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CASE REPORT

Werner syndrome presenting as early-onset diabetes: A case report

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ABSTRACT

Werner syndrome is a rare autosomal recessive premature progeroid syndrome caused by mutations in the *WRN* gene. It is characterized by early onset of age-related diseases, such as cataracts, atherosclerosis, diabetes mellitus, osteoporosis and malignancies, in which diabetes often onset in patients' 30–40s. Herein, we report a Chinese patient with Werner syndrome with uncommon early-onset diabetes at 18 years-of-age, who had low body mass index, insulin resistance, negative antibodies of diabetes and early onset of cataracts. Genome sequencing and reverse transcription polymerase chain reaction confirm the diagnosis. A novel heterozygous splice-site mutation in the *WRN* gene (c.1270-2A>T) was identified. The present case reminds clinicians that when young diabetes patients are encountered, if they are accompanied by premature aging, attention should be paid to identifying the possibility of Werner syndrome based on diagnostic criteria.

INTRODUCTION

Werner syndrome (WS; OMIM #277700) is a rare autosomal recessive premature progeroid syndrome characterized by early onset of age-related diseases, such as cataracts, atherosclerosis, type 2 diabetes, osteoporosis and malignancies[1,2]. The prevalence of diabetes is exceptionally high (55–71%) in WS, and it usually appears at 30–40 years-of-age, marked by accumulated visceral fat, insulin resistance with low body mass index[2,3]. WS's clinical criteria are now available at the International Registry of Werner Syndrome (www.wernersyndrome.org), and new diagnostic criteria have been revised according to clinical experience with Japanese cases of WS[4]. However, confirmation of diagnosis still requires *WRN* gene testing.

Here, we report a young woman with diabetes. The early onset age (18 years) of diabetes with very low body mass index (15.43 kg/m^2), insulin resistance, negative antibodies of diabetes and early onset of cataracts drove us to seek a genetic etiology. WS was confirmed by next-generation sequencing and reverse transcription polymerase chain reaction. Also, we summarized all Chinese genetically confirmed WS in the literature.

CASE REPORT

An 18-year-old female patient presented with hyperglycemia for 2 months and was admitted to the Department of Endocrinology and Metabolism, First Affiliated Hospital of China Medical University, Shenyang, China. She has no apparent symptoms of thirst, polydipsia, polyphagia and polyuria. Before she came to our hospital, she was treated for type 1 diabetes with insulin for 1 week. Her parents were healthy and were not consanguineous. Her grandfather had type 2 diabetes mellitus. Her older brother had a history of cataracts since the age of 2 years.

The patient appeared like she was aged in her 30s and showed the following features: height 163 cm; weight 41 kg; body mass index 15.43 kg/m^2; heart rate 74 b.p.m., blood pressure 115/68 mmHg; and a bird-like face, slim limbs, dry hair, and dry and atrophic skin (Figure 1). Ophthalmic examination showed upper eyelid trichiasis, rough corneal epithelium, lens posterior capsule opacity and vitreous opacity. Her voice was normal.

Laboratory examinations showed the presence of hypertriglyceridemia, insulin resistance with elevated blood glucose level and hemoglobin A1c, normal levels of glutamic acid decarboxylase and insulin autoantibody, normal level of plasma lactic acid, negative urine ketone and decreased level of sex hormone-binding globulin (Table 1).

Abdominal color Doppler ultrasound showed fatty liver. The color Doppler ultrasound of the carotid artery showed that the carotid intima-media thickness was 0.6 mm on the left and 0.7 mm on the right. Audiological examinations did not show any abnormalities. Dual-energy X-ray absorptiometry showed normal bone density in the lumbar vertebrae ($Z = 0.8$). X-ray of her feet did not discover Achilles tendon calibration.

