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Significant expressivity of Wolfram syndrome: phenotypic assessment of two known and one novel mutation in the *WFS1* gene in three Iranian families

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Abstract Wolfram syndrome also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness) is a rare neurodegenerative autosomal recessive disorder. There is evidence of variable expressivity both in patients and heterozygous carriers. In this study, we describe three Persian Wolfram syndrome families with differences in the age of onset, signs and symptoms of the disease. We clinically evaluated affected families for verifying WS clinical diagnosis. After linkage analysis via 5 STR markers, molecular analysis for *WFS1* was performed by direct sequencing for patients and available family members. Three homozygous mutations were identified including c.1885 C>T, c.2205C>A both in exon 8 and c.460+1G>A in intron 4. The mutation c.2205C>A was found to be novel. We report interesting phenotype-genotype correlations: homozygous c.1885C>T and c.2205C>A variants were correlated with quite different disease severity and onset in the siblings. We report a rare case of WS with homozygous c.1885C>T who is married and has a healthy child. c.460+1G>A showed a possible partial dominant inheritance put forth by a heterozygous parent showing partial WS symptoms while her daughter displayed typical WS symptoms. Due to variable expressivity, detailed clinical examination and molecular diagnostics should be used to confirm WS and a more exact recurrence risk data.

Keywords Wolfram syndrome · Variable expressivity · Mutation · Iran

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Introduction

Wolfram syndrome (WS) is a rare disorder (MIM222300) inherited as an autosomal recessive trait with the prevalence ranging from 1 in 770,000 in the UK to 1 in 68,000 in Lebanon [1]. Juvenile onset diabetes mellitus (DM) and optic atrophy (OA) are the key features of the disease diagnosis [2]. In the majority of patients, other indications such as diabetes insipidus, sensorineural deafness, urinary tract abnormalities, peripheral neuropathy, and psychiatric disorders are also evident. The gene responsible for the syndrome (*WFS1*) was identified on chromosome 4p16.1 in 1998 [3, 4]. It encodes an 890 amino acid protein (wolframin), with nine predicted helical transmembrane segments, participating in the regulation of cellular Ca^{2+} homeostasis. The protein is found in various tissues such as the pancreas, brain, heart, bones, muscles, lungs, liver, and kidneys [5].

Clinical manifestations of WS are variable. In addition, there is evidence for genetic heterogeneity [1, 6]. So far, there are several reports implying that WS may exist in a wide range of clinical presentations, from mild to severe or with different constellation of signs and symptoms observed in cases with the same mutation in a given family

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[6]. Awareness of the prevalence, severity, and diversity of signs and symptoms among WS patients could improve our ability to properly diagnose the disease.

In the present study, clinical and molecular investigations of three Iranian families suspected of WS were carried out. We report a novel mutation and interesting atypical cases of variable expressivity including two families each with a couple of siblings displaying considerable variable expressivity. We encountered quite rare case of WS mother who has experienced marriage and has a child. Finally, we found late onset partial WS symptoms in a heterozygous mother after her child was diagnosed with WS.

Materials and methods

Patients and families

We included five patients with Persian ethnicity from three different families. All of the parents were consanguineous. Criteria for diagnosis of WS included the manifestation of diabetes mellitus (DM) along with optic atrophy (OA) unexplained by any other disease. In a clinical evaluation, physical exams including endocrinological, ophthalmological, neurological, urogenital and psychiatric assessments were also considered (Tables 1, 2). The participants provided informed written consent. This study was approved by the Institutional Review Board of Tehran University of Medical Sciences.

Sampling and DNA extraction

Blood samples from parents, all siblings and non-affected individuals were collected. One hundred healthy individuals from the same ethnic background were examined in case a novel variant was found. DNA was extracted from peripheral blood collected in EDTA using QIAamp DNA Blood kit (Qiagen, Germany). DNA concentration and purity was measured by a spectrophotometer (nanodrop 2000c, Thermo scientific, USA) and agarose gel electrophoresis using routine procedures.

Genotyping STR markers, SLINK and linkage analyses

Five short tandem repeat (STR) markers (*D4S2366, D4S431, D4S3023, D4S2925* and *D4S394*) and their primers linked to the *WFS1* gene on 4p16 were selected based on their physical distance from NCBI UniSTS and NCBI map viewer (http://www.ncbi.nlm.nih.gov/mapview). For STR markers a touchdown thermal cycling was programmed. Silver staining was followed and bands were visualized. After linkage analyses, haplotypes were drawn.

