoclonus, brisk reflexes, developmental, and learning delay. The second had p.Leu159TrpfsTer10 and p.Arg227Leu variants and PED with epilepsy (Steel et al. 2020). In addition to prolonged exercise, triggers also included heat, emotional stress, and prolonged computer use. Interictal exam was normal.

A family with PED-Writer's Cramp-Rolandic Epilepsy (PED-WC-RE) carrying p.Arg360His and p.Gly501Arg variants (affecting the TLDc domain) was reported. The epilepsy was self-limited, and the PED was WC. Interictal nystagmus and postural hand tremor were treated with trihexyphenidyl (Lüthy et al. 2019). Three other cases have been reported. An individual with p.Thr182Met and p.Gly511Arg with infantile RE developed episodic dysarthria and paroxysmal truncal dystonia triggered by fatigue or excitement, and WC. All symptoms except the WC responded

to oxcarbazepine, levodopa, and clonazepam (Lüthy et al. 2019). Two unrelated individuals with p.Ile81_Lys84del and p.Ala500Val have been identified. Both had RE preceding PED. One patient improved with benzodiazepines, and the other's seizures were controlled on lamotrigine but his PED persisted (Lüthy et al. 2019).

Transportopathies

This group of diseases involves alterations to transmembrane proteins that transport molecules across the cellular membrane.

SLC2A1

SLC2A1 (OMIM 138140) on 1p34.2 encodes glucose transporter 1 (GLUT1), the main protein responsible for glucose transport across the blood brain barrier Table 1. GLUT1 deficiency syndrome (GLUT1-DS) manifests as paroxysmal movement disorders (mainly PED), but also early-onset epilepsy, cognitive impairment, and non-neurologic features (see Table 2) (Pearson et al. 2013; Koch and Weber 2019; De Giorgis et al. 2016; De Vivo et al. 1991), and should be suspected in any patient presenting with epilepsy with microcephaly, paroxysmal dyskinesia, or the aforementioned features (Castellotti et al. 2019). Of note, only a minority of PED is caused by SLC2A1 variants (Schneider et al. 2009; Erro et al. 2014b).

Missense *SLC2A1* variants account for more than half of GLUT1-DS cases (Leen et al. 2013) and tend to be have milder phenotypes (Pearson et al. 2013). Interestingly, 10% of GLUT1-DS cases have no identifiable *SLC2A1* variants (Leen et al. 2013), suggesting that other genes also cause GLUT1-DS. Lumbar puncture is indicated in the absence of pathogenic *SLC2A1* variants. CSF glucose ≤ 10th percentile, CSF:serum glucose ≤ 25th percentile, and CSF lactate level < 90th percentile is highly suggestive of GLUT1-DS (Leen et al. 2013).

ATP7B/Wilson Disease

ATP7B (OMIM 606882) on 13q14.3 encodes a copper-transporting ATPase. Dysfunction leads to copper overload in brain, liver, cornea, and other tissues, a condition called Wilson Disease. The most frequent neurological manifestations include dysarthria, dystonia, tremor, parkinsonism, choreoathetosis, and ataxia (Ferenci et al. 2012), but paroxysmal dyskinesias can be the initial symptom as well (Dutta 2018; Kim and Yoon 2017). One individual with PKD, minimal interictal dystonia, and a positive *ATP7B* variant (specifics not disclosed) was reported (Dutta 2018). Attacks lasted for seconds to 2 min and completely resolved on carbamazepine. Another individual had PNKD and a clinical diagnosis of Wilson Disease via a Leipzig score of 5 (Kim and Yoon 2017), with attacks lasting seconds and relieved by smoking. He had elevated 24-h urinary copper excretion and Kayser–Fleischer rings but normal MRI brain, liver biopsy, and *ATP7B* gene sequencing. His symptoms responded to trientine. PKD later in the course of Wilson Disease has also been reported, and was responsive to oxcarbazepine (Micheli, Tschopp, and Cersosimo 2011).

SLC16A2

SLC16A2 (OMIM 300095) on Xq13.2 encodes monocarboxylate transporter type 8 (MCT8), a thyroid hormone (T3) transporter for CNS neurons (Gika et al. 2010). Pathogenic variants on *SLC16A2* can manifest as Allan–Herndon–Dudley Syndrome (AHDS) including dystonia, choreoathetosis, tremor, ataxia, and paroxysmal dyskinesia.

Individuals present in infancy with hypotonia, poor feeding, and developmental delay (Gika et al. 2010). Lab testing reveals high free T_3, low reverse T_3, and mildly reduced total and free T_4. TSH is normal or slightly elevated (Remerand et al. 2019). Patients develop myopathic facies, muscle wasting, contractures, pectus excavatum, scoliosis, rotatory nystagmus, and disconjugate gaze (Dumitrescu et al. 2004). Delayed or hypo-myelination is common (Vancamp, Demeneix, and Remaud 2020). Severe hypotonia is gradually replaced by spastic paraplegia. Intellectual disability emerges (Kurian and Jungbluth 2014).

ADHS with PKD have been reported with a missense c.1535T > C (p.Leu512Pro) variant, and a separate case with c.1212delT frameshift leading to stop codon (Dumitrescu et al. 2004). Clinically, these patients had severe developmental delay and hypotonia with PKD triggered by *passive* movements. Similarly to PNKD, excitement, happiness, or crying can also trigger attacks (Brockmann et al. 2005). Attacks can also be more prevalent in sleep (Boccone et al. 2010). Attacks included head tilt or retroversion, lasted up to 3 min, up to 30 times per day. Several other variants have been reported (Gika et al. 2010; Fuchs et al. 2009; Rego et al. 2017; Boccone et al. 2010; Anık et al. 2014) (see Table 3).

Second-messenger related

This group of diseases involves alterations to the second-messenger signaling systems, cAMP and cGMP.

Table 1 Features of main genetic paroxysmal dyskinesias

Condition	PKD	PNKD	PED	PHD
Primary gene	*PRRT2*	*PNKD*	*SLC2A1*	*ADCY5*
Proportion of cases due to primary gene	40–90%	71%	< 30%	Unclear
Onset age	1–20	< 5	2–30	Childhood
Duration	Seconds–5 min	Minutes to hours	15–45 min	"Typical" < 1 min "Atypical" < 1 h
Frequency	10–100 per day	Weekly	Several per week	1–10 × per night
Trigger	Sudden movement (nearly all) Half also have non-kinesigenic triggers	Caffeine, alcohol (nearly all) Temperature, stress, excitement	Sustained movement, fasting, stress, anxiety	NREM sleep
Dyskinetic features of attacks	Unilateral, focal, or generalized chorea + dystonia	Unilateral, focal, or generalized chorea + dystonia	Focal or unilateral chorea + dystonia most common (in *SLC2A1*)	Varied, dystonia + purposeless movements of trunk and limbs
Non-dyskinetic features of attacks	Aura (paresthesias, tension) 48%, can be used to abort	Aura (weakness, shortness of breath, migraine) 40–60%	Can be aborted by rest. Migraine, oculogyric crisis, gait disturbance, clumsiness, weakness	No epileptiform activity on EEG
Associated conditions	Infantile convulsions, febrile convulsions, episodic ataxia, paroxysmal torticollis, epilepsy, hemiplegic migraine	Migraine	Epilepsy, learning difficulties, ataxia, pyramidal signs, hemolytic anemia	Have other paroxysmal dyskinesias, axial hypotonia, orofacial jerks, intellectual disability, seizures
Treatment*	Carbamazepine, antiepileptics, good response	Avoid triggers. Clonazepam, diazepam, gabapentin, levetiracetam, acetazolamide, variable response	Ketogenic/Adkins diet, triheptanoin, levodopa, acetazolamide	Clonazepam, levetiracetam, carbamazepine Oxcarbazepine
Prognosis	Remission by middle age is possible. Improves during pregnancy	Attack frequency decreases with age	Depends on treatment compliance	Can be favorable

