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CASE REPORT AND REVIEW

WS1 gene mutation analysis of Wolfram syndrome in a Chinese patient and a systematic review of literatures

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Abstract Wolfram syndrome is a rare hereditary disease characterized by diabetes mellitus and optic atrophy. The outcome of this disease is always poor. WFS1 gene mutation is the main cause of this disease. A patient with diabetes mellitus, diabetes insipidus, renal tract disorder, psychiatric abnormality, and cataract was diagnosed with Wolfram syndrome. Mutations in open reading frame (ORF) of WFS1 gene was analyzed by sequencing. Mutations in WFS1 gene was also summarized by a systematic review in Pubmed and Chinese biological and medical database. Sequencing of WFS1 gene in this patient showed a new mutation, 1962G>A, and two other nonsense mutations, 2433A>G and 2565G>A. Systematic review included 219 patients in total and identified 172 WFS1 gene mutations, most of which were located in Exon 8. These mutations in WFS1 gene might be useful in prenatal diagnosis of Wolfram syndrome.

Keywords Wolfram syndrome · DIDMOAD · WFS1 gene · Mutation · Genetic diagnosis

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Introduction

Wolfram syndrome is a rare, autosomal recessive disease characterized as diabetes mellitus and progressive optic atrophy. It is also named DIDMOAD, because the most symptoms of Wolfram syndrome include diabetes insipidus, diabetes mellitus, optic atrophy, and deafness. The incidence of Wolfram syndrome is about 1/700,000 in UK and 1/100,000 in South America [1]. Diabetes mellitus is the most common manifestation of Wolfram, which always starts before the age of 10. But the most frequent causes of morbidity and mortality are neurological disorders and urinary tract complications [2].

Since the first cases of Wolfram syndrome reported by Wolfram et al. in 1938 [3], more and more cases have been reported. In order to fully understand the pathophysiology and early diagnose of this disease, many studies are carried out to find out the genetic basis of this hereditary disease, and it is becoming clear that WFS1 gene (NM_006005) is the most important gene responsible for Wolfram syndrome. WFS1 gene encodes a transmembrane protein, wolframin, which is located primarily in the endoplasmic reticulum and ubiquitously expressed with highest levels in brain, pancreas, heart, and insulinoma beta-cell lines. Mutation in WFS1 gene may lead to instability and significantly reduced half-life of wolframin [4]. Other than this, the WFS2 gene and mitochondrial mutation have also been reported to be related to Wolfram syndrome [5]. In

the present study, we report a new mutation in a Chinese patient with Wolfram syndrome. Besides, we made a systematic review on Wolfram syndrome so as to fully understand WFS1 gene mutation related to Wolfram syndrome.

Patient and methods

Clinical details

This study was approved by the specialty committee on ethics of biomedicine research of the Second Military Medical University, and written informed consent was obtained from the patient and his parents. Polydipsia, diuresis, and uroclepsia were present in this young male patient after birth. He was diagnosed with a nervous bladder by kidney CT scan, urodynamic study (Fig. 1a, b) and ultrasonography (Fig. 1c) in the department of urinary surgery when he was 16 years old. Then, suprapubic cystostomy was performed. But no symptom relief was obtained. One year later, water deprivation test was performed in the department of endocrinology and he was diagnosed with central diabetes insipidus and chronic renal dysfunction. Oral desmopressin was given and polydipsia was significantly relieved. But frequent micturition and uroclepsia were still present. During the hospitalization period, he attempted to commit suicide but failed. Then, antipsychotic medication was given. After then on, he was treated by self-catheterization every other day.

When he was 21 years old, polydipsia and acratia were aggravated without any incentive. The drinking amount was as high as 4000–5000 ml/day. The accompanied symptoms included dizziness, eye distension, blurred vision, and unstable gait. Meanwhile, it was demonstrated by blood biochemistry tests that serum glucose was extremely high (38.9 mmol/l). Type 1 diabetes mellitus was diagnosable because of a positive islet cell antibody and protein tyrosine phosphatase antibody. Cranial MRI, psychological and visual examination were also performed to improve the diagnosis of Wolfram syndrome. Cranial MRI showed a satiated pituitary (Fig. 1d). Psychological examination showed compromised calculation ability. Eye examination showed lateral nystagmus and cataract. Visual acuities of bilateral eyes were both 4.3. No abnormality was observed in brainstem electric response audiometry test. Serum creatinine was not monitored intermittently until this patient was 26 years old, when his serum creatinine was as high as 2413 μmol/l and received long-term hemodialysis therapy. Supporting therapy including insulin, fluid, and potassium administration and anti-infection treatment were given, but renal function was not recovered