Mutation analysis of the *WFS1* gene

The information of *WFS1* coding sequence (NM-006005) was obtained from Genbank. The gene has eight exons (including one noncoding and seven coding). Primers were designed by Primer 3 web based software (University of

Table 1 The clinical features of the cases in relation with each mutation

Family number	Age	Variant, status	Clinical findings
(IR-WS-1) IV-1	26	c.1885C>T, homozygous	DM, DI, OA, hearing loss, urological manifestations, neurological manifestations
(IR-WS-1) IV-2	24	c.1885C>T, homozygous	DM, OA, hearing loss
(IR-WS-2) V-1	25	c.2205C>A, homozygous	DM, DI, OA, hearing loss, urological manifestations, neurological manifestations cerebellar ataxia
(IR-WS-2) V-2	20	c.2205C>A, homozygous	DM, OA
(IR-WS-3) V-2	7	c.460+1 G>A, homozygous	DM, OA, urological manifestations,
(IR-WS-3) IV-5	31	c.460+1 G>A, heterozygous	DM, OA

DM diabetes mellitus, *DI* diabetes insipidus, *OA* optic atrophy

Table 2 Clinical features of patients with Wolfram syndrome

Patient ID	Sex (F/M)	Diabetes mellitus (age at diagnosis)	Optic atrophy (age at diagnosis)	Diabetes insipidus (age at diagnosis)	Deafness
(IR-WS-1) IV-1	F	7	17	17	20
(IR-WS-1) IV-2	F	5	20	20	20
(IR-WS-2) V-1	F	3	12	13	14
(IR-WS-2) V-2	M	7	11	20	20
(IR-WS-3) V-2	F	2.5	7	8	–
(IR-WS-3) IV-5	F	25	30	–	–

Table 3 WFS1 gene mutation among patients and their family members

Family	Patient no.	Exon	Nucleotide change	Amino acid change	Type of mutation	Reference
1	(IR-WS-1) IV-1, IV-2	8	c.1885C>T	R629W	Missense	Kadayifci [6]
2	(IR-WS-2) V-1,V-2	8	c.2205C>A	Y735X	Nonsense	New
3	(IR-WS-3) V-2	4	460+1G->A	Intron	Splicing site	Strom [4]