*Note: Certain underlying conditions have specific treatments, see text for details. Sources per article text. Additional sources include (Bruno et al. 2004)

Table 2 Clinical spectrum of GLUT1 deficiency syndrome

Epilepsy	Movement disorders	Cognitive/behavioral disturbances	Other neurological symptoms	Non-neurologic features
Early-onset absence epilepsy (EOAE)	PED	Developmental delay	Spasticity	Hemolytic anemia
	PNKD	Cognitive impairment of variable severity	Alternating hemi/quadriplegia	Hepato-splenomegaly
	PKD		Hypotonia	Cataracts
Childhood-absence epilepsy (CAE)	Episodic choreoathetosis and progressive spastic paraparesis	Intellectual disability	Abnormal eye movements	Microcephaly
Epilepsy with myoclonic-atonic seizures (Doose syndrome)	Intermittent ataxia	Language delay	Migraine headaches	
	Chorea	Dysphoria	Cyclical vomiting	
Focal epilepsy	Dystonia	Inconsolable crying	Sleep disturbance	
Febrile seizures	Parkinsonism		Encephalopathy	
	Myoclonus			
	Oculogyric crises			

ADCY5

ADCY5 (OMIM 600293) on 3q21.1 encodes the membrane-bound ADCY5 that converts adenosine triphosphate (ATP) to pyrophosphate and cyclic adenosine monophosphate (cAMP), the second messenger in a broad range of cellular activities. *ADCY5* is expressed largely in striatum and myocardium (Chen et al. 2014). Clinically, variants cause axial hypotonia, facial chorea, dystonia, myoclonus, or PHD. Additional clues include pain during movements, fluctuating severity, mild to no cognitive impairment, normal MRI, and little to no progression (Chen et al. 2014). Attacks can be triggered with or without movement, fatigue, or intercurrent illness, and last from minutes to weeks (Chen et al. 2014). Several variants have been identified, and can have features of all paroxysmal dyskinesias (see Table 3) (Friedman et al. 2016).

Unique clinical features of *ADCY5* include a frog-like gait in childhood, and worsening of choreoathetosis during drowsiness (Chang et al. 2016). The PHD and hyperkinetic (Table 4) movements can be treated with clonazepam or levetiracetam (Chen et al. 2015). Caffeine can also reduce hyperkinetic movements (Aurélie Méneret et al. 2019) via adenosine receptor antagonism, which likely inhibits adenylyl cyclase. Finally, bilateral GPi DBS is moderately effective (Dy et al. 2016; Eisenberg et al. 2021; de Almeida Marcelino et al. 2020) Table 4.

PDE10A

PDE10A (OMIM 610652) encodes the cyclic nucleotide phosphodiesterase 10A, which is selectively expressed in striatal medium spiny neurons. Striatal cAMP modulates movement, and is synthesized by ADCY5 and degraded by PDE10A. *PDE10A* (and *ADCY5*) variants lead to decreased dopamine transporter expression in the striatum, loss of substantia nigra neuromelanin-containing neurons, and microstructural white and gray matter changes (Niccolini et al. 2018). Variants can cause childhood-onset chorea (Esposito et al. 2017). In addition, a single case of PNKD with a p.Ile625Phe and p.Glu67Gln variant was reported (Niccolini et al. 2018).

PDE2A

PDE2A (OMIM 602658) on 11q13.4 encodes phosphodiesterase 2A, which catalyze cAMP and cGMP (cyclic guanosine monophosphate). *PDE2A* is highly expressed in striatal medium spiny neurons (Salpietro et al. 2018). One of its isoforms localizes to mitochondria and regulates cellular energy metabolism (Monterisi et al. 2017).

PNKD/PKD-like movements were reported in one individual with a homozygous loss-of-function c.1439A > G (p.Asp480Gly) variant. Attacks were sudden falls followed by dystonic postures and choreic movements with no reported trigger. Additional chorea and dystonia was triggered by motor tasks such as writing. Eventually he developed a progressive choreic disorder, language/cognitive difficulty, and interictal EEG abnormalities (Salpietro et al. 2018).

Table 3 Genes and variants identified in paroxysmal dyskinesias

Gene chromosome	Protein	Function	Variants related to paroxysmal dyskinesia	Paroxysmal dyskinesia type	Other paroxysmal disorders	Classic presentation Other features MRI findings
Synaptopathies						
PRRT2 16p11.2	Proline-rich transmembrane protein 2	Modulates SNARE complex (SNAP25 and synaptotagmin)	p.Arg217ProfsTer8 (78.5%) c.649delC (3.9%) c.718C > T (1.5%) c.291delC (1.2%) c.649C > T (1.2%)* (partial list, see mdsgene.org)	PKD PNKD PED PHD	EA, ICCA, BFIS, epilepsy, hemiplegic migraine	PKD
PNKD 2q35	PNKD (three isoforms: *PNKD*-L; *PNKD*-M; *PNKD*-S)	Modulates neurotransmitter release	p.Ala7Val p.Ala9Val p.Ala33Pro p.Arg320AlafsTer45 (partial list, see mdsgene.org)	PNKD PED PKD	Episodic ataxia Hemiplegic migraine Epilepsy	PNKD Oculogyric crises, blepharospasm, risus sardonicus, pain. Progressive chorea, myoclonus
TBC1D24 16p13.3	Tre2-Bub2-Cdc16 (TBC)	Regulation of vesicular membrane trafficking	p.Gln301Ter + p.Ser202Leu p.Leu159TrpfsTer10 + p.Arg227Leu p.Arg360His + p.Gly501Arg p.Thr182Met + p.Gly511Arg p.Ile81_Lys84del + p.Ala500Val p.Pro102Ser + p.Val137Ala	PED	Epilepsy Myoclonus Ataxia Tremors	DOORS, familial epilepsies, hearing loss Onychodystrophy, osteodystrophy, intellectual disability
Transportopathies						
SLC2A1 1p34.2	GLUT1 glucose transporter	Mediates glucose transport across BBB	p.Ser95Ile p.Asn219GlnfsTer18 p.Val145Met p.Asn317Thr p.Glu282_Ser285del p.Arg333Gln p.Arg91Trp	PED PNKD PKD	EA Epilepsy Migraine Episodic choreoathetosis Myoclonus Oculogyric crises	GLUT-DS (Table 2)
ATP7B 13q14.3	Transmembrane copper-transporting ATPase	Copper transporter, defects lead to copper overload in brain, liver, cornea, and other tissues	Specific variants not reported	PKD PNKD		Wilson Disease Dysarthria, dystonia, chorea, myoclonus, ataxia, tremors, liver dysfunction, hemolytic anemia, Kayser–Fleischer ring

Table 3 (continued)