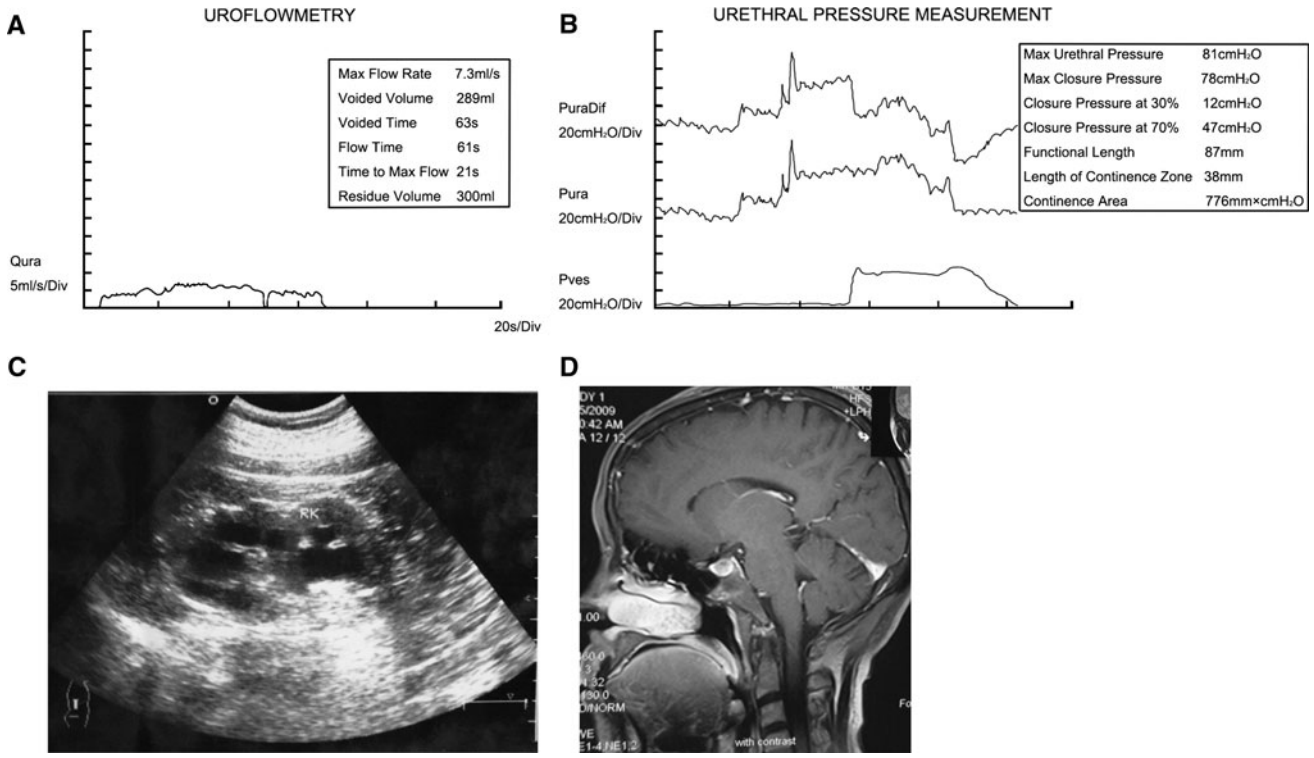

Fig. 1 Clinical data of the patients with Wolfram syndrome. **a** Uroflowmetry, **b** urethral pressure measurement, **c** ultrasonography of the kidney, **d** cranial CT. Urodynamic data showed a nervous bladder. Ultrasonography showed that bilateral hydronephrosis and enhanced echo in cortex. Cranial CT showed a satiated pituitary

at all. No similar symptom was present in his relatives, but his grandfather married the consanguineous cousin.

