European Journal of Medical Genetics 55 (2012) 37–42

Contents lists available at SciVerse ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Original article

Rapidly progressive renal disease as part of Wolfram syndrome in a large inbred Turkish family due to a novel *WFS1* mutation (p.Leu511Pro)

Sevil Ari Yuca[a,*,1], Nanna Dahl Rendtorff[b,**,1], Houda Boulahbel[c], Marianne Lodahl[b], Lisbeth Tranebjærg[b,d], Yasar Cesur[a], Murat Dogan[a], Cahide Yilmaz[e], Cihangir Akgun[f], Mehmet Acikgoz[g]

[a] *Yuzuncu Yil University, School of Medicine, Department of Pediatric Endocrinology, Van, Turkey*
[b] *Wilhelm Johannsen Centre for Functional Genome Research, Department of Cellular and Molecular Medicine (ICMM), The Panum Institute, University of Copenhagen, Copenhagen, Denmark*
[c] *Biotech Research & Innovation Centre (BRIC) and Centre for Epigenetics, University of Copenhagen, Copenhagen, Denmark*
[d] *Department of Audiology, Bispebjerg Hospital, Copenhagen, Denmark*
[e] *Yuzuncu Yil University, School of Medicine, Department of Pediatric Neurology, Van, Turkey*
[f] *Yuzuncu Yil University, School of Medicine, Department of Pediatric Nephrology, Van, Turkey*
[g] *Yuzuncu Yil University, School of Medicine, Department of Pediatrics, Van, Turkey*

ARTICLE INFO

Article history:
Received 31 March 2011
Accepted 27 August 2011
Available online 23 September 2011

Keywords:
Autosomal recessive
Hearing impairment
Inbred
Missense
Mutation
Renal failure
WFS1
Wolfram syndrome

ABSTRACT

Wolfram syndrome, also named “DIDMOAD” (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness), is an inherited association of juvenile-onset diabetes mellitus and optic atrophy as key diagnostic criteria. Renal tract abnormalities and neurodegenerative disorder may occur in the third and fourth decade. The wolframin gene, *WFS1*, associated with this syndrome, is located on chromosome 4p16.1. Many mutations have been described since the identification of *WFS1* as the cause of Wolfram syndrome. We identified a new homozygous *WFS1* mutation (c.1532T>C; p.Leu511Pro) causing Wolfram syndrome in a large inbred Turkish family. The patients showed early onset of IDDM, diabetes insipidus, optic atrophy, sensorineural hearing impairment and very rapid progression to renal failure before age 12 in three females. Ectopic expression of the wolframin mutant in HEK cells results in greatly reduced levels of protein expression compared to wild-type wolframin, strongly supporting that this mutation is disease-causing. The mutation showed perfect segregation with disease in the family, characterized by early and severe clinical manifestations.

1. Introduction

Wolfram syndrome (WS), also named “DIDMOAD” (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness), is an inherited autosomal recessive disease associated with juvenile-onset diabetes mellitus (DM) and optic atrophy, as key diagnostic criteria [1]. It is a progressive neurodegenerative disorder. Urinary tract atony, ataxia, peripheral neuropathy and psychiatric illness develop in many patients [2]. Typically, diabetes insipidus (DI) and sensorineural hearing loss (HI) occur in the second decade, renal tract abnormalities occur in the third and neurological complications in the fourth decade [2,3].

Linkage between WS and the *WFS1* gene (encoding wolframin) was reported earlier [4,5,6]. Mutations (mainly missense) in *WFS1* can also cause isolated autosomal dominant low-frequency non-syndromic sensorineural hearing loss (LFSNHL) [7,8]. In addition, a *WFS1* missense mutation has been reported in two families with dominantly inherited HI and some members being affected by optic atrophy and impaired glucose regulation/diabetes [9,10]. Wolframin localizes primarily to the endoplasmic reticulum, as demonstrated in a variety of neurons in hippocampus CA1, amygdaloid areas and olfactory tubercule, as well as in inner hair cells [11,12]. Many mutations have been described since the identification of *WFS1* as the cause of Wolfram syndrome (KRESGE database: http://www.khri.med.umich.edu/research/lesperance_lab/low_freq.php). Disease-causing mutations include missense mutations, nonsense mutations, frameshift mutations, amino acid deletions and insertions. Genotypes associated with WS include homozygosity or compound heterozygosity, and disease mutations are distributed all over the gene.

* Corresponding author. Tel.: +90 533 523 90 50.
** Corresponding author. Tel.: +45 35 32 78 21; fax: +45 35 32 78 45.
E-mail addresses: sevilyuca@yahoo.com (S.A. Yuca), nannad@sund.ku.dk (N.D. Rendtorff).
[1] These authors contributed equally to this work.

1769-7212/$ – see front matter © 2011 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmg.2011.08.005

In the present study, we sequenced *WFS1* in patients with WS from four branches of an extended inbred Turkish family. We aimed to identify the disease-causing mutation, to correlate the mutation with the clinical findings in our patients, and to determine whether a molecular genetic screening strategy of predictive value in apparently unaffected siblings from WS families would be feasible.

