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ORIGINAL ARTICLE

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Clinical and molecular assessment of 13 Iranian families with Wolfram syndrome

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Abstract

Purpose Wolfram syndrome (WS) is a rare genetic disorder described by a pattern of clinical manifestations such as diabetes mellitus, diabetes insipidus, optic nerve atrophy, sensorineural hearing loss, urinary tract abnormalities, and psychiatric disorders. *WFS1* and *WFS2* loci are the main genetic loci associated with this disorder.

Methods In the current study, we investigated associations between these loci and WS *via* STR markers and homozygosity mapping in 13 Iranian families with WS. All families were linked to *WFS1* locus.

Results Mutation analysis revealed four novel mutations (Q215X, E89X, S168Del, and E391Sfs*51) in the assessed families. Bioinformatics tools confirmed the pathogenicity of the novel mutations. Other identified mutations were previously reported in other populations for their pathogenicity.

Conclusions The current study adds to the mutation repository of WS and shows a panel of mutations in Iranian population. Such panel would facilitate genetic counseling and prenatal diagnosis in families with WS cases.

Keywords Wolfram Syndrome · WFS1

Introduction

Wolfram syndrome (WS) was first described in 1938. It is a rare genetic disorder characterized by a constellation of clinical manifestations such as diabetes mellitus (DM), diabetes insipidus (DI), optic nerve atrophy (OA), sensorineural hearing loss (SNHL), urinary tract abnormalities, and psychiatric disorders. The underlying etiology includes a neurodegenerative process, although recent studies suggest a neurodevelopment abnormality beginning early in the disease course [1]. WS is associated with a high rate of morbidity and mortality depending on the organ systems involved. Chronic progressive and debilitating nature of the disease and the severe behavioral and psychological abnormalities associated with this disorder including depression and suicidal tendency further contribute to the morbidity and mortality [2, 3].

This genetic disorder is usually considered to have an autosomal recessive inheritance [4]. So far, two loci namely *WFS1* and *WFS2* are known. The main responsible gene is *WFS1* for which over two hundred mutations have been reported from different ethnic groups. The protein encoded by the *WSF1* gene is wolframin. Wolframin is localized in endoplasmic reticulum (ER) membrane of pancreatic β-cells, neurons [5], and several other tissues including spinal cord, heart, muscle, liver, and kidneys [6]. This protein participates in several aspects of ER functions such as membrane trafficking, excretion, processing, and calcium

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balance [7]. As a calmomodulin-binding protein, it might contribute in calcium signal transduction [7]. Animal studies have shown the role of wolframin in the processing of the arginine vasopressin-precursor and the survival of the supraoptic and the supraventricular hypothalamic nuclei cells [8]. Such critical functions of wolframin explain the wide range of signs and symptoms in WS. For instance, the WS-associated diabetes is caused by insulinopenia due to degeneration of β-cells [7]. Moreover, as calcium discharges are crucial for neuron excitability and survival, it is plausible that retinal ganglion cells that have high activity are damaged by wolframin deficiency [9]. The same mechanism might be involved in the pathogenesis of WS-associated deafness.

The relatively high incidence of the disease in the Middle East including Iran and Northern Africa might be attributed to marriages among relatives. Our institution being one of the referral centers for pediatric diseases in the country admits and handles quite a considerable number of otherwise rare diseases, in different pediatric specialties and subspecialties. Therefore, we have been able to evaluate a considerable number of WS patients for different aspects of clinical manifestations. To our knowledge, this is the largest series reported to date in the country. In this study, we report 23 cases of WS from consanguineous marriages presented to the Children's Medical Center along with a review of relevant literature. Although the medical and family histories and clinical findings are essential for the diagnosis of WS, genetic testing must confirm the diagnosis.

Methods

Over a period of 10 years, all children with insulin-dependent DM presented to our center (inpatient/outpatient) that had optic atrophy, DI or a positive family history of WS were enrolled in this study. Diagnosis of WS was based on the following criteria: presence of insulin dependent DM along with optic atrophy unexplained by any other disease and/or some other abnormalities unassociated with WS. Children were clinically investigated for additional symptoms of WS in various organ systems. All children underwent a thorough physical exam including endocrinological, ophthalmological, neurological, urogenital, and psychiatric assessments performed by a specialized team. Audiological evaluation included routine physical examination, audiography (across a range of frequencies from 125 to 18000 Hz) to explore hearing impairments. A brainstem auditory evoked potential test and the visual evoked potential were also performed. Thirteen families consisting of 23 WS patients were studied. This study was approved by the ethical committee of the Tehran University of Medical Sciences. Written and informed consent were obtained from patients or caregivers.