Gene chromosome	Protein	Function	Variants related to paroxysmal dyskinesia	Paroxysmal dyskinesia type	Other paroxysmal disorders	Classic presentation Other features MRI findings
SLC16A2 Xq13.2	Monocarboxylate transporter type 8 (MCT8)	Required for transmembrane uptake of free T3 from blood into neurons	p.Leu512Pro c.1212delT (early stop codon) del ex2-6 p.Cys436fs p.delPhe229 p.Arg271His p.Gly463Arg p.Gly495Ala 2.8 kb deletion of exons 3–4 c.1343e1344insGCCC	PKD (passive movements) PNKD PHD	Seizures	Allan–Herndon–Dudley Syndrome Raised serum free T3 Hypotonia, muscular hypotrophy, microcephaly, developmental delay. Progressive ataxia, spasticity, dysarthria
Second-messenger related						
ADCY5 3q21.1	Membrane-bound adenylyl cyclase	Expressed in striatum. Integrates signals from adenosine and dopamine receptors Synthesizes striatal cAMP	p.Arg418Trp p.Arg418Gln p.Arg438Pro (partial list, see mdsgene.org)	PKN PNKD PED PHD	Facial chorea or dystonia; Oculogyric crisis, RLS	Hyperkinetic movements, axial hypotonia, frog-like gait, worsening during drowsiness Attacks can last up to weeks. Fluctuations
PDE10A 6q27	Phosphodiesterase 10A	Regulate degradation of striatal cAMP	p.Ile625Phe + p.Glu67Gln	PNKD		Childhood-onset chorea MRI: bilateral striatal lesions
PDE2A 11q13.4	Phosphodiesterase 2A	Catalyzes the hydrolysis/degradation of both cGMP and cAMP	Homozygous p.Asp480Gly Homozygous p.Gln394Ter p.Pro149Leu + p.Ala618Valfs56	PKD PNKD	Epilepsy	Intellectual disability, paroxysmal dyskinesia, seizures Progressive chorea, dystonia, falls
Channelopathies						
SCN8A 12q13.13	Sodium voltage-gated channel alpha subunit	Responsible for rapid depolarization during AP formation. Pathogenesis unknown	p.Glu1483Lys p.Ala1214Thr	PKD	BFIS/ICCA	Epilepsy Intellectual disability, autism spectrum disorder Myoclonus ataxia
KCNMA1 10q22.3	Large conductance voltage and calcium-activated potassium channel, α subunit	Control smooth muscle tone and neuronal excitability	p.Asp434Gly p.Arg458Ter p.Glu884Lys p.Asn1053Ser	PNKD	Epilepsy Hypotonia	PNKD ± epilepsy Intellectual disability Developmental delay Oculomotor abnormalities Long tract atrophy

Table 3 (continued)

Gene chromosome	Protein	Function	Variants related to paroxysmal dyskinesia	Paroxysmal dyskinesia type	Other paroxysmal disorders	Classic presentation Other features MRI findings
ATP1A3 19q13.2	ATPase Na+/K+ transporting subunit	Major determinant of membrane resting potentials	p.Asp923Asn p.Leu815Arg p.Glu277Lys	PED PNKD	Plegic attacks EA Epilepsy Dysautonomia Migraine Oculomotor abnormally Transient hypotonia	AHC, RDP, CAPOS Developmental delay, ataxia, parkinsonism, dystonia
KCNA1 12p13.32	K(V)1.1 Voltage-gated potassium channel subunit	Strongly expressed in cerebellum, hippocampus, and motor axons. Variants impair channel dynamics and affect neuronal excitability	p.Leu319Arg p.Asn255Lys	PKD PNKD	EA1 Epilepsy Paroxysmal dyspnea Cataplexy Migraines	EA1 ± myokymia, neuromyotonia Hyperthermia, cerebellar dysfunction, developmental delay, hypomagnesemia, lower-limb weakness, cataplexy
CLCN2 3q27.1	Voltage-gated chloride channel-2	Possible role in brain ion and water homoeostasis, and regulation of cell excitability	Homozygous p.Ser375CysfsTer6	PKD		CC2L Ataxia, tremors, spasticity, chorioretinopathy or optic atrophy, neuropsychiatric symptoms, male infertility
CHRNA4 20q13.33	Neuronal-type nicotinic acetylcholine receptor α4 subunit	Component of $\alpha_4ß_2$-nAChR, affects synaptic excitability	p.Val327Met	PKD	ADSHE GEFS+	Epilepsy
Mitochondrial						
SACS 13q12.12	Sacsin	Mitochondrial surface molecular chaperone	p.Pro3007Ser and p.His3392fs p.Trp1376Ter	PKD		ARSACS
POLG 15q26.1	DNA polymerase gamma	Replication of mitochondrial DNA	p.Ser147Ile	PKD	Spasmodic torticollis Epilepsy	Progressive external ophthalmoplegia, spinocerebellar ataxia, epilepsy, neuropathy
DLAT 11q23.1	Dihydrolipoamide S-acetyltransferase	Component E2 of PDC	Homozygous p.Phe576 > Leu Homozygous p.Val157Gly p.Glu138Ter	PNKD PED	Seizures	PDC deficiency. For all in this group: developmental delay, abnormal tone, ptosis, choreoathetoid movements, seizures, ataxia Elevated CSF lactate MRI abnormalities in globus pallidus

Table 3 (continued)

Gene chromosome	Protein	Function	Variants related to paroxysmal dyskinesia	Paroxysmal dyskinesia type	Other paroxysmal disorders	Classic presentation Other features MRI findings
PDHA1 Xp22.12	Pyruvate dehydrogenase E1 alpha 1 subunit	Mitochondrial multi-enzyme complex link between glycolysis and TCA cycle	p.Arg72Cys p.Leu216Ser p.Ile280Ser	PED PNKD	Ranges from none to EA, Epilepsy	PDC deficiency Elevated CSF lactate MRI abnormalities in globus pallidus
PDHX 11p13	Pyruvate dehydrogenase complex component X	Catalyzes conversion of pyruvate to acetyl CoA. Minor antigen for anti-mitochondrial antibodies	p.Gly27Thrfs23/p.Asp322AlafsTer6	Recurrent dystonia		PDC deficiency Elevated CSF lactate MRI abnormalities in globus pallidus
BCKDHB 6q14.1	Branched-chain keto acid dehydrogenase E1 beta polypeptide	Involved in branched-chain amino acid oxidation	Heterozygous p.Arg359Lys + p.Cys235Ter	PNKD	Lethargy, vomiting, seizures, dementia, developmental delay	Maple syrup urine disease Elevated branched-chain amino acids
ECHS1 10q26.3	Short-chain enoyl-CoA hydratase	Involved in fatty acid beta-oxidation	Heterozygous p.Glu78Ter + p.Ala173Val Heterozygous p.Ala132Thr + p.Ala173Val	PED	Ranges from none to vomiting, reduced consciousness, and dehydration	T2 hyperintensities in bilateral globus pallidus
HIBCH 2q32.2	Encodes beta-hydroxyisobutyryl-Coenzyme A hydrolase	Involved in branched-chain amino acid catabolism	Heterozygous p.His343Asp + p.Val128Asp p.Thr305Ala	PED PNKD	Ranges from none to ketoacidosis	T2 hyperintensities in bilateral globus pallidus Can have elevated ammonia and creatine kinase
PRKN 6q26	E3 ubiquitin ligase	Proteasome-dependent degradation of proteins, involved in mitochondrial quality control	Deletion exon 3–6 and exon 3 (heterozygous) Other variants not reported	PED		Early-onset parkinsonism, dystonia
Miscellaneous						
DEPDC5 33q12.2-q12.3	Subunit of Rags 1 complex GTPase-activating protein	Modulates mTOR pathway, regulating cell growth	p.Ser1104Leu	PKD	Seizures	FFEVF, focal cortical dysplasia
GCH1 14q22.2	GTP cyclohydrolase	Catalyzes first step in tetrahydrobiopterin synthesis, essential for dopamine synthesis. Variants reduce striatal dopamine levels	c.172-175delC (frameshift) p.Glu84Ter	PED		Dopa-responsive dystonia Lower limb dystonia, Parkinsonism Marked diurnal fluctuation

Table 3 (continued)