2. Materials and methods

2.1. Subjects

The present study included DNA analysis of 20 individuals (11 males, 9 females) from a large Turkish family (Fig. 1). The diagnosis of WS was based on manifestation of DM, optic atrophy (OA) and other abnormalities associated with WS. As diagnostic criteria for diabetes mellitus, fasting blood glucose >126 mg/dl and HbA1c >6.5% were used. These rather low values were justified by the early diagnosis in all of the patients (from age 2–7 years).

Audiological evaluation included routine physical examination, audiography to determine hearing status, and a brain stem auditory evoked potential (BAEP) test to examine the central conduction time of the auditory pathways. The ophthalmological tests consisted of examination of fundus with slit lamp biomicroscopy, indirect funduscopy, corrected visual acuity, color vision tests using Ishihara color plates and visual fields testing by Goldman perimeter.

In all patients, we performed a water restriction test followed by arginine vasopressin administration (Desmopressin nazal) to diagnose DI. We discriminated between complete DI when the maximal urine concentration was less than 300 mOsm/kg and partial DI when the maximal urine concentration was 300–800 mOsm/kg.

Urinary tract was investigated by using ultrasonography and voiding cysto-ureterography. Fluoroscopy with contrast infusion was performed if there was any suspicion of reflux or detrusor external sphincter dyssynergia (DESD). Reduced flow rate and abnormal flow rate patterns were also taken into consideration in the diagnosis of DESD. In four patients, urodynamic evaluation consisted of pressure-flow studies. Cystometry was followed by uroflowmetry and simultaneous recording of intravesical pressure during voiding with a catheter in place. Renal failure was defined as glomerular filtration rate (GFR) <25 ml/min/1.73 m^2 and/or serum creatinine >2 mg/dl.

Cranial magnetic resonance imaging (MRI) was performed in all patients.

This study was approved by The Ethical Committee at Yuzuncu Yil University Medical School and followed the Helsinki Declaration. Parents of juvenile patients were informed about the study and gave written consent.

2.2. WFS1 mutation analysis

Blood samples were obtained from all available family members and genomic DNA was extracted from leukocytes by standard phenol chloroform procedure. For the molecular analysis of *WFS1*,

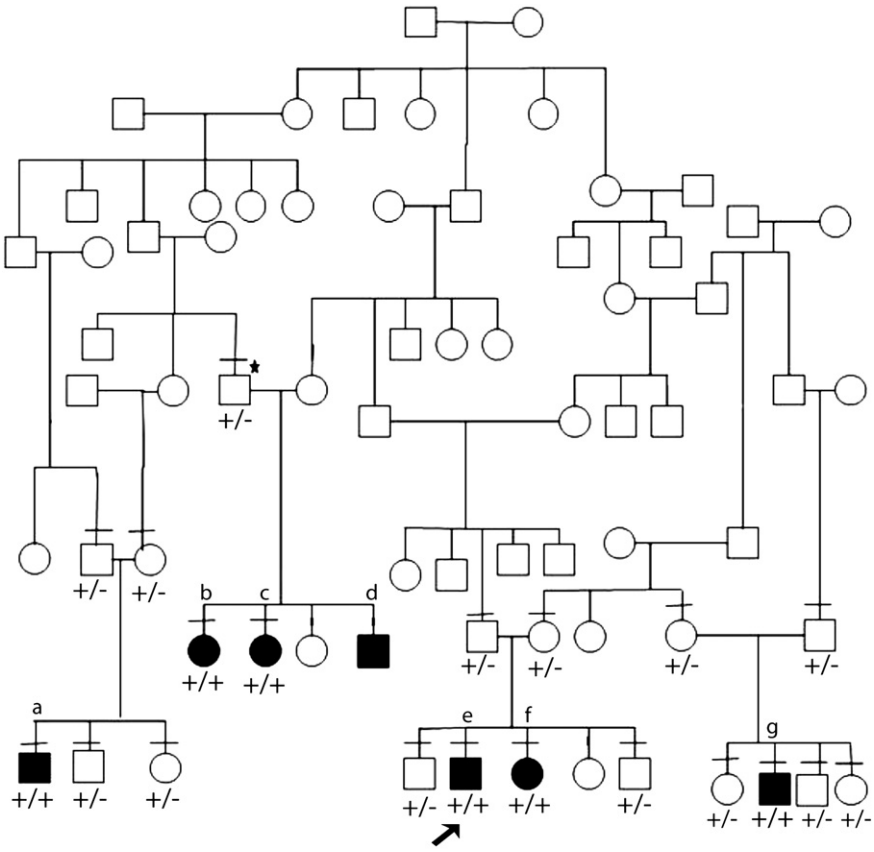

Fig. 1. Pedigree of the family investigated in this study. Affected individuals are denoted by a filled symbol. Individuals who were tested for mutation are indicated by a horizontal bar above the symbol. A man, denoted by an asterisk, has IDDM.

primers were designed to PCR amplify exons and surrounding intronic regions of *WFS1* (RefSeq NM_006005.2). Primer sequences and PCR conditions are available upon request. A DNA sample from the proband was used for sequence analysis of all 8 exons of *WFS1*. PCR products were sequenced using Big Dye Terminator Kit v1.1 (Applied Biosystems). Sequencing products were separated on an ABI 3130XL genetic analyzer (Applied Biosystems) according to the manufacturer's instructions. The identified mutation was checked against databases of published polymorphisms and mutations (http://www.khri.med.umich.edu/research/lesperance_lab/low_freq.php; http://www.hgmd.cf.ac.uk/ac/index.php). In order to study the segregation of the c.1532T>C mutation with the disease in the family we used direct sequencing of PCR amplified genomic DNA. The mutation in question was absent when tested in 126 control chromosomes from 63 UK Caucasian control individuals (from Sigma Aldrich).

