TITLE:
PHENOTYPES, GENOTYPES AND MANAGEMENT OF PAROXYSMAL MOVEMENT DISORDERS

RUNNING TITLE:
Paroxysmal Movement Disorders

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ABSTRACT

As a consequence of the genomic revolution, a large number of publications describing paroxysmal movement disorders have been published in the last few years, shedding light on their molecular pathology. Routine gene testing is not necessary to guide treatment for typical forms of paroxysmal kinesigenic dyskinesia (PKD), paroxysmal non-kinesigenic dyskinesia (PNKD), and episodic ataxia type 1 (EA1) or 2 (EA2). It can, however, be helpful in the management of atypical or complex cases, especially for genetic counselling, treatment strategies and the offer of preimplantation genetic diagnosis. Anti-epileptic drugs remain the treatment of choice for PKD and EA1, benzodiazepines are often useful for PNKD, and EA2 benefits from acetazolamide regardless of the genetic etiology.

Keywords: paroxysmal dyskinesia, episodic ataxia, PRRT2, PNKD, SLC2A1

What this paper adds:

- A growing number of genes has been associated with classic and newly described paroxysmal movement disorders including PRRT2, SLC2A1, PNKD, KCNA1, CACNA1A, CACNB4, KCNMA1, SLC1A3, SCN2A, KCNA2, SCN1A, ATP1A2, ATP1A3, ADCY5, GNAO1.
- Paroxysmal movement disorders share common mechanisms and clinical features with other neurologic paroxysmal phenomena including epilepsy and migraine.

MANUSCRIPT

INTRODUCTION

Primary paroxysmal dyskinesias are distinguished from episodic ataxias on clinical grounds as the latter involve episodes of incoordination and imbalance, but not dyskinesias. However, recent genetic findings have led to the two different clinical presentations being considered together. They are characterized by episodic symptoms that usually begin in childhood or adolescence and tend to improve or even resolve later in life.

Most of the identified genetic mutations leading to paroxysmal disorders are related to membrane proteins expressed in neurons and often linked with the regulation of cellular excitability. This review focuses on how new genetic findings have influenced the nosology

Structural damage to the CNS can manifest as paroxysmal movement disorder in an exceedingly small proportion of patients. Nevertheless, because true primary paroxysmal movement disorders are rare, secondary paroxysmal movement disorders, which include demyelination, tumours, stroke and neurodegenerative diseases need to be clearly distinguished as part of the diagnostic process. Functional (psychogenic) paroxysmal movement disorders are not uncommon and should be promptly recognized and appropriately treated. Motor stereotypies, complex motor tics, developmental movement disorders (e.g. gratification phenomenon) and epileptic seizures need to be considered in the differential diagnosis, in particular in younger children.

PHENOTYPES
The clinical phenomenology of the primary paroxysmal dyskinesias was largely delineated and described in the second half of the twentieth century and has subsequently been embellished by advances in genetics particularly in the last decade.

INITIAL DESCRIPTIONS
Although descriptions of attacks of paroxysmal kinesigenic dyskinesia actually date as far back as 1892, it was Mount and Reback who described the first family with paroxysmal attacks of a movement disorder characterized by a combination of dystonia and choreoathetosis, which could be precipitated by alcohol, coffee, tea, fatigue, and smoking. The names “paroxysmal choreoathetosis of Mount and Reback”, “familial paroxysmal choreoathetosis” and others were used until 1967 when Kertesz described very clearly that some patients (but not all) could present with “kinesigenic” triggers: attacks could be caused by sudden movement, like suddenly standing up from a chair, or suddenly starting to run after being still for a while. Various names were used over time to differentiate between the different forms, with a general agreement that “kinesigenic” and “non-kinesigenic” dyskinesias seemed to be different conditions, to which some applied the terms “paroxysmal kinesigenic choreoathetosis (PKC) and paroxysmal dystonic choreoathetosis (PDC), both no longer in use.
CURRENT CLASSIFICATIONS

