Paroxysmal motor disorders: expanding phenotypes lead to coalescing genotypes

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Abstract
Paroxysmal movement disorders encompass varied motor phenomena. Less recognized features and wide phenotypic and genotypic heterogeneity are impediments to straightforward molecular diagnosis. We describe a family with episodic ataxia type 1, initially mis-characterized as paroxysmal dystonia to illustrate this diagnostic challenge. We summarize clinical features in affected individuals to highlight underappreciated aspects and provide comprehensive phenotypic description of the rare familial KCNA1 mutation. Delayed diagnosis in this family is emblematic of the broader challenge of diagnosing other paroxysmal motor disorders. We summarize genotypic and phenotypic overlap and provide a suggested diagnostic algorithm for approaching patients with these conditions.

Introduction
Episodic, neurologic dysfunction is a feature of common disorders such as migraine and seizure, as well as rare, childhood onset, genetic disorders characterized by intermittent motor perturbation. The term paroxysmal choreoathetosis was first used to describe such episodic nonepileptic movement events by Mount and Reback in 1940 and included bouts of dystonia, chorea, athetosis or a combination of these movements. Classification of the paroxysmal dyskinesias based on phenomenology was subsequently proposed by Lance in 1977 and later replaced by one based upon precipitating factor including kinesigenic, nonkinesigenic, exercise induced, and hypnotogenic. Over time, the term paroxysmal movement disorders has grown to include not only the paroxysmal dyskinesias but episodic ataxias as well. Even more broadly, paroxysmal movement disorders may encompass alternating hemiplegias, benign paroxysmal torticollis of infancy, tics, stereotypies, and shuddering spells among others.

With increasing awareness of genetic etiologies for these conditions it is clear that classification based upon either phenomenology or precipitating factor is insufficient to distinguish between distinct molecular etiologies. Overlapping clinical features may hinder accurate classification. Specific phenotypes may result from mutations in several genes and conversely mutations in a single gene may result in multiple phenotypes of varied severity. Consequently, a patient’s predominant symptoms may not match the clinical features associated with their classically defined paroxysmal movement disorder subtype and/or genetic etiology and may require a more broad molecular approach for accurate diagnosis.

With these issues in mind, we present a family with paroxysmal movement disorder, initially mis-categorized, to exemplify the challenges associated with establishing the correct molecular diagnosis in these conditions. We emphasize and provide images and video to demonstrate key clinical features that may serve as clues to accurate diagnosis. Additionally, based upon evaluation of 17 affected members spanning multiple generations, less well...
recognized aspects of the disorder are highlighted to increase awareness of these features and to establish more comprehensive phenotypic description of the rare variant identified in the family. In reviewing the approach to diagnosis, this report highlights the importance of familiarity with features of distinct paroxysmal movement disorder subtypes while simultaneously drawing attention to the limitations of such classification schema.

Case Report

A mother and daughter (Fig. 1 V:13 and VI:8) presented with paroxysmal muscle cramping. The child was born without complication at term by caesarian-section due to maternal pre-eclampsia. Development was normal. She was noted to toe-walk at 10 months with gait gradually normalizing. Episodic painful cramping manifest as hand fisting and lower extremity posturing with transient toe walking began at 18 months and gradually increased in frequency. During severe episodes the child was unable to grasp objects or walk. Upon presentation at age 6, episodes occurred monthly with duration of hours to days. Initial neurologic examination was normal with the exception of mild bilateral dysdiadochokinesia, a right Babinski sign, steady gait with pes planus with mild bilateral foot eversion and mild difficulty with hopping.

Family history was notable for similar cramping episodes primarily involving the hands in her mother (Fig. 2) and multiple maternal relatives. The mother reported improvement of symptoms with potassium containing foods and also carbamazepine that was initiated after a single postpartum seizure. A nonspecific history of epilepsy was noted on the maternal side. CPK was minimally elevated (187 U/L; nl 29-143). Brain MRI and nerve conduction testing were normal. Initial diagnostic impression was of myotonia. EMG in the mother, however, did not show myotonia but instead revealed myokymia. The significance of this finding was not initially appreciated, the hand posturing observed in the mother was labeled dystonia (Fig. 2), and the mother and daughter were referred for movement disorder specialist evaluation for presumed paroxysmal dystonia.