Gene chromosome	Protein	Function	Variants related to paroxysmal dyskinesia	Paroxysmal dyskinesia type	Other paroxysmal disorders	Classic presentation Other features MRI findings
SLC20A2 8p11.21	Solute carrier family 20 phosphate transporter member 2	Involved in phosphate balance	p.His362GlnfsTer54 p.Gln523Ter p.Pro568Leu Exon1 and 2 deletion	PKD	Focal chorea Migraine	Basal ganglia calcifications. For all in this group: dystonia, parkinsonism, chorea, ataxia, neuropsychiatric symptoms, migraine, vertigo
PDGFB 22q13.1	Platelet-derived growth factor, beta polypeptide	Implicated in PFBC	p.Leu110Pro	PKD	Migraine	Basal ganglia calcifications Head CT can be normal
MYORG 9p13.3	Myogenesis-regulating glycosidase	Unknown	Homozygous p.Arg611Trp	PKD	None	Basal ganglia calcifications Recurrent miscarriages due to placental calcifications
XPR1 1q25.3	Murine virus receptor	Involved in phosphate balance	p.Asp262GlufsTer6 + p.Arg448Trp	PKD	Epilepsy	Basal ganglia calcifications
HTT 4p16.3	Huntingtin	Nuclear protein that regulates transcription	CAG expansion	PHD (longer duration, > 1 min)		Huntington Disease
Neuroacanthocytosis			No specific variants reported	PNKD PED	Myoclonus, chorea, epilepsy	Acanthocytes, chorea, dystonia, parkinsonism, neuropathy, ataxia, epilepsy, neuropsychiatric
HPRT1 Xq26.2-q26.3 T	HPRT	Central role in purine salvage pathway	c.212G > T	PKD	Dystonia, chorea, athetosis, seizures (rare)	Lesch-Nyhan, *HPRT*-related neurological dysfunction, *HPRT*-related hyperuricemia Self-mutilation, developmental delay
ABAT 16p13	GABA-transaminase	Breakdown of GABA	p.Arg92Gln	PNKD	Epilepsy Myoclonus	Severe epileptic encephalopathy, growth acceleration

* Mdsgene.org maintains a database of variants for *PNKD*, *PRRT2*, *SLC2A1*, and other conditions including *ADCY5*, *GCH1*, *PRKN*, *KCNA1*, *PDHA1*. Supplementary material for (Ebrahimi-Fakhari et al. 2015) also contains prevalence of each variant for *PRRT2* only. For non-*PRRT2*/*PNKD*/*SLC2A1* variants, we focused on cases presenting with PxD

PKD (paroxysmal kinesigenic dyskinesia), PNKD (paroxysmal non-kinesigenic dyskinesia), PED (paroxysmal exertion induced dyskinesia), PHD (paroxysmal hypnagogic dyskinesia), EA (episodic ataxia), *ICCA* (infantile convulsions with choreoathetosis), BFIS (benign familial infantile seizures), ADSHE (Autosomal Dominant Sleep-related Hypermotor Epilepsy), DOORS (deafness, onychodystrophy, osteodystrophy, intellectual disability, and seizures), GEFS+ (Genetic Epilepsy with Febrile Seizures Plus), GLUT-DS (glucose transporter 1 deficiency syndrome), AHC (alternating hemiplegia of childhood), RDP (rapid-onset dystonia-parkinsonism), CAPOS (Cerebellar ataxia, Areflexia, Pes-cavus, Optic atrophy, Sensorineural hearing loss), CC2L (CLCN2-related leukoencephalopathy), FFEVF (autosomal dominant familial focal epilepsy with variable foci), ARSACS (Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay), PFBC (Primary Familial Brain Calcification), HPRT (hypoxanthine phosphoribosyltransferase)

Table 4 Acquired causes of paroxysmal dyskinesia with workup

Category	Disease	Workup
Immune-mediated	Multiple sclerosis	MRI, CSF study
	Acute disseminated encephalomyelitis	
	Post-streptococcal autoimmune neuropsychiatric syndrome	ASO, anti-DNase B
	Voltage-gated potassium channel complex protein antibody encephalitis Anti-Caspr2 syndrome LGI-1 syndrome	Auto-antibody panel
	Steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT)	TPO and TG antibodies
	Antiphospholipid syndrome	aCL, anti-β-2-glycoprotein I Ab, LA
	Sjögren syndrome	Anti-SSA (Ro), anti-SSB (La), RF, ANA
	Behcet disease	Clinical
	Celiac disease	Anti-TG antibody
Vascular	Limb-shaking syndrome (carotid stenosis)	Neuroimaging + vessel study
	Transient ischemic attack/stroke	
	Moyamoya	
	Arteriovenous malformation	
Metabolic	Hypo/hyperglycemia	Serum glucose
	Hypocalcemia/hypoparathyroidism/pseudohypoparathyroidism	Serum calcium, PTH, VitD
	Thyrotoxicosis/hypothyroidism	Thyroid hormones
Infections	Encephalitis/postinfectious	HIV, CMV, RPR, VDRL, measles
Other	Parry–Romberg syndrome Cryopyrin-associated periodic syndrome (CAPS) Kernicterus Central pontine myelinolysis Perinatal hypoxia (cerebral palsy)	Neuroimaging *NLRP3* genetic analysis Newborn bilirubin levels Osmotic changes Perinatal history
	Chiari malformation Intracranial neoplasm Traumatic brain injury	Neuroimaging

Table modified from Erro and Bhatia (2019)

Similar PNKD/PKD-like phenotypes have been reported with biallelic variants. One case of homozygous nonsense variant c.1180C > T; p.(Gln394Ter) presented with PKD at age 17 months and eventually developed permanent choreodystonia, developmental delay, hypotonia, and interictal (but not ictal) EEG abnormalities. Another case of heterozygous missense c.446C > T (p.Pro149Leu) and splice-site variant c.1922 + 5G > A presented as PNKD at age 7 triggered by emotional stress or sensory stimuli. He also had mild intellectual disability and developmental delay (Doummar et al. 2020). These cases were pharmacoresistant (Doummar et al. 2020). DBS has similarly been unsuccessful (Salpietro et al. 2018).

Channelopathies

This group of disorders involves changes to behavior of transmembrane ion channels that affect neuronal excitability.

SCN8A

SCN8A (OMIM 600702) on 12q13 encodes the α-subunit of Nav1.6 voltage-gated sodium channel, which localizes to axons and regulates the initiation and propagation of action potentials throughout the CNS (O'Brien and Meisler 2013). Variants can manifest as PKD. Most pathogenic variants in *SCN8A* are missense and cluster in transmembrane domains. Gain-of-function variants manifest with epilepsy, while loss-of-function variants manifest as intellectual disability, autistic spectrum disorder, myoclonus, and ataxia, often without epilepsy (Gardella and Møller 2019).

Several cases of paroxysmal dyskinesia have been described. A common variant is c.4447G > A (p.Glu1483Lys) manifesting as BFIS/PKD/ICCA with normal cognitive and motor milestones (Gardella et al. 2016). This variant is associated with abnormal ictal EEGs, suggesting an epileptic origin. However, another variant c.3640G > A (p.Ala1214Thr) manifesting as PKD with normal 24-h video EEG was reported. This individual had

sensory aura, carbamazepine response, and spontaneous remission after age 23 (Tian et al. 2018).

KCNMA1

KCNMA1 (OMIM 300150) on 10q22.3 encodes the pore-forming α subunit of the "Big K+" large conductance calcium and voltage-activated K+ channel (KCa1.1) that is highly expressed in the brain. They affect action potential repolarization, mediating the fast phase of after-hyperpolarization, and regulate neurotransmitter release and dendritic excitability (Bailey et al. 2019). Variants primarily cause seizures, movement disorders, developmental delay, and intellectual disability (Du et al. 2005).

PNKD with or without generalized epilepsy is linked to at least two gain-of-function variants. The p.Asp434Gly variant was identified in a family (Du et al. 2005) of whom 7/13 had PNKD, 1/13 had epilepsy, and 5/13 had both. Clonazepam was partially effective. The p.Asn1053Ser variant was identified in an individual with mild developmental delay and PNKD triggered by excitement (Wang et al. 2017). Additional variants include p.Glu884Lys and p.Arg458Ter (Zhang et al. 2015; Yeşil et al. 2018) with additional features including oculomotor abnormalities, transient hypotonia, esotropia (Zhang et al. 2015), developmental delay, or corticospinal-cerebellar tract atrophy (Yeşil et al. 2018). For p.Arg458Ter, the paroxysmal dyskinesia features were not well characterized.

