Mitochondrial diseases can be caused by pathogenic variants in the nuclear DNA or in the mitochondrial DNA itself.1 They can result in variable clinical signs and symptoms. A total of 19 different mitochondrial tRNA synthetases exist and are essential for mitochondrial protein synthesis. Mutations in all 19 tRNA have been related to human disease2,3; for clinical phenotypes of mitochondrial disorders as a result of nuclear DNA mutations, see Table S1. In 2017, 9 individuals were reported with biallelic variants in WARS2, a nuclear gene encoding for mitochondrial triptophanyl-tRNA synthetase. All presented neurodevelopmental as well as complex movement disorders and variable other findings such as epilepsy or retinitis pigmentosa4–6 classified as “Neurodevelopmental disorder, mitochondrial, with abnormal movements and lactic acidosis, with or without seizures” (neurodevelopmental disorder (NEMMLAS), MIM #617710).

Here, we further increase the knowledge on the clinical presentation of WARS2 deficiency by presenting the first case with a clinically prominent hyperkinetic movement disorder with dystonia, chorea, and ballism.

Case Report

A 31-year-old man was referred to our movement disorders outpatient clinic at the age of 30 years. He was born at term to healthy parents after an uncomplicated pregnancy; neonatal and early infancy course were unremarkable. A younger sister of 4 years had no medical complaints.

At the age of 15 months, the patient had first come to medical attention because of ballistic movements and a stepwise loss of already acquired skills. Since the age of 2 years, the patient showed a severe hyperkinetic movement disorder with uncontrollable
ballistic and dystonic movements. He could communicate nonverbally with the parents on a basic level and react to orders.

The clinical presentation of the patient at the age of 31 years is demonstrated in the accompanying Video S1.

The cranial magnetic resonance imaging showed gross cerebellar atrophy of both hemispheres, but no white matter lesions or signs of leukencephalopathy. To quantify the cerebellar volume, additional computerized volumetry was performed. This confirmed the atrophy pattern including the complete cerebellar hemispheres (Fig. 1), more extensive than in previously reported mitochondrial disease patients with movement disorders. Cerebral spinal fluid results were unremarkable, including lactate. Serum lactate levels were not elevated at the time of presentation at our center, and documented lactate levels during childhood ranged between 0.3 and 6.0 mmol/l (reference <2 mmol/l), whereas creatine kinase (191 U/l) was marginally increased.

The patient received symptomatic treatment with tiaprid hydrochloride up to 450 mg per day, which reduced the occurrence and the amplitude of the hyperkinetic movements and did not cause drowsiness.

Trio exomic sequencing from leucocyte-derived DNA was performed after written informed consent as reported earlier. No pathogenic or likely pathogenic variants were detected in the mitochondrial DNA. Based on the suspected autosomal recessive pattern of inheritance, we prioritized genes carrying biallelic variants in WARS2. All identical ENSPTRG00000001173 58 S G I Q P T G I L H L G N Y L G A I E S W V R L

**TABLE 1** Phylogenetic conservation of WARS2 variant c.149G>A

| Species               | Match       | Gene                               | aa      | Alignment                  |
|-----------------------|-------------|------------------------------------|---------|----------------------------|
| Human                 | Not conserved| ENSPTRG00000001173                 | 58 S G I Q P T G I L H L G N Y L G A I E S W V R L |
| Ptroglyptes           | All identical| ENSPTRG00000001173                 | 58 S G I Q P T G I L H L G N Y L G A I E S W V R L |
| Mus musculus          | All identical| ENSMUSG00000004233                 | 58 S G I Q P T G I L H L G N Y L G A I E S W V R L |
| Galus gallus          | All identical| ENSGALG00000004233                 | 58 S G I Q P T G I L H L G N Y L G A I E S W V R L |
| Danio rerio           | All identical| ENSDARG000000011881                 | 58 S G I Q P T G I L H L G N Y L G A I E S W V R L |
| Drosophila melanogaster| All identical| FBg0036763                     | 95 S G I Q P T G S L H L G N Y L G A I E S W V R L |
| Caenorhabditis elegans| All identical| C34E10.4                      | 46 T G I Q P T G I P H L G N F F G S I E P W T E |

In summary, WARS2-related mitochondrial disease can cause heterogeneous clinical presentations, but developmental cognitive delay and complex movement disorders seem to be a consistent feature. In children and young adults with otherwise unexplained progressive hyperkinetic movement disorders, WARS2-related mitochondrial disease should be included in the list of differential diagnoses.

**Discussion**

Here we present a patient with biallelic variants in WARS2 and a clinical phenotype consisting of a severe hyperkinetic movement disorder and cognitive deficits. This case broadens the differential diagnostic approach to juvenile hyperkinetic movement disorders with dystonia, chorea, and ballism. It further substantiates the role of WARS2 in syndromes comprising developmental and cognitive delay combined with hyperkinetic movement disorders. Because the majority of published patients were reported to have had epileptic seizures, the absence of this clinical finding might explain the survival beyond 25 years in our patient.

In summary, WARS2-related mitochondrial disease can cause heterogeneous clinical presentations, but developmental cognitive delay and complex movement disorders seem to be a consistent feature. In children and young adults with otherwise unexplained progressive hyperkinetic movement disorders, WARS2-related mitochondrial disease should be included in the list of differential diagnoses.

**Author Roles**

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

**Disclosures**

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. Informed consent to be videotaped and to publish the clinical data including video was obtained by the patient’s parents. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.
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Supporting Information

Supporting information may be found in the online version of this article.

**Video S1.** Clinical presentation of the 31-year-old patient in the movement disorders outpatient clinic in 2018 showing a severe hyperkinetic movement disorder with uncontrollable dystonic and ballistic movements. He can communicate nonverbally with the parents on a basic level and react to orders.

**Table S1.** Differential diagnosis of mitochondrial disorders as a result of nuclear DNA mutations resulting in similar phenotypes.