Though the primary complaint of intermittent hand and leg cramping and posturing was consistent with paroxysmal dystonia, the finding of myokymia and the hand positioning, atypical for dystonia (Fig. 2 and Video S1–S4), suggested instead a diagnosis of episodic ataxia type 1. Therefore, a more focused, detailed history was obtained from mother with that differential in mind. Mother reported normal birth and development with onset of painful leg cramps beginning at 10 years. She reported paroxysmal episodes of painful muscle cramping in hands and legs associated with twitching in her face (Video S3) and occasional tongue involvement with duration of hours up to 1 week. Episodes sometimes were associated with blurred vision, dizziness, imbalance, and vomiting, though these were not prominent symptoms. During episodes, her fingers would assume a fixed flexed posture (Fig. 2) and at times she would have difficulty speaking. Episodes of painful leg stiffening occasionally woke her from sleep. The patient reported a generalized tonic-clonic seizure 1 week postpartum and a second possible seizure a few weeks prior to the birth of her third child. Sleep and wake EEG were normal twice. Carbamazepine initiated after the initial seizure improved paroxysmal episodes, though the patient was nonadherent with this medication. Examination at age 22 was notable only for occasional vocal tics, mild tongue tremor and irregular tremulous movements of her fingers (Video S1). These movements were initially considered to be minmyoclonus or distal chorea but over time it became clear

Figure 1. Family Pedigree. Dark Symbols – Symptomatic; Light Symbols – Asymptomatic; “+” – KCNA1 c.748_750delTTC; “-” – KCNA1 wild type; “*” – Phenotypically positive per report, individuals not examined. A single noncarrier (V9) reported multiple symptoms (Vertigo, Muscle cramp, muscle twitch, weakness, headache, nausea, blurred vision, light sensitivity, dyspnea, hypothermia, altered mental status, chest pain, irregular heartbeat). This individual most likely represents a negative phenocopy but false negative genetic testing cannot be excluded.
these movements resulted from myokymic contraction of the intrinsic hand muscles.

Sequencing of KCNA1 gene revealed an in-frame deletion of phenylalanine 250, a strictly conserved residue (c.748_750delTTC). This change has previously been reported in a single family.9

Family Evaluation

Evaluations of probands and family members were undertaken in accordance with institutional regulations. Standardized history and physical examination was completed on 24 individuals (ages 4–80 years) on a single day during a family educational seminar with findings summarized in Table 1 and Figure 1. All individuals were at baseline at the time of the evaluation. As part of routine clinical care over several years prior to the seminar, Sanger sequencing of the KCNA1 exons and exon/intron boundaries was completed in individuals V:10, V:13, and VI:1 (Fig. 1) before family relationships were known. Subsequent targeted sequencing of exon two of the KCNA1 gene was used to investigate the presence of the variant in 19 additional family members. All testing was conducted in a clinical genetic testing laboratory.

Results and Discussion

Episodic ataxia type 1 (EA1) is an autosomal dominant potassium channelopathy first described by Van Dyke in 1975,10 and characterized by brief episodes of ataxia with persistent myokymia.11–16 Episodic events may typically include dizziness, unsteady, wide-based gait, incoordination, dysarthria, weakness, stiffness, headache, nausea, vomiting, visual disturbance, and/or vertigo.11 Myokymia

Figure 2. Characteristic Hand Posture. Typical hand posture of adducted thumb and extended fifth finger present in mother (D) and daughter (C). These postures are similar to those pictured in the original description of EA1 in Van Dyke et al., 1975 (A, B). (Reprinted with permission).
manifests as fine twitching or intermittent cramps and stiffness. To the examiner, myokymia most commonly appears as subtle peri-ocular or peri-oral rippling/twitching or fine lateral finger movements with hands in prone, relaxed position (Videos S1–S4).17–21 Myokymia at baseline or heightened during an attack, may be misinterpreted as tremor.11,17 Onset of symptoms is typically in childhood and paroxysms may wane in adulthood.10,11,17 Typical attack duration is minutes though events may persist for hours.11,22–24 Episode frequency varies widely from several times per day to infrequent (<1 per month).10,11,17,25 Typical triggers include physical exertion, emotional stress, and environmental temperature extremes. Events may occur without precipitant and numerous other triggers have been reported including fever, caffeine, alcohol, sudden movement, diet, rest after exertion, startle, movement after prolonged rest, pregnancy, menstruation, fatigue, strong smells, or bending over/looking down.11,12

Numerous other paroxysmal symptoms have been reported including dyspnea,9 distal weakness with prolonged attacks lasting days,26 malignant hyperthermia,27 paresthesias, palpitations, hot flashes11 choreoathetosis, dystonia, carpal spasm, clenching of the fists, and isolated neuromyotonia.20,21,28–30 In addition to episodic symptoms, fixed deficits may occur in some. Delayed motor development20 and cognitive dysfunction including mild to moderate learning disabilities and severe expressive and receptive language delays have been reported.31,32 Shortened Achilles tendons that may result in tiptoe walking and generalized increase in muscle tone may manifest as bilateral calf hypertrophy, hypercontracted posture, or isolated contracture of abdominal wall muscles, elbow, hip, and knee joints.20 Skeletal deformities including scoliosis, kyphoscoliosis, high-arched palate, and minor craniofacial dysmorphism have also been described.13,26 Though most individuals with EA1 do not have seizures, abnormal electroencephalograms (EEG) have been reported10,24,31 and various seizure types have been described.11,12,16,31,33 Neuroimaging is typically normal though cerebellar atrophy has been reported32 and persistent and progressive ataxia may rarely occur.11,32 Psychiatric symptoms have also been reported though it is not confirmed that these are related to EA1.11 EA1 results from mutation in the KCNA1 gene, which encodes the Kv1.1 subunit of a potassium channel.18,34 At least 39 pathogenic variants have been identified in this gene15 and significant inter- and intrafamilial phenotypic variability has been reported.20 The pathogenic variant in this family (c.748_750delTTC) was noted only

