



## Case Report

# PARS2-associated mitochondrial disease: A case report of a patient with prolonged survival and literature review



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## ABSTRACT

Biallelic pathogenic variants in mitochondrial aminoacyl-tRNA synthetase (mt-aaRS) *PARS2* are associated with mitochondrial cytopathy. Here, we report the tenth case of an individual with biallelic *PARS2* pathogenic variants, detected by exome sequencing (ES), and a literature review of ten cases of *PARS2* mutations. Our patient displayed symptoms and clinical and laboratory findings similar to those reported previously with normal lactate levels. These symptoms included seizure disorder (which was managed with antiepileptics), developmental delay, and progressive cardiomyopathy which manifested at 19 years of age. The patient received a vitamin regimen including antioxidants as part of his treatment regimen. While further studies are required to conclusively establish the beneficial role of vitamin and cofactor administration on the mitochondria in *PARS2*-associated mitochondrial disease, these factors may have delayed the onset of cardiomyopathy.

## 1. Introduction

Mitochondrial aminoacyl tRNA synthetases (aaRSs) are essential for mitochondrial protein biosynthesis and oxidative phosphorylation [1–6]. Nineteen nuclear genes encode the aaRSs, including prolyl-tRNA synthetase 2, or *PARS2*, which charges mitochondrial prolyl-tRNA with its cognate amino acid, proline.

Biallelic pathogenic *PARS2* variants are associated with early infantile epileptic encephalopathy (EIEE75, MIM 618437), a multi-system mitochondrial disorder. Clinical features previously observed in nine individuals with *PARS2* deficiency include microcephaly, hypotonia, seizures, intellectual disability, structural brain abnormalities, and other systemic findings including lactic acidemia. All patients generally have similar characteristics and symptoms, with most dying during the first 10 years of age [6–11] (Table 1).

Herein, we report the case of an individual with heterozygous pathogenic *PARS2* variants diagnosed through exome sequencing. Unlike most previous cases, chronic lactic acidemia was not present, and cardiomyopathy did not occur until adulthood (19 years). He died of cardiac failure at 21 years of age. To our knowledge, this patient had the longest lifespan with this disorder.

## 2. Case presentation

**Clinical Course.** This male patient presented initially at eight months with epilepsy, global delays, and recurrent respiratory infections. Electroencephalography (EEG) revealed high-amplitude, posteriorly accentuated spikes consistent with hypsarrhythmia. Initial seizures were intractable, despite antiepileptics, but were gradually controlled with adrenocorticotrophic hormone (ACTH). Biochemical analysis revealed a single serum lactate elevation during infancy (which was normal on follow-up evaluations), normal amino acid levels in plasma and cerebrospinal fluid, and normal urine organic acids. Peroxisomal studies yielded normal results. Brain MRI revealed frontal and anterior parietal atrophy with signal changes involving the caudate, lentiform nuclei, and bilateral thalami. Karyotype was normal and fluorescence *in situ* hybridization revealed negative results for Angelman syndrome. Initial ophthalmologic and audiologic examinations and mitochondrial enzyme assays in fibroblasts revealed normal findings. Because an older deceased sibling had a similar presentation, an unknown mitochondrial disorder was speculated and an antioxidant vitamin mixture including vitamins C, B1, B2, B3 (100 mg twice daily), and E (200 mg twice daily), Q10, lipoic acid, and levocarnitine (250 mg thrice daily) was

Abbreviations: EE, electroencephalography; ACTH, adrenocorticotrophic hormone; MRI, magnetic resonance imaging

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**Table 1**  
Overview of different cases with PARS2-related mutations (our case and other previously published cases).

