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ADCY5 Mutation Carriers Display Pleiotropic Paroxysmal Day and Nighttime Dyskinesias

Jennifer R Friedman, MD[1,*,○], **Aurélie Méneret, MD**[2,3,○], **Dong-Hui Chen, MD, PhD**[4], **Oriane Trouillard**, **Marie Vidailhet, MD**[2,3], **Wendy H. Raskind, MD, PhD**[5,6], and **Emmanuel Roze, MD, PhD**[2,3]

[1]Department of Neurosciences and Pediatrics, University of California San Diego and Rady Children's Hospital, San Diego, CA

[2]Inserm U 1127, CNRS UMR 7225, *Sorbonne Universités*, UPMC *Univ* Paris 06 UMR S 1127, Institut du Cerveau et de la *Moelle épinière*, F-75013, Paris, France

[3]AP-HP, Département de Neurologie, Hôpital Pitié-Salpêtrière, Paris, France

[4]Department of Neurology, University of Washington, Seattle

[5]Department of Psychiatry and Behavioral Sciences and Department of Medicine (Medical Genetics), University of Washington, Seattle

[6]Mental Illness, Research, Education, and Clinical Center, Department of Veteran Affairs, Seattle Washington

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Paroxysmal dyskinesias are characterized by delineated episodes of dystonia and/or chorea resulting from genetic and non-genetic etiologies.[1] Paroxysmal dyskinesias are classified by precipitating factor as kinesigenic, non-kinesigenic, exercise-induced or hypnogenic.[1–3] *ADCY5* mutations have recently been added to the growing list of genetic paroxysmal dyskinesias.[4]

ADCY5-mutation carriers display mixed hyperkinetic movements including dystonia, chorea, myoclonus and tremor.[4] In addition to baseline abnormal movements often associated with axial hypotonia, many exhibit paroxysmal exacerbations.[4] Paroxysmal

[*]Correspondence to Jennifer Friedman, Rady Children's Hospital, San Diego, 8010 Frost St, Suite 400, San Diego, CA 92123, jrfriedman@rchsd.org, Phone:858-966-5819; Fax: 858-966-4930.
[○]equal contribution

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None.

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1) Research project: A. Conception, B. Organization, C. Execution; 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3) Manuscript: A. Writing of the first draft, B. Review and Critique.
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episodes may last minutes with discrete on- and off-set. In addition, motor dysfunction and the presence of paroxysmal episodes may wax and wane over weeks to months.[4] We present case videos to illustrate the baseline motor manifestations and pleiotropic paroxysmal dyskinesias encountered in this disorder (video1a;video1b;video2;video3;video4 and table).

An expanding list of genes have been associated with paroxysmal dyskinesia including mutations in *PRRT2* (mono- and bi-allelic), *PNKD(MR-1), SLC2A1, ATP1A3, GCH1, KCNMA1, SLC16A2(MCT8), PDHA1, PDHX* and *DLAT*.[1, 5] Hypnogenic paroxysmal dyskinesia usually is an epileptic condition and may be associated with other gene mutations.[2] Recent reports indicate overlap between paroxysmal dyskinesia semiology among the genetic disorders.[6] Paroxysmal exacerbations in *ADCY5* mutation carriers similarly do not fit clearly within previously identified clinical paroxysmal dyskinesia categories and instead may manifest, even within the same patient, as multiple different paroxysmal dyskinesia sub-types. Uniquely, ADCY5-related paroxysmal dyskinesia patients may have non-epileptic nocturnal paroxysmal dyskinesia, without ictal EEG abnormalities. When present, the combination of various forms of paroxysmal dyskinesia and/or nocturnal paroxysmal dyskinesia is a striking clue to diagnosis of *ADCY5* mutation.

ADCY5 patients typically have early-onset protean paroxysmal dyskinesia superimposed upon baseline movement disorder in contrast to patients with mutations in *PRRT2* or *PNKD*, whose interictal examination is usually normal. Additional diagnostic clues to ADCY5-dyskinesia are the presence of axial hypotonia, orofacial jerks, and marked fluctuations, typically without ataxia, marked intellectual disability or seizures. In this setting, the main differential diagnoses include mutations in *SLC2A1, ATP1A3, GCH1* and biallelic mutations in *PRRT2*. In contrast to ADCY5-dyskinesia patients, GCH1 patients have pure dystonia or dystonia-parkinsonism, and rarely dyskinesia, rather than a mixed hyperkinetic disorder with axial hypotonia. Instead of nocturnal paroxysmal dyskinesia as in ADCY5-dyskinesia patients, ATP1A3 patients may experience relief of paroxysms with sleep, often have paroxysmal plegia in addition to paroxysmal dyskinesia and often have intellectual disability. Recessive PRRT2-related paroxysmal dyskinesia differs from ADCY5-related paroxysmal dyskinesia by the frequent occurrence of seizures and episodic ataxia.[7] There may be overlap between patients with severe ADCY5-related paroxysmal dyskinesia and patients with *SLC2A1, PDHA1, PDHX* or *DLAT* mutations. The latter, are more likely to have mental retardation, seizures, ataxia and attacks triggered by fasting or prolonged exercise.

Classification based upon precipitant factors may guide initial genetic investigations. Elucidation of the molecular underpinnings of paroxysmal dyskinesia sub-types and recent evidence of partial clinical overlap between the different genetic disorders highlight the limitations of such classification. A new classification scheme for paroxysmal dyskinesia based on both clinical characteristics and genetics has been proposed.[6] This classification may eventually be highly relevant for targeted therapeutics when pathophysiology is better understood. Our report further supports this classification and suggests that it can be updated by including ADCY5-related paroxysmal dyskinesia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table

Characteristics of the patients

CASE ID	AGE (years)	MOTOR DELAY	LANGUAGE DELAY	MOVEMENT ONSET (months)	DEVELOPMENTAL REGRESION	CONTINUOUS MOVEMENTS	PNKD	PKD	PED	PND	INTERICTAL EEG	ICTAL EEG	AXIAL HYPOTONIA	LIMB HYPERTONIA	PYRAMIDAL SIGNS[1]	DYSTONIA	MYOCLONUS	CHOREA	TREMOR	PAIN WITH DYSKINESIA	MUTATION
1	8	Y	Y	15	Y	Y	Y	Y	Y	Y	ab[2]	nl	Y	Y	Y	Y	Y	Y	N	Y	p.R418W (c.1252C>T)
2	22	Y	N	14	N	Y	Y	N	N	N	nl	nd	Y	N	N	N	Y	Y	N	N	p.R418Q (c.1253G>A)
3	37	N	N	12	N	Y	N	N	N	Y	nl	nd	Y	N	N	Y	Y	Y	N	N	p.R418W (c.1252C>T)
4	34	N	N	24	N	Y	Y	N	Y	N	nd	nd	Y	N	N	Y	N	N	Y	N	p.R438P (c.1313G>C)

PNKD – Paroxysmal Nonkinesigenic Dyskinesia; PKD – Paroxysmal Kinesigenic Dyskinesia; PED – Paroxysmal Exercise Induced Dyskinesia; PND – Paroxysmal Nighttime Dyskinesia; N – not present; Y – present; nd – not done; ab – abnormal; nl - normal.

[1]Pyramidal Signs = hyperreflexia and or extensor plantar reflex.

[2]Routine EEG was normal during sleep and waking. Video EEG at 3 years 9 months showed no epileptiform discharges associated with multiple paroxysmal choreiform/myoclonic spells during waking. During early drowsiness there were two brief bursts of hypnagogic irregular atypical spike wave discharges without associated movement.