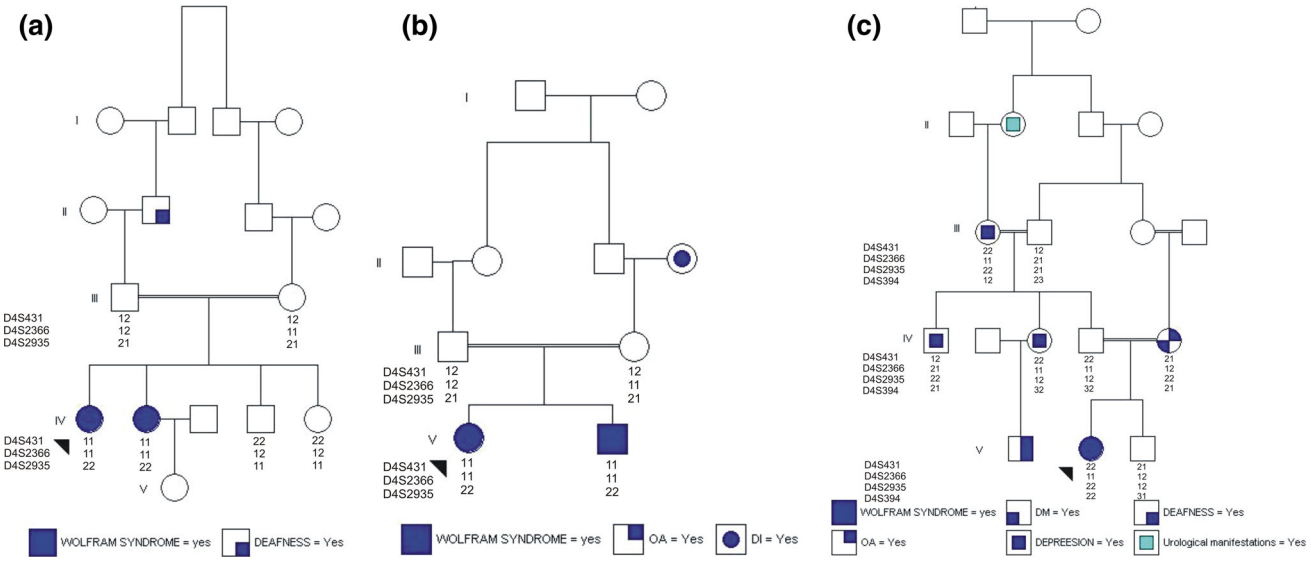

Fig. 1 The pedigrees of WS families IR-WS-1 (**a**), IR-WS-2 (**b**) and IR-WS-3 (**c**)

Massachusetts Medical School, USA). For the purpose, exon 8 was subdivided into seven overlapping parts. For the molecular analysis of the *WFS1* gene, PCR was performed using a thermocycler (Engine Dyad and Dyad disciple, Bio-Rad, USA), followed by direct bi-directional DNA sequencing on an Applied Biosystems 3730/3730×1 DNA Analyzers Sequencing (Applied Biosystems, USA). At first, one patient from each family was screened for potential *WFS1* mutations, and then the mutation was identified in other siblings and parents. For a novel variant, 100 healthy controls of the same ethnicity as the patients were screened using PCR-DNA sequencing of the exon of interest. The sequence data were compared to RefSeq NM-006005 using Lasergene sequence analysis tools EditSeq and SeqMan (DNASTAR Inc., USA).

Results

Three mutations, including one novel mutation, were found, two of which were in exon eight and one in intron four (Table 3; Fig. 1). The phenotypes related to each of the genotypes are described separately for each of the three families (Table 1). Below, the clinical and molecular results are described separately for each of the three families,

Family #1 (IR-WS-1)

The patient IV-1 (Fig. 1a), 24 years old, is the first of four siblings. She was a known diabetic case since age of 7 years having received insulin but with poor compliance to treatment. Her fasting blood sugar (FBS) level was 472 mg/dl and hemoglobin A1C was 11.5 %. Her ophthalmic evaluation revealed bilateral OA at age 17, decreased vision and peripheral constriction of visual field. Her specific gravity of urine was 1,009. Renal sonography demonstrated neurogenic bladder dysfunction with bilateral reflux. Voiding cystourethrography (VCUG) showed grade IV hydronephrosis in the right and grade I in the left kidney with dilation in the proximal urethra and bladder enlargement secondary to polyuria. Her Tc-99 m DMSA result suggested globally decreased activity with irregularity of the left kidney. There was also reduced cortical uptake in the upper portion of the right kidney.

Patient IV-2 (Fig. 1a) (20 years old) showed milder symptoms than her affected sister (IV-1). She was a known diabetic case since age of 5 and with some urologic