ATP1A3

ATP1A3 (OMIM 182,350) on 19q13.2 encodes the α3 isoform of the Na+/K+ ATPase transmembrane pump, which is expressed almost exclusively in neurons. This isoform is specifically required as a rescue pump for rapid restoration of large transient increases in intracellular Na+ concentration. Conditions associated with α3 deficiency are, therefore, likely aggravated by supra-threshold neuronal activity (Dobretsov and Stimers 2005). The three classic *ATP1A3* syndromes are: (1) Rapid-onset Dystonia-Parkinsonism (RDP), (2) Alternating Hemiplegia of Childhood (AHC), and (3) Cerebellar ataxia, Areflexia, Pes-cavus, Optic atrophy, Sensorineural hearing loss (CAPOS) syndrome (Salles and Fernandez 2020). However, *ATP1A3* disorders are a heterogenous spectrum including paroxysmal symptoms (PED, PNKD, weakness, and encephalopathy), a rostro-caudal gradient, ataxia, seizures, sensorineural hearing loss, pes cavus, optic atrophy, and areflexia (Salles and Fernandez 2020). Typical triggers include alcohol, fever, stress, exercise, or environmental factors such as light, temperature, water, or sounds (Brashear et al. 1993).

A single family with PED and a p.Asp923Asn variant was reported (Roubergue et al. 2013). Symptoms started with AHC and became PED over time. The same variant manifested as RDP as well in separate individuals. A separate case of PED with preceding mild intellectual disability and RDP was reported with a p.Glu277Lys variant (Nomura et al. 2021). In addition to prolonged exercise, triggers included mentally stressful situations. PNKD has also been reported with a p.Leu815Arg variant (Zúñiga-Ramírez et al. 2019). These individuals had speech arrest, intellectual disability, and interictal mild generalized dystonia. Attacks were triggered by weather changes, mood swings, caffeine intake, exercise, fever, and infections.

KCNA1

KCNA1 (OMIM 176260) on 12p13.32 encodes the shaker-related voltage-gated K+ channel Kv1.1a subunit, which regulates neuronal excitability by hyperpolarizing the membrane. To date, 34 variants have been associated with symptoms including episodic ataxia 1 (EA1) with or without myokymia, PKD, PNKD, epilepsy, isolated neuromyotonia, EA with hyperthermia or paroxysmal dyspnea, persistent cerebellar dysfunction with cognitive/motor development delay, primary hypomagnesemia, distal lower-limb weakness, and isolated cataplexy (Yin et al. 2018). A c.959T > G (p.Leu319Arg) missense variant was identified in a family with PKD, seizures, and migraines. Symptoms responded to carbamazepine or oxcarbazepine, and symptoms remitted by age ~ 35. Some family members manifested PNKD, with longer attacks up to 20 min, triggered by stress and anger (Yin et al. 2018). A c.765C > A (p.Asn255Lys) variant was reported in a family with PKD, migraines, and infantile seizures. PKD attacks partially resolved in the third decade without medication. Exam and workup were normal (Tian et al. 2018).

CLCN2

CLCN2 (OMIM 600570) on 3q27.1 encodes a voltage-gated chloride channel-2 (ClC-2) present in plasma membranes and has widespread tissue expression. This channel is activated by hyperpolarization, acidic extracellular pH, and osmotic cell swelling, and has a role in CNS homoeostasis and cell excitability (Jordt and Jentsch 1997).

Loss-of-function variants cause *CLCN2*-related leukoencephalopathy (CC2L) with intramyelinic edema. Clinical features include ataxia, tremors, spasticity, chorioretinopathy, optic atrophy, headache, neuropsychiatric symptoms, and male infertility. Typically, brain MRI shows confluent, symmetric T2-weighted hyperintensities along the fiber tracts including the posterior limbs of the internal capsules, cerebral peduncles, and middle cerebellar peduncles (Guo et al. 2019).

A homozygous p.Ser375CysfsTer6 variant was confirmed in a patient manifesting with mild hand tremors since age 7 and PKD since age 21. Additional symptoms included blepharospasm, executive dysfunction, and interictal ataxia. The MRI was typical for CC2L, and carbamazepine eliminated PKD (Hanagasi et al. 2015).

CHRNA4

CHRNA4 (OMIM 118504) on 20q13.33 encodes the neuronal-type nicotinic acetylcholine receptor α4 subunit. Along with the product of *CHRNB2*, this forms the $\alpha_4\beta_2$-nAChR which is particularly expressed in cortex, basal ganglia, thalamus, cerebellum, and hippocampus, and affects synaptic excitability. *CHRNA4* variants have been implicated in PKD (Jiang et al. 2018), Genetic Epilepsy with Febrile Seizures Plus (GEFS+) (Jiang et al. 2018), and Autosomal Dominant Sleep-related Hypermotor Epilepsy (ADSHE) (Ferini-Strambi, Sansoni, and Combi 2012; Hirose et al. 1999). One family with a p.Val327Met variant was identified with two individuals manifesting as PKD and one as GEFS+. The PKD responded to oxcarbazepine (Jiang et al. 2018). Of note, seizures in ADSHE can manifest as PHD, arise during NREM sleep, and respond to carbamazepine (Ferini-Strambi, Sansoni, and Combi 2012; Hirose et al. 1999), sharing some features with paroxysmal dyskinesias.

Mitochondrial

This group of disorders involves genetic variations of mitochondrial proteins. Many of these variants affect oxidative energy-producing processes, leading to neuronal dysfunction.

SACS

SACS (OMIM 604490) on 13q12.12 encodes sacsin, a protein located on the mitochondrial surface that may function as a molecular chaperone (Ménade et al. 2018). Variants are responsible for ARSACS (Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay), a neurodegenerative disorder characterized by a childhood-onset triad of cerebellar ataxia, peripheral neuropathy, and pyramidal tract signs (Richter et al. 1999; Vermeer et al. 1993). Atypical features can include PKD (Lu et al. 2020), spastic paraplegia, cognitive decline, supratentorial abnormalities, and epilepsy (Vermeer et al. 1993). Two cases of PKD in setting of ARSACS have been reported. Clinically, individuals had ataxia and weakness or learning disability and then developed PKD at 8–10 years old. One individual had a missense and frameshift variant (p.Pro3007Ser and rp.Hise392fs), the other had a homozygous variant (p.Trp1376Ter). Attacks responded to carbamazepine (Lu et al. 2020).

POLG

POLG (OMIM 174763) on 15q26.1 encodes DNA polymerase gamma, involved in replication of mitochondrial DNA. *POLG* disease includes progressive external ophthalmoplegia, sensory ataxic neuropathy, spinocerebellar ataxia, epilepsy, and movement disorders (Zhou et al. 2021). One case of isolated carbamazepine-responsive PKD plus spasmodic torticollis was reported with a c.440G > T (p.Ser147Ile) variant (Zhou et al. 2021). This individual also carried a missense *PLA2G6* variant (associated with parkinsonism) thought less likely pathogenic.

PDHA1/DLAT/PDHX (Pyruvate Dehydrogenase Complex Deficiency)

Pyruvate dehydrogenase complex (PDC) is a mitochondrial enzyme that is the rate-limiting step in aerobic glucose oxidation (Patel et al. 2012). It is composed of the products of several genes (*PDHA1*/*PHHB1*/*PDHX*/*DLAT*/*DLD*). Deficiency is associated with developmental delay, abnormalities in muscle tone, ptosis, choreoathetoid movements, seizures, ataxia, paroxysmal dystonia, and more, with few surviving past age 20 (Patel et al. 2012; Barnerias et al. 2010). Testing typically reveals an elevated lactate level or a low lactate/pyruvate ratio (Garone et al. 2020). MRI abnormalities are seen in most patients with ventriculomegaly being the most common (Patel et al. 2012). However, variants can also present as isolated paroxysmal dyskinesia.

