# A new mutation in WFS1 gene (c.1522–1523delTA, Y508fsX421) may be responsible for early appearence of clinical features of Wolfram syndrome and suicidal behaviour

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## Abstract

**OBJECTIVE**: Wolfram syndrome (WS) is an autosomal recessive disorder characterized by the association of juvenile-onset diabetes mellitus and optic atrophy. It is also known by the acronym DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness).

**PATIENTS, METHODS AND RESULTS**: We diagnosed Wolfram syndrome in 2 male siblings and determined a new mutation (c. 1522–1523delTA, Y508fsX421). Both affected siblings were homozygous, other family members were heterozygous. Dilated renal outflow tracts in the third decade, and neuropsychiatric disorders including bipolar disorder and neurosensorial deafness appear in the fourth decade in ordinary WS, whereas these features appeared in second decade in our patients. This mutation may be responsible for early appearance of dilated renal outflow tracts and multiple neurological abnormalities. Psychiatric disturbances such as suicide were reported at increased frequency in Wolfram patients and in heterozygous carriers. Suicidal behaviour occurred in our patients when they were yet 11 and 13 years old. Therefore, our findings may indicate that there may be a relationship between this WFS1 mutation and mood disorder such as suicidal behaviour.

**CONCLUSIONS**: We determined a new mutation (c. 1522–1523delTA, Y508fsX421) in WS1 gene in 2 siblings with Wolfram syndrome. This mutation may be responsible for early appearance of clinical features of Wolfram syndrome, and there may be a relationship between this mutation and suicidal behaviour.

ORIGINAL ARTICLE

## Introduction

Wolfram syndrome (WS) is an rare recessive disorder (estimated autosomal prevalence of 1 in 770 000, and with a carrier frequency of 1 in 354) characterized by the association of juvenile-onset diabetes mellitus and optic atrophy [2,5,17] . It is also known by the acronym DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). Genetic linkage studies linked WS to the short arm of chromosome 4 [12] and in 1998 the gene for WS, wolframin/*WFS1* was identified [9,14]. WFS1 is a novel gene and encodes an 890 amino-acid glycoprotein (wolframin), predominantly localized in the endoplasmic reticulum. WS results in most cases from mutations in the WFS1 gene [3]. Since the identification of the WFS1 gene, numerous mutations have been identified in WS patients, most likely resulting in a loss of wolframin function [6, 10]. Mutations, including stop codon, frameshift, deletion and insertion mutations, mostly located in exon 8, have been identified in WS families [9,10,14 ].

Although diabetes and optic atrophy represent the minimal diagnostic criteria, neurodegenerative or psychiatric features may evolve over time. Diabetes insipidus, sensori-neuronal deafness, urinary tract atony, ataxia, peripheral neuropathy, mental retardation and psychiatric illness are additional symptoms seen in the majority of patients [14]. Urinary manifestations constitute an integral part of the syndrome, as they are present in up to 62% of cases and represent one of the major causes of morbidity [3]. Urological findings are cardinal aspects in Wolfram syndrome due to its high frequency and prognostic value in natural history of disease. The urinary tract is commonly involved with upper tract dilatation, and bladder dysfunction, usually in the form of a large capacity, atonic bladder [11]. There is evidence suggesting that subjects affected with the WS and normal carriers present an increased risk of psychiatric disorders, particularly depression and suicidal behaviour [13]. It was claimed that there was a role of WFS1 gene mutation in the pathophysiology of increased risk of suicidal behaviour in WFS homozygotes and heterozygotes [13]. An excess of psychiatric hospitalizations and suicides has been reported in the blood relatives of patients suffering from Wolfram syndrome, an observation that led to the suggestion that heterozygous carriers of the gene for WS are predisposed to psychiatric illness [15].

In the present study, we aimed to report a new mutation in WFS1 gene that may be related to severe suicidal behaviour and urological abnormalities in a Turkish family.