| Episodic Symptom | # affected | Avg. Age of onset (years) | Frequency | Duration typical (Range) | Most frequent triggers |
|------------------|-----------|--------------------------|-----------|--------------------------|-----------------------|
| Ataxia           | 15        | 8                        | ***       | Minutes (Minutes-Days)   | Fever/Exertion/Illness/Startle |
| Muscle stiffness or cramping | 13 | 10 | ****** | Minutes (Seconds-Days) | Exertion |
| Myokymia         | 11        | 12                       | ****  | Minutes (Minutes-Day)    | Fever Stress |
| Dizziness or vertigo | 10  | 18                       | ***    | Minutes (Minutes-Day)    | Exertion/Fever/Stress/Temperature Extreme/Sudden Movement |
| Dysrhythmia       | 9         | 11                       | *****  | Minutes (Minutes-Hours)  | Illness/Startle |
| Weakness          | 7         | 22                       | *****  | Minutes (Minutes-Weeks)  | Exertion/Stress |
| Headache or migraine | 5       | 23                       | *****  | Minutes (Minutes-Hours)  | Stress/Illness |
| Blurred vision    | 4         | 12                       | **     | Minutes (Seconds-Hours)  | Stress/Fatigue |
| Altered mental status | 4     | 20                       | ***    | Minutes (Minutes)        | Exertion/Stress/Fatigue/Startle |
| Dyspnea           | 4         | 9                        | ***    | Minutes (Minutes-Half Hour) | Stress/Startle |
| Sweating          | 3         | 33                       | *      | Minutes (Minutes)        | Stress/Fatigue/Diet |
| Posturing of limb | 3         | 20                       | *      | Minutes (Minutes)        | N/A |
| Chorea-athetosis  | 2         | 9                        | **     | Minutes (Minutes-Half Hour) | Fatigue |
| Hemiplegia        | 2         | 34                       | *      | Minutes (Varial (Half Hour-Days) | Exertion/Stress/Fatigue/Illness |
| Nausea/or vomiting | 1       | NR                       | *      | Days (Days)               | N/A |
| Palpitations or chest pain | 1  | 10                       | *      | Minutes (Minutes)        | Exercise/Stress/Alcohol/Vestibular Change/Temperature Extreme |

Affected individuals were queried systematically regarding episodic symptoms reported previously in the literature. Symptom character, age of onset, frequency, duration and most common trigger are shown; # – Number of 17 affected reporting the symptom; Frequency: D- daily; W- once to several times per week; M- once to several times per month; Y – several times per year to rare; Number of asterisks represent number of individuals reporting each symptom frequency. *Data were incomplete and thus total number of asterisks does not always equal the number reporting a specific symptom; NR – not reported; N/A numerous triggers reported by a single individual only.
The signs and symptoms identified in our family reinforce previous descriptions of EA1 families and highlight less commonly appreciated aspects. Among mutation carriers, ataxia (15/17), painful muscle stiffness/cramping (13/17), myokymia (reported as tremor or trembling) (11/17), and dizziness/vertigo (10/17) were the most prominent symptoms (Table 1). Paroxysmal dyspnea has been noted to be characteristic of the KCNA1c.748_750-delTTC variant, occurring in 6/7 cases previously described.9 In our family only 4/17 of the mutation carriers identified this symptom. Nonspecific headache and migraine were reported in 5/17 variant carriers, but were also reported by all five non-carriers and thus the association of this symptom with EA1 is unclear. Seizures were reported in 2/17 carriers. However, due to potential misdiagnosis of “spells” as seizures, the number of individuals with true epileptic events is unknown.

Interestingly, orthopedic issues that have not previously been highlighted were problematic for numerous members of our family. Six of the seventeen carriers (and none of the five wild-type individuals) reported a history of toe walking, tight heel cords, heel cord lengthening or other lower extremity orthopedic surgery and/or wore braces to correct abnormal foot postures. An additional six carriers (and no wild type individuals) were noted to have mild to moderate Achilles tendon shortening on examination. Several members reported chronic and disabling progressive gait abnormalities in later adulthood. We are unable to definitively conclude that these features are related to KCNA1 variant as some also had obesity and/or diabetic neuropathy that may confound the gait abnormality. Myopathy, previously reported,10,13 is another potential cause of gait abnormality. No individuals had muscle biopsy so we are unable to evaluate this possibility. Learning disabilities and/or delayed motor and/or language development were noted in 7/17 carriers but none of the noncarriers. These symptoms have been reported in individuals with EA120 but have not been previously associated with this variant.9,11 In keeping with prior reports,11 interictal abnormalities suggestive of underlying mild cerebellar dysfunction were noted in some individuals with SARA scores in carriers of 0–3.5,36,37 As noted above, orthopedic issues and diabetic neuropathy may confound this measurement.

