

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

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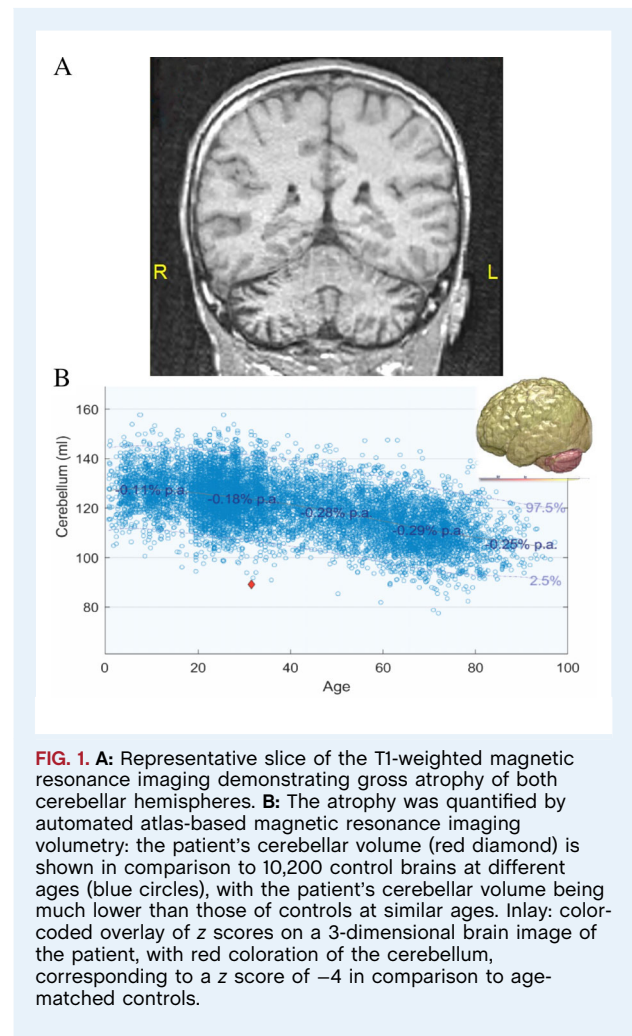
Mitochondrial diseases can be caused by pathogenic variants in the nuclear DNA or in the mitochondrial DNA itself.¹ They can result in variable clinical signs and symptoms. A total of 19 different mitochondrial tRNA synthetases exist and are essential for mitochondrial protein synthesis. Mutations in 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



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Keywords: Hyperkinetic movement disorder, neurodevelopmental disorder, aminoacyl tRNA synthetase, mitochondria.

Relevant disclosures and conflicts of interest are listed at the end of this article.

Received 18 June 2019; revised 4 October 2019; accepted 10 October 2019.

Published online 00 Month 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.12855

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	ENSMUSG0000004233	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 leukoencephalopathy. 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.

Funding Sources and Conflicts of Interest: There was no funding for this study. All authors have no conflicts of interest to report.

Financial Disclosures for the Previous 12 Months: J.K. has received consulting fees as an advisory board member and honoraria as a speaker from UCB Pharma, Biogen, Novartis Pharma, BIAL, Zambon, AbbVie, Teva Pharmaceuticals, Medtronic, Desitin, Boehringer Ingelheim, and GlaxoSmithKline and serves as an editorial board member of *Frontiers in Neurology*. All other authors have nothing to declare.

References

1. Wortmann SB, Mayr JA, Nuoffer JM, Prokisch H, Sperl W. A guideline for the diagnosis of pediatric mitochondrial disease: the value of muscle and skin biopsies in the genetics era. *Neuropediatrics* 2017;48:309–314.
2. Fuchs SA, Schene IF, Kok G, et al. Aminoacyl-tRNA synthetase deficiencies in search of common themes. *Genet Med* 2019;21:319–330.
3. Angelini C, Bello L, Spinazzi M, Ferrati C. Mitochondrial disorders of the nuclear genome. *Acta Myol* 2009;28:16–23.
4. Musante L, Puttmann L, Kahrizi K, et al. Mutations of the aminoacyl-tRNA-synthetases SARS and WARS2 are implicated in the etiology of autosomal recessive intellectual disability. *Hum Mutat* 2017;38:621–636.
5. Theisen BE, Rumyantseva A, Cohen JS, et al. Deficiency of WARS2, encoding mitochondrial tryptophanyl tRNA synthetase, causes severe infantile onset leukoencephalopathy. *Am J Med Genet A* 2017;173:2505–2510.
6. Wortmann SB, Timal S, Venselaar H, et al. Biallelic variants in WARS2 encoding mitochondrial tryptophanyl-tRNA synthase in six individuals with mitochondrial encephalopathy. *Hum Mutat* 2017;38:1786–1795.
7. Huppertz HJ, Kroll-Seiger J, Kloppel S, Ganz RE, Kassubek J. Intra- and interscanner variability of automated voxel-based volumetry based on a 3D probabilistic atlas of human cerebral structures. *NeuroImage* 2010;49:2216–2224.
8. Schreglmann SR, Riederer F, Galovic M, et al. Movement disorders in genetically confirmed mitochondrial disease and the putative role of the cerebellum. *Mov Disord* 2018;33:146–155.
9. Kremer LS, Distelmaier F, Alhaddad B, et al. Bi-allelic truncating mutations in TANGO2 cause infancy-onset recurrent metabolic crises with encephalocardiomyopathy. *Am J Hum Genet* 2016;98:358–362.
10. Wagner M, Berutti R, Lorenz-Depiereux B, et al. Mitochondrial DNA mutation analysis from exome sequencing—A more holistic approach in diagnostics of suspected mitochondrial disease. *J Inher Metab Dis* 2019;42(5):909–917.

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