

## Short Communication

# Early-onset urological disorders due to Wolfram syndrome: A case of neonatal onset

Mami Fukuma, Daisuke Ariyasu, Megumi Hatano, Hiroko Yagi, and Yukihiro Hasegawa

*Division of Endocrinology and Metabolism, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan*

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### Introduction

Wolfram syndrome (WS) is an autosomal recessive neurodegenerative disorder characterized by DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). Genetic analysis has demonstrated mutations of the *WOLFRAMIN* gene (*WFS1*) in patients with this syndrome (1), which may be complicated by other conditions, among them urological disorders (UDs). According to one study, UD were found to occur in 19.39% (76/392) of WS patients with an average age of 20 yr (2), with only two patients presenting UD before the age of 5 yr, both during infancy. We report here a neonatal case of WS presenting UD.

### Case Report

The patient was a 15-yr-old Japanese boy with WS. He was the second child of healthy, non-consanguineous Japanese parents and was

born through spontaneous vaginal delivery after 39 wk of gestation following an uncomplicated pregnancy. He suffered from urinary tract infection at the age of 10 d. The Society for Fetal Urology (SFU) classifications in renal sonography were grade 2 (right) and grade 1 (left). Urethral dilatation and bladder enlargement were also observed. Voiding cystourethrogram showed vesicoureteral reflex in the right kidney (grade V). The patient underwent surgery for reflux nephropathy and urinary tract enlargement at the age of 5 mo.

A clinical diagnosis of WS was made based on the fact that the patient showed all the major clinical features of WS before the age of 7 yr. Diabetes mellitus was diagnosed at the age of 3 yr. The patient has been treated with insulin since then. At the age of 5 yr, neurogenic bladder was diagnosed, and deafness was confirmed by audiometric test (left ear > 50 dB, right ear > 60 dB). At the age of 6 yr, he was found to have bilateral optic atrophy without diabetic retinopathy. Diabetes insipidus developed at the age of 7 yr. The patient was treated for epilepsy with valproate after the age of 11 yr. His renal function, thyroid function, and blood tests were normal (Table 1).

### Mutational Analysis

Genomic DNA was extracted from white blood cells. PCR and direct sequencing were

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Corresponding author: Yukihiro Hasegawa, Department of Endocrinology and Metabolism, Tokyo Metropolitan Children's Medical Center, 2-8-29 Musahi-dai, Fucyu, Tokyo 183-8561, Japan

E-mail: yhaset@gmail.com

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**Table 1** Patient's laboratory data at the age of 15 yr

WBC	5000/ $\mu$ l	fT3	2.80 pg/ml
Neut	57.60%	fT4	0.86 ng/dl
		TSH	1.11 $\mu$ IU/ml
BUN	11.8 mg/dl	T	1.32 ng/ml
Cr	0.59 mg/dl	IGF-1	269 ng/ml
HbA1c	7.10%	DHEA-S	121 $\mu$ g/dl

conventionally performed. Informed consent for a mutational analysis was obtained from his guardians.

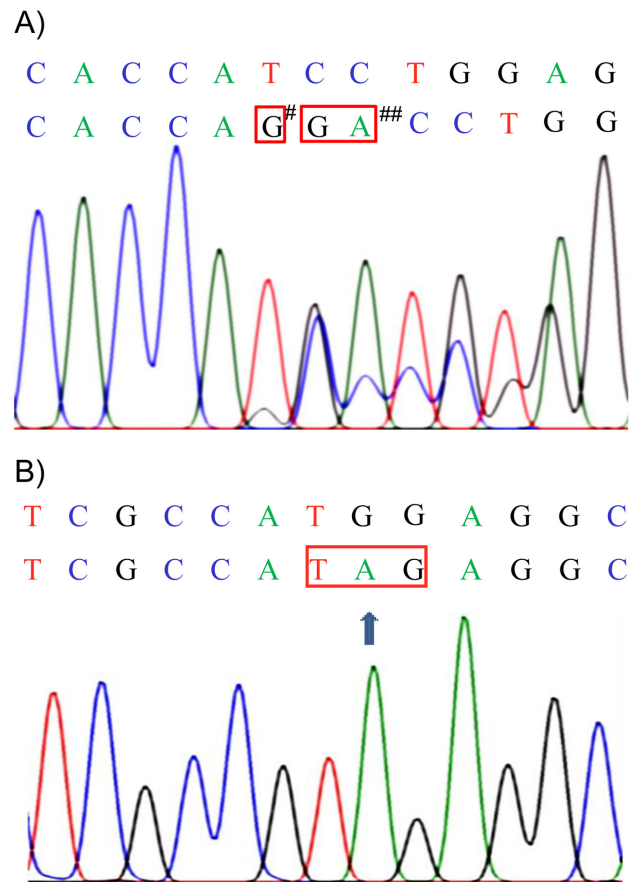
PCR-direct sequence analysis of the patient's WFS1 gene revealed two mutations in exon 8, namely, c.2483T>G, c.2483\_2484 ins GA, resulting in a frameshift and premature stop codon (p. I 828 R fs\*35), and c.2510G>A (p.W837\*; Fig. 1), both of which had already been documented in a previous study (3). PCR and direct sequence analysis after subcloning confirmed that these two mutations resided in two separate alleles. A work-up for the family showed that the c.2483T>G, c.2483\_2484 ins GA mutation was inherited from the father. The c.2510G>A mutation was not present in either the father or the mother, suggesting that it had occurred de novo on the maternal allele.

Both the patient and his father displayed a c.2209 G>A, p.E737K variant, one of the previously reported SNPs. This variant was detected in normal controls as well in several studies (rs147834269) (4–6).

## Discussion

The subject in the present case report was among the youngest WS patient on record to have developed UDs. The first clinical manifestation was UTI caused by renal abnormalities at the age of ten days, indicating an unequivocally early onset of UDs.

The patient's clinical course suggested that hydronephrosis was not secondary to polyuria. Neither our case nor the two previously reported



**Fig. 1.** Sequence of the patient's WFS1 gene. A) A nucleotide change at position 2483<sup>(#)</sup> and a heterozygous two-base insertion (c.2483\_2484 ins GA)<sup>(##)</sup> in exon 8 are shown in this figure. The insertion resulted in a premature stop codon (p. I 828 R fs\*35; data not shown here). B) The results of sequencing after subcloning of the patient's DNA is shown in (B). The patient had a nucleotide change at position 2510 and a nonsense mutation of p.W837\* in exon 8. This mutation appeared after the frame shift, as seen in (A).

ones (2) presented diabetes mellitus or diabetes insipidus at the onset of UDs (2). Although the high urine flow seen in diabetes mellitus and diabetes insipidus is theoretically one reason for hydronephrosis, there should be another reason for hydronephrosis in the disorder.

Further study is needed to determine whether a genotype-phenotype correlation may apply to UDs. The correlation between the

genotype and phenotype of WS in some of the phenotypes was reported in an earlier study (2); the ages of onset for diabetes mellitus, diabetes insipidus, and hearing defects were considered to depend on the patient's genotype. Mutations in severe cases of WS were found to concentrate in two regions (2). Since the mutations in our case were present in one of the two regions, a genotype and the severity of UDs may be correlated.

In conclusion, we reported a case of WS with neonatal onset of UDs. As far as we know, this is the earliest onset of UDs in this syndrome.

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