By 1995 Dermirkiran and Jankovic\textsuperscript{5} published the classification that is mostly used today based on the analysis of 46 patients. In their study, they applied and revised the prevailing criteria previously used for classification: i) type of triggers ii) duration of attacks, iii) existence of a family history iv) presence of previous or ongoing CNS injury. This series reflects usual findings in clinics elsewhere: secondary paroxysmal dyskinesias were more frequent than primary, and the frequency of non-kinesigenic dyskinesia was almost double that of kinesigenic. The authors classified paroxysmal dyskinesias into kinesigenic (paroxysmal kinesigenic dyskinesia, PKD), non-kinesigenic (PNKD), exertion induced (PED, which some call also “exercise-induced”), and hypnogenic (PHD). PHD had been described in 1981 by Lugaresi and Cirignotta\textsuperscript{6} as nocturnal attacks of dystonia during non-REM sleep and without detectable epileptiform activity on concomitant EEG; these were also called “nocturnal hypnogenic paroxysmal dystonia” or “nocturnal paroxysmal dystonia” until in 1990 the same group established the epileptic nature of such episodes in three patients\textsuperscript{7}. Currently, in almost all patients, this condition is no longer considered a dyskinesia but a familial form of frontal lobe epilepsy in which frontal lobe discharges may not be easily detected with conventional EEG, and it has been renamed nocturnal frontal lobe epilepsy (NFLE) which can be caused by mutations in several different genes (NFLE phenotypic series - \url{http://omim.org/phenotypicSeries/PS600513}).

PAROXYSMAL KINESIGENIC DYSKINESIA (PKD)

In 2004 Bruno and colleagues\textsuperscript{8} reviewed clinical details of a multicentre retrospective cohort of 121 affected individuals from 73 kindreds with PKD, and proposed the diagnostic criteria that is still largely used today to diagnose primary PKD: (1) Identified kinesigenic trigger for the attacks; (2) Short duration of attacks (<1 minute); (3) No loss of consciousness or pain during attacks; (4) Exclusion of other organic diseases and normal neurologic examination; (5) Control of attacks with phenytoin or carbamazepine, if tried; (6) Age at onset between 1 and 20 years, if no family history of PKD. These criteria are summarized in Figure 1 (insert A). In their own cohort, 95 patients had what they called “classic PKD” and fulfilled the criteria, while the remaining ones had atypical clinical features including 12 patients with infantile (<1y of age) onset of PKD, and 14 patients in an “outlier group” in which alternative diagnosis were considered including psychogenic movement disorder, non-kinesigenic or
exercise-induced paroxysmal dyskinesia. They also highlighted that linkage analysis had associated a specific region of chromosome 16 with both PKD and infantile convulsion with choreoathetosis (ICCA, OMIM # 602066, "#" indicating a phenotype entry in OMIM), suggesting that PKD, ICCA and infantile convulsions could all be part of the phenotypic spectrum from mutations in the same gene.

**PAROXYSMAL NON-KINESIGENIC DYSKINESIA (PNKD)**

The phenotype of PNKD continues to evolve and presents with greater variability than PKD, and much more often is secondary to neurological conditions. After the discovery of the mutations on a gene causing classic familial PNKD in various families (see below), Bruno and others reviewed 49 patients from eight mutation positive kindreds, and 22 patients from six kindreds who were mutation negative. The criteria they suggested for the diagnosis of classic PNKD were: (1) Hyperkinetic involuntary movement attacks, with dystonia, chorea, or combination of these, typically lasting 10 minutes to 1 hour, but up to 4 hours (2) Normal neurologic examination between attacks, and exclusion of secondary causes (3) Onset of attacks in infancy or early childhood, (4) Precipitation of attacks by caffeine and alcohol consumption, (5) Family history of movement disorder meeting Criteria 1 through 4. These are summarized in Figure 1 (insert B), which highlights that in addition to different triggers, PNKD attacks are longer than PKD attacks, less frequent, and respond to different medications.