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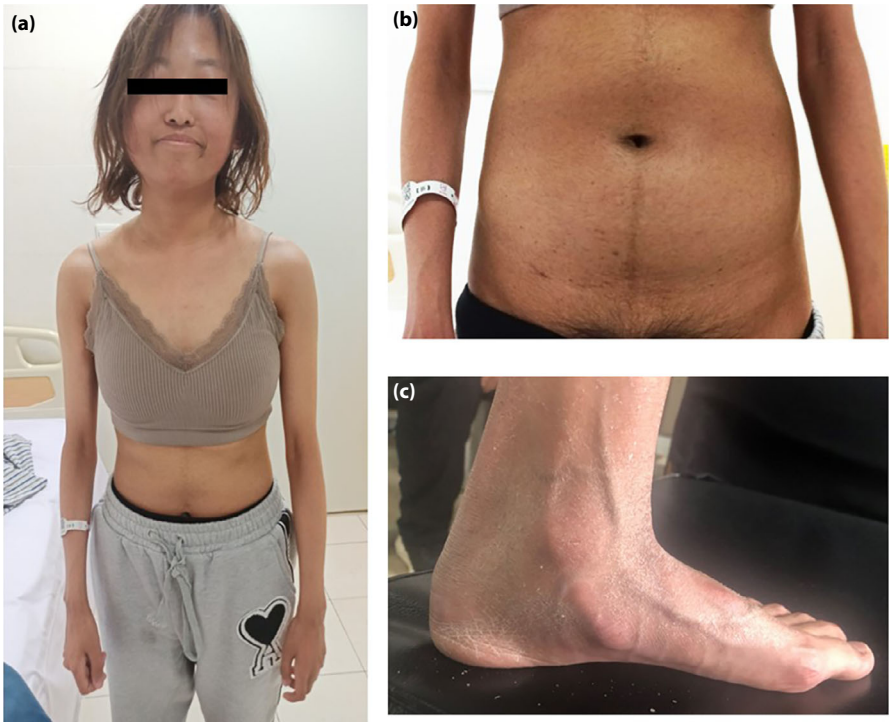

Figure 1 | Physical characteristics of the patient. (a) Senile appearance with dry hair. (b) Slim limbs, but with abdominal obesity. (c) Dry and atrophic skin on the foot.

Blood samples were collected from the patient and her parents. Genomic deoxyribonucleic acid (DNA) was extracted from the peripheral blood using a Blood DNA Kit (CWE9600, CoWin Biosciences Inc., Beijing, China). IDT xGen Exome Research Panel v1.0 (Integrated DNA Technologies, Inc., Coralville, IA, USA) was used for exon trapping. Illumina NovaSeq (San Diego, CA, USA) was used for high-throughput sequencing. Emphasis was laid on the analysis of all known genes (total 195) involved in diabetes mellitus. Two heterozygous variants found in the *WRN* gene were believed to be responsible for the prominent phenotype of the patient. The first variants was NM_000553.4 c.3020delG from the paternal origin, can be classified as pathogenic according to American College of Medical Genetics and Genomics guidelines (PVS1 + PM2 + PM3[5]). The second variant, NM_000553.4 c.1270-2A>T, is a novel splice-site mutation from the maternal origin, and it can also be classified as pathogenic (PVS1 + PM2 + PM3; Figure 2a). In addition, several other variants were also found with uncertain significance, including variants in the *ABCC8* gene (NM_00035 2.3 exon6, c.824G>A, p.R275Q) and *APPL1* gene (NM_01209 6.2 exon19, c.1829A>G, p.N610S), which are genes responsible for maturity onset diabetes of the young 12 and maturity onset diabetes of the young 14, respectively.

Total ribonucleic acid of the patient and her mother were isolated from the fresh blood samples using RNA extraction Kit Dnase I (abs60029, Absin Bioscience Inc., Shanghai, China). Reverse transcription was carried out by ABScript II RT Mix for qPCR with gDNA Remover Kit (RK20403, ABclonal Technology Co., Ltd., Wuhan, China). The complementary deoxyribonucleic acid was amplified and sequenced using flanking primers located in exons 6–15 of the *WRN* gene, surprisingly confirming exon 14 skipping in the patient and partial intron 13 fragment inclusion in her mother, which was instead of exon 10 skipping (Figure 2b). Then we sequenced parts of intron 13, exon 14 and intron 14. However, only one single-nucleotide polymorphism (rs2247189, c.1720+24T>A) in intron 14 was identified with unknown significance. Thus, we could not identify the cause of the skipping of exon 14 or partial intron 13 fragment inclusion.