The evolutionary conservation of wolframin amino acids among *WFS1* orthologues was investigated using the ClustalW2 multiple sequence alignment program and the BoxShade 3.21 program.

2.3. Protein expression analysis of the p.Leu511Pro wolframin mutant

Expression vector for wild-type, N-terminally myc epitope-tagged wolframin was kindly provided by Dr. Timothy G. Barrett, UK [40]. Mutations were introduced in wolframin using the QuickChange procedure (Stratagene) and confirmed by sequencing. Human embryonic kidney (HEK) cells were cultured and transfected as described [13]. Briefly, 2×10^5 cells were seeded per 9.6 cm^2 dish and co-transfected the following day, using 0.5 μg of wolframin and EGFP expression plasmid, respectively, complexed with 3 μl FuGENE 6 reagent (Roche), according to the manufacturer's instructions. After 16 h, the cells were lysed with SDS-PAGE sample buffer (2% sodium dodecyl sulphate, 62 mM Tris–HCL (pH 6.8), 10% glycerol, 50 mM dithiothreitol, 0.12% bromophenol blue). Aliquots of the cell lysates were subjected to SDS-PAGE and immunoblotting analysis with antibody against the myc-tag on wolframin or EGFP, using standard immunoblotting procedures.

3. Results

The mean age of the seven affected patients was 10.8 ± 4.4 years, with the range of 6–19 years, at the time of this study. The clinical features are summarized in Table 1. All seven patients had DM and six clearly had WS. One patient (number IV in Table 1) and his mother refused DNA analysis. The seven patients were all related (Fig. 1).

The patients were diagnosed with type I DM in early age and the mean age for diagnosis was 4.5 ± 1.9 years (minimum 2 years, maximum 7 years). Moreover, the father (unaffected in the pedigree) of patients II, III and IV, respectively, had IDDM at age 40 but no other components of WS.

Although hyperglycemia and glycosuria revealed diabetes mellitus in all patients, only two cases presented with diabetic ketosis (serum C-peptide level was <0.5 iU/ml at the time of analysis). C-peptide levels showed mild insulin deficiency in all the rest of the cases (mean serum C-peptide values were 0.8 iU/ml). Median glaciated hemoglobin (HbA1c) was 8.5% at the time of DM diagnosis. All of the patients receive treatment for type 1 diabetes mellitus. Subsequently patients were diagnosed with DİDMOAD syndrome. Neither diabetic retinopathy nor nephropathy have been detected after 11 years of follow up.

The diagnosis of DI by water deprivation test was made for five patients, whereas the remaining three were negative. One patient (number VII in Table 1) was responsive to intranasal ADH treatment. The urine osmolality and specific gravity of three of the other patients with DI did not improve with nasal desmopressin, and analysis of renal function revealed chronic renal failure. Two patients with no manifestation of DI were under 7 years of age (number I and VI in Table 1). Urodynamic studies revealed atonic bladder, detrusor weakness and residual urine in the bladder after miction in the three female patients who subsequently developed renal failure within two years, defined as glomerular filtration rate (GRF) <25 ml/min/1.73 m^2 and/or serum creatinine values >2 mg/dl. Our patients had end-stage renal failure with GFR <10 ml/min/1.73 m^2. The cause of renal failure was therefore likely to be secondary to residual urine and retrograde renal injury due to neurogenic bladder and free water loss due to central diabetes insipidus. These patients are subjected to haemodialysis.

Sensorineural HI was present in five patients. The hearing impairment was progressive and showed variable audiological patterns. Patient V (Fig. 1: individual e) had at age 14 bilateral 40–60 dB HL at all frequencies between 500 and 4000 Hz. Patient VI (Fig. 1: individual f) had at age 11 bilateral profound >110 dB HL at all frequencies. Patient VII (Fig. 1: individual g) had at age 19 bilateral 50 dB HL at 500–1000 Hz and sloping audiogram with 70–110 dB HL at frequencies 2000–4000 Hz, indicating a more severe HI at higher frequencies in the latter individual, but equal affection across low and high frequencies in individuals V and VI (audiograms are available, but not shown). Two of the patients use a hearing aid.

Six patients had optic atrophy without evidence of rapid progression, and despite severe visual impairment as measured by visual acuity (Table 1), no individuals were completely blind.

Cranial imaging was performed in six patients, and revealed, bilaterally, thinning of the optic nerves in one of these and hypoplasia of the hypophysis gland in three patients. Cerebral atrophy was not observed in any patients.

Table 1
Clinical manifestations in seven Wolfram syndrome patients.