**PAROXYSMAL EXERCISE-INDUCED DYSKINESIA (PED)**

Paroxysmal exercise-induced dyskinesia (PED) was first brought to attention in 1977 by Lance who reported a family in which 3 affected members (grandfather, mother and daughter) all suffered from episodes of dystonia with superimposed mild chorea, only after prolonged exercise, but no other triggers such as sudden movement, alcohol or tobacco. He also noted that the duration of the episodes (mostly between 5 and 30 minutes) were longer than PKD, but shorter than PNKD attacks. In one person who had tried medication, neither carbamazepine, phenytoin or clonazepam worked. It took another 7 years until Plant et al. described the second family (mother and daughter) with what they termed “Familial paroxysmal dystonia induced by exercise”, and demonstrated that the dystonic movements could also be precipitated by prolonged sensory stimulation either with passive movement or vibration. Although the episodes were reported in the lower limbs in both
families reported then, Plant could elicit PED in the upper limbs with prolonged exercise or sensory stimulation, and reasoned that the lower limbs predominance could be situational because they are more often under prolonged exercise. There was family history of epilepsy. No formal diagnostic criteria were proposed, instead the clinical features described by Plant" and Lance are still used as guidelines to diagnose this rather rare condition; these are also summarized in Figure 1 (insert C).

GENOTYPES AND EXPANDED PHENOTYPES

The genes underlying the main types of episodic ataxia (EA) were described in the 1990s. EA type 1 (EA1 OMIM # 160120), which causes short episodes of ataxia (seconds to minutes) several times per week and interictal myokymia, is associated with mutations in a gene that codes for one of the potassium channels, KCNA1 (K stands for potassium, CN for channel, and A1 is the type of potassium channel subunit, which can form homomeric or heteromeric channels).

In EA2 (OMIM # 108500) episodes are longer, less frequent, lasting up to hours, and interictal nystagmus (and not myokymia) is often seen. EA2 is associated with mutations in the gene for one of the subunits of the calcium channel, CACNA1A (CA stands for calcium, CN for channel, and A1A is a subunit of the channel, which is a heteromer composed of various different subunits coded by different genes). CACNA1A was also associated with other paroxysmal disorders including hemiplegic migraine (OMIM # 141500), epilepsy (OMIM # 617106 and others), benign paroxysmal torticollis of childhood and paroxysmal tonic upward gaze, reflecting phenotypic pleiotropy: the fact that mutations in one single gene can cause several distinct phenotypes. In addition, a different type of mutation on CACNA1A causing trinucleotide repeat also caused a non-paroxysmal disease: progressive cerebellar atrophy as in spinocerebellar atrophy type 6 (SCA6, OMIM # 183086).

The gene underlying classic cases of PNKD was described in 2004 as MR-1 (myofibrillogenesis regulator 1, OMIM *609023, “*” indicating a gene entry in OMIM) later renamed PNKD, which is the currently accepted name. Other names used for this gene or locus include MR1; MR-1; PDC; DYT8; FPD1; BRP17; PKND1; FKSG19; TAHCP2; KIPP1184. Unlike CACNA1A this gene is not associated with significant phenotypic pleiotropy, and in some cohorts was found to underlie the majority of classical familial cases of PNKD. Later in
2008 various cases of PED were shown to be caused by mutations in the gene GLUT-1 (glucose transporter type 1), now officially called SLC2A1 (OMIM # 138140). SLC stands for solute carrier, and 2A1 for the family number 2, member number 1 in the family. The current nomenclature for genes coding non-active transporters is SLC. SLC2A1 (which many clinicians still continue to call GLUT-1) was described previously in association with infantile epilepsy with low CSF glucose, initially described by De Vivo in 1991. Today it is apparent that although isolated PED caused by SLC2A1 mutations is rare, episodes of PED in sufferers from GLUT-1 deficiency syndrome (GDS) are common, but often go unnoticed in the setting of epilepsy and other more severe findings. Isolated dystonia after exercise (usually affecting only the lower limbs) has also been observed in carriers of mutations causing early onset parkinsonism (such as PARKIN, OMIM # 602544) or dopa-responsive dystonia (such as GCH1, OMIM # 602544), but are rather unusual initial presentations of these conditions.