## Patients, methods and results

*Patients*

Two diabetic male siblings (22 and 17 yr) whose parents were consanguineous were hospitalized at the same time due to diabetic ketoacidosis. **First patient** treated with insulin has been diabetic since 6 yr old and was being followed for aggressive behaviour and negativism by psychiatry department. Short stature and weakness were determined at physical examination (height: 137 cm, weight: 25 kg, BMI: 13.3 kg/m$^2$, below –5 SD). The stage of pubic hair and genital development were P2, G2 in according to Tanner classification. Fasting plasma glucose: 523 mg/dl, urea: 214 mg/dl, creatinin: 3.25 mg/dl, Na: 115 mEq/L, K: 5.4 mEq/L and plasma osmolality was 308 mosm/kg, HbA1c:17.78%, insülin: 5.52 mU/ml and c peptid was <0.5 ng/ml. Anti GAD65 and islet cell antibodies were negative. Urine analysis: density: 1 000, pH: 6, glucose: 300 mg/dl, protein: 25 mg/dl, ketone: 150 mg/dl and osmolality was 250 mosm/kg. Urine density was changing between 1 000 and 1 005. In spite of dehydration serum ADH level was 0.9 pg/ml. Hereupon, we suspected from diabetes insipidus and, after correction of status, we performed water restriction test followed by arginine vasopressin administration (4 µg Desmopressin iv). The patient had still diluted urine after 8 hours of water deprivation (urine osmolality: 261 mosm/kg), and urinary density and osmolality increased after desmopressin administration (urine density 1 020, urine osmolality 550 mosm/kg). Bilateral optic atrophy was found in ophthalmologic examination (Figure 1). Mixt type sensorioneural hearing loss in audiometric examination and bilateral grade 2–3 hydronephrosis were observed in renal ultrasonographic examination. With these findings the patient accepted as a Wolfram syndrome. **Second patient** was younger brother of the first patient. Diabetes mellitus had started when he was 6 yr old, and treated with insulin at various doses. He had been taken Na valproate due to severe suicidal behaviour for two years, and he was hospitalized for bipolar disorder one year ago. On the physical examination, patient was short and cachectic (height: 137 cm, weight: 29 kg below –5 SD, BMI: 13,3 kg/m$^2$). Stage of male genital development in according to Tanner classification was P1, G1. Urine densities were low in different times (1 000–1 005). Biochemical parameters were as follow; fasting plasma glucose: 524 mg/dl, Na: 138 mEq/L, K: 4,6 mEq/L, urea: 30 mg/dl, creatinine: 0.7 mg/dl, plasma osmolality: 313 mosm/kg, Insulin: 2.97 mU/ml, C peptid: 0.5 ng/ml, HbA1C: 12,3%. Urine density was also changing between 1 000 and 1 005, and plasma ADH level was 0.7 pg/ml. Like his older brother, urine osmolality did not increase after water restriction test (250 mosm/kg), and showed significant increment after desmopressin administration (4 µg iv) (urine osmolarity: 650 mosm/kg). Bilateral optic atrophy and horizontal nystagmus were found in ophthalmologic examination like 1$^{st}$ patient. Neural and sensory hearing loss was detected by an audiometric evaluation. Ultrasonographic evaluation revealed bilateral grade 4 hydronephrosis and vesicular distension (Figure 2). Hypophyseal magnetic resonance imaging showed signal loss in neurohypophysis in both patients (Figure 3). We diagnosed Wolfram Syndrome in 2 siblings with these results, and blood samples were obtained from all patients and available family members

for genetic study. Informed and written consent were obtained from all patients and family members.

*B-PCR Amplification and Sequencing of the WFS1 Gene*

Blood samples were obtained from all patients and available family members after informed consent was given. Total DNA was extracted from leukocytes by standard procedures. The WFS1 gene was amplified, and screened by polymerase chain reaction (PCR) and direct sequencing in Essen University Children's Hospital, Department of Pediatric Endocrinology- Germany.