Patient No.	Pedigree No.	Age (year)	Gender	DM	Optic atrophy	Visual acuity	Dİ	Hearing impairment	Puberty	Neurogenic Bladder	Renal failure	MRI
I	a	6	M	2	–	–	–	–	–	–	–	Normal
II	b	10	F	7	8	0.2	8	8	10	8	9	Normal
III	c	12	F	6	9	0.15	9	10	11	9	11.5	Hypoplastic hypophysis and nervus opticus
IV[a]	d	6	M	3	6	0.3	–	–	–	–	–	NI
V	e	17	M	4	6	0.05	10	9[b]	13	17	–	Hypoplastic hypophysis
VI	f	14	F	5	6	0.05	8	7[b]	11	8.5	10	Normal
VII	g	19	M	2	6	0.3	4	8[b]	14	–	–	Hypoplastic hypophysis

Notes: Age is patient age at the time of this study. Numbers indicate age at the time of diagnosis in years (except for visual acuity). M: male; F: female; (–) absence of condition; DM: Diabetes mellitus; DI: Diabetes insipidus; NI: Not investigated.

[a] Not analyzed at the DNA level, but examined clinically.

[b] Audiograms available (not shown).

3.1. Growth and puberty

The height of four patients (Patients II, V, VI, and VII) was below the third percentile for the age and gender. While growth patterns on the growth charts of patients II, V and VI were normal until age 7, decreased growth velocity was evident subsequently. The height of these three patients decreased to below the third percentile at the age of 10 years. The height of patient VII was found to be below the third percentile at age 8 at the time of referral to our clinic. No evidence of growth hormone deficiency was found in the patients. Pubertal onset was normal in all patients, and the mean age of pubertal onset was 12 ± 2 years.

3.2. WFS1 sequencing analysis

To establish a molecular diagnosis, DNA was collected from 20 individuals, six of whom were affected with Wolfram syndrome (I, II, III, V, VI and VII, Table 1) (patient IV, and his mother declined DNA analysis). Sequencing of *WFS1* in the proband identified a homozygous sequence change c.1532T>C in exon 8, leading to a substitution of leucine for proline at position 511 of wolframin (p.Leu511Pro) (Fig. 2a). The mutation is novel and was absent in 126 control chromosomes from 63 Caucasian control individuals. We identified homozygosity for the *WFS1* p.Leu511Pro mutation in six WS patients (patient IV was not analyzed due to aforementioned refusal of DNA analysis), thus showing perfect segregation for a recessive disease in the family (Fig. 1). As expected, the father of patients II–IV, who only had IDDM but not WS, was heterozygous for the p.Leu511Pro mutation Leucine at position 511 is conserved in evolutionary distant species such as mouse, rat, chicken, frog, and zebrafish (Fig. 2b) strongly indicating that the p.Leu511Pro mutation underlies Wolfram syndrome in the family.

3.3. Protein expression analysis of the identified p.Leu511Pro wolframin mutant

We next performed functional expression analysis to investigate whether the identified mutation may be pathogenic. Thus, we transiently transfected human embryonic kidney (HEK) cells with plasmid expressing myc epitope-tagged wild-type wolframin or wolframin harboring the p.Leu511Pro mutation and analyzed the cells for the expression level of the exogenous wolframin by immunoblotting for the myc-tag. This analysis revealed that the p.Leu511Pro wolframin mutant showed greatly decreased expression compared to wild-type wolframin (Fig. 3, upper panel). The p.Arg629Trp mutation previously shown to result in an unstable wolframin protein and WS [14] was included as a control. Furthermore, to control for equal transfection efficiencies across all cell populations and equal loading of the samples, we immunoblotted for EGFP that we had co-transfected together with wolframin. As shown in (Fig. 3, lower panel), the samples showed equal expression of EGFP, confirming equal transfection across all cell populations and equal loading of the samples. In conclusion the protein expression analysis suggests that the p.Leu511Pro wolframin mutation is pathogenic by causing decreased wolframin expression levels.