The most common precipitators for spells noted in this family are similar to those previously described9,11 and include fever, stress, exertion, illness, and fatigue. There were no factors that consistently resolved spells though all affected members indicated relaxation would lessen or abort episodes. Interestingly, two individuals reported that foods high in potassium and/or potassium supplementation would shorten or decrease severity of attacks. This has not been previously reported but bears further study. Potassium levels evaluated during spells have been normal in the mother of the proband but have not been systematically studied in other members.

Age of affected family members ranged from 4 to 80 years. Symptom onset was at 2.5 to 18 years. In keeping with previous reports, many patients reported shortened duration, frequency, and even complete cessation of spells in later adulthood,38 with all individuals over age 40 reporting decreasing frequency or resolution of symptoms and most under 30 years reporting increasing frequency of symptoms. A single patient age 31 reported stable symptom frequency. Only a subset of affected individuals were aware of the etiology of their symptoms prior to the family educational seminar.

The delay to diagnosis in this family is notable though is not uncommon for EA1.25 For multiple family members, symptoms were ascribed to alternative diagnoses including epilepsy, anxiety and/or hyperventilation. Though signs and symptoms in this family were consistent with those previously described for EA1, it is remarkable that, despite numerous prior neurologic evaluations in multiple individuals by numerous clinicians, this diagnosis was not considered due to absence and/or failure to recognize the hallmark features of EA1. In the mother, symptoms of ataxia including gait instability and/or incoordination were elicited only after detailed and probing questioning in retrospect once the diagnosis was suspected, and even then were identified as only minor features. Similarly, the daughter denied gait imbalance or episodes of unsteadiness or dizziness (Video S5).

Another hallmark feature of EA1, myokymia, was observed and recorded in the medical record as “twitching” but was not recognized as a clue to the correct diagnosis. Myokymia, which has been previously described as constant piano-playing movements, was either absent on examination or when present was mis-characterized by clinicians as tremor, mini-myoclonus or distal chorea, as has been reported previously in EA1.10 Peri-ocular, peri-
oral, and hand myokymia on examination were correctly identified only after detection by EMG. Of note, none of the four children under age 10 years or the two eldest individuals, aged 79 and 80, displayed myokymia. Myokymia was present in 8/11 individuals between ages 12 and 56 interictally during examination. Similarly, despite awareness of the diagnosis, numerous examinations (1F) of multiple family members over 7 years after establishing the EA1 diagnosis, the presence and severity of myokymia was quite variable and mostly absent in the children. As in our experience, there have been other reports in the literature of episodic ataxia without myokymia or ataxia, the two “hallmark” features of the disorder.12,13,24

The primary complaints in the proband and her mother were painful muscle cramping, stiffness and posturing suggesting initially myotonia and subsequently a diagnosis of paroxysmal dystonia (Video S5). Paroxysmal dystonia has been previously reported in EA1 patients.11 Postures described in the child proband’s record include hand clenching, leg extension and walking on the balls of the feet. Though it is unclear if the postures noted historically were characteristic of dystonia, hand postures documented in mother and daughter and multiple other family members after the diagnosis was suspected are consistent with carpal spasms described by Van Dyke in his original report (Fig. 2) and may best be considered neuromyotonia. Neuromyotonia may mimic dystonia though the latter is rarely painful.39 In the literature, there is inconsistent application and understanding of this term calling into question whether our patients and even others described historically displayed neuromyotonia, dystonia or combination of both.

It is important to emphasize that stiffness, cramping and posturing, as for our family, may be the primary symptoms leading EA1 patients to seek medical evaluation, rather than the namesake ataxia. Van Dyke, in his original report documented cramping, posturing and jerking limb movements in his patients.10 The term ataxia, however, has come to overshadow the other features he described. In fact, though the term ataxia was used initially by Van Dyke and continues to be applied throughout the literature, it is unclear if gait imbalance and incoordination reflect cerebellar and/or vestibular dysfunction or alternatively are due to muscle stiffness, posturing and jerking, weakness or some combination of the multiple motor abnormalities that have also been described. Lack of familiarity with these additional characteristics and over-reliance for classification on the name of the condition – that is ataxia, may lead to mis-categorization and delay to diagnosis. Characteristic but less well recognized signs of myokymia and neuromyotonia may not be correctly identified and are highlighted in Figure 2 and Videos S1–S5 to enhance familiarity with these aspects.