The gene underlying most cases of PKD was the latest one to be identified and was described at a time when genomic technology had advanced significantly, therefore allowing for a very swift description of a vast array of disparate phenotypes, demonstrating impressive phenotypic pleiotropy. PRRT2 (OMIM # 614386) which stands for Proline-Rich Transmembrane Protein 2 codes for a transmembrane protein whose function is relatively unknown, but seems to be involved in synaptic transmission. Between 2011 and 2013 it was associated not only with PKD, but also shown to be the cause for the majority of cases of benign infantile familial seizures (OMIM # 605751) and infantile convulsions with paroxysmal choreoathetosis (ICCA, OMIM # 602066), and as a frequent cause of hemiplegic migraine, in addition to one sporadic case of benign paroxysmal torticollis of infancy, and a few cases of episodic ataxia (some with homozygous mutation and accompanying features including developmental delay or epilepsy). The odyssey of PRRT2 into one of the most notable examples of phenotypic pleiotropy has been chronicled in various review articles and commentaries. Figure 2 compares the phenotypic pleiotropy seen in PRRT2 with that of CACNA1A, KCNA1 and SLC2A1.

IMPACT ON PATIENT MANAGEMENT

Given the significant phenotypic pleiotropy observed in genetic paroxysmal movement disorders, and the overlap with clinical spectrums associated with other genes, history
taking must encompass not only one type of episode, but also any history of the various possible paroxysmal phenomena in the patient and family members. Paroxysmal phenomena in these overlapping syndromes include: paroxysmal weakness, paroxysmal ataxia, paroxysmal chorea, paroxysmal dystonia, paroxysmal myokymia, paroxysmal eye movement abnormalities, migraine, and epilepsy. Table 1 provides a summary of clinical information that might suggest a particular gene is involved.

The diagnosis of paroxysmal conditions is often hampered by the lack of findings on neurological examination. Therefore, history and when possible video recordings of paroxysmal events are often the most useful tool. It can also be useful to ask the patient to mimic their actual episodes. Videos may be very useful but also have many caveats. Whenever possible they should be obtained with appropriate settings (frame, angle, lighting, duration, screen resolution, etc) and the largest number of episodes possible. This can help differentiate between dyskinesias (dystonia and chorea) and ataxia, although gait ataxia can only be seen if the patient is filmed while walking, and ataxic uncoordinated movements in children can be confused with dyskinesias. Older children will report dizziness and vertigo, but smaller children may not be able to. Both episodic ataxias and paroxysmal dyskinesias tend to start in childhood or teenage years, rendering the initial diagnosis challenging.

Myokymia may be difficult to document and sometimes to interpret, but is a useful finding. It is a hallmark of EA1 caused by KCNA1 mutations, and some family members may present with isolated myokymia. Familial Dyskinesia with Facial Myokymia (OMIM # 606703) which is caused by mutations on the ADCYS gene (OMIM * 600293) and presents with facial movements now believed to represent facial dyskinesia (chorea) or facial myoclonus, and not true myokymia. ADCYS mutations present with a broad phenotypic spectrum and can initially manifest with paroxysmal dyskinesias (often sleep-related), making for an important differential diagnosis.

It is paramount to differentiate between episodes of positive symptoms (like dystonia or chorea) from negative symptoms, in particular paroxysmal hemiplegia which is seen in hemiplegic migraine and also in alternating hemiplegia of childhood (AHC, OMIM # 104290), both conditions which show clinical and genetic overlap with paroxysmal dyskinesia.
Mutations in *PRRT2*, the main known cause of classic PKD can also cause hemiplegic migraine, and this condition may co-exist within families or individuals. Mutations in *ATP1A3* (OMIM * 182350), the causative gene for AHC, are associated with a broad spectrum of phenotypic manifestation including episodes of hemiplegia and hemidystonia (isolated or combined), in addition to other features like developmental delay or loss of milestones. *ATP1A3* mutations also cause rapid onset dystonia parkinsonism (RPD, previously called DYT12, OMIM # 128235), cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS, OMIM # 601338). Although RDP and CAPOS themselves do not manifest with paroxysmal dystonia, there is a growing notion that *ATP1A3* mutations cause various intermediate phenotypes with clinical overlap.