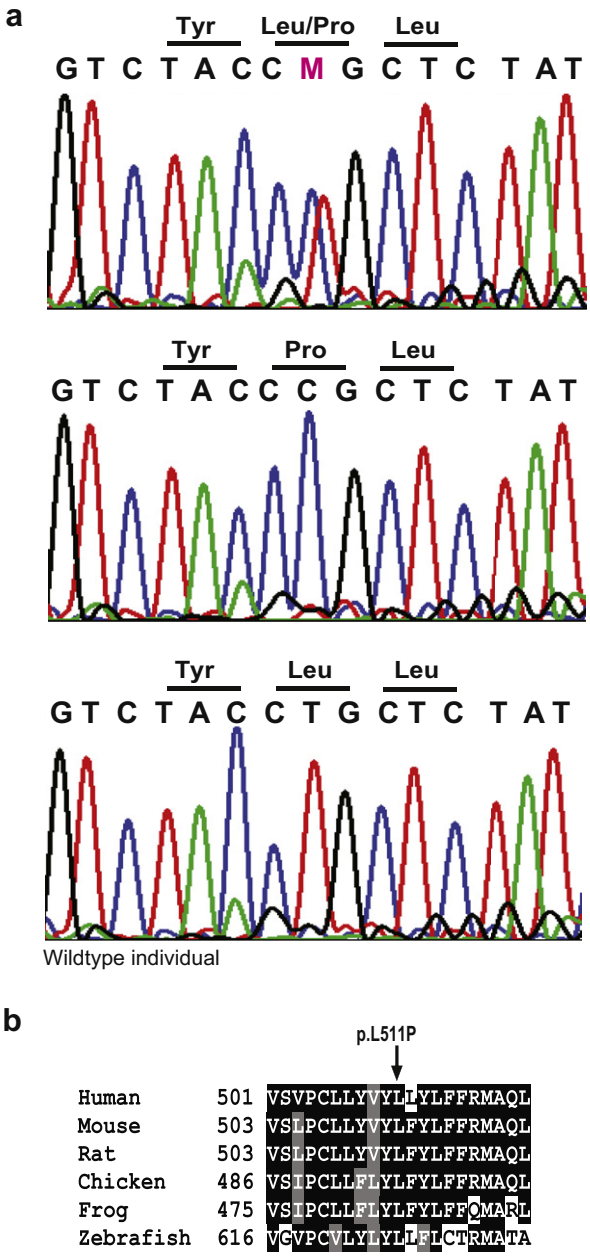

Fig. 2. (a) Representative sequence chromatogram for the *WFS1* missense mutation in an heterozygous and homozygous individual, respectively, for the c.1532T>C mutation compared to a normal control. Nomenclature of the mutation refers to the *WFS1* RefSeq NM_006005.2, with nucleotide number +1 being A of the start codon ATG. The mutation is homozygous in individuals affected with Wolfram syndrome. (b) Evolutionary conservation of the amino acid mutated in the patients.

4. Discussion

The essential features of Wolfram syndrome diagnosis are juvenile-onset diabetes mellitus and optic atrophy [1,15]. Patients usually present with DM followed by OA in the first decade. IDDM is often the first clinical sign of Wolfram syndrome, but differs from classical IDDM because of normal autoimmune laboratory parameters [16,17], and not being prone to diabetic ketosis [18] nor to diabetic retinopathy [17,19]. Central DI and sensorineural HI are mostly detected in the second decade, dilated renal outflow tracts early in the third decade and multiple neurological abnormalities early in the fourth decade [15]. In our patients, DM was diagnosed at 4.5 ± 1.9 years of age, and presented with hyperglycemia and glycosuria, but only two cases displayed diabetic ketosis. C-peptide levels showed mild insulin deficiency in all cases. Median glaciated hemoglobin (HbA1C %) was 8.5% at the time of diagnosis. Islet antibodies were not analyzed. None of the patients showed diabetic retinopathy or nephropathy at any time of the study. Six patients had OA from age six (6.3 ± 1.3 years). Sensorineural hearing impairment was found in five patients who were affected at 8.3 ± 1

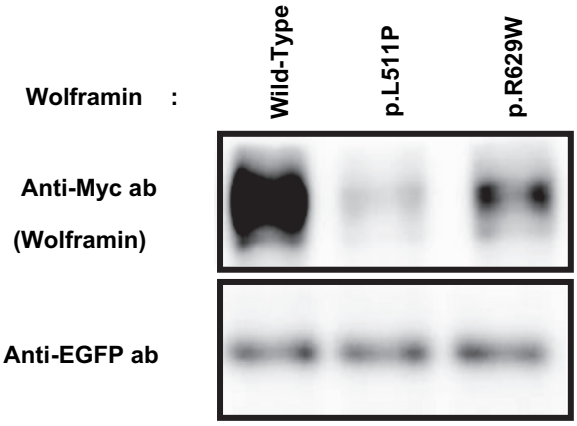

Fig. 3. Functional protein expression analysis of the wolframin missense mutant. Wild-type or mutant myc epitope-tagged wolframin was transiently co-expressed with EGFP in HEK293 cells. The cells were lysed after 24 h and the cell extracts were subjected to SDS-PAGE and immunoblotting for the myc-tag and EGFP.

years. DI was diagnosed in five patients (II, III, V, VI, and VII) with a mean age at diagnosis of 8.3 ± 0.5 years. While one male patient responded to intranasal ADH treatment, three female patients were resistant to ADH therapy. Two patients (both age six) had no evidence of DI yet.

Urological abnormalities in WS are variable, including various degrees of upper urinary tract dilatation and bladder dysfunction. An atonic bladder with a large capacity has been reported most commonly. Cremers et al. [19] and Barrett et al. [15] reported the prevalence of urinary tract abnormalities to be 13% and 58%, respectively. The changes reported are variable, but urinary tract dilatation is frequent [22,23,24]. In the present study, 57% of the patients had urological complications which began at age 8. In our patients, urethral dilatation, vesico-urethral reflux, neurogenic bladder and recurrent urinary infections were demonstrated. Although sterile intermittent catheter application was used in female patients, renal failure was observed only two years after the detection of neurogenic bladder. The three female patients with renal failure were younger than previously reported [24,25].

Imaging findings in WS have rarely been reported. Cerebellar, cerebral and pontine atrophy, and enlarged ventricles have rarely been observed [26,27,28]. Pakdemirli et al. [29] showed typical MRI findings, including absence of high signal of the neurohypophysis, thinning of left optic nerve, optic chiasm and tracts, and atrophy of the brain stem, vermis, and cerebral cortex. Ari et al. [30] described thinning of the optic nerve and thinning and localized atrophy of the optic chiasm in cranial MRI. In our patients, cranial MRI examinations revealed bilateral thinning of the optic nerves (Patient III) and hypoplasia of hypophyseal gland (Patient III, V and VII).