Table 1 The nucleotide sequences of primers used for amplification of *WFS1* markers

Markers	Primer sequences	PCR product size
D4S3023	ACCTCACTGGAAACTAAATGG	125–155 bp
	TGAACAGCAGCGGTCT	
D4S2366	TCCTGACATTCCTAGGGTGA	120–140 bp
	AAAACAAATATGGCTCTATCTATCG	
D4S431	AGGCATACTAGGCCGTATT	246–270 bp
	TTCCCATCAGCGTCTTC	
D4S2935	GCTCACAGAAGTGCCCAATA	104–120 bp
	CCCTGGGTGAAGTTTAATCTC	
D4S394	CCCTTGAGCATCCTGACTTC	189–223 bp
	GAGTGAGCCCCTGTACTCCA	

Table 1 demonstrates the nucleotide sequences of primers used for amplification of *WFS1* markers. For identification of mutations, DNA sequencing of the linked gene including all the exons, exon–intron boundaries and the promoter was performed. Table 2 shows the nucleotide sequences of primers used for amplification of *WFS1* exons.

Statistical and bioinformatics analyses

The frequencies of certain clinical signs and symptoms were described as percentages. Genetic linkage analysis via STR markers and homozygosity mapping were applied for screening of two known loci. Slink and LOD score were calculated. All steps were similar to our previously published article [10]. Bioinformatics analysis of the mutations were further investigated and validated with various software like SIFT, POLYPHEN, and CONSURF.

Results

Clinical result

All 23 patients (14 males and 9 females) were born of consanguineous marriages. The median age of the patients was 19 years (range: 4–40). All the participants were Persian. Written consent to participate in the study was obtained from members of all families.

Diabetes mellitus was present in all of the cases diagnosed at 1–25 years of age; it was the first manifestation of WS in 70% ($n = 16$) of our patients. Optic atrophy was present in nearly all of patients and it was diagnosed in half

of the patients before 11 years of age. The age of diagnosis could not be identified in four patients. With disease progression and advancing age, there was a more severe reduction in vision and a more severe involvement of the optic nerve, leading eventually to blindness, as occurred in three of our cases later in the second decade of life. In none of our patients, even those suffering from DM for long, were there any ophthalmic complications due to diabetes such as hemorrhage, cataract or retinal detachment. Three patients had constriction of visual fields and one patient was colorblind. MRI, as done in majority of the cases, disclosed a chiasmatic optic atrophy around optic canal. Half of our patients suffered from high-frequency SNHL confirmed by Auditory Brainstem Response examinations. Hearing loss was sensorineural in the majority of patients, and conductive hearing loss was found in only one case, which had simultaneous sensorineural problems. Urodynamic studies were performed in all patients. A substantial majority of patients (86%) had renal tract abnormalities including hydroureteronephrosis, neurogenic bladder, vesicoureteral reflux, and increased post voiding residue. Less frequent comorbidities were ataxia, anosmia, severe allergy, dysrhythmia, celiac disease, and epigastric pain each detected in one patient.

Table 2 The nucleotide sequences of primers used for amplification of *WFS1* exons