	Our Case	Sofou et al. [10] (1st case report of PARS2 mutation)	Pronicka et al. [9]	Mizuguchi et al. [6]	Clara et al. [8]	Yin et al. [7]	Al Balushi et al. [11]
Sex	Male	Male	Male	2 sisters	3 siblings (Two brothers and one sister)	2 sisters	Female
Family history	Elder brother has same phenotype.	Not mentioned	Affected siblings (no details given)	2 affected sisters, no mention of any other family member	3 affected siblings (2 brothers and 1 sister).	2 affected sisters, no mention of any other family member	Not mentioned
Longevity	Died at 21 years, brother died at 5 years	Died at the age of 16 years	Died under 2 years	Both alive at the time of report publishing (9 and 3 years of age)	Elder brother and sister died at 8.5 years; youngest brother alive at the time of report (6.5 years)	Younger one died at 4 months; older one alive at the time of report (3 years)	Alive at time of report publishing (3.3 years)
Clinical findings	+	+	+	+	+	+	+
Developmental delay							
Hypotonia	+	+	+	+	+	+	Hypertonia
Microcephaly	+	+	+	+	+	+	-
Type of seizure	Infantile spasms, generalized seizure	Intractable epileptic encephalopathy	Generalized seizure	Generalized seizure	Generalized seizure	Generalized seizure	Infantile spasms
Cardiomyopathy	+	+	Not known	Not examined	+	Nil	Nil
Other organ involvements	Frequent episodes of respiratory infection, feeding difficulty	Visual impairment, feeding difficulty	Not known	Nil	Facial dysmorphism; visual impairment, hyperacusis	Feeding difficulty	Coagulation abnormalities
Diagnostic findings							
MRI brain	Frontal and anterior parietal atrophy with signal changes involving caudate, lentiform nuclei, and thalami bilaterally	Supratentorial atrophy of the cerebral cortex, complete agenesis of the corpus callosum, and hypomyelination of the white matter	Done; findings not known	Diffuse hypomyelination,	Progressive volume loss of frontal lobes; widening of cortical sulci and frontal horns of lateral ventricles	Hypomyelination with cortical atrophy, decreased frontal lobe volume.	Cerebral atrophy, Bifrontal subdural hematomas.
EEG findings	High amplitude and posteriorly accentuated spike activity hypsarrhythmia	Bilateral synchronous spikes and polyspikes, mainly in posterior regions of hemispheres, with generally depressed background activity	Done; findings not known	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia, multifocal spikes, sharp waves with a symmetric background pattern	Not reported
Lactate levels	Normal; high only on one occasion	Elevated (serum and CSF)	Elevated (only mentioned that lactate excretion was elevated)	Elevated lactate (serum and CSF); not tested in CSF of the second sibling	CSF lactate level high	Elevated serum lactate levels; CSF levels were not tested	normal
Muscle/skin biopsy	Negative (skin biopsy)	Increased fiber caliber variation; no mitochondrial proliferation, and structurally abnormal mitochondria	Done; findings not known	Not done	Normal histological and histochemical picture and activities of respiratory chain complexes I-IV at the control range, except for citric synthase activity (increased at 281 nmol/min/mg)	Not done	Not done
ECHO	Initially normal. Severe degree of heart failure; EV 20%	Dilated cardiomyopathy, left ventricular hypertrophy	Done; findings not known	Not done	Dilated/hypertrophic cardiomyopathy	Normal	Normal
Genotype (ES)	Compound heterozygous variants: maternally-inherited c.283G > A (p.Val95Ile) and paternally-inherited 1091C > G (p.Pro364Arg)	Compound heterozygous variants: c.1130dupC, (p.K378 fs*1); 836C > T; (p.S279L), located in a conserved motif of unknown function	Compound heterozygous variants: c.1091C > G (p.Pro364Arg); c.239 T > C (p.Ile80Thr)	Compound heterozygous variants in both siblings: c.283G4A (p.Val95Ile); c.607G4A (p.Glu203Lys)	Compound heterozygous variants: c.239 T > C, (p.Ile80Thr) c.1091C > G, (p.Pro364Arg)	Compound heterozygous variants c.283 G > A (p.V95I) and c.604G > C (p.R202G)	Compound heterozygous variants c.1091C > G (p.Pro364Arg) c.283G > A (p.Val95Ile)
Treatment	ACTH, and other antiepileptics; low dose aspirin, lisinopril, digoxin,	Antiepileptic drugs and other supportive treatment; did not	Antiepileptic drugs and other supportive treatment; did not	Antiepileptic drugs and other supportive treatment;	Antiepileptic drugs and other supportive treatment; did not receive mitochondrial "cocktail"	Antiepileptic drugs and other supportive treatment;	Not reported

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Table 1 (continued)

Our Case	Sofou et al. [10] (1st case report of PARS2 mutation)	Pronicka et al. [9]	Mizuguchi et al. [6]	Clara et al. [8]	Yin et al. [7]	Al Balushi et al. [11]
carvedilol; mitochondrial “cocktail”	receive mitochondrial “cocktail”	receive mitochondrial “cocktail”	did not receive mitochondrial “cocktail”		did not receive mitochondrial “cocktail”	

prescribed. Other medications included levetiracetam to control seizures. Throughout childhood, his cardiovascular function was stable, presenting normal findings on echocardiography, and only several illnesses requiring hospitalizations for respiratory distress and occasionally increased seizure frequency. Surgeries included posterior spinal fusion for scoliosis and surgical release of bilateral knee contractures. He had global developmental delay throughout childhood, but no developmental regression.

At 19 years, the patient presented with viral illness and dehydration, and echocardiography showed mildly depressed cardiac function with left ventricular ejection fraction of 50%; low-dose lisinopril was administered. Physical examination revealed normal height and weight, microcephaly (circumference below the second percentile), with flattened occiput, mildly dysmorphic facial features including synophrys, malar hypoplasia, and mild prognathism, chin crease, and diffuse hypotonia (Fig. 1). He was nonverbal but responded to simple commands, interacted with his family, and was independently ambulatory.