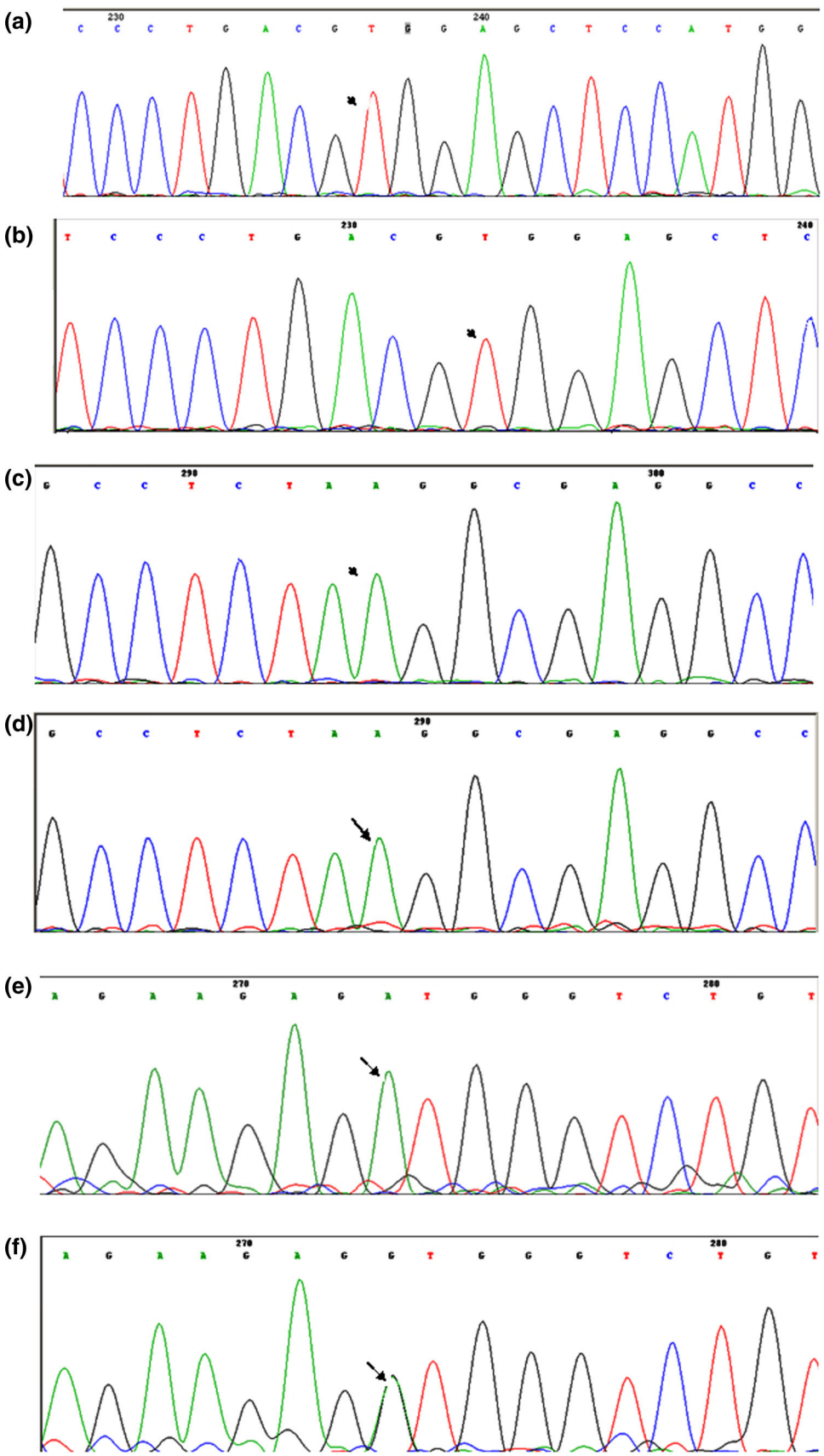

Fig. 2 Electropherograms of mutant alleles

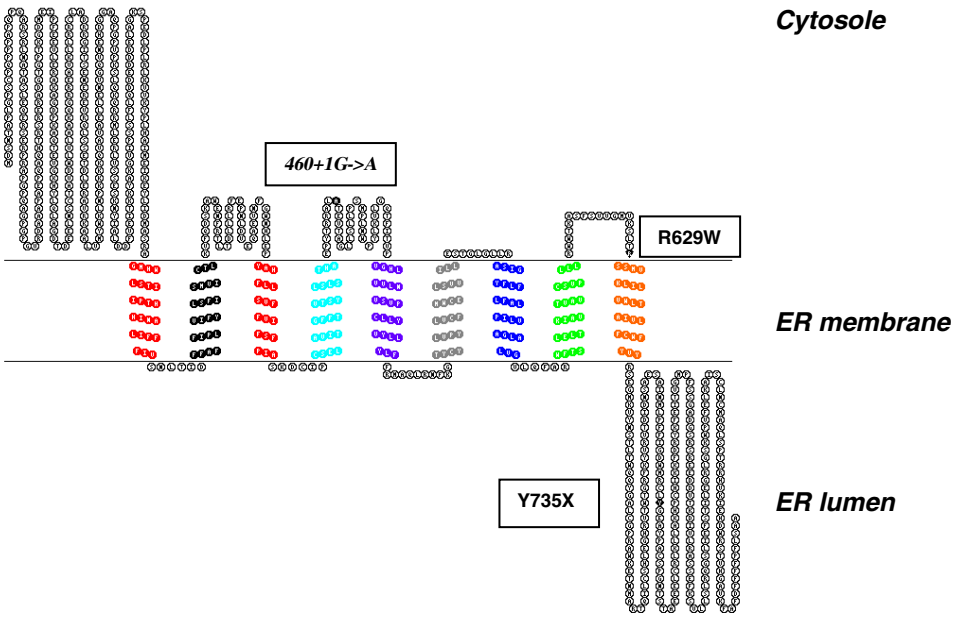

Fig. 3 The position of the three mutations investigated in this study

problem but without any other signs or symptom until recently. Her FBS level was 222 mg/dl, and her hemoglobin A1C was 11.5 %, and with urinary gravity of 1,009. Many other aspects of the phenotypes, such as age of onset, were different between the two affected sisters; interestingly, patient IV-2 is married and has a healthy daughter (V-1). Her phenotypic expression appeared very late, about two year after her daughter was born. During pregnancy, she did not run into any problem except experiencing increased levels of glucose which was controlled.

Preliminary evidence of linkage was found for the *WFS1* gene. Haplotypes are shown in Fig. 1a. Molecular analysis showed both sisters to be homozygous for 1885 C to T transversion in exon eight of *WFS1* resulting in change in codon 629 (c.1885C>T) in the ER membrane domain of the protein causing tryptophan to be replaced by arginine (R629 W) (Figs. 2a, b, 3). Both parents were heterozygote for this mutation but their healthy siblings were homozygous for the normal allele.

Family #2 (IR-WS-2)

In this family (Fig. 1b), there are two siblings with variable expressivity in the disease signs and symptoms. They had been born to a first cousin couple. The patient V-1 is a 25 year old girl, the eldest child. She had Type 1 DM for twenty-two years and used insulin with poor compliance to treatment. At age of 13, she started to complain about polyuria, nocturia and incontinency, and diagnosis of the neurogenic bladder was made. She had visual disturbances at age of 12 and hearing loss at age of 14. Her brother, V-2, who is 22 years old, showed differences in disease severity. DM and OA were diagnosed at age of 7 and 11, respectively, but he had not presented any other signs and symptom until recently.

Laboratory investigations showed FBS level of 400 mg/dl, hemoglobin A1C of 8.1 %, for patient V-1 and blood FBS of 250 mg/dl, hemoglobin A1C of 7.6 % and specific gravity of urine of 1,014 for V-2. In audiometric examination of the individuals, no wave II ABR responses were detected up to 50 dB nHL with click stimulus indicating moderate hearing loss at high frequencies in both ears.

