# Paroxysmal Non-Kinesigenic Dyskinesias Associated with Biallelic *POLG* Variants: A Case Report

Mutations in mitochondrial DNA polymerase γ (*POLG*) have been described to cause a wide variety of phenotypes.[1,2] Although less commonly reported, movement disorders have also been described, mainly parkinsonism or complex hyperkinetic movement disorder.[3,4] We present a child carrying two variants in the *POLG* gene presenting paroxysmal non-kinesigenic dyskinesias (PNKD) as the only manifestation of the disease.

The patient is a 12-year-old girl born to healthy unrelated parents. There was no family history of neurological disease. Early psychomotor development was normal. At the age of 18 months, she began to have paroxysmal dyskinesias, characterized by hyperkinetic complex movements mainly involving the limbs and face, with mixed choreic, dystonic, myoclonic, and ballistic features often resulting in falling to the ground (Video 1).

These episodes, lasting 3 to 5 to 20 minutes, were most commonly observed in the morning after 10 to 20 minutes of wakefulness, but could occur at any time during the day. No precipitating factor was identified. The frequency varied from 1 to 2 times a week to several times a day. Episodes never occurred during sleep.

The patient was first referred to our department at the age of 2.5 years. Neurological examination between episodes was always unremarkable, and cognitive assessment at the last follow-up (age 11 years) was completely normal (Wechsler Intelligence Scale for Children-IV: Full Scale Score: 100). Extensive metabolic investigations of plasma, urine, and CFS were negative. Brain magnetic resonance imaging (ages 3, 4, 7, 9, and 11 years) was normal. Longitudinal video electroencephalography (EEG) monitoring showed a normal organization of brain activity in both wakefulness and sleep and rare interictal posterior slow abnormalities. Ictal EEG ruled out the epileptic nature of the episodes. Next-generation sequencing analysis of a customized epilepsy/movement disorder gene panel revealed the presence of two variants in the *POLG* (NM_002693.2): a heterozygous missense variant c.3212 G>A; p.Arg1071His (rs774851005) reclassified as likely pathogenic of maternal origin and a novel de novo heterozygous frameshift variant: c.651dupC; p.Ser218LeufsTer26 absent in parents and classified as likely pathogenic. Long-read sequencing and RNAseq confirmed the presence of the two variants in trans (Supporting information Data S1). Whole exome sequencing excluded other genetic causes. Muscle histology and respiratory chain enzyme activity in muscle and fibroblasts were normal. Macrodeletions and multiple deletions of mitochondrial DNA were excluded by Southern

**Video 1.** Segment 1, age 19 months, during nappy changing, the child presents with an episode of generalized chorea predominantly of the right upper limb, associated with tongue protrusion. Segment 2, age 2.5 years. While standing, the child presents sudden hypertonus of the legs and trunk with a fall to the ground, followed by a choreo-ballic phase in the left limbs, while the right upper limb remains flexed and adducted. Segment 3, age 4 years. Another episode of generalized hyperkinesia at rest, clearly involving the cranial muscles.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.30029



**Key Words**: DNA polymerase gamma (POLG), paroxysmal non-kinesigenic dystinesias (PNKD), next generation sequencing (NGS)

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blotting. Treatments with carbamazepine, clobazam, clonazepam, valproic acid, levetiracetam, acetazolamide levodopa were all ineffective. Following the identification of variants in *POLG*, at age 9, daily supplementation with riboflavin (300 mg) and coenzyme Q (300 mg) reduced intensity (no longer reported falling to the ground) and frequency (weekly or monthly) of the episodes.

The paroxysmal disorder in our patient can be classified as PNKD according to the following characteristics: lack of association with exercise and movement, prolonged duration, poor response to medication.[5] Interestingly, the ictal EEG at age 7 (Video S1) showed a persistent slowing triggered by hyperpnea similar the EEG pattern observed in hemiplegic attacks described in alternating hemiplegia of childhood and hemiplegic migraine and in paroxysmal hemiplegia of GLUT1 deficiency syndrome, suggesting a possible common mechanism.[6,7] Paroxysmal dyskinesias, mainly exercise induced, are associated with deficiency of a number of mitochondrial enzymes involved in energy production and branched-chain amino acids catabolism: pyruvate dehydrogenase complex, short-chain enoyl-CoA hydratase, 3-hydroxyisobutyryl-CoA hydrolase, succinic semialdehyde dehydrogenase.[8] Our report broadens the etiological and clinical spectrum to include POLG-related condition.

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## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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# Supporting Data

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## Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Manuscript: A. Writing of the first draft, B. Review and Critique.

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## Financial Disclosures

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