Variants of *PDHA1* (OMIM 300502) on Xp22.12 have been associated with PED. A c.214C > T (p.Arg72Cys) variant was identified in a boy with PED and heat-triggered dystonia with elevated CSF lactate and MRI with abnormal signal in globus pallidus. His symptoms were greatly improved with levodopa (Head et al. 2004). Another case with a c.647T > C (p.Leu216Ser) variant presenting as isolated PED, normal lactate, and abnormal MRI (Castiglioni et al. 2015) was treated with thiamine. This individual had two asymptomatic family members who carried the same variant, suggesting reduced (or incomplete) penetrance. Another family with a c.839T > G (p.Ile280Ser) variant presenting as PNKD responsive to zonisamide was identified (Egel et al. 2010).

Variants of *DLAT* (OMIM 608770) on 11q23.1 have been associated with PNKD. One case presented at 11 months with episodic dystonia, normal lactate, abnormal MRI, triggered by stress or fever, with homozygous c.1728C > A (p.Phe576 > Leu) variant is described (Head et al. 2005). This individual had delayed development and developed generalized dystonia by age 8. Another family with a c.412G > T (p.Glu138Ter) heterozygous variant resulting in mis-splicing was identified, presenting with delayed motor milestones and then episodic dystonia (McWilliam et al. 2010). No triggers

were reported. A case presenting as delayed milestones and PED with a homozygous c.470T > G (p.Val157Gly) variant has also been reported (Friedman et al. 2017). This individual also had intellectual disability, microcephaly, disconjugate gaze, increased tone, and brisk reflexes.

Variants of *PDHX* (OMIM 608769) on 11p13 have been associated with recurrent dystonia, learning disability and MRI abnormalities in an individual who presented with neonatal lactic acidosis harboring c.87del86/c.965del59 (p.Gly27Thrfs23/p.Asp322AlafsTer6) variant (Barnerias et al. 2010). There was no mention of triggers.

BCKDHB/Maple Syrup Urine Disease

BCKDHB (OMIM 248611) on 6q14.1 encodes branched-chain keto acid dehydrogenase E1 beta polypeptide. This is part of a mitochondrial enzyme complex implicated in Maple Syrup Urine Disease (MSUD). Patients with MSUD can present as PNKD (Temudo et al. 2004; Liu et al. 2019). Laboratory testing reveals elevated branched-chain amino acids, and patients ultimately develop the MSUD phenotype. If treated, as adults, there can be tremor, dystonia, parkinsonism, scissoring gait, epilepsy, or neuropsychiatric symptoms (Carecchio et al. 2011). Compound heterozygous variants c.1076G > A (p.Arg359Lys) and c.705delT (p.Cys235Ter) have been identified in a family with MSUD presenting as PNKD (Liu et al. 2019).

ECHS1 Deficiency

ECHS1 (OMIM 602292) on 10q26.3 encodes short-chain enoyl-CoA hydratase, involved with mitochondrial fatty acid beta-oxidation. Variants typically present with lactic acidosis or Leigh syndrome, but can present as isolated PED. One individual had no other symptoms and normal lab tests. His PED resolved spontaneously by age 15 (Olgiati et al. 2016). He had a compound heterozygous c.232G > T (p.Glu78Ter) and c.518C > T (p.Ala173Val) variant. His brother had the variants but a more severe phenotype with severe persistent generalized dystonia worsening during action, severe spasticity, learning difficulties, OCD, and depression. Both had abnormal T2 hyperintensities in bilateral globus pallidus. Two additional cases have been reported with compound heterozygous c.394C > T (p.Ala132Thr) and c.518C > T (p.Ala173Val) (Korenke et al. 2016).

HIBCH Deficiency

HIBCH (OMIM 610690) on 2q32.2 encodes beta-hydroxyisobutyryl-Coenzyme A hydrolase, a mitochondrial enzyme involved in branched-chain amino acid catabolism (Yamada et al. 2014). *HIBCH* deficiency presents with episodic ketoacidosis and Leigh-like basal ganglia disease and most individuals die in adolescence. However, mild phenotypes with PED have been reported. One girl who had a compound heterozygous c.1027C > G (p.His343Asp) and c.383T > A (p.Val128Asp) variant presented with isolated PED, with elevated ammonia and creatine kinase and bilateral globus pallidus MRI abnormalities (Xu et al. 2019). Attacks resolved on a low-valine diet. Additional cases presenting as isolated PED or isolated PNKD, with a c.913A > G (p.Thr305Ala) variant, have been identified (Spitz et al. 2021).

PRKN

PRKN (OMIM 602544) on 6q26 encodes parkin, a cytosolic E3 ubiquitin ligase that regulates mitochondrial quality by promoting the selective autophagy of depolarized mitochondria. Parkin ubiquitinates a variety of cytosolic and outer mitochondrial membrane proteins (Seirafi, Kozlov, and Gehring 2015). Variants cause autosomal-recessive early-onset Parkinson disease (PD), which can present solely as PED (Erro et al. 2014b; de Schipper, Boon, and Munts 2015; Bozi and Bhatia 2003). Symptoms tend to start with lower-limb dystonia after extended periods of exercise and eventually other signs of parkinsonism develop. There is an association with RLS (Erro et al. 2014b), and there is partial levodopa response (de Schipper, Boon, and Munts 2015). Only one paper included details of the *PRKN* variant, a compound heterozygous deletion of exons 3–6 and exon 3.

Miscellaneous

This diverse group of disorders does not have mechanisms that clearly fit into one of the above categories.

DEPDC5

DEPDC5 (OMIM 614191) on 33q12.2-q12.3 encodes a subunit of GTPase-activating protein toward Rags 1 complex (GATOR). *DEPDC5* is a negative regulator of mTOR complex 1 (Bar-Peled et al. 2013), which regulates cell growth. Variants have been associated with autosomal dominant familial focal epilepsy with variable foci (FFEVF) (Dibbens et al. 2013), focal cortical dysplasia (Baulac et al. 2015), and can also manifest as pure PKD. One family is identified with a heterozygous *DEPDC5* c.3311C > T (p.Ser1104Leu) variant, with 30–40 attacks of PKD per day, responsive to carbamazepine. He had an "almost normal" brain MRI and interictal neurological exam. Initial 24-h video EEG was normal, but a repeat EEG 2 years later showed bilateral temporal spikes (Tian et al. 2018).

GCH1

GCH1 (OMIM 600225) on 14.q22.2 encodes GTP Cyclohydrolase 1 (Furukawa Y. 2002), which catalyzes the synthesis of tetrahydrobiopterin (BH4). This is a tyrosine hydroxylase (TH) cofactor required for dopamine synthesis (Ichinose et al. 1994). BH4 is also a cofactor for tryptophan hydroxylase and phenylalanine hydroxylase, which synthesize serotonin and phenylalanine (Siu 2015). *GCH1* typically presents as dopa-responsive-dystonia, characterized by asymmetric lower-limb action dystonia, exacerbated when walking, accompanied by marked diurnal fluctuation (Segawa 2011). *GCH1* can also present as PED (Erro et al. 2014b). Particular variants identified include a single base pair deletion c.172-175delC leading to frame shift (Tsao 2012), or nonsense variant p.Glu84Ter (Dale et al. 2010). These manifest as paroxysmal lower-limb dystonia triggered by walking or prolonged exercise.

SLC20A2/PDGFB/MYORG/XPR1 (Basal Ganglia Calcifications)

SLC20A2 (OMIM 158378) on 8p11.21 encodes solute carrier family 20 phosphate transporter member 2, which is involved in phosphate balance. Variants are the major cause of Primary Familial Brain Calcification (PFBC) or Fahr disease (Hsu et al. 2013). This typically presents with abnormal head CT showing basal ganglia calcifications and hyperkinetic movements including dystonia, parkinsonism, chorea, as well as ataxia, psychosis, dementia, and other neuropsychiatric symptoms. A family with isolated PKD with autosomal dominant PFBC (Zhu et al. 2014) has been identified, with a heterozygous deletion c.1086delC (p.His362GlnfsTer54) in exon 8. Attacks started in their youth, and where data are available, attack duration was 3–10 s, 10–35 × per day, and completely responded to carbamazepine. Attacks gradually disappeared by age 30. Similar symptoms have been reported in two others carrying c.C1567T (p.Gln523Ter) and c.C1703T (p.Pro568Leu) variants, respectively (Zhan et al. 2020). Another family had PKD and deletions of exons 1 and 2 (Mitsutake et al. 2020). Their deletion also involved another gene (*SMIM19*). Interestingly, a variant in *SCN4A* known to cause paramyotonia congenita was also identified in this family (Mitsutake et al. 2020).