## Results

We determined a deletion of 2 bp at nucleotide 1 522–1 523, Y508C frameshift, STOP codon 34 aminoacids apart (mutation is c.1522–1523delTA and at protein level Y508fsX421. c.1522–1523delTA, Y508fsX421) [7] . Both affected children were homozygous. The other family members were heterozygous. We could not investigate wolframin protein levels in mutant fibroblast cells derived from two siblings with mutation in the WFS1 gene due to technical failure.

## Discussion

WS is a rare disorder and since the identification of the WFS1 gene, more than 150 mutations (such as stop, frameshift, splice site and missense mutations) have been identified in WS patients, most likely resulting in a loss of wolframin function [6,10]. We determined a mutation (c. 1522–1523delTA, Y508fsX421) in exon 8. Affected 2 siblings were homozygous other family members were heterozygous in terms of this mutation. This mutation is probably a new mutation, because we checked for corresponding mutations in the literature and we determined 59 deletion mutations in WFS1 gene [8]. Nevertheless, we could find only 3 mutations at nucleotide 1 522–1 523 (c.1522–1536del15, c.1523–1524delAT and c.1523–1524delAT), [4,14,16].

Patients with WS present with diabetes mellitus followed by optic atrophy in the first decade, cranial diabetes insipidus and sensorineural deafness in the second decade, dilated renal outflow tracts early in the third decade, and multiple neurological abnormalities early in the fourth decade in ordinary WS [3]. On the contrary, severe dilated renal outflow tracts, and multiple neurological abnormalities appeared in second decade in our patients. We think that this mutation in WFS1 gene may be related to early development and appearance of clinical features of Wolfram syndrome, because clinical features of WS earlier appeared than expected time of classically WS. Both of our patients showed suicidal behaviour in they were yet 11 and 13 years old. Suicidal attemption is rare in normal conditions in these ages; therefore we think that WS may be responsible for this suicidal behaviour. Indeed psychiatric disturbances including psychosis, mood disorder and suicide have been reported at increased frequency in Wolfram patients

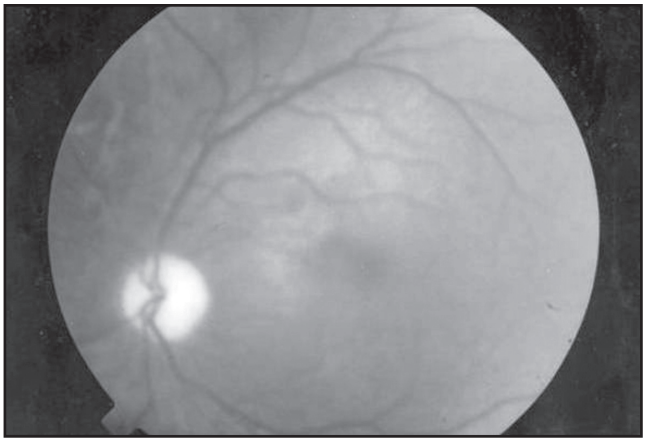

**Figure 1.** Bilateral optic atrophy of the index patient (patient 1).

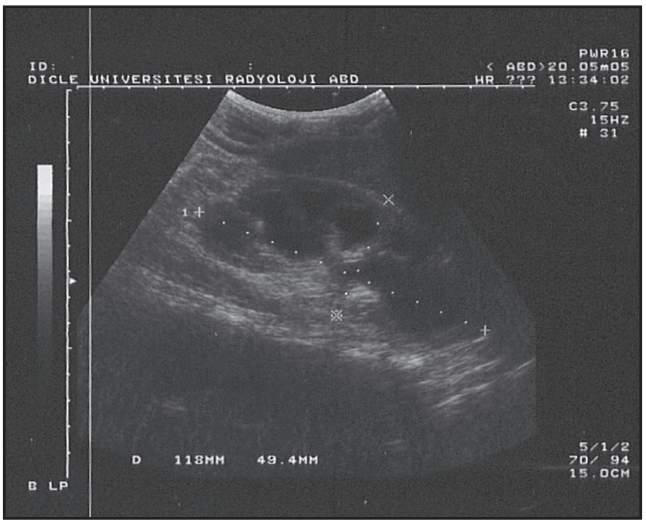


**Figure 2.** Bilateral grade 4 hydronephrosis and vesicular distension of the index patient in ultrasonographic evaluation (patient 1).