Metformin hydrochloride (0.5 g three times a day) and pioglitazone hydrochloride (30 mg once a day) were given instead of insulin to the patient. The patient's compliance was poor due to the gastrointestinal reaction to metformin. After 2 months, the hemoglobin A1c was rechecked and found to be 7.8%, and the treatment was changed to linagliptin (5 mg once a day) and pioglitazone hydrochloride.

DISCUSSION

The present article reports a Chinese woman with WS who presented early-onset diabetes. Patients with WS have been reported in many populations, but the prevalence is high in some populations, resulting in founder effects, such as in Japan

Table 1 | Laboratory investigations

Test	At diagnosis				Follow up (2 months)	Normal values
	Fasting	30 min after OGTT	60 min after OGTT	120 min after OGTT	Fasting	
PG (mmol/L)	7.84	13.18	18.17	11.56	6.82	–
INS (mIU/L)	25.33	45.76	84.64	133.70	30.07	–
CP (pmol/L)	1,379.4	1,729.8	2,853.2	4,098.3	1,495.0	–
HbA1c (%)	8.6				7.8	4.4–6
LDL-c (mmol/L)	2.13				2.47	0–3.64
TC (mmol/L)	3.54				3.72	0–5.72
TG (mmol/L)	1.72				0.78	0–1.7
HDL-c (mmol/L)	0.94				0.95	0.91–1.92
UA (μmol/L)	266				258	155–357
TSH (mIU/L)	4.7195				–	0.35–4.94
fT4 (pmol/L)	11.94				–	9.01–19.05
fT3 (pmol/L)	5.04				–	2.63–5.7
TRAb (IU/L)	0.42				–	0–1.75
GAD (IU/mL)	9.16				–	0–17
IAA (IU/mL)	4.96				–	0.41–20
LAC (mg/dl)	17.4				–	4.5–19.8
E2 (pmol/L)	322.7					45.40–854.00
T (nmol/L)	0.78					0.69–2.53
FT (pmol/L)	9.89					0.77–33.03
LH (mIU/mL)	2.84					1.1–11.6
FSH (mIU/mL)	1.64					2.8–11.3
AND (nmol/L)	13.40					1.0–11.5
DHEA (μmol/L)	4.97					0.95–11.67
SHBG (nmol/L)	10.30					18–144
Urine ketone	(–)					(–)

AND, androstenedione; CP, serum C peptide; DHEA, dehydroepiandrosterone; E2, estradiol; FSH, follicle-stimulating hormone; FT, free testosterone; fT3, free triiodothyronine; fT4, free thyroxine; GAD, glutamic acid decarboxylase; HbA1c, hemoglobin A1c; HDL-c, high density lipoprotein cholesterol; IAA, insulin autoantibody; INS, serum insulin; LAC, lactic acid; LDL-c, low density lipoprotein cholesterol; LH, luteinizing hormone; PG, plasma glucose; SHBG, sex-hormone binding globulin; T, testosterone; TC, total cholesterol; TG, triglyceride; TRAb, TSH receptor antibody; TSH, thyrotropin-releasing hormone; UA, uric acid.

and Sardinia[6]. The prevalence of WS is estimated at 1:380,000–1:1,000,000, but it is seldom reported in Chinese people. There have been just 10 genetically confirmed WS cases so far, including the present case (Table 2, references in Appendix). The male : female ratio is 7:3. Most patients (7/10) presented first with skin change and sought medical advice in many different departments. It is necessary to raise awareness regarding WS among ophthalmologists and internal medicine doctors to promote early diagnosis[6].

Among these reported Chinese WS cases, four patients (4/10) had developed diabetes at the time of consultation, with a lower frequency than reported in the literature (55–71%). The onset age of diabetes in WS patients is generally 30–40 years[3]. However, the onset age of diabetes is much earlier in the present case, which other genes and environmental factors might modify. For example, the patient's lifestyle was unhealthy, as she especially liked drinking sugary drinks and rarely exercised. Next-generation sequencing identified two variants in diabetes-related genes with uncertain significance: the *ABCC8* gene and *APPL1* gene. Digenic or oligogenic causality might modify the etiology of diabetes development, which could partially explain the very early onset of diabetes in the present patient.