PDGFB (OMIM 190040) on 22q13.1 encodes platelet-derived growth factor beta, and variants have been implicated in PFBC. One individual was identified with a PKD phenotype with migraines, completely resolved on carbamazepine. This individual had a normal head CT, and was found to have a c.329T > C (p.Leu110Pro) variant (Zhan et al. 2020).

MYORG (OMIM 618255) on 9p13.3 encodes a glycosidase with a transmembrane domain. Variants in this protein have been associated with PFBC. There is one reported case of a homozygous c.1831C > T (p.Arg611Trp) variant presenting as isolated PKD (Saranza et al. 2020). Attacks started at age 8, triggered by sudden movements, with up to 10 attacks per day. Attacks ceased during pregnancy. Head CT showed bilateral calcifications throughout subcortical structures, brainstem, and cerebellum.

XPR1 (OMIM 605237) on 1q25.3 encodes a transmembrane protein that serves as a virus receptor, that is also involved with phosphate homeostasis. Variants have been associated with PFBC, and manifest as movement disorders, seizures, and neuropsychiatric symptoms (Tang et al. 2021). There is one reported case of an individual with history of GTCs who developed PKD at age 16, with attacks 4–10 s long provoked by sudden activity, occurring > 5 times per day. There were paresthesias but no pain or change in consciousness during attacks. Attacks resolved with oxcarbazepine. Head CT showed bilateral globus pallidus calcifications. Whole-exome sequencing identified heterozygous c.786_789delTAGA (p.Asp262GlufsTer6) and c.1342C > T (p.Arg448Trp) variants (Tang et al. 2021).

Two additional cases of PFBC presenting with PKD are mentioned in the literature, without specific genes identified (Chung, Cho, and Kim 2012; Diaz et al. 2010).

Huntington disease

HTT (OMIM 613004) on 4p16.3 encodes huntingtin, a nuclear protein that affects DNA transcription. A pathological CAG expansion at 40 or more repeats classically manifests with motor, cognitive, and behavioral features, with incomplete penetrance from 36 to 39. HD is characterized by choreoathetotic movements. These can manifest during sleep (Neutel et al. 2015) as atypical PHD, and be the first symptom of HD (Provini, Plazzi, and Lugaresi 2000).

Neuroacanthocytosis

Neuroacanthocytosis is a group of genetic disorders associated with abnormal red blood cells. These present with a range of neurological symptoms including chorea, dystonia, parkinsonism, peripheral neuropathy, ataxia, and psychiatric symptoms (Walker et al. 2007). One family with acanthocytosis and PED with epilepsy was identified (Storch et al. 2004), treated with ketogenic diet. Another case with PNKD was reported (Tschopp et al. 2008) that improved on carbamazepine. The latter individual had mild chorea, right leg weakness, and myoclonic jerks between attacks, with normal brain imaging. No specific gene variants were identified.

HPRT

HPRT1 (OMIM 308000) on Xq26.2-q26.3 encodes hypoxanthine phosphoribosyltransferase, which has a central role in the generation of purine nucleotides via the purine salvage pathway (Keebaugh, Sullivan, and Thomas 2007). Deficiency increases purine and uric acid synthesis, and causes neurological and metabolic symptoms. Inheritance is typically X-linked recessive and can manifest as Lesch–Nyhan disease (LND), HPRT-related Neurological Dysfunction, or HPRT-Related Hyperuricemia. Severity depends on residual HPRT activity and ranges from severe dystonia, cognitive impairment, and self-injurious behavior, to nearly asymptomatic (Madeo et al. 2019). Rearrangements, nonsense, deletions, and splicing variants are associated with LND, and missense variants tend to be benign (Madeo et al. 2019).

One individual with HPRT-related Neurological Dysfunction developed PKD and had a c.212G > T variant (De La Casa-Fages, Pérez-Sánchez, and Grandas 2014). Carbamazepine, gabapentin, levetiracetam, baclofen and pregabalin were ineffective.

ABAT

ABAT (OMIM 613163) on 16p13 encodes GABA-transaminase (GABA-T), which is involved in GABA catabolism and mitochondrial nucleotide salvage (Besse et al. 2015). Deficiency is autosomal recessive and typically presents in infancy with profound neurodevelopmental impairment including encephalopathy, hypotonia and hypersomnolence (Koenig et al. 2017).

Two siblings with milder disease (developmental delay, hypotonia, hyporeflexia, ataxia, and seizures) developed PNKD associated with drowsiness (Morales-Briceño et al. 2019). Whole-exome sequencing in both sisters revealed c.275G > A (p.Arg92Gln) pathogenic variants in the *ABAT* gene.

CLCN1

CLCN1 (OMIM 118425) on 7q35 encodes muscle chloride channel, which regulates skeletal excitability. Deficiency causes myotonia congenita (MC), which can be misidentified as dystonic PKD (A. Kim et al. 2018). Unlike PKD, MC does not involve choreic movements and only involves the body part where the triggering muscle was active. Presence of myotonia on EMG is also useful for differentiation.

Discussion

With widespread use of whole-exome/genome sequencing, there is an ever increasing number of variants and genes identified associated with paroxysmal dyskinesias. It is not sufficient to identify the clinical syndrome based on triggers, frequency, and duration, because each variant has reduced or incomplete penetrance and can express as different types of paroxysmal dyskinesias.

There are no *reliable* clinical features to distinguish between *PRRT2* and non-*PRRT2* PKD, but in general, non-*PRRT2* PKD is 2 years older in onset, less likely to have family history of PKD, is less associated with other neurological syndromes, and more likely to manifest as pure dystonia (Huang et al. 2015). An alcohol trigger can potentially distinguish *PNKD*-PNKD from non-*PNKD* PNKD (Bruno et al. 2007; Erro, Sheerin, and Bhatia 2014a). However, it is likely that at typical ages of presentation, individuals have not been exposed to alcohol. Hence, there are no *reliable* distinguishing features. In general, non-*PNKD* PNKD has an older age of onset (12 years). Fewer individuals report caffeine and stress triggers, and up to 68% report exercise as a trigger (Bruno et al. 2007). Finally, attacks are more likely to have pure dystonia or pure chorea, as opposed to combined semiologies in *PNKD*-PNKD (Bruno et al. 2007). PED is even more heterogenous, and there are no *reliable* clinical features to distinguish between the various etiologies (Sethi, Erro, and Bhatia 2021).

Finally, we prefer the terminology "genetic" vs "acquired" rather than "primary" vs "secondary". Genetic disorders as reviewed above can present with paroxysmal dyskinesias and with non-movement symptoms, which can be considered secondary to the genetic variant. Conditions previously thought to have distinctive clinical or imaging features can present as isolated paroxysmal dyskinesias (e.g., *PDGFB* with normal brain imaging (Zhan et al. 2020)).

Diagnostic approach

See Fig. 2 for a proposed approach for new cases of paroxysmal dyskinesia where there is no genetically confirmed family history. Functional movement disorder (FMD) should be excluded *if possible* based on positive features such as distractibility, inconsistency, and entrainability (Yu and Stone 2018). Additional supportive features (See Table 5) (Ganos et al. 2014; Dreissen, Cath, and Tijssen 2016) can raise suspicion for FMD, but if attacks are infrequent (as in PNKD or PED), the diagnosis of FMD may not be possible to ascertain.

