



## CASE REPORT

# A novel detrimental homozygous mutation in the WFS1 gene in two sisters from nonconsanguineous parents with untreated diabetes insipidus

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## Abstract

Given the limited lifespan and with the recent progress in experimental treatments for WS, timely diagnosis and multidisciplinary treatment for DI/DM, hydronephrosis, and visual/psychiatric status—maintaining quality of life—are of crucial importance.

## KEYWORDS

diabetes insipidus, diabetes mellitus, novel mutation, WFS1 gene, Wolfram syndrome

## 1 | INTRODUCTION

WS is a rare neurodegenerative disorder. Two sisters, a 19-yr blind since 13 (died at 21, due to brain stem atrophy) and a 7-yr-old, from nonconsanguineous parents originated from Trapezund, had poorly treated DM since 3 years and

untreated DI. Genetic testing revealed a novel homozygous c.2069G > A mutation in WFS1.

Wolfram syndrome (WS), also called DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness), is a rare autosomal recessive neurodegenerative genetic disorder.<sup>1</sup> The prevalence of WS has been estimated between 1

All contributors have read and approved the submission to Clinical Case Reports.

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in 770 000 in the United Kingdom and 1 in 100 000 in North America.<sup>2</sup> Two causative genes have been identified: WFS1 and CISD2 (WFS2).<sup>3</sup> Classical WS is the result of autosomal recessive mutations affecting the WFS1 gene, which is implicated in endoplasmic reticulum (ER) function,<sup>2</sup> although WS was first described as a mitochondriopathy. However, the localization of the protein on the endoplasmic reticulum (ER) membrane challenged this hypothesis. ER contacts mitochondria to ensure effective Ca<sup>++</sup> transfer and lipids transfer, and apoptosis within stabilized and functionalized microdomains, termed “mitochondria-associated ER membranes” (MAMs).<sup>4</sup> The prognosis of the syndrome is currently poor. The median age at death is 30 years (range, 25–49 years), usually from respiratory failure as a result of brain stem atrophy.<sup>5</sup>

## 2 | CASE REPORT

Two sisters from nonconsanguineous parents presented to our pediatric endocrinology clinic due to severe polyuria-polydipsia. They both had poorly treated diabetes mellitus since the age of 3 years and untreated diabetes insipidus (DI).

A 19-yr-old girl totally blind since the age of 13 had primary amenorrhea and bladder incontinence. Cranial nerve examination was normal except oculomotion with roving eye movements. Muscle strength was normal with deep tendon reflexes 2/4. There were no signs of ataxia nor extrapyramidal signs. Mental status was appropriate for age but suffered from insomnia and apparent depression. Her HbA1c was 8.2%, biochemical values being normal. Gonadotropins in GnRH testing as well as estradiol levels and thyroid function tests were normal. Abdominal ultrasonography revealed normal uterus and ovaries but inappropriate for pubertal stage along with mild (Grade II) hydronephrosis. Comprehensive ophthalmic examination showed “No Light Perception” in both eyes. The pupillary light reflex was completely absent, and both pupils were mid-dilated. The anterior segment was normal, and the intraocular pressure was 12 mm Hg in both eyes (Goldman application tonometer). Dilated fundus examination revealed complete optic nerve atrophy. Otologic and audiological evaluation was performed. They included otomicroscopy, tympanometry, transient otoacoustic emissions (TOAE), and automated auditory brainstem response (aABR). Her tympanogram was type A, TOAEs “pass” bilateral, as well as aABRs.

The patient had severe salt-wasting diuresis when treatment for diabetes insipidus was started,<sup>6</sup> and fludrocortisone was necessary to be added, along with frequent bladder catheterizations for her neurogenic bladder. Six months after appropriate treatment for diabetes mellitus and insipidus, she had menstrual onset. Unfortunately, 2 years after presentation, she died unexpectedly in her sleep. Autopsy showed severe brain stem atrophy.

Her 7-year-old sister had normal neurological examination. She was prepubertal. Her HbA1c was 10.1%, the rest

biochemical values being normal. Abdominal ultrasonography revealed mild to severe hydronephrosis (Grade III). Ophthalmic examination showed a visual acuity 6/15 (0.40 LogMAR) in her right eye and 6/19 (0.50 LogMAR) in her left eye with + 1.00 diopters sphere corrective lens in both eyes. The pupillary light reflex was reduced symmetrically in both eyes, but there was not relative afferent pupillary reflex. The anterior segment was normal, and the intraocular pressure was 12 mm Hg in the right and 11 mm Hg in the left eye (Goldman application tonometer). Dilated fundus examination revealed moderate optic nerve atrophy. Otologic and audiological tests revealed a type C tympanogram, right side “pass” and left “fail” of TOAEs, whereas aABRs were “pass” bilateral.