Genetic analysis

Peripheral venous blood (5 ml) was collected in this patient and also his parents, and DNA was extracted with QIAamp DNA Blood Midi kit (Qiagen, USA). Thirteen primers were designed and generated by Invitrogen (USA) to amplify the open reading frame (ORF) of WS1 gene (NM_006005) as previously reported [6]. PCR was performed with Advantage-GC Genomic Polymerase Mix (Clontech, USA) in ABI PCR amplifier 9700 (Applied Biosystems, USA). After confirmation by electrophoresis, the PCR product was purified with QIAquick PCR Purification Kit (Qiagen, USA). The ORF of WFS1 gene was amplified and sequenced in ABI sequencer 3270 (Applied Biosystems, USA). Then, the sequencing results were analyzed by nucleotide blast in NCBI.

Literature retrieval and data extraction

A search of the Pubmed database from 1966 to 2009 and Chinese biological and medical database (CBM) from 1978 to 2009 was conducted to identify clinical trials and case reports using the keyword Wolfram syndrome or DIDMOAD. The search was restricted to the English- and Chinese-language literature. The resulting publications were further sorted to the most relevant studies to this topic. Literature retrieval and data extraction were conducted by two authors independently (M.-l. Yu and J.-f. Wang). Studies were excluded if they met the following criteria: (1) analyzed the microsatellite polymorphisms or mitochondrial DNA mutations, but not WS1 gene polymorphism; (2) included patients with psychiatric disorders or other diseases but not Wolfram Syndrome. Data including patient characters and WS1 gene mutations were recorded; (3) different publications reported the same patients.

Results

A total of three mutations were found in Exon 8 of WS1 gene of this patient, 1962G>A, 2433A>G, and 2565G>A. The first SNP leaded to substitution of amino acid (glutamic acid to lysine), while the two latter SNPs were nonsense mutations (lysine and serine, K811K and S855S, respectively). Genotype of 1962G>A was homozygote of AA in this patient, while the genotypes were both heterozygote of AG in his father and mother, respectively (Fig. 2).

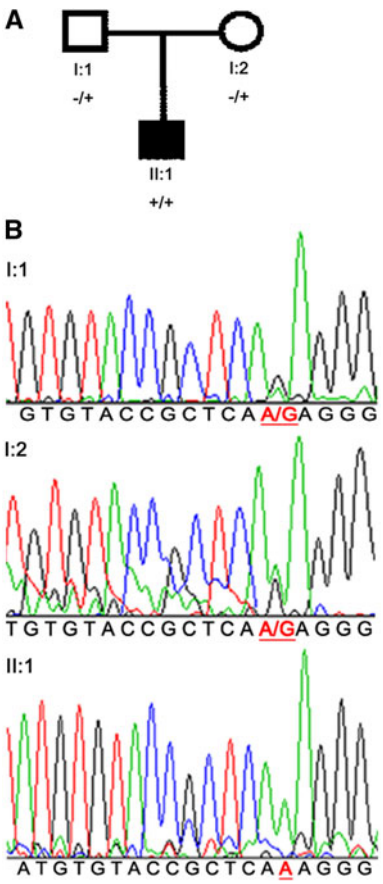

Fig. 2 Pedigree (**a**) and sequence chromatograms (**b**) of the family. These images were generated based on 1962G>A

After literature retrieval, we identified 24 articles reporting the WS1 gene polymorphism related to Wolfram Syndrome but among which full text [7] of one article was not available. A total of 219 patients were included in the 24 articles with full text [4, 6, 8–29]. Clinical characters were described in 211 patients and WFS1 mutations were described in 218 patients. Diabetes mellitus (100%) and optic atrophy (96.7%) were the most common symptoms of Wolfram Syndrome, followed by deafness (59.0%), renal tract disorder (53.8%), diabetes insipidus (52.8%), neurological disorders (40.1%), psychological disorders (17.5%), and cataract (6.6%) (Table 1).

In these patients, a total of 172 polymorphisms were reported, but 1962G>A had never been reported. In order to facilitate investigators on Wolfram syndrome to further understand current knowledge of genetic polymorphism in WFS1, we summarize all these polymorphisms in Table 2, except three polymorphisms reported as amino acid changes but not the exact nucleotide, including S443I, A684V, and R708C [27]. These mutations were mainly distributed in Exon 8 (79.7%), followed by Exon 7 (4.7%), Exon 6(4.1%), Exon 3 (3.5%), Exon 2 (2.9%) and 4 (2.9%) and Exon 5 (2.3%).