These diagnostic challenges are not unique to EA1 but are emblematic of the complexity of accurately diagnosing a broad range of paroxysmal movement/motor disorders. Like KCNA1, other genes may be associated with varied and ever expanding phenotypes or presentation may lack the namesake feature and may overlap multiple other genetically defined paroxysmal movement disorders. For example mutation in PRRT2, classically associated with paroxysmal kinesigenic dyskinesia (PKD) may also present as nonkinesigenic dyskinesia, exercise-induced dyskinesia, nocturnal dyskinesia, seizure or with hemiplegic spells.42–47 Conversely, across the broad category of paroxysmal movement disorders multiple genes may converge on similar phenotypes. For example, though PKD is typically associated with PRRT2 gene mutation, kinesigenic spells have also been described with mutation in SLC16A2, KCNA1, ADCY5, SLC2A1, SCN8A, SLC20A2, and CLNCl.28,48–54 Similarly, other clinical features have been associated with mutations in numerous genes. This may occur because these symptoms result from multiple genetic causes. For example though plegic episodes are classically associated with mutation in ATP1A3, or CACNA1A, such episodes have also been described in individuals with mutation in ATP1A2, PRRT2, SLC2A1, SLC1A3, MRI and SCNIA.46,47,55–61 Similarly, nocturnal spells, though most suggestive of mutation in ADCY5, have also been described in patients with PRRT2 and SLC16A2 mutations. Though not previously associated with KCNA1, nocturnal spells present in our family broaden the range of conditions to be considered when night-time symptoms are present.

The pathophysiologic mechanism underlying overlapping phenotypes is unknown. In a recent report, Yin and colleagues hypothesize that the influence of basal ganglia and cerebellum may converge on cortical excitability as a common final pathway for paroxysmal dystonic movements to account for presence of both cerebellar features (ataxia) and extrapyramidal features (dystonia, dyskinesia) in KCNA1 gene mutation carriers. In other instances, apparently overlapping phenotypes may simply result from mischaracterization of certain difficult to classify signs that are phenomenologically similar. As we have demonstrated, neuromyotonia may be mistaken for dystonia. Similarly dyskinetic spells may cause imbalance and dyscoordination that, especially if not directly observed, may be difficult to distinguish from or labeled as ataxia.29 Epileptic and nonepileptic events may co-exist and may be clinically indistinguishable. This poses challenges not only to accurate diagnosis but also for the selection of appropriate therapy. Full review of paroxysmal movement disorders is beyond the scope of this report though can
be found in part in Méneret, and Roze, 2016, and Erro et al., 2017,5,62 the latter providing a useful pathophysiological framework from which to conceptualize the phenotypic overlap among these conditions. To further aid in diagnosis and concisely illustrate the phenotypic expansion and genotypic heterogeneity, we have summarized features across a wide array of paroxysmal motor disorders (Table 2).

Genotypic and phenotypic overlap may be a discouraging impediment to the clinician tasked with diagnosing a patient with a paroxysmal movement disorder. Méneret and Roze5 outline a traditional diagnostic algorithm for a subset of paroxysmal movement disorders based on phenomenology. This approach is most useful when symptoms are classic and result from mutation in the most commonly associated gene in each category. In other situations, classification may be difficult and even if categorization is correct, there may be simply too many genetic etiologies to practically screen for each systematically as suggested in diagnostic algorithms previously proposed.5,63 Difficulties with traditional paroxysmal movement disorder classification approaches due to phenotypic overlap have been raised previously17,62–66 and are becoming increasingly problematic with expanding genotypic and phenotypic heterogeneity.

We suggest the traditional approach reliant on clinical acumen and historical classification remains useful as an initial step as some cases may be diagnosed with screening of a single gene. This step should be supplemented with broader hypothesis free genetic testing in cases that remain undiagnosed after initial screening as the number of potential genetic etiologies is too large to practically target one by one. Our suggested approach is outlined in Figure 3. We have chosen the term paroxysmal “motor” rather than “movement” disorder to acknowledge the wide range of conditions that may share genetic etiology but may present either with positive movements such as dyskinesia and/or with absence of motor movement such as hemiplegia. To enhance initial success, collecting a broad history with attention to a wide array of potential associated symptoms in patient and family members as well as careful examination for less obvious signs may be helpful in categorization. In particular diagnostic clues such as myokymia, nystagmus, and/or neuromyotonia may be quite characteristic of episodic ataxias. Similarly, classic presentations such as brief duration dyskinetic attacks brought on by movement in a developmentally normal teenager are quite characteristic of mutation in PRR2. Developmental delay may lead toward or away from certain diagnoses. If the clinician is confident in categorization then targeted screening for the most commonly associated gene associated with that category may be performed. If initial attempts at categorizing and/or targeted screening are not successful, we suggest a more broad approach to screen simultaneously for numerous potential etiologies. This testing should include not only known genes that have previously been associated with the patient’s phenotype, but also, recognizing that there will likely be continued phenotypic expansion, should include genes that may not yet have been defined as etiologic in association with the patient’s presenting symptoms. Care should be taken in particular to exclude treatable disorders with specific metabolic therapy such as GLUT1 deficiency among others (Table 3, Table S1).