Although genetic testing is advisable, it is not always necessary for the treatment of patients, but can help define the prognosis, and aid in reproductive counselling, which is particularly important for conditions which carry greater disability like *ATP1A3* phenotypes, which can be inherited or are often caused by de-novo mutations, in which case they bear low recurrence risk except when there is underlying germline mosaicism. Figure 3 shows how phenotypic spectrums for various paroxysmal movement disorders overlap with migraine and epilepsy. Because the sequential testing for multiple genes is usually more expensive than a gene panel, most experts these days recommend that either gene panel or exome sequencing might be preferable when there is not a very strong suspicion for a single gene. Gene panels are usually designed by different labs based on a central phenotype (like “dystonia”, “chorea”, “paroxysmal movement disorder”, etc) while exome sequencing will look at sequencing changes in the exons of roughly 20,000 genes. The main advantage of the panels over exome sequencing is that many include coverage for deletions or duplications, which do not alter sequence per se, and are not detected by standard sequencing techniques. Therefore, knowledge of the phenotypes, genotypes, and techniques is necessary before requesting the test, and when necessary the opinion of a specialist in neurogenetics or movement disorders is of great value.

Treatment for paroxysmal movement disorders remains mostly unchanged, and with the exception of a randomized controlled trial for 4-aminopyridine in EA2, all options are based on observational studies, expert consensus or anecdotal evidence, and are mainly directed at the phenotype and not genotype. There is emerging evidence that triheptanoin
might be useful in SLC2A1-related PED$^{24}$. However, because a therapeutic trial with any of the available options (acetazolamide, anti-epileptic drugs, benzodiazepines, levodopa, ketogenic diet, and potentially triheptanoin) is unlikely to support a specific diagnosis in patients with PED, diagnosis usually requires additional testing including CSF glucose and neurotransmitters, erythrocyte glucose uptake, erythrocyte GLUT-1 expression or testing for SLC2A1 mutations$^{25}$. This is likely due to a combination of the rarity of these conditions, and the fact that effective treatments were described before the era of genomics: PKD responds to low dose carbamazepine (or phenytoin), PNKD often responds to benzodiazepines, and PED tends to respond poorly to medication, although benzodiazepines, levodopa, acetazolamide, antiepileptic drugs and even ketogenic diet can be tried depending on severity$^{1}$. A few cases of good response to deep brain stimulation have been reported in refractory severe PNKD$^{26,27}$ and also on life-threatening exacerbations of dyskinesias in patients carrying mutations in GNAO1$^{28}$. GNAO1 mutations have recently been described as a cause of early life movement disorder with or without epileptic encephalopathy, often wrongly labelled as “dyskinetic cerebral palsy” with episodic “dyskinetic storms” with poor response to oral medications. Acetazolamide, an carbonic anhydrase inhibitor which was initially used for epilepsy as an alternative to the ketogenic diet, remains the standard treatment for EA2, in addition to flunarizine or 4-aminopyridine; EA1 responds to carbamazepine, valproic acid and acetazolamide, but the response to acetazolamide in EA1 is not as dramatic as in EA2$^{1,29}$. Therefore, although genetic testing might be useful for various different reasons, it is not necessary to target initially pharmacotherapy in patients with classic phenotypes.

CONCLUSION
Although genetics has so far had relatively little impact on the treatment of primary paroxysmal movement disorders it has played a significant part in changing our understanding of the likely mechanisms involved in their causation. It is to be hoped that as a greater understanding of the chemical processes involved in the mediation of this fascinating group evolves more specific and efficacious therapies can be developed.

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Figure 1 – Classic phenotypes of primary paroxysmal dyskinesia

Legend: this figure summarizes the main clinical criteria used to differentiate between the 3 classic phenotypes of paroxysmal dyskinesia. All criteria require exclusion of secondary causes of paroxysmal dyskinesia such as brain lesions, metabolic derangements, etc. Although the term primary is used, classic paroxysmal dyskinesia is often familial, and mostly cause by known genetic mutations. PED = paroxysmal exercise-induced dyskinesia, PKD = paroxysmal kinesigenic dyskinesia, PNKD = paroxysmal non-kinesigenic dyskinesia, h = hours, min = minutes, y = years.
Legend: this figure summarizes the main phenotypes associated with PRRT2 (upper left figure) and how it compares with that of CACNA1A (lower left) and KCNA1 (upper right), and with the summarized phenotypic spectrum of SLC2A1 (lower right). PRRT2, CACNA1A and KCNA1 have been associated with discrete phenotypes as well with intermediate phenotypes, suggesting there is a large spectrum of clinical manifestations like SLC2A1. Although there is significant overlap, clinical features in history and examination (or video documentation) may be enough to differentiate between the main phenotypes and guide management without need for genetic diagnosis. Age of onset for almost all paroxysmal conditions associated with these genes have onset in infancy (BPT, infantile convulsions, epileptic encephalopathy) or childhood/adolescence (EAs, PKD) but they may occasionally start in adult life (PED, epilepsy, progressive ataxia).
Figure 3 - Phenotypic overlap for genes associated with paroxysmal movement disorders