Table 1 Clinical characters of patients with Wolfram syndrome

Author [Ref.]	No.	DM	OA	DF	RTD	DI	ND	PD	CA
Aluclu [7]	2	2	2	2	2	2	0	2	0
Cano [8]	12	12	11	3	7	2	5	4	1
Colosimo [9]	19	19	19	15	11	11	–	–	–
Domenech [10]	7	7	7	5	2	3	1	2	0
Eller [11]	3	3	3	1	1	1	1	0	1
Fang [12]	1	1	1	1	1	1	0	0	0
Gasparin [13]	27	27	27	4	26	11	10	4	4
Giuliano [14]	19	19	17	12	11	11	9	2	0
Gomez-Zaera [15]	23	23	22	12	11	11	14	5	0
Hansen [16]	10	10	10	5	0	2	2	0	5
Hardy [17]	30	30	30	20	16	27	20	3	0
Hofmann [18][a]		–	–	–	–	–	–	–	–
Hong [4]	1	1	1	1	1	1	0	0	0
Inoue [19][a]		–	–	–	–	–	–	–	–
Inukai [20]	1	1	1	1	1	1	0	0	0
Kadayifci [21]	2	2	1	2	1	2	2	0	0
Nakamura [22]	1	1	1	1	1	1	0	0	0
Sam [23]	1	1	1	0	0	0	1	0	0
Shu [24]	2	2	2	1	2	2	0	0	0
Smith [25]	13	13	13	5	3	4	6	7	0
Strom [26]	15	15	14	14	9	6	7	3	2
Tessa [27]	6	6	6	5	2	5	2	3	0
van ven Ouweland [28]	12	12	12	11	5	7	4	1	0
Zenteno [30]	4	4	4	4	–	–	–	–	–
The present study	1	1	0	0	1	1	1	1	1
Total	212	212	205	125	114	112	85	37	14
Percentage (%)		100	96.7	59.0	53.8	52.8	40.1	17.5	6.6

No. number of patients included, *DM* diabetes mellitus, *OA* optic atrophy, *DI* diabetes insipidus, *DF* deafness, *RTD* renal tract disorder, *ND* neurologic disorder, *PD* psychological disorder, *CA* cataract

[a] Clinical characters were not described in these studies

Discussion

Although incidence of Wolfram syndrome is much lower than diabetes mellitus, diabetes insipidus, optic atrophy or any other single symptom manifested in Wolfram syndrome, it should be known by every clinician, especially those specialized in endocrinology, nephrology, ophthalmology and otorhinolaryngology, because there is still no effective therapy against it and the mortality is very high. It was reported that 60% of patients with Wolfram syndrome died by the age of 35 [2]. In the present study, genetic analysis of a patient with Wolfram syndrome was made and we also conducted a systematic review in WFS1 gene mutation related to Wolfram syndrome.

Diabetes mellitus was the earliest manifestation of Wolfram syndrome [2], however, not only is DM present in all or most of patients but that with time, other alterations can also affect most, if not all of patients with Wolfram syndrome [30]. For example, the patient in our present study was diagnosed with renal tract disorder at first. Diabetes mellitus was not diagnosed until he was 21 years old, 5 years after the renal tract disorder was diagnosed. This suggested that Wolfram syndrome should be suspected when continuous renal tract disorder was present without clear cause. From the literatures, one can observe that most diagnosis of Wolfram syndrome was based on the presence of diabetes mellitus and optic atrophy. This, as in the case of the present reported here, could delay the diagnosis, and there can also be a dissociation between the pathological findings and the clinical presentation in some patients [31].