Next Generation Sequencing (NGS) tools are likely most useful in this regard. These include sequencing of phenotype-driven panels, or sequencing of the whole exome (WES) or the whole genome (WGS). Here we offer a few caveats: 1. NGS tools may fail to identify copy number variation (CNV), chromosomal rearrangement and trinucleotide expansion, and the ability to detect such variants varies by laboratory and technique employed. In particular CNV’s may be difficult to detect with WES and may be more easily identifiable utilizing panels with high depth of coverage or WGS; 2. NGS tools may inadequately cover all regions, particularly high GC rich regions, and these gaps may not be apparent to the ordering clinician unless specifically queried. For some panels, NGS techniques are supplemented with other strategies such as Sanger Sequencing to optimize poorly covered regions or alternative techniques to detect copy number variation such as Multiplex Ligation-dependent Probe Amplification (MLPA). However, the use of supplemental techniques varies widely by laboratory and specific panel and is not typically evident to the ordering clinician; 3. Mosaicism has been described for ATP1A3, ADCY5, SLC2A1, PHDAI, SCN1A and SCN2A67–72 gene mutations and is likely to be associated with other conditions in the future. Low-level mosaicism may not be identified by Sanger and though mosaicism may be detected by WES or WGS, low-level mosaicism may be excluded by filtering protocols. For these reasons, it is critical that the ordering clinician be familiar with the limitations of testing. Additionally, familiarity with historically defined PD subtypes and associated genotypes will enable clinicians to suspect specific gene mutations, which, if not identified by NGS, may be pursued with alternative more targeted techniques. This is especially important with regard to genes associated with a specific metabolic therapy for which mutation should be thoroughly ruled out (Table 3, Table S1); 4. Hypothesis free screening techniques such as NGS may lead to variants of unknown significance in genes related to phenotype. Though it is tempting to ascribe pathogenicity when variants occur in plausible genes, it is important to exercise caution unless the genetic data is supplemented with functional studies or
Table 2. Phenotypic and genotypic heterogeneity in paroxysmal motor disorders.

| Phenotype                          | Spell trigger | Spell character | Other reported features |
|------------------------------------|---------------|-----------------|-------------------------|
|                                    | Kinesigenic   | Exercise-Induced| Non-Kinesigenic         |
| Paroxysmal                         |               |                 |                         |
| Motor                              | Sleep         | Ataxic          | Plegic                  |
| Phenotype                          | Headache/Vomiting | Seizure         | Cerebellar Features 1  |
|                                    |               |                 | Dystonia                |
|                                    |               |                 | Dykenosis 2            |
|                                    |               |                 | Myasthenia              |
|                                    |               |                 | Myoclonus               |
|                                    |               |                 | Tremor                  |
|                                    |               |                 | Muscle Cramps           |
|                                    |               |                 | Learning Disability 3   |
|                                    |               |                 | Motor Delay             |
|                                    |               |                 | Dysarthria              |
|                                    |               |                 | Visual Disturbance       |
|                                    |               |                 | Weakness                |
|                                    |               |                 | Nausea/Vomiting         |
|                                    |               |                 | Hypotonia               |
|                                    |               |                 | Parkinsonism            |
|                                    |               |                 | Pyramidal Signs 4       |
|                                    |               |                 | Encephalopathy          |
|                                    |               |                 | Microcephaly            |
|                                    |               |                 | Regressive Course       |
| Paroxysmal Kinesigenic Dyskinesia  |               |                 |                         |
| PRRT2; PMD-PRRT2                   | SLC16A2; HSP-SLC16A2; MCT8 |
| SCN8A                              |                |                 |
| SLC20A2                            |                |                 |
| CLNC1                              |                |                 |
| Paroxysmal Exercise Induced Dyskinesia | SLC2A1; PMD-SLC2A1 |
| GCH1; DYT1/PARK-GCH1; DYT5          | PDHA1; PMD-PDHA1 |
| PDHX                               | DLAT           |
| ECHS1                              | PRKN, PARK2, PARKIN |
| ALDHS1                             |                |
| Paroxysmal Non-Kinesigenic Dyskinesia | PNKD2; MR1     |
| KCNMA1; SLC1; SLC8                 | BCKD Complex   |
| PDGFB                              |                |
| Episodic Ataxia                    |                |                 |
| EA1; KCN1; PMD-KCN1                |                |                 |
| EA2; CACNA1; PMD-CACNA1            |                |                 |
| EA5; CACNB4                        |                |                 |
| EA6; SLC1A3; PMD-SLC1A3; EAAT1; GLAST |
| EA8; UBR4                          |                |                 |
| Other                              |                |                 |
| KCNA2                              |                |                 |
| SCN2A                              |                |                 |
| NALCN                              |                |                 |
| DAR52                              |                |                 |

(Continued)
Systematic literature review was performed for genes associated with paroxysmal motor disorders. Presence, absence and frequency of paroxysmal and nonparoxysmal symptoms were identified. Other reported features may occur between or during discrete spells. Typical features are shaded black. Features reported at least once but not commonly are shaded gray.

Paroxysmal motor categories and associated genes are listed on the left. Spell trigger and character are specified.