Exon	Primer Sequence	Size of PCR products
Exon 1	CGGAGATGTGGAGTGATTGG	401
	ATCAGCTCGGAAGGGGAAAC	
Exon 2	CCATGGGGACTGTACTGAGTG	321
	CAATGCTGAACTGCAGAGGAC	
Exon 3	GAAGACCCTCATGCCTTGTC	272
	ATCTCAGGCACCGACACTTC	
Exon 4	GCCTAGCCTAGTGGACATGC	222
	GAAACTGAAATTTCCCAACAGC	
Exon 5	AGAGTTGGCAGGGTCAGAGTG	375
	GGAAGGTCCTGGCTCCTGTG	
Exon 6	CCAGCTACTGGAGGTACAGAGG	486
	CTACTCCCAGCGTCCAGAAC	
Exon 7	AGCCCATTGCTCTGTGTGAGG	354
	GGCACGGCTGTAAGACACTCT	
Exon 8-1	GTCAGAGGGAGGCGTGAGAT	392
	GCCTGCTCCACATCCAGGTT	
Exon 8-2	GGTGTTCCAGGACAGCAAGG	393
	CCGACAGGCACGGTGATGAA	
Exon 8-3	GCTATCGCTGCTGCCCTCCA	381
	AGCTCCAGAGACGTGAACCAC	
Exon 8-4	GTGAGCTCTCCGTGGTCATC	346
	CCCTCTGAGCGGTACACATAG	
Exon 8-5	CTCCATGGTCAAGCTCATCCT	431
	TGTAGCGGTCGAACTTCTTGAT	
Exon 8-6	GAGTCTGCCATCAACATGCTC	507
	TGGGAAGAAAAAGAAGTCGAAG	
Exon 8-7	CTTCGAGCTCAAGGCCATCAG	342
	AGAGCTACACAGCAGCCTTCC	

Molecular result

In all 13 families, linkage analysis indicated linkage to the *WFS1* region. Gene mutation analyses identified several new mutations. Mutations were classified into two groups: missense and inactivating. The mean age of onset of OA and DM were lower in patients with inactivating mutations. Table 3 summarizes the mutations identified in each family.

Discussion

WS also known as DODMOAD (DI, DM, OA, and deafness) is a rare genetic dysmorphgenesis disorder with an autosomal recessive pattern of inheritance. A mutation on chromosome 4 is identified. The mutant gene is responsible

Table 3 The list of identified mutations in *WFS1* in the assessed families

Family number (number and gender of patients)	Mutation position	Nucleotide change	Amino acid change	Mutation type	Associated phenotypes in the current study	References
I (1 male)	Exon 8	c.1619G > A	W540X	Nonsense	DM, DI, OA, RTC	[19]
II (1 female), VIII (1 male, 1 female), X (1 male)	Exon 8	c.1523_1524delAT	Y508del_fsX541	Frameshift	DM, HI, DI, OA, RTC	[20]
III (2 females)	Exon 6	c. 643C > T	Q215X	Nonsense	DM, OA	Novel
IV (3 males, 1 female)	Exon 5	c.631G > A	Asp211Asn	Missense	DM, HI, OA, RTC	[21]
V (1 male)	Exon 3	c. 265G > T	E89X	Nonsense	DM, OA	Novel
VI (1 male)	Exon 5	c.502_504delTCC	S168DEL	Deletion	DM, HI, OA, RTC	Novel
VII (2 males)	Exon 8	1361_1376del	Y454_L459del_fsX454	Frameshift	DM, DI, OA	[22]
IX (1 female), XII (3 females, 1 male)	Exon 8	c.1456C > T	Q486X	Nonsense	DM, HI, OA, RTC	[22]
X (1 male)	Exon 4	c.387G > A	W129X	Nonsense	DM, HI, DI, OA, RTC	[23]
XI (2 males)	Exon 8	c.1380_ 1388del	T461_V463del	Deletion	DM, HI, DI, OA, RTC	[6]
XIII (1 male)	Exon 8	c.1171delG	E391Sfs*51	Deletion	DM, OA	Novel

DM diabetes mellitus, *OA* optic atrophy, *HI* hearing impairment, *DI* diabetes insipidus, *RTD* renal tubular dysgenesis

for encoding a transmembrane protein called Wolframin, which is normally present in several tissues, including heart, brain, pancreas, liver, kidney, skeletal muscle, and inner ear [5]. Nonetheless, mitochondrial mutations [11] and autosomal dominant patterns [12] have also been detected. The reported prevalence ranges from 1 in 100,000 [13] to 1 in 770 000 in UK [14].

The present report is the largest series on WS in Iranian population. There was a high rate of consanguineous marriages in our patients. The rate of consanguineous marriages is reported as high as 38% in our country [15] suggesting a high index of suspicion for WS in Iran while managing diabetic children in consanguineous families.