Genetic diagnosis of Wolfram syndrome brings us a new insight for early diagnosis and even prenatal diagnosis of Wolfram syndrome. This might be rather useful in atypical patients without all the manifestations of Wolfram syndrome. Many different mutations have been reported in WFS1 gene, but there is still lack of definite mutations that all patients with Wolfram syndrome share. Therefore, the only diagnostic method of Wolfram syndrome based on WFS1 gene is sequencing. Although most patients have mutations in Exon 8 of WFS1 gene, there are some patients in which mutations within Exon 8 have not been detected [14]. And in another patient reported by Gasparin et al. [14], no mutation was found at all within all exons and intron–exon boundaries. Mutations in introns might be neglected because they did not sequence the total length of WFS1 ORF. There are many types of mutations in WFS1 gene, as shown in Table 2, such as deletion, insertion, single nucleotide mutation, and also frameshift. However, there seems to be less frameshift mutations in Chinese population (for example, references [12] and [4], as well as the present study) than population of other races, such as the Brazilians [14] or other Latin Americans [29] reported recently. Fewer reports in Chinese might be one of the causes. Some of the mutations are non-sense mutations, such as 2433A>G and 2565G>A identified in the present study. As reported previously, most of the mutations were distributed in Exon 8 [14].

It remains unclear how does mutation screening contribute to clinical therapy of Wolfram syndrome. But prenatal diagnosis may be a promising method to prevent Wolfram syndrome. As reported by Domenech et al. [32] for the first time, Wolfram syndrome affected the older daughter in a family, and her parents were heterozygote carriers of 2206G>C. When the second pregnancy was present, they did a prenatal diagnosis by transabdominal chorionic villus sample and found that the fetus was also a

Table 2 Clinical characters of patients with Wolfram Syndrome

Mutation [Ref.]
Single nucleotide polymorphism
328T>A [15], 376G>A [16], 387G>A [25], 397G>A [15, 17], 406C>T [18], 460 + 1G>A [26, 28], 461-9A>G [9], 472G>A [14], 505G>A [7], 530G>C [29], 580C>T [17, 26], 631G>A [28], 676C>T [28], 684C>G [9, 12, 18], 817G>T [18], 854G>C [19], 861 + 1G>A [15], 873C>A [11, 15, 26], 887T>G [18], 906C>A [18], 937C>T [17], 993C>T [16], 997A>G [9, 10, 12, 18, 27], 1023C>T [10, 12, 18], 1032-5C>G [19], 1067C>T [9], 1096C>T [9, 26], 1112G>A [10], 1112G>A [4], 1113G>A [15], 1145T>C [14], 1167G>A [19], 1185T>C [9, 10, 12, 18], 1280T>G [9], 1294C>G [9], 1309G>C [18], 1346C>T [25], 1355T>C [19], 1367C>A [9, 18], 1371G>T [15], 1433G>A [18], 1456C>T [10, 19], 1500T>C [9, 10, 12, 18], 1511C>T [15], 1514G>A [10], 1517T>G [25], 1537A>G [19], 1542C>A [10], 1545C>T [19], 1545C>T [9, 15, 16, 26], 1584C>G [10], 1602C>G [10], 1628T>G [10], 1628T>G [17], 1637T>A [10], 1672C>T [9], 1673G>A [9, 10, 25], 1675G>A [12, 25], 1681C>T [19], 1725C>T [12, 18], 173C>T [16], 1761G>T [18], 1815C>T [19], 1816G>C [10], 1820C>G [28], 1832A>G [9, 10, 18, 27], 1838G>A [25], 1885C>T [4, 15, 21], 1925C>T [19], 1941C>A [14], 1944G>A [18], 1962G>A[a], 1980C>G [15], 1991T>C [14], 1997G>A [7], 1999C>T [9, 18, 24], 2002C>T [18, 19], 2007T>G [14, 28], 2012C>T [25], 2020G>A [16], 2068T>C [18], 2099G>A [15], 2100G>T [18, 25], 2105G>A [14], 2114G>A [19], 2206G>A [11, 15, 18], 2206G>C [11], 2209G>A [16], 2254G>T [18, 19, 25], 2292C>T [18], 2322G>A [12, 18], 2327A>T [25], 2338G>C [16], 2341C>T [19], 2378G>C [10], 2433A>G [9, 10, 12, 18][a], 2452C>T [16, 25, 26], 2513C>T [9], 2565A>G [9, 10, 12, 18][a], 2578C>G [25], 2590G>T [25], 2601G>A [15], 2603A>G [19], 2654C>T [18], 2720C>T [9], 2735G>A [19],
Insertion or deletion
197-214dup18 [9], 409-424dup16 [11, 15], 424-425ins16 [9, 16, 25], 532-538del6 [10], 599delT [26], 639-642delGGCG [9], 862-1357del2514 [25], 876dupC [14], 877delC [9], 937-941dup5 [17], 1029insC [4], 1032ins9 bp [20, 25], 1038insC [12], 1046delTCT [16], 1060-1062delCTT [9, 14, 16, 18], 1140-1163dup24 [14], 1230_1233delCTCT [10, 14, 15, 28], 1232_1233delCT [15], 1234-1237delGTCT [16], 1240_1242delTTC [15], 1243_1245delGTC [14, 15, 17, 18, 25], 1249-1251delTTC [13], 1279ins5 [22], 1300-1302delGTC [7], 1355-1370dup16 [14], 1355-1370del16 [29], 1362-1377del16 [10], 1380del9 [26], 1387delCTCT [27], 1401-1403delGCT [15], 1504ins24 [18], 1507-1519del13 [9], 1519del16 [27], 1522-1523delTA [8], 1522-1536del15 [28], 1523delAT [26], 1525-1537del13 [28], 1546delTTC [10], 1549delC [18], 1546delTTC [19], 1581insC [28], 1610insCTGAAGG [19], 1611-1624del14 [18], 1620-1622delGTG [10, 15], 1661-1687del27 [15], 1685del15 [19], 1698-1703del6 [15, 18], 1775-1776delTG [15], 1813-1814insA [9], 1949-1950delAT [11, 14], 2164-2165dup24 [10], 2164ins24 [26], 2224-2225insT [15], 2315insT [12], 2392-2393insGAC [10], 2433delA [18], 2504-2505insC [10], 2638-2643del6 [12], 2642delTC [25], 2643-2646delCTTT [14], 2646-2649delTTTC [17], 2648-2651delTCTT [15, 18], 2649delC [9, 17], 2812delTC [19]