Table 2. Continued.

| Spell trigger | Spell character | Other reported features |
|---------------|-----------------|------------------------|
| Regressive course | Micropsy | Genetic diagnosis |
| | Dyskinesia | |
| | Cerebellar ataxia | |
| | Nystagmus | |
| | Myoclonus | |
| | Myotonia | |
| | Headache | |
| | Epilepsy | |
| | Atonic | |
| | Pyramidal, dystonic | |
| | Sleep | |
| | Enuresis, incontinence | |
| | Craniosynostosis | |

| | | Alternative Genotype |
| | | ATP1A2, DVD, RARK1, ATRAP1A3 |
| ADCA5 | GLDC | SCWA |
| SCMA | GM1101 | FGF14 |

Cerebellar features include ataxia, nystagmus, not definitely associated with spells. Learning disability also includes intellectual disability and language delay. Pyramidal signs include spasticity and spastic paraparesis.

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Figure 3. Paroxysmal motor disorder diagnostic algorithm. I. Seizures should be considered in any patient with a paroxysmal motor disorder; II. Age of onset, family history, examination and imaging findings may guide diagnosis. Abnormal neurologic examination or imaging findings may occur with secondary and metabolic etiologies. Care should be taken to exclude treatable metabolic causes (Table 3). Developmental delay, if present should be evaluated independent of the movement disorder. Benign paroxysmal motor disorders may be considered if phenotype is consistent. Evolution of motor findings over time may provide clues to diagnoses that are not immediately apparent; III. Identifying the predominant character of the spells is the first step in categorization; IV. Distinguishing features including triggers or other characteristic aspects may enable accurate phenotypic classification; V. Phenotypic characterization limits the genes to consider. Most commonly associated genes in bold with less commonly associated genes in plain type. Where phenotype is classic, targeted gene testing or small gene panel may be considered first. If phenotype is not well defined or varies then multi-gene panel or exome is a preferred initial step; Paroxysmal epileptic events may result from mutations in PRRT2, SCN1A, KCNA1, ATP1A3, CACNA1A, KCNMA1, etc.; Only genes with seizure as a typical feature are listed. See Table 2 for other genes associated with epileptic events; Secondary causes may include trauma, stroke, demyelinating event, electrolyte disturbance, etc.; See Table 3; Paroxysmal Benign/Developmental Disorders most commonly include tic disorders but may also include stereotypes, shuddering spells, benign myoclonus of early infancy, benign neonatal sleep myoclonus and infantile griffation. Paroxysmal torticollis during infancy is also typically considered benign as symptoms typically resolve over months to years. However, patients should be monitored as there may be later development of various migrainous symptoms including paroxysmal vertigo and hemiplegic migraine and there may be associated developmental issues. Mutations in CACNA1A and PRRT2 may be found; Consider classification as “ataxia” if patient complains of vertigo, dysarthria, headache, nausea, or visual disturbances without specific complaint or examination finding of ataxia; Nonkinesigenic triggers include alcohol, fatigue, caffeine, stress, menses, and excitement; BCKDc = BCKD complex; Other genes associated with dyskinesia and nonkinesigenic trigger include: SLC16A2, SCN8A, PDHA1, PDHX, DLAT, ECHS1, SCN1A, and ALDH5A1; Also consider genes associated with EA1, EA2, EA6, EA6, and EA8; FHx, family history; PND, paroxysmal nocturnal dyskinesia; AHC, alternating hemiplegia of childhood; FHM, familial hemiplegic migraine; PKD, paroxysmal nocturnal dyskinesia; AHC, alternating hemiplegia of childhood; FHM, familial hemiplegic migraine; PKD, paroxysmal nocturnal dyskinesia; AHC, alternating hemiplegia of childhood; FHM, familial hemiplegic migraine; PKD, paroxysmal nocturnal dyskinesia; AHC, alternating hemiplegia of childhood; FHM, familial hemiplegic migraine; 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### Table 3. Metabolic disorders that may present as paroxysmal motor disorders.