Molecular genetic analysis is important in monogenic diabetes in order to diagnose WS so that adequate treatment can be provided [31]. Many mutations have been described since the identification of *WFS1* as the cause of Wolfram syndrome [5,6,12,20,21,32,33]. A few mutations have been reported in patients from Turkey [34,35]. The splice-site mutation at c.460+1G->A was reported in a Turkish family from Germany [36]. Aluclu et al. [34] diagnosed Wolfram syndrome in two male siblings and found a new homozygous mutation, p.Tyr508fsX421 (c.1522-1523delTA). A p.Arg629Trp (c.1885C>T) mutation in *WFS1* was found in homozygosity in two Wolfram syndrome patients by Kadayifci et al. [35]. In our study, a previously unreported homozygous *WFS1* mutation, p.Leu511Pro, was identified. Ectopic expression in HEK cells of wolframin with the p.Leu511Pro mutation resulted in strongly reduced levels of mutant wolframin as compared to wild-type wolframin, supporting the conclusion that the mutation is disease-causing. The mutation segregated in perfect agreement with recessive inheritance of the disorder. Evidence for genotype/phenotype relevance on the clinical variety of WFS was demonstrated in recent studies [37,38]. The family reported here illustrates exceptionally early onset, and rapid progression to renal insufficiency at a very early age. It is noteworthy that the severe and early clinical affection did not include any signs of psychiatric or neurological disease, but the patients are still young and should be followed closely in the future.

In one report, an individual homozygous for a missense *WFS1* mutation (p.Ala716Thr) was described displaying features of WS, specifically juvenile diabetes mellitus and cataracts, but lacking optic atrophy that is part of the definition of WS (OMIM 606201) [8]. In another report, a patient, homozygous for another missense mutation (p.Pro885Leu) had a mild phenotype and had not developed diabetes insipidus, renal dysfunction, or neurological abnormalities [33]. Our WS patients also had a homozygous mutation, but we observed a more severe and a more rapid progression of clinical manifestations as compared to other cases [15,33]. Thus, most patients above age >10 had full blown WS and the three female patients had neurogenic bladder and renal failure.

Heterozygous carriers of *WFS1* mutations may have an increased incidence of psychiatric illness [39]. Heterozygous *WFS1* mutations were identified in 14 members of our family (14/22). A father had type 1 DM at age 40. All heterozygous individuals were evaluated for hearing impairment, optic atrophy and psychiatric illness, but none of these diseases were observed.

In conclusion, we report seven familial patients with WS. A severe clinical picture and rapid progression of renal disease were observed since 80% of the patients had developed all the typical features by age 10 years, but they had escaped, so far psychiatric and neurological features. Strikingly, severe renal affection was diagnosed in the three female patients, two of whom had chronic renal failure by the age of 12.

Our report strongly supports efforts for early detection of WS and very close clinical follow up in order to treat and prevent the severe medical symptoms and the possibility of providing comprehensive genetic counseling in affected families.

Conflict of interest

Authors have no competing interests to declare.

Acknowledgements

We are grateful to the family who participated in this study. The Lundbeck Foundation (grant no. 32011) and Widex AS are acknowledged for financial support to the Audiogenetic Research Group at ICMM. The molecular genetic studies were performed at the Wilhelm Johannsen Centre for Functional Genome Research, established by the Danish National Research Foundation.

References

[1] D.J. Wolfram, H.P. Wagener, Diabetes mellitus and simple optic atrophy among siblings: report of four cases, Mayo. Clin. Proc. 13 (1938) 715–718.
[2] T.G. Barrett, S.E. Bundey, Wolfram (DIDMOAD) syndrome, J. Med. Genet. 34 (1997) 838–841.
[3] F. Khanim, J. Kirk, F. Latif, T.G. Barrett, WFS1/wolframin mutations, Wolfram syndrome, and associated diseases, Hum. Mutat. 17 (2001) 357–367.
[4] M.H. Polymeropoulos, R.G. Swift, M. Swift, Linkage of the gene for Wolfram syndrome to markers on the short arm of chromosome 4, Nat. Genet. 8 (1994) 95–97.
[5] H. Inoue, Y. Tanizawa, J. Wasson, P. Behn, K. Kalidas, E. Bernal-Mizrachi, M. Mueckler, H. Marshall, H. Donis-Keller, P. Crock, D. Rogers, M. Mikuni, H. Kumashiro, K. Higashi, G. Sobue, Y. Oka, M.A. Permutt, A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome), Nat. Genet. 20 (1998) 143–148.