[a] Identified in the present study

heterozygote of 2206G>C. Prenatal diagnosis of Wolfram syndrome was especially useful in such conditions when the parents are both carriers of a heterozygote of WFS1 mutation. We speculated that when a child is affected with Wolfram syndrome, his future siblings might benefit from prenatal detection of WFS1 mutations. When there is a family history of consanguineous marriage, prenatal diagnosis of WFS1 mutation was also helpful for pre-diagnosis of Wolfram syndrome. For example, the grandparents had a consanguineous marriage, which significantly increased risks of hereditary diseases.

Wolframin, the product of WFS1 gene, is mainly distributed in endoplasmic reticulum. It appears to be important in the regulation of intracellular Ca^{2+} homeostasis. Osman et al. [33] injected cRNA from WFS1 cDNA into X. *laevis* to investigate its influence on Ca^{2+} channel activity. It was demonstrated that over-expression of WFS1 increased cytosolic calcium levels in oocytes. After stimulation with IP3, they found that calcium channel activity increased significantly by detecting the slope conductance. Therefore, WFS1 mutation induced calcium regulation dysfunction might be responsible for the progression β-cell loss and neuronal degeneration associated with Wolfram syndrome. In the same chromosome of WFS1, there is another gene named WFS2 encoding CISD2 which might be also related to Wolfram syndrome. Amr et al. [34] reported that WFS1 mutation was absent in three families with Wolfram syndrome. But they found that a polymorphism in WFS2 gene inducing an amino acid change might be related to this disease. They also found that CISD2 encoded by WFS2 gene was also located in endoplasmic reticulum but it had no any correlation with wolframin encoded by WFS1 gene. Chen et al. [35] made further investigation on the pathophysiological effect of CISD2 and found that CISD2 was primarily localized in the mitochondria. CISD2-deficient mice had similar phenotypes to Wolfram syndrome, including a progressive neurodegeneration and an impaired glucose tolerance, which might be related to mitochondrial breakdown and dysfunction after CISD2 knockdown.

In summary, we describe a patient with Wolfram syndrome and identified a new mutation of WFS1 gene, 1962G>A. A systematic review of Wolfram syndrome was also conducted in the present study. Diabetes mellitus and optic atrophy were the most common manifestations of Wolfram syndrome, but the first manifestation of Wolfram syndrome was not necessarily these two manifestations. Many mutations in WFS1 gene were reported, which might be related to Wolfram syndrome. These mutations might be useful in prenatal diagnosis of Wolfram Syndrome.

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