


Mutation of the *WARS2* Gene as the Cause of a Severe Hyperkinetic Movement Disorder

Annemarie Hübers, MD,¹ Hans-Jürgen Huppertz, MD,² Saskia B. Wortmann, MD, PhD,^{3,4,5} and Jan Kassubek, MD^{1,*} 

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 disease^{2,3}; 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 pigmentosa,^{4–6} 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 infantile 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

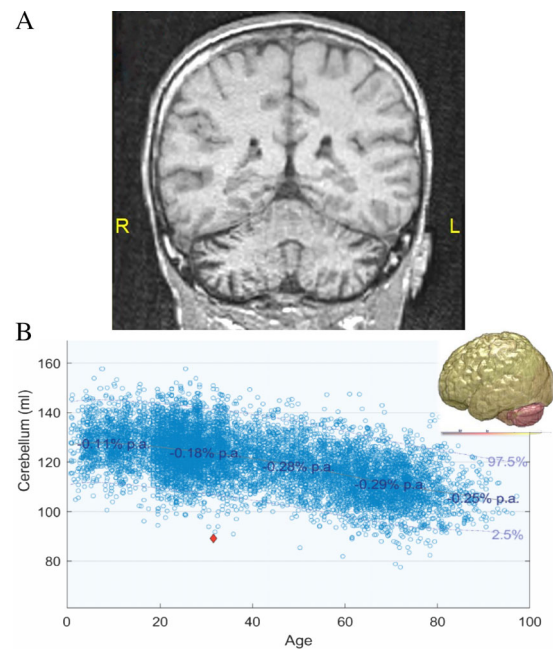


FIG. 1. A: Representative slice of the T1-weighted magnetic resonance imaging demonstrating gross atrophy of both cerebellar hemispheres. **B:** The atrophy was quantified by automated atlas-based magnetic resonance imaging volumetry: the patient's cerebellar volume (red diamond) is shown in comparison to 10,200 control brains at different ages (blue circles), with the patient's cerebellar volume being much lower than those of controls at similar ages. Inlay: color-coded overlay of z scores on a 3-dimensional brain image of the patient, with red coloration of the cerebellum, corresponding to a z score of -4 in comparison to age-matched controls.

¹Department of Neurology, University of Ulm, Ulm, Germany; ²Swiss Epilepsy Clinic, Klinik Lengg, Zürich, Switzerland; ³University Children's Hospital, Salzburg, Austria; ⁴Institute of Human Genetics, Technische Universität München, München, Germany; ⁵Institute of Human Genetics, Helmholtz Zentrum München, Neuherberg, Germany

*Correspondence to: Prof. Dr. Jan Kassubek, Department of Neurology, University of Ulm, Oberer Eselsberg 45, 89081 Ulm, Germany; E-mail: jan.kassubek@uni-ulm.de

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

Species	Match	Gene	aa	Alignment
Human			50	S G I Q P T G I L H L G N Y L G A I E S W V R L
mutated	Not conserved		50	S G I Q P T G I L H L D N Y L G A I E S W V
<i>Ptrogodytes</i>	All identical	ENSPTRG0000001173	50	S G I Q P T G I L H L G N Y L G A I E S W V
<i>Mus musculus</i>	All identical	ENSMUSG00000004233	50	S G I Q P T G I L H L G N Y L G A I E S W V
<i>Gallus gallus</i>	All identical	ENSGALG00000014772	19	S G I Q P T G T P H L G N Y L G A I Q N W V N
<i>Danio rerio</i>	All identical	ENSDARG00000011801	56	S G I Q P T G I P H L G N Y L G A L E S W V A
<i>Drosophila melanogaster</i>	All identical	FBgn0036763	95	S G I Q P T G S L H L G N Y L G A V R K W V Q
<i>Caenorhabditis elegans</i>	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

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.⁷ This confirmed the atrophy pattern including the complete cerebellar hemispheres (Fig. 1), more extensive than in previously reported mitochondrial disease patients with movement disorders.⁸ 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 tiapridhydrochloride 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.^{9,10} 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 the index and detected 2 variants in *WARS2* (NM_201263.2). The paternally inherited missense variant c.37T>G, p.(Trp13Gly) is listed as pathogenic in ClinVar (www.ncbi.nlm.nih.gov/clinvar/). The predicted effect on the structure and function of *WARS2* was shown to impair the mitochondrial localization of the protein.¹ This might, even in a homozygous state, only subliminally impair protein function, which is underlined by the 9 homozygous carriers listed in GnomAD. However, in combination with a more deleterious variant, this variant has been found in association with disease and is hence considered a hypomorphic allele.⁴ The maternally inherited c.149G>A, p.Gly50Asp missense variant has not been previously described. It is absent from the >125000 exome datasets listed in GnomAD and is not found in heterozygous state in our in-house database (18,000 exome datasets). The affected position is conserved down to *Caenorhabditis elegans* and is predicted to be disease causing by mutation taster (Table 1). No other rare and potentially protein damaging variants were detected on an exome broad search.

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.

A.H.: 1B, 2C, 3A

H.J.H.: 1C, 2B, 3B

S.B.W.: 1C, 2B, 3B

J.K.: 1AC, 2A, 3B

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.³