[6] T.M. Strom, K. Hortnagel, S. Hofmann, F. Gekeler, C. Scharfe, W. Rabl, K.D. Gerbitz, T. Meitinger, Diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD) caused by mutations in a novel gene (wolframin) coding for a predicted transmembrane protein, Hum. Mol. Genet. 7 (1998) 2021–2028.
[7] I.N. Bespalova, C.G. Van, S.J. Bom, D.J. Brown, K. Cryns, A.T. DeWan, A.E. Erson, K. Flothmann, H.P. Kunst, P. Kurnool, T.A. Sivakumaran, C.W. Cremers, S.M. Leal, M. Burmeister, M.M. Lesperance, Mutations in the Wolfram syndrome 1 gene (WFS1) are a common cause of low frequency sensorineural hearing loss, Hum. Mol. Genet. 10 (2001) 2501–2508.
[8] T.L. Young, E. Ives, E. Lynch, R. Person, S. Snook, L. MacLaren, T. Cater, A. Griffin, B. Fernandez, M.K. Lee, M.C. King, Non-syndromic progressive hearing loss DFNA38 is caused by heterozygous missense mutation in the Wolfram syndrome gene WFS1, Hum. Mol. Genet. 10 (2001) 2509–2514.
[9] H. Eiberg, L. Hansen, B. Kjer, T. Hansen, O. Pedersen, M. Bille, T. Rosenberg, L. Tranebjaerg, Autosomal dominant optic atrophy associated with hearing impairment and impaired glucose regulation caused by a missense mutation in the WFS1 gene, J. Med. Genet. 43 (2006) 435–440.
[10] R. Valero, S. Bannwarth, S. Roman, V. Paquis-Flucklinger, B. Vialettes, Autosomal dominant transmission of diabetes and congenital hearing impairment secondary to a missense mutation in the WFS1 gene, Diabet. Med. 25 (2008) 657–661.
[11] K. Takeda, H. Inoue, Y. Tanizawa, Y. Matsuzaki, J. Oba, Y. Watanabe, K. Shinoda, Y. Oka, WFS1 (Wolfram syndrome 1) gene product: predominant subcellular localization to endoplasmic reticulum in cultured cells and neuronal expression in rat brain, Hum. Mol. Genet. 10 (2001) 477–484.
[12] K. Cryns, S. Thys, L.L. Van, Y. Oka, M. Pfister, N.L. Van, R.J. Smith, J.P. Timmermans, C.G. Van, The WFS1 gene, responsible for low frequency sensorineural hearing loss and Wolfram syndrome, is expressed in a variety of inner ear cells, Histochem. Cell Biol. 119 (2003) 247–256.
[13] U. Doehn, C. Hauge, S.R. Frank, C.J. Jensen, K. Duda, J.V. Nielsen, M.S. Cohen, J.V. Johansen, B.R. Winther, L.R. Lund, O. Winther, J. Taunton, S.H. Hansen, M. Frodin, RSK is a principal effector of the RAS–ERK pathway for eliciting a coordinate promotile/invasive gene program and phenotype in epithelial cells, Mol. Cell 35 (2009) 511–522.
[14] S. Hofmann, C. Philbrook, K.D. Gerbitz, M.F. Bauer, Wolfram syndrome: structural and functional analyses of mutant and wild-type wolframin, the WFS1 gene product, Hum. Mol. Genet. 12 (2003) 2003–2012.
[15] T.G. Barrett, S.E. Bundey, A.F. Macleod, Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome, Lancet 346 (1995) 1458–1463.
[16] T. Gunn, R. Bortolussi, J.M. Little, F. Andermann, F.C. Fraser, M.M. Belmonte, Juvenile diabetes mellitus, optic atrophy, sensory nerve deafness, and diabetes insipidus–a syndrome, J. Pediatr. 89 (1976) 565–570.
[17] J.P. Monson, B.J. Boucher, HLA type and islet cell antibody status in family with (diabetes insipidus and mellitus, optic atrophy, and deafness) DIDMOAD syndrome, Lancet 1 (1983) 1286–1287.
[18] C. Blasi, F. Pierelli, E. Rispoli, M. Saponara, E. Vingolo, D. Andreani, Wolfram's syndrome: a clinical, diagnostic, and interpretative contribution, Diabetes Care 9 (1986) 521–528.
[19] C.W. Cremers, P.G. Wijdeveld, A.J. Pinckers, Juvenile diabetes mellitus, optic atrophy, hearing loss, diabetes insipidus, atonia of the urinary tract and bladder, and other abnormalities (Wolfram syndrome). A review of 88 cases from the literature with personal observations on 3 new patients, Acta Paediatr. Scand. Suppl. (1977) 1–16.
[20] K. Cryns, M. Pfister, R.J. Pennings, S.J. Bom, K. Flothmann, G. Caethoven, H. Kremer, I. Schatteman, K.A. Koln, T. Toth, S. Kupka, N. Blin, P. Nurnberg, H. Thiele, P.H. van de Heyning, W. Reardon, D. Stephens, C.W. Cremers, R.J. Smith, C.G. Van, Mutations in the WFS1 gene that cause low-frequency sensorineural hearing loss are small non-inactivating mutations, Hum. Genet. 110 (2002) 389–394.