Next, if there is a family history of similar attacks and symptoms began in childhood, it is reasonable to proceed directly to genetic testing. Otherwise, the acquired causes

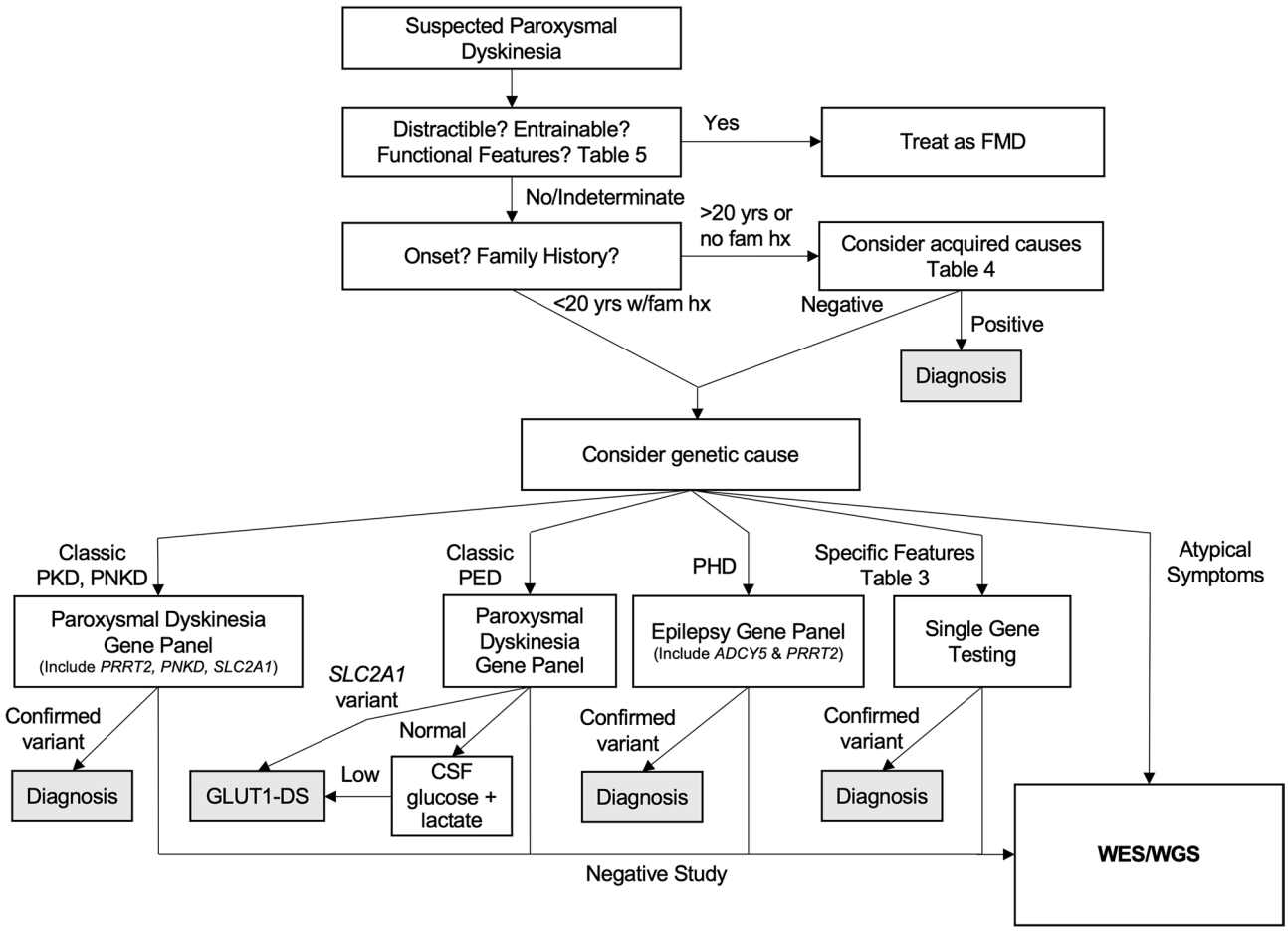

Fig. 2 Proposed diagnostic approach for new cases of paroxysmal dyskinesia where family does not have a confirmed genetic diagnosis. If possible, functional movement disorder (FMD) should be ruled out and referred for multidisciplinary treatment. If there is childhood-onset and positive family history, genetic testing is indicated. Otherwise, acquired causes should be considered with additional testing tailored to clinical suspicion per Table 4. If presentation is classic for PKD, PNKD, or PED, it is reasonable to proceed with gene panel testing. PED is unique as ~ 10% of GLUT1-DS cases have normal *SL2A1* genes and lumbar puncture is indicated. If PED is the presentation and available CSF results are already diagnostic for GLUT1-DS, genetic testing is not necessary. PHD should be evaluated with an epilepsy gene panel that includes *ADCY5* and *PRRT2*. If a particular etiology is highly suspected based on specific features, it is reasonable to proceed with single-gene testing. In some cases, the choice between single gene vs panel may be determined by ethical concerns. See text for more information. Finally, if workup is negative or if symptoms are not suggestive of a particular etiology, proceed to whole-exome/genome sequencing (WES/WGS)

should be considered (Table 4) with diagnostic testing tailored according to clinical suspicion. If testing is unrevealing or if there is no clinical suspicion for such causes, genetic testing is indicated.

If symptoms are classic for PKD, PNKD, PED, or PHD, it is reasonable to test for common underlying etiologies *PRRT2*, *PNKD*, *SLC2A1*/GLUT1-DS, and *ADCY5*. Note that up to 10% of GLUT1-DS is not caused by *SLC2A1*, so for PED, CSF glucose and lactate is required if gene testing is negative. If there are classic features for specific etiologies (e.g., DOORS, *ADCY5*, GLUT-DS, Wilson Disease, AHL-RDP-CAPOS, and *KCNA1*), targeted gene testing is reasonable.

The cost difference of panels versus single-gene sequencing is negligible ("Invitae" 2021), so, the decision to use a panel can be driven by ethical concerns. If the panel is likely to be broader than necessary based on the level of clinical suspicion, the risk of revealing additional genetic information irrelevant to the diagnosis is high. On the other hand, if there is weak clinical suspicion for any particular cause, a panel is of higher yield and leads to faster diagnosis (van Egmond et al. 2017).

In atypical presentations, or if workup is thus far negative, whole-exome or whole-genome sequencing (WES/WGS) is indicated. WGS has a slightly higher diagnostic yield, but WES may be more affordable with certain insurances. Out of pocket costs are comparable ($1000–1250 USD ("Invitae"

Table 5 Features of functional paroxysmal dyskinesia

Positive features	Distractibility
	Entrainability
	Inconsistency
Supportive features	Unresponsiveness to medication
	Unusual triggers
	Inconsistent attack duration
	Inconsistent attack frequency
	Onset in adulthood
	Acute-onset/precipitating event
	Static course
	Waxing and waning course
	Dramatic placebo response
	Unresponsiveness to medications

2021; "Nebula Genomics" 2021). WGS is preferred if cost-to-patient is similar.

If a known pathogenic variant is identified, treatment can be tailored for the underlying cause (if such a treatment exists). However, WES/WGS may identify variants of unknown significance. In addition, there are ethical considerations (Di Fonzo, Monfrini, and Erro 2018) involving incidentally found pathogenic variants.

As genetic databases ("MDSGene" 2020) grow, basic scientists, geneticists, and clinicians need to collaborate to verify pathogenicity of newly identified variants. Simultaneously, despite genotype–phenotype variability, careful characterization of clinical features is still important for symptomatic treatment and to define the features of these variants.

Conclusion

Diagnosis of paroxysmal dyskinesia is difficult due to large genotype–phenotype overlap and phenotypic variability. An algorithmic approach with judicious use of WES/WGS is indicated. We view this as an opportunity that will increase understanding of pathophysiology and ultimately improve patient care.

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Declarations

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