Two years later, echocardiography revealed severe cardiac failure with a left ventricular ejection fraction of 20%. Aspirin, digoxin, carvedilol, and lisinopril were prescribed at low doses. He was readmitted twice with respiratory distress and suspected viral illness and was then discharged to home hospice and died of cardiac failure at 21 years of age.

**Family History.** The patient's eldest brother presented at 4 months with infantile spasms, which progressed to seizures, nystagmus, and profound intellectual disability. Brain magnetic resonance imaging (MRI) revealed cerebral atrophy. At 5 years, he died from severe cardiomyopathy and lactic acidosis. An underlying mitochondrial disease was suspected. Muscle biopsy indicated variations in myofiber size, reduced activity of multiple respiratory chain enzymes, and normal electron microscopic findings. Cytochrome c oxidase activity ranged from 0.04 (control  $0.52 \pm 0.17$  in the brain) to 0.64 ( $2.8 \pm 0.52$ ). Cytochrome c oxidase staining revealed equivocal results. Increased citrate synthase activity was consistent with mitochondrial proliferation. Autopsy revealed frontal cerebral cortex atrophy and normal cortical mitochondria. The patient had another healthy older brother.

**Molecular Findings.** Written consent was obtained from the family for trio-exome sequencing. The patient harbored compound heterozygous variants of uncertain significance: c.1091C > G (p.P364R), inherited paternally, and c.283 G > A (p.V95I), inherited maternally. This exact genotype has been reported recently by Al Balushi et al. [11]. Monoallelic P364R in PARS2 was reported in four different individuals with congenital microcephaly, early infantile epileptic encephalopathy, dilated cardiomyopathy, and Leigh syndrome-like disease [8,9]. *In silico* analyses predicted deleterious effects. V95I was previously reported in four individuals with early infantile epileptic encephalopathy and hypotonia [6,7]. It has also been reported in the homozygous state by Maddirevula et al. [12]. The c.1091C > G (p.P364R) allele has been found in 295 out of 281,922 alleles, whereas the c.283 G > A (p.V95I) was found in 31 out of 282,762 alleles in the GnomAD database. However, neither were found in the homozygous state in GnomAD.

### 3. Discussion

Herein, we report the oldest documented patient harboring biallelic PARS2 pathogenic variants with cardiac function preserved until shortly before death, who had the longest lifespan in this condition reported thus far.

PARS2 mutations are rare, previously reported in only nine patients (Table 1). Our patient harbored one mutation (P364R) in common with the eldest of three affected siblings (Table 1). The elder brother and sister both died at 8.5 years of age [8]. Two sisters harboring PARS2 mutations [7] shared one pathogenic variant with our patient, c.283 G > A (p.V95I) (Table 1). The younger sister died at 4 months, while the elder sibling was 3 years at the time of publication. None of these patients were treated with antioxidants. All had elevated lactate



**Fig. 1.** The patient at age 15 years. Findings included: microcephaly with flattened occiput, mildly dysmorphic facial features with synophrys, malar hypoplasia, mild prognathism, and chin crease.

levels, unlike our patient.

Though our patient periodically required hospitalization, he survived for two decades. Among supportive therapies, he received a regimen of antioxidant supplements targeting mitochondrial dysfunction since infancy. Furthermore, he had an affected older brother, who received no treatment and died during early childhood from cardiac failure.

Some treatment strategies for mitochondrial diseases involve bypassing mitochondrial functions, including natural substances directly involved in ATP production, such as creatine (when the ATP demand exceeds the mitochondrial supply, creatine releases phosphate to increase ATP production), carnitine (improves ATP efficiency by clearing the toxic byproducts of ATP synthesis and facilitating ATP production by importing fuel molecules in the mitochondria), and coenzyme Q10 (essential for mitochondrial respiration) [13].

Mitochondrial cytopathies are associated with reduced transduction of aerobic energy (decreased ATP synthesis), increased oxidative stress, apoptosis, and necrosis. Theoretically, combinations of specific nutraceuticals bypass deficiencies in mitochondrial respiration, potentially providing an alternate energy source [13,14]. A previous randomized placebo-controlled trial involving patients with mitochondrial cytopathies reported that creatine monohydrate, alpha lipoic acid, and coenzyme q10 reduced lactate levels and oxidative stress (as indicated by its markers) [13].

While numerous factors could have contributed to significant differences in disease severity between our patient and his sibling, we hypothesize that antioxidant supplementation may have delayed the onset of cardiomyopathy and contributed to normal lactate levels. Further prospective studies with larger cohorts and well-defined clinical and laboratory markers are required to establish the beneficial roles of antioxidants and other vitamins in individuals with *PARS2*-associated disease.

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#### Ethics approval

Not applicable.

#### Patient consent statement

The patient's family provided informed consent for the publication of this case report.

#### Declaration of Competing Interest

The authors disclose no conflict of interest.

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