Clinical criteria of WS are now available at the International Registry of Werner Syndrome (www.wernersyndrome.org), and new diagnostic criteria have been revised according to clinical experience with Japanese cases of WS, including six cardinal signs and symptoms (onset >10 years-of-age until 40 years-of-age): progeroid changes of hair, cataract, changes of skin, soft-tissue calcification, bird-like face, abnormal voice, as well as seven further signs and symptoms, including abnormal glucose and/or lipid metabolism, deformation and abnormality of the bone, hypogonadism, and so on[4]. Only one of the 10 Chinese patients reached the confirmed diagnosis, and the rest were suspected, suggesting the importance of genetic diagnosis. According to Human Gene Mutation Database Professional 2020.4, 95 mutations of *WRN* gene-causing WS have been recorded, most of them are predicted to result in a protein truncation, resulting

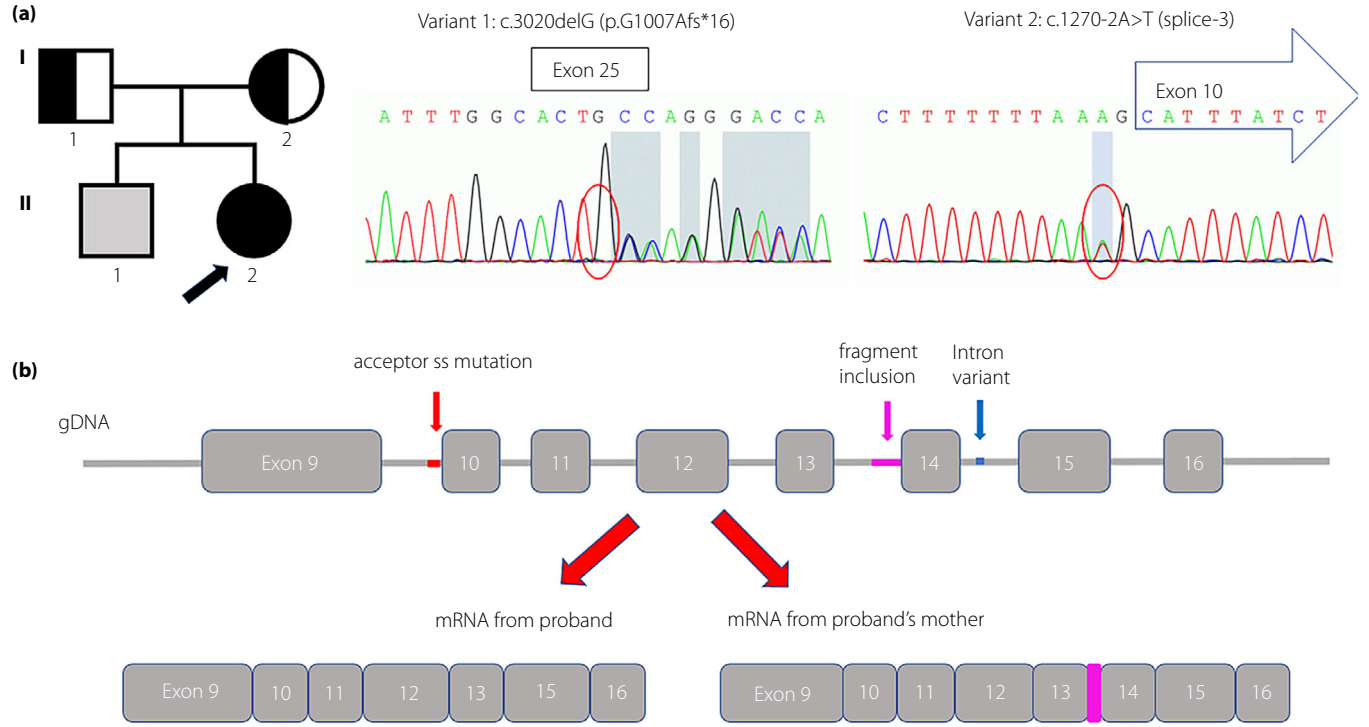

Figure 2 | Pedigree of the proband and genetic analysis of the *WRN* gene. (a) Pedigree of the relatives with Werner syndrome. Males and females are indicated by squares and circles, respectively. Filled symbols indicate an affected individual. Half-filled symbols indicate heterozygous carriers. The proband is indicated by a black arrow. Electropherogram of the *WRN* gene sequence shows two heterozygous variants. The first one is c.3020delG from the paternal origin, and the second variant, c.1270-2A>T, is a novel splice-site mutation from the maternal origin. (b) The complementary deoxyribonucleic acid was amplified and sequenced using flanking primers located in exons 6–15 of *WRN*, surprisingly confirming exon 14 skipping in the patient and partial intron 13 fragment inclusion (pink) in her mother, instead of exon 10 skipping. There was no mutation in intron 13, exon 14 and intron 14, except one intron variant c.1720+24T>A (blue) in intron 14 with unknown significance.