Linkage screening showed preliminary evidence of linkage to the *WFS1* gene (Fig. 1b). Both patients V-1 and V-2 were homozygous for the nonsense mutation c.2205C>A, resulting in the introduction of a premature stop signal at codon 735 (Tyrosine) in the luminal domain and a truncated protein of only 735 amino acids (aa) instead of 890 aa (Figs. 2c, d, 3). Both parents were heterozygous for this mutation.

Family #3 (IR-WS-3)

Depression and type 2 DM are the most frequent findings in the family (Fig. 1c). The patient V-2 is an eight year old girl. Her DM was diagnosed at the age of 2.5 year. She was diagnosed with OA at the age of seven and DI at eight. Laboratory test results indicated following data: blood FBS = 230 mg/dl, hemoglobin A1C = 6.8 % and urinary gravity = 1,012.

Renal ultrasonography showed mild hydronephrosis with dilation in ureters. The scan findings suggested

moderate vesicoureteral reflux in either side to moderate dilatation of pelvicalyceal system. ABR responses indicated normal hearing in the left ear with the traditional wave V traced down to 20 dB nHL, but in the left ear it was approximately 40 dB nHL suggesting a mild hearing loss (at high frequencies).

Her 31 year old mother, IV-5, has had DM since the age of 25. Ophthalmologic examination revealed OA, also confirmed by MRI. The laboratory tests showed the following data: FBS: 145 mg/dl, hemoglobin A1C: 6.5 % and urinary gravity: 1,018. Linkage was found to the *WFS1* gene (Fig. 1c). Molecular analysis results revealed patient V-2 was homozygous for a splice site mutation: a homozygous G > A transition at nucleotide position 460 + 1 at the donor splice site of intron 4 (c.460+1G>A). This mutation eliminates the correct splicing site leading to the creation of a truncated protein with 157 aa. Mutation analysis confirmed that her parents, IV-4 and IV-5 (who showed a partial WS symptoms, were heterozygous carriers for this mutation and her healthy sibling, V-3, was homozygous for the wild type allele (Fig. 2e, f). Patient V-1 had optic atrophy and deafness, without other wolfram symptoms. Unfortunately, we did not have access to his specimen.