Legend: this figure summarizes how the genes associated with paroxysmal movement disorders (paroxysmal dyskinesias and episodic ataxias) can also manifest with other paroxysmal episodes including hemiplegic migraine and epilepsy. Only epilepsy genes associated with other paroxysmal events (e.g. migraine, movement disorder) are included in this figure.
# Table 1 – Clinical features of paroxysmal dyskinesia associated with different genes

Legend: this table summarizes the main clinical features in paroxysmal dyskinesia which are suggestive of association with mutations in a particular gene.

<table>
<thead>
<tr>
<th>Genes</th>
<th>Suggestive clinical features in patient or family members</th>
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| **PRRT2** | More common phenotypes: classic paroxysmal kinesigenic dyskinesia (PKD), benign familial infantile seizures, hemiplegic migraine  
PKD with short duration (<1min), high frequency (>daily), often asymmetric or unilateral, but also bilateral; may be chorea/dystonia/mix; may present sensory aura before attack; may present episodes at rest; excellent response to low dose antiepileptic (carbamazepine and phenytoin are the most used, in this order); onset on the 2nd decade of life and improvement or remission on the 4th decade of life. Family history of epilepsy or migraine is common. All phenotypes can be inherited as autosomal dominant traits. |
| **SLC2A1** | More common phenotypes: infantile epilepsy, classic paroxysmal exercise-induced dyskinesia (PED), PED associated with epilepsy.  
PED after exercise, often in lower limbs (probably because they are more often exercised for prolonged periods); dystonia > chorea; low glucose CSF in some but not all patients; usually does not respond well to antiepileptic drugs; age of onset is quite variable from childhood to adulthood. Family history of epilepsy is common. Variable penetrance and variable expressivity. |
| **PNKD** | More common phenotype: paroxysmal non-kinesigenic dyskinesia (PNKD)  
PNKD starting in infancy—childhood; mix of chorea and dystonia; attacks lasting between minutes to 1h, not triggered by sudden movement or exercise, but triggered by caffeine or alcohol intake, as well as emotional stress; response to benzodiazepines; not associated with epilepsy. |
| **PARKIN, GCH1** | More common phenotypes: dopa responsive dystonia, levodopa responsive parkinsonism  
PED with dystonic features is a rare initial presentation, usually in the lower limbs, with excellent response to levodopa; family history for consanguinity for Parkin, GCH1 can have autosomal dominant or rarely a recessive inheritance; Parkin usually starts in young adulthood, GCH1 starts in children. Family history for dystonia or parkinsonism can happen for both genes. Not associated with epilepsy. |
| **ACDY5** | More common phenotypes: familial dyskinesia with facial myokymia  
Paroxysmal dyskinesia brought on by stress may be the initial presentation, but older family members may present with persistent dyskinesias (chorea and dystonia). Abnormal facial movements (myoclonus/dyskinesia, not truly myokymia). Dyskinesias tend to improve with adult life. Patients may present with history of developmental delay or hypotonia. Likely to have phenotypic pleiotropy and reduced penetrance due to mosaicism which are still being described in the literature. |
| **ATP1A3** | More common phenotypes: alternating hemiplegia of childhood (AHC), rapid onset dystonia parkinsonism (RDP), cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS) and intermediate phenotypes  
AHC starts in infancy and presents with episodes of hemiplegia and often hemidystonia. It usually evolves with epilepsy and loss of developmental milestones, and often persistent movement disorder. The RDP phenotype does not usually cause paroxysmal dystonia, but persistent dystonia and/or parkinsonism of subacute onset. Paroxysmal ataxia, later on becoming persistent is also described in ATP1A3 mutations. |