She also presented severe salt-wasting diuresis when treatment for diabetes insipidus was started, and fludrocortisone was necessary to be added for 1 month only, along with frequent urinary catheterizations for her neurogenic bladder. On the contrary, we were not able to discontinue fludrocortisone in her sister.

They both normalized their HbA1c (<7%) under intensified multiple insulin daily injections with the 24-hr analogue degludec (Tresiba<sup>®</sup>) and the newest faster formulation of aspart (Fiasp<sup>®</sup>). Glucose variability was also optimized using the FlashStyle Libre System, minimizing hypoglycemia and confining postprandial hyperglycemic excursions. Adjunctive treatment with idebenone 600 mg × 3 p.o. was given to the younger sister aiming to visual stabilization<sup>7</sup>—proven successful for 2.5 years now—while both sisters received additional pioglitazone therapy 45 mg/d × 1 p.o. aiming to mitigate β-cell death.<sup>8</sup>

Genetic testing was performed to confirm the clinical diagnosis of WS. DNA was tested with PCR amplification and sequencing analysis (Sanger sequencing) of the entire coding region and all exon-intron splice junctions of the WFS1 gene (chromosome 4): reference sequence: NM\_006005.3, with the A of the ATG start codon at position 1. A homozygous c.2069G > A mutation in WFS1 gene was found in both sisters, whereas the parents were carriers. This point mutation is a missense mutation in amino acid position 690 (p.C690Y) replacing cysteine with tyrosine in exon 8. To our knowledge, this is a novel variant in WFS1 gene, not previously reported in patients with WS. According to the Prediction Program PolyPhen-2, the mutation is predicted to be damaging with a score of 1000. A different heterozygous—not related to disease manifestation—missense mutation at the same codon has been reported (690Cys- > Arg).

## 3 | DISCUSSION

We have previously reported a novel homozygous WFS1 gene mutation due to maternal uniparental disomy of chromosome

4.<sup>9</sup> Now we present a novel detrimental homozygous WFS1 gene mutation, adding to the genotype-phenotype correlation reported so far.<sup>10</sup> The two sisters affected were born from nonconsanguineous parents of Greek descent born in distant regions of Russia. However, detailed genealogical history proved that both originated 5-6 generations before from Trapezund, an ancient Greek colony located in the Greek—until 1922—Pontus, presently in the state of Turkey, indicating a founder mutation effect.

Even though a correct diagnosis of WS had been made several years ago, none of the girls had ever received treatment for DI. Their diabetes was poorly controlled, and their quality of life was poor. No care had been ever provided for their hydronephrosis nor their psychiatric status. Given the known effect of glycemic control on the neurodegenerative process<sup>10</sup> and the severe consequences of untreated DI such as failure to thrive and hydronephrosis, proper treatment of endocrine dysfunctions is crucial not just to avoid consequences but also to improve quality of survival.<sup>11</sup> In our center, proper multidisciplinary care along with adjunctive treatment with idebenone<sup>7</sup> and pioglitazone<sup>8,12</sup> has resulted in stabilization of visual status, resume in growth and pubertal development, normalization of BMI and improved quality of life in our previously reported patient<sup>9</sup> as well as the younger of the two sisters currently reported. The fact that the life span in WS is limited but progress in experimental treatments—that hopefully will be soon widely available—has been made<sup>13</sup> underlines the importance of timely diagnosis and effective multidisciplinary approach in centers with experience in complex endocrine pathologies such as WS.

## CONFLICT OF INTEREST

All authors declare no conflict of interest.

## AUTHOR CONTRIBUTIONS

PDT: was the treating physician in Athens Medical Center and wrote the paper. KK: was the treating physician in Attikon University Hospital. ME: performed the genetic analysis in all family members in Greece—Access to Genome. TA: put the initial genetic diagnosis in one of the two sisters in Russia. NT. and DA: performed the otologic and audiologic evaluations. VG: performed the ophthalmic examination and follow-up. DA: performed the neurological evaluation. ZG: performed the urologic evaluations and follow-up. PA: supervised hospitalization in Attikon University Hospital. MG: followed the older sister in the transition to the adult endocrine unit of Aretaieion University Hospital. UF: coordinated and supervised explorations and treatment.

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**How to cite this article:** Papadimitriou DT, Kleanthous K, Manolagos E, et al. A novel detrimental homozygous mutation in the WFS1 gene in two sisters from nonconsanguineous parents with untreated diabetes insipidus. *Clin Case Rep*. 2019;7:2355–2357. <https://doi.org/10.1002/ccr3.2494>