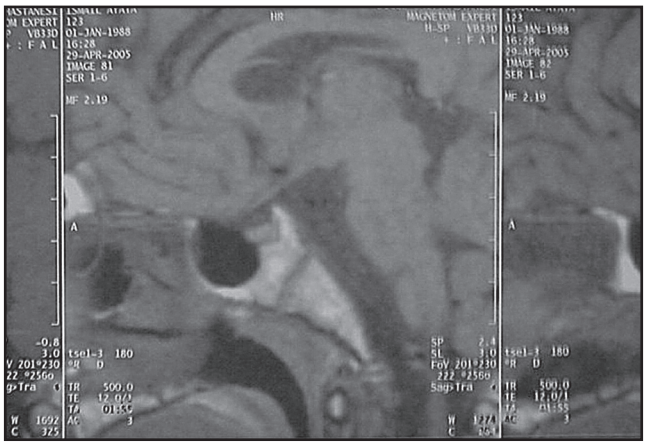

**Figure 3.** Pituitary MRI of the index patient. Signal loss was being showed in neurohypophysis (patient 1).

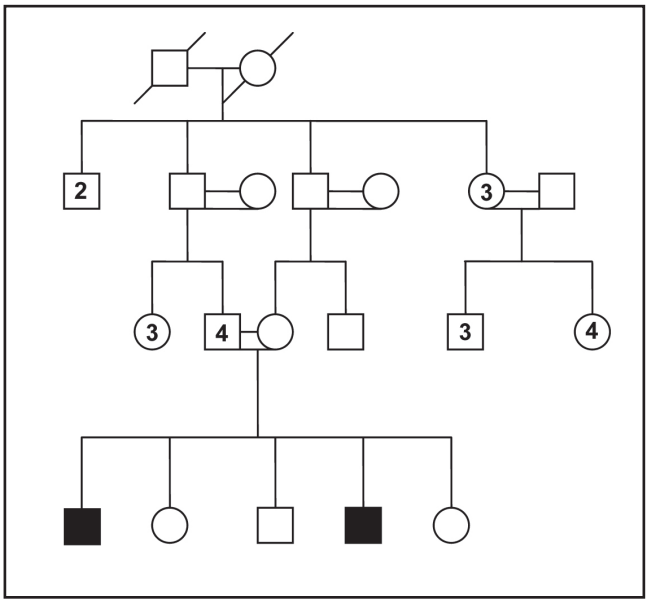


**Figure 4.** Pedigree of the all family. ■ - Patients with Wolfram's syndrome (male siblings).

and in heterozygous carriers of a Wolfram mutation. But whether there is a relation between type of mutation and clinical findings is not clear. Several studies have been published analyzing the WFS1 gene for mutations and/or polymorphisms that are associated with diabetes and psychiatric disorders. Although most studies showed no association between type of mutation and suicidal behaviour, two missense mutations demonstrated significant association with psychiatric disorders and diabetes mellitus [10]. Our findings may indicate that there is a relationship between type of mutation of WFS1 gene and mood disorder such as suicidal behaviour. Nevertheless private nature of the mutations in WS patients and the low frequencies make it difficult to determine the biological or clinical relevance of these mutations. The main handicap of this study was being limited only two patients with WS and their blood relatives. We could not find any data about suicidal behaviour in the heterozygous family members and blood relatives of the patients. Therefore, population association studies and functional studies of these variants will need to be performed to confirm these preliminary results.

**Conclusions:** We determined a new mutation in 2 siblings with Wolfram syndrome (c. 1522–1523delTA, Y508fsX421) and this mutation may be responsible for early appearance of clinical features of Wolfram syndrome, and there may be a relationship between this mutation and psychiatric disorders such as suicidal behaviour.

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