There was no significant sex predominance and all the patients were from Iranian origin. The earliest manifestation in our patients was DM occurring at a median age of 5 years, which is almost the same as reported in the literature. There was not a homogenous trend of manifesting clinical features in siblings in a family. For example in one girl, the clinical manifestations started with DM at the age of 3, while her brother exhibited polyuria, polydipsia, and elevated blood sugar not earlier than age of 7. In the majority of families with more than one affect child, the chronological pattern of clinical presentation was the same. None of our patients developed complications of DM such as proliferative retinopathy, glomerulosclerosis, and neuropathy despite long standing DM. The order of clinical manifestation in our patients was somewhat different from what is reported in the literature. The earliest symptom was DM; however the next symptom detected was DI followed by OA.

In almost all the patients suffering from hearing problems, there was a simultaneous involvement of the visual and renal system. With advancing age, all of these symptoms revealed a progressive course. An underlying neurologic degeneration etiology could be considered for this synchronous clinical deterioration. Once the diagnosis is confirmed, it is suggested that the physician look of other associated symptoms such as urologic abnormalities that might have an insidious course early in the disease and remain unidentified for a long time.

Reduced vision was present in the majority of our cases, and some of our older patients were almost completely blind. Visual signs and symptoms of WS start with loss of visual acuity and gradually progress over time with constriction of the visual field, such that, excluding a few case reports, almost all patients will eventually suffer from some kind of visual problem [16]. Absence of visual loss in some of our patients was probably due to their younger age at the time of study. Visual problems appear to be independent from DM, as indicated by the absence of diabetic retinopathy in our patients and progression of vision loss despite proper glycemic control. Although contribution of diabetic retinopathy to vision loss has been reported in some patients with longer duration of diabetes [17, 18], most studies indicate optic atrophy as the main cause of vision loss [16]. Evaluation for color blindness and reduced peripheral vision was performed in a minority of the patients. Therefore, there is a chance of their presence in more cases if investigated.

The current study has shown diverse mutations in *WFS1* gene in the assessed patients in which four were novel mutations (two deletions and two nonsense mutations). Studies in other populations have also indicated wide range of mutations. Table 4 has summarized the novel mutations identified in each population and the related phenotypes.

Table 4 The reported cases with WS, the number of patients with each clinical sign and the detected mutations

Population	Number of cases	DM	OA	HI	RTD	DI	NA	New mutation reported	Reference
Italian	1	0	1	0	0	1	0	Structural rearrangement	[24]
Turkish	7	7	6	5	3	5	0	c.1532T > C p.Leu511Pro	[25]
Italian	9	9	9	4	1	3	4	c.2663C.A S888X c.1381A.C T461P	[26]
Indian	7	7	7	4	6	4	1	0	[27]
Chinese	1	1	0	0	1	1	1	1962 G > A	[28]
Polish	9	9	9	4	5	4	2	c. 501del, S167fs c. 1330C > G, S443R c. 1174C > T, Q392X c. 1539delAT,Y513fs c. 1619G > A, W539X	[29]
Turkish	2	2	2	2	2	2	0	c. 1522-1523delTA, Y508fsX421	[30]
French	19	19	17	12	11	11	9	328T > A, Y110N c.873C > A, Y291X c.1113G > A, W371X	[31]

Table 4 (continued)

Population	Number of cases	DM	OA	HI	RTD	DI	NA	New mutation reported	Reference
								c.1661_1687del27, L554_G562del c.1885C > T, R629W c.1775_1776delTG, L592fsX604 c.1980C > G, V415del c.2099G > A,W700X 2224-2225insT, C742fsX758	
Spanish	7	7	7	5	2	3	1	c.873C > A, Y291X c.1949_50delAT, T710X c.2206G > C, G736A	[32]
Lebanese	27	27	27	8	–	11	5	c.2106delTGCTGTT, F646fs708X	[33]
Mexican	4	4	4	4	–	–	–	c.1354del16, P451fsX515 c.530G > C, R177P	[34]
Brazilian	27	27	27	4	26	11	10	c.1355_1370dup16, Ala460HisfsX88 1234_1237delGTCT, Val412SerfsX29 c. 1145T > C, Leu382Pro c. 876dupC, Leu293ProfsX13 1991T > C, Leu664Arg 2007T > G, Tyr669X 2643_2646delCTTT, Phe882SerfsX69 2105G > A, Gly702Asp 472G > A, Glu158Lys	[35]
United Kingdom	30	30	30	20	16	27	20	406C > T, Q136X 505G > A, E169K 817G > T, E273X 874C > T, P292S 887T > G, I296S 906C > A, Y302X 1433G > A, W478X 2002C > T, Q668X 887T > G, C690R 2100G > T, W700C 2206G > A, G736S 2654C > T, P885L 1060-1062del (TTC), Del354F 1243-1245del (GTC), Del415V 1549del (C), Del517fs/ter521 1611-1624del (CTTCATGTGGTGTG), Del538-542fs/ter537 1698-1703del (CTCTTT), Del567-568LF 2648-2651del (TCTT), Del883fs/ter949	[36]