in nonsense-mediated decay (of mutant messenger ribonucleic acids and/or functionally null protein due to truncations of C-terminal nuclear localization signals. The most common mutations in Japanese patients are c.3139-1 G>C (50.4%) and c.1105 C>T (17.5%)[7], whereas the most common mutation in non-Japanese patients is c.1105 C>T (18.6%)[8], suggesting that c.1105 C>T (rs17847577) is a hotspot mutation across ethnic groups. These two mutations have also been found in two Chinese cases of WS separately, but no hotspot mutation has been implied among Chinese WS patients, which might require more cases to be found.

Initially, the variants of the *WRN* gene found in the present case were both believed to result in protein truncations. The first variant, c.3020delG, located in exon 25, leads to a premature stop codon downstream, yielding a truncated protein (p. Gly1007AlafsTer16). This variant was previously reported in another Chinese WS patient[5]. The second novel splice site variant, c.1270-2A>T, in intron 9, is predicted to cause exon 10 deletion. However, reverse transcription polymerase chain reaction showed no skipping of exon 10, but a surprising skipping of exon 14 or inclusion of intron 13 fragment. We further sequenced the whole intron 13, exon 14 and intron 14, and only one single-nucleotide polymorphism (rs2247189, c.1720+24T>A) in intron 14 was identified with unknown significance. It is challenging to elucidate why acceptor splice site mutation of one exon leads to a distant exon skipping. Still, it underlines the importance of reverse transcription polymerase chain reaction sequencing for the confirmation of suspected splice site mutations. Similarly, an instance of exon skipping not associated with splice acceptor or donor sites mutation was found in WS patients, suggesting a leaky deep intronic mutation[9].

Thiazolidine derivatives and metformin are recommended for glycemic control in WS patients[3]. However, clinicians should be aware of the side-effect of bone fracture from thiazolidine derivatives, especially in WS patients with osteopenia and osteoporosis. Dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists have also been reported to be effective in small numbers of WS patients[10,11]. Dietary and exercise therapies to prevent increased visceral fat are also essential for palliating the diabetes progression in WS patients.

In conclusion, the present report described a Chinese WS patient who had uncommon early-onset diabetes. This case