[21] L. Tranebjærg, Wolframin 1-related disease and hearing. in: S. Kóks, E. Vasar (Eds.), Emerging Link between the Emotional Brain and Endocrine Pancreas. Research Signpost, 2008, pp. 107–124 (Chapter 7).
[22] S. Tekgul, O. Oge, E. Simsek, N. Yordam, S. Kendi, Urological manifestations of the Wolfram syndrome: observations in 14 patients, J. Urol. 161 (1999) 616–617.
[23] S. Aboseif, M. Gasparini, R. Schmidt, E. Tanagho, Wolfram's (DIDMOAD) syndrome and its urological manifestation, Br. J. Urol. 72 (1993) 106–111.
[24] G.B. Piccoli, E. Mezza, A. Jeantet, G.P. Segoloni, An uncommon genetic syndrome with acute renal failure in a 30-year-old diabetic patient, Nephrol. Dial. Transplant. 18 (2003) 206–208.
[25] A. Sumboonnanonda, A. Vongjirad, V. Suntornpoch, K. Angsusingha, P. Parichatikanond, T. Laohapand, Renal failure in two patients with Wolfram syndrome, J. Pediatr. Endocrinol. Metab. 10 (1997) 645–651.
[26] O. Kehl, U. Keller, DIDMOAD syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, deafness) with cerebello-pontine atrophy, Schweiz. Med. Wochenschr. 112 (1982) 348–352.
[27] A.T. Soliman, B. Bappal, A. Darwish, A. Rajab, M. Asfour, Growth hormone deficiency and empty sella in DIDMOAD syndrome: an endocrine study, Arch. Dis. Child. 73 (1995) 251–253.
[28] C. Leiva-Santana, A. Carro-Martinez, A. Monge-Argiles, A. Palao-Sanchez, Neurologic manifestations in Wolfram's syndrome, Rev. Neurol. (Paris) 149 (1993) 26–29.
[29] E. Pakdemirli, N. Karabulut, L.S. Bir, Y. Sermez, Cranial magnetic resonance imaging of Wolfram (DIDMOAD) syndrome, Australas. Radiol. 49 (2005) 189–191.
[30] S. Ari, U. Keklikci, I. Caca, K. Unlu, H. Kayabasi, Wolfram syndrome: case report and review of the literature, Compr. Ther. 33 (2007) 18–20.
[31] A.S. Slingerland, Monogenic diabetes in children and young adults: challenges for researcher, linician, and patient, Rev. Endocr. Metab. Disord. 7 (2006) 171–185.
[32] E. Domenech, M. Gomez-Zaera, V. Nunes, Wolfram/DIDMOAD syndrome, a heterogenic and molecularly complex neurodegenerative disease, Pediatr. Endocrinol. Rev. 3 (2006) 249–257.
[33] C. Hardy, F. Khanim, R. Torres, M. Scott-Brown, A. Seller, J. Poulton, D. Collier, J. Kirk, M. Polymeropoulos, F. Latif, T. Barrett, Clinical and molecular genetic analysis of 19 Wolfram syndrome kindreds demonstrating a wide spectrum of mutations in WFS1, Am. J. Hum. Genet. 65 (1999) 1279–1290.
[34] M.U. Aluclu, M. Bahceci, A. Tuzcu, S. Arikan, D. Gokalp, A new mutation in WFS1 gene (C.1522-1523delTA, Y508fsX421) may be responsible for early appearance of clinical features of Wolfram syndrome and suicidal behaviour, Neuro. Endocrinol. Lett. 27 (2006) 691–694.
[35] A. Kadayifci, Y. Kepekci, Y. Coskun, Y. Huang, Wolfram syndrome in a family with variable expression, Acta Medica. (Hradec. Kralove) 44 (2001) 115–118.
[36] J.M. van den Ouweland, K. Cryns, R.J. Pennings, I. Walraven, G.M. Janssen, J.A. Maassen, B.F. Veldhuijzen, A.B. Arntzenius, D. Lindhout, C.W. Cremers, C.G. Van, L.D. Dikkeschei, Molecular characterization of WFS1 in patients with Wolfram syndrome, J. Mol. Diagn. 5 (2003) 88–95.
[37] P.A. Zalloua, S.T. Azar, M. Delepine, N.J. Makhoul, H. Blanc, M. Sanyoura, A. Lavergne, K. Stankov, A. Lemainque, P. Baz, C. Julier, WFS1 mutations are frequent monogenic causes of juvenile-onset diabetes mellitus in Lebanon, Hum. Mol. Genet. 17 (2008) 4012–4021.
[38] A. Cano, C. Rouzier, S. Monnot, B. Chabrol, J. Conrath, P. Lecomte, B. Delobel, P. Boileau, R. Valero, V. Procaccio, V. Paquis-Flucklinger, B. Vialettes, Identification of novel mutations in WFS1 and genotype–phenotype correlation in Wolfram syndrome, Am. J. Med. Genet. A 143A (2007) 1605–1612.
[39] R.G. Swift, M.H. Polymeropoulos, R. Torres, M. Swift, Predisposition of Wolfram syndrome heterozygotes to psychiatric illness, Mol. Psychiatry 3 (1998) 86–91.
[40] M. Zatyka, C. Ricketts, G. da Silva Xavier, J. Minton, S. Fenton, S. Hofmann-Thiel, G.A. Rutter, T.G. Barrett, Sodium–potassium ATPase 1 subunit is a molecular partner of Wolframin, an endoplasmic reticulum protein involved in ER stress, Hum. Mol. Genet. 15 (2008) 190–200.