DM diabetes mellitus, *OA* optic atrophy, *HF* hearing impairment, *DI* diabetes insipidus, *RTD* renal tubular dysgenesis, *NA* neurologic abnormalities

We have previously identified a novel frameshift (c.2177_2178insTCTTC) and a novel missense mutation (c.2205 C > A) in *WFS1* gene in Iranian population [4, 10]. Similar to studies in other populations, exon 8 of the *WFS1* gene includes the largest proportion of the mutations in Iranian population. Figure 1 summarizes the location of identified mutations in relation with different domains of WFS1.

Based on the diversity of mutations in each population, identification of population-specific panels for mutation screening is of practical value. The current study adds to the mutation repository of WS and shows a panel of mutations in Iranian population. Such panel would facilitate genetic counseling and prenatal diagnosis in families with WS cases.

There is currently no effective cure for WS. Current treatment strategies are mainly focused on managing specific manifestation. Although the genetic basis of the syndrome is elucidated to a large extent, there is no genetic intervention to prevent or treat the disease.

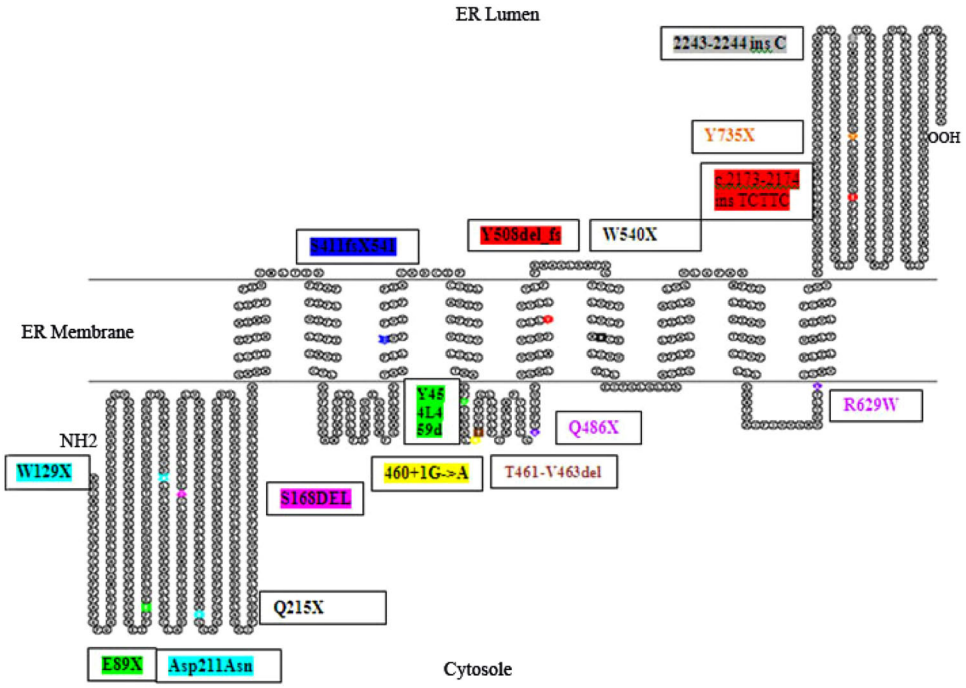

Fig. 1 Summary of identified mutations in *WFS1* gene in relation with protein helices as depicted by TOPO2 (http://www.sacs.ucsf.edu/TOPO2). Amino acids 311–333, 340–362, 405–422, 422–451, 493–515, 527–549, 588–610, and 630–652 construct intermembrane helices

Conclusion

This study is the largest series of WS in Iran and could have an important role in the diagnosis of this disorder.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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