| Paroxysmal movement phenomenology | Metabolic disorder group | Disease name | Gene | Treatment |
|----------------------------------|--------------------------|--------------|------|-----------|
| PED                              | Glucose transport defects | GLUT1 deficiency | SLC2A1 | KD, alpha-lipoic acid, L-carnitine, triheptanoin |
| Mitochondrial Disorders          | Pyruvate dehydrogenase deficiency | PDHA1 | KD, thiamine, carnitine, lipoic acid, dichloroacetate |
|                                  | Pyruvate dehydrogenase deficiency | PDHX | KD, thiamine |
|                                  | Pyruvate dehydrogenase deficiency | DLAT | KD, thiamine |
|                                  | Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency | ECHS1 | Low valine diet, cysteamine, N acetylcysteine, thiamine, riboflavin, carnitine, CoQ10, pyridoxine, vitamin C |
| Biogenic Amines Disorders        | GTP cyclohydrolase 1 deficiency | GCH1 | L-DOPA/carbidopa |
| Organic acidurias                | Succinic semialdehyde dehydrogenase deficiency | ALDH5A1 | |
| PKD                              | Glucose transport defects | GLUT1 deficiency | SLC2A1, ATP7B | see above |
| Copper metabolism                | Wilson disease | ATP7B | D-penicillamine, trientine, zinc |
| PNKD                             | Glucose transport defects | GLUT1 deficiency | SLC2A1, BCKDHA, BCKDHB, DBT | see above |
| Aminoacidopathies                | Maple Syrup Urine disease<sup>3</sup> | GLDC | BCAA-free formulas |
|                                  | Nonketotic hyperglycinemia | GLDC | sodium benzoate, dextromethorphan, KD |
| PAROXYSMAL DYSTONIA              | Mitochondrial Disorders | Pyruvate dehydrogenase deficiency | DLAT | See above |
|                                  | 3-hydroxyisobutyryl-CoA hydrolase deficiency | HIBCH | Low valine diet, cysteamine, N acetylcysteine |
|                                  | Thiamine Transporter 2 deficiency | SLC19A2 | Thiamine, biotin, riboflavin, CoQ10 |
|                                  | Aminoacidopathies | Hartnup disease<sup>3</sup> | SLC6A19, GLDC, SUOX | Niacin, L-tryptophan |
|                                  | Nonketotic hyperglycinemia | GLDC | see above |
| Biogenic amines disorders        | Isolated Sulfite Oxidase deficiency | SUOX | Hydratation, potassium citrate, D-penicillamine, tiopronin |
|                                  | Cystinuria<sup>3</sup> | SLC3A1, SLC7A9 | L-DOPA/carbidopa, 5 HTP, selegiline |
|                                  | Sepiapterin reductase deficiency | SR | |
| PAROXYSMAL CHOREA                | Aminoacidopathies | Isolated Sulfite Oxidase deficiency | SUOX | |
|                                   | Glucose transport defects | GLUT1 deficiency | SLC2A1, PDHA1 | see above |
|                                   | Mitochondrial disorders | Pyruvate dehydrogenase deficiency | PDHA1 | see above |
|                                   | Pyruvate carboxylase deficiency | PC | biotin, triheptanoin, thiamine, lipoic acid, citrate, aspartic acid |
|                                   | Mitochondrial complex V deficiency | MT-ATP6 | |
|                                   | Urea cycle defects | Ornithine transcarbamylase deficiency | OTC | Protein restriction, sodium benzoate, sodium PBA, L-arginine, L-citrulline |
|                                   | CPS1 deficiency | CPS1 | see OTC |

(Continued)
supported by segregation in multiple family members or replication in independent families. Sharing of data is crucial with regard to advancing knowledge of such variants. Various outlets are available in which to deposit genotypic and phenotypic information in attempt to more systematically catalogue and characterize variants including ClinVar, MatchmakerExchange, and MDSGene among others. Participation in such efforts is critical to avoid siloed information and to more precisely establish genotype phenotype correlations so that more patients may benefit from knowledge gained.

Lastly, we acknowledge that advanced molecular techniques are not available in all regions and thus this approach may not be universally applicable. In such circumstances, clinicians may rely upon traditional classification schemas guided by Figure 3 and Table 2. In these settings, even without identification of the precise molecular etiology, approximation of diagnosis may enable appropriate empiric therapy and most importantly, avoidance of missing metabolic conditions for which a specific recommended treatment exists (Table 3, Table S1).

In conclusion, though expanding phenotypes and coalescing genotypes may increase the challenge of diagnosing patients with paroxysmal motor disorders, accurate diagnosis is possible by employing historical strategies of careful phenotypic categorization paired with current and future tools to refine the diagnosis when phenotype defies expected genotype. The knowledge gained from understanding the genetic etiology of distinct and overlapping paroxysmal motor conditions will lead to better understanding of pathophysiologic mechanisms. Better understanding of how diverse genetic etiologies result in overlapping phenotypes will lead to improved understanding of underlying disease process and ultimately to development of better therapies for individuals with paroxysmal motor disorders.

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### Author Contributions

Conception and Design of Study: JF, LZ, SC, GR; Acquisition and Analysis of Data: JF, LZ, SC, GR, DC, MS, RH, KH, SG; Drafting of Significant Portion of Manuscript: JF, LZ.
Conflicts of Interest

KH is employed by and has a financial interest in Medical Neurogenetics Laboratories, a company that provides sequencing of the KCN1A gene on a clinical basis. Other authors have no conflicts of interest.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Metabolic disorders that may present as paroxysmal motor disorders.

Video S1. Patient V:13; Myokymia manifesting as small semirhythmical finger movements in the prone and supine position associated with neuromyotonia, appearing as thumb adduction and slight extension of the fifth finger.

Video S2. Patient VI:8; Myokymia manifesting as fine semirhythmical finger movements in the hand in prone and supine positions.

Video S3. Patient V:13; Myokymia manifesting as bilateral infraocular twitching movements with exacerbation in superior gaze position.

Video S4. Patient VI:8; Myokymia is visible both as movement of the foot across the ankle joint and also as undulating movements under the skin on the bottom of the foot.

Video S5. Patient VI:8; The child proband describes the major symptoms of her condition.