Discussion

Wolfram syndrome (WS) is a rare neurodegenerative disorder. Although it is an autosomal recessive disorder, there are some reports of higher prevalence of DM [7], hearing loss [8], psychological problems [9, 10] among heterozygous carriers. OA is one of the main characteristic findings of WS. However atypical ophthalmic findings such as cataract [11, 12], strabismus, pigmentary and diabetic retinopathy, abnormal papillary light reflexes, nystagmus and glaucoma are reported among WS patients indicating variable clinical presentation, also known as expressivity which measures the extent to which a genotype shows signs of its phenotypic expression [2, 13–15].

In this study, we describe families with variable expressivity in severity of symptoms, age of onset and other aspects of their phenotypes. So far, over two hundred mutations have been reported from different ethnic groups including Iran [16, 17]. Three mutations and their phenotypic effects that were investigated in this study included one splicing (c.460+1G>A) mutation which probably activates the mechanism used by the cell to degrade aberrant mRNAs (nonsense-mediated decay), leading to the absence of wolframin due to mRNA degradation [16, 18], one missense (1885C>T) which would lead to cellular depletion or reduced expression of the protein [16, 19, 20] and finally, one novel nonsense (c.2205C>A) mutation, which might result in complete degradation of wolframin. Protein expression analyses in homozygous patients are warranted to check the hypotheses [16].

The c.1885C>T (p.Arg629Trp) identified in family #1 in our study, was first described by Kadayifci et al. [6] in a Turkish family with six siblings in which two members had the main features of the syndrome and were homozygous for the mutation while a third heterozygous sibling had only sensorineural deafness. Their grandfather committed suicide that might have reflected variable expressivity among homozygous and heterozygous individuals. Our results correspond to this research confirming that the mutation can cause variable expressivity among siblings.

We found a new homozygous mutation c.2205C>A (codon 735) not reported previously in any population. Hardy et al. [21] reported a compound heterozygous mutation involving c.2206G>A (G736S), a missense mutation, and 906C>A (Y302X), a nonsense mutation, in two siblings. In the French population a 21 year old female with the same mutation (c.2206G>A) has been reported [22]. Domenech et al. [23] reported another mutation in this codon (codon 736) resulting in c.2206G C (G736R). The patient was an 8-year-old girl who received a diagnosis of OA at the age of 5 and DM at 5.5 years of age.

The third mutation identified in this study, had been previously reported in a 17 year old male with retarded sexual maturation and renal tract abnormalities [4]. In addition, Van Ven Ouweland et al. [24] identified the same mutation in a family of Turkish decent in both affected siblings from consanguineous parents. They had variable age of onset of OA and deafness but were rather the same in the case of other signs and symptoms. In our study, there is coincidence of disease progression in the mother and her child in the third family and it was very odd to see that the mother was heterozygous but demonstrated the main clinical feature of WS. In line with the observation, Bonnycastle et al. reported variants segregating with diabetes in a multigenerational Finnish family. At least 8 members of this family had diabetes with age-of-diagnosis ranging from 18 to 51 years suggesting autosomal dominant inheritance. They found a novel non-synonymous variant (p.Trp314Arg) in *WFS1* segregating with the diabetic phenotype. [25]. Rendtorff and his colleague illustrated OA and hearing loss as a phenotype caused by dominant mutations in *WFS1* in eight families. Therefore, they suggested that patients who are heterozygous for *WFS1* missense mutations should be subject to careful clinical examinations for OA and other manifestations of WS [26].

Notably, in the research by Strom and Van Ven Ouweland et al. heterozygous individuals did not demonstrate any feature of WS [4, 24]. This might be due to several factors among which are modifier genes, environmental factors, allelic variation and gene–environment interactions.

In summary, in view of the variable expressivity found in WS patients segregating the same mutations and the possible onset of some of the symptoms in a subset of heterozygous individuals, we suggest considering detailed clinical examination and molecular analysis when dealing with the genetic counseling of WS patients and their family members.

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Conflict of interest The authors declare no conflict of interest.

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