Table 2 | Summary of all Chinese genetically confirmed WS in the literature

Reported department	WS of Chinese											2020 Survey in Japan[8]
	P1 Dermatology	P2 Orthopedics	P3 Ophthalmology	P4 Endocrinology	P5 Neurosurgery	P6 Orthopedics	P7 Rheumatology	P8 Dermatology	P9 Neurology	P10 Endocrinology	Summary Dermatology and Orthopedics (40%)	Dermatology and Plastic surgery (15.6%)
Diagnosed age (years)	31	38	26	40	30	41	36	22	31	18	24.5 ± 7.3	42.5 ± 8.6
Sex	Male	Male	Male	Female	Female	Male	Male	Male	Male	Female	Male (70%)	Male (55%)
Bodyweight (kg)	27	N.M.	40	32	46	42	49.8	N.M.	52.5	41	46.8 ± 8.0	44.1 ± 9.5
Hight (cm)	154	N.M.	150	147	N.M.	150	161	165	163	163	163.0 ± 6.7	154.0 ± 10.7
BMI (kg/m^2)	11.4	N.M.	17.8	14.8	N.M.	18.7	19.2	N.M.	19.8	15.4	17.6 ± 2.8	18.5 ± 3.1
Cardinal signs and symptoms												
Progeroid (changes of hair	Yes	Yes	Yes	Yes	N.M.	Yes	Yes	N.M.	No	Yes	87.5% (7/8)	97.5%
Cataract	Yes	N.M.	Yes	Yes	Yes	Yes	Yes	N.M.	Yes	Yes	100% (8/8)	100%
Changes of skin, Intractable skin ulcers	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100% (10/10)	97.5%
Soft-tissue calcification	Yes	N.M.	Yes	N.M.	N.M.	N.M.	N.M.	N.M.	Yes	No	75% (3/4)	87.5%
Bird-like face	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	90% (9/10)	90%
Abnormal voice	Yes	Yes	N.M.	Yes	Yes	Yes	Yes	Yes	Yes	No	88.9% (8/9)	87.5%
Other signs and symptoms												
Abnormal glucose and/or lipid metabolism	No	N.M.	N.M.	Yes	N.M.	Yes	Yes	N.M.	N.M.	Yes	40% (DM)	67.5% (DM/IGT)
Deformation and abnormality of the bone	Yes	N.M.	N.M.	Yes	Yes	Yes	Yes	Yes	Yes	No	87.5% (7/8)	N.E.
Malignant tumors	N.M.	N.M.	N.M.	N.M.	Yes	N.M.	N.M.	N.M.	N.M.	No	N.E.	20%
Parental consanguinity	No	Yes	Yes	No	N.M.	Yes	No	N.M.	No	Yes	50% (4/8)	29.7%
Premature atherosclerosis	N.M.	N.M.	N.M.	N.M.	N.M.	N.M.	N.M.	N.M.	N.M.	No	N.E.	17.5%
Hypogonadism	Yes	N.M.	N.M.	Yes	N.M.	Yes	Yes	Yes	N.M.	No	50%	N.E.
Short stature and low body weight	Yes	N.M.	Yes	Yes	N.M.	Yes	Yes	No.	Yes	No	75% (6/8)	N.E.
Diagnosis based on signs and symptoms	Confirmed	Suspected	Suspected	Suspected	Suspected	Suspected	Suspected	Suspected	Suspected	Suspected	–	
Gene testing	Homozygous, c.3020delG	Homozygous, c.IVS28+2T>C	Homozygous, c.3460_3461insTTGTG	Compound heterozygous, **c.1105C>T** and c.1134delA	Heterozygous, c.2806insA	Homozygous, c.2229_2230delAG	Compound heterozygous, c.1662G>A and c.3019delG	Compound heterozygous, **c.3139-1G>C** and c.1960C>T	Homozygous, c.2959C>T	Compound heterozygous, c.3020delG and c.1270-2A>T	–	–

DM, diabetes mellitus, IGT, impaired glucose tolerance, hot spot mutations in Japanese are indicated in bold; N.E., not evaluated; N.M., not mentioned.

reminds clinicians that when young diabetes patients are encountered, if they are accompanied by premature aging, attention should be paid to identifying the possibility of WS based on diagnostic criteria.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The ethics committee approved the study of First Affiliated Hospital of China Medical University.

Informed consent: The patient and her family members provided written informed consent for publication of their clinical details and clinical images.

Approval date of registry and the registration no. of the study/-trial: N/A.

Animal Studies: N/A.

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APPENDIX

REFERENCES OF CHINESE GENETICALLY CONFIRMED WERNER SYNDROME IN TABLE 2

Number	Reference
P1	[1]
P2	[2]
P3	[3]
P4	[4]
P5	[5]
P6	[6] (In Chinese)
P7	[7] (In Chinese)
P8	[8] (In Chinese)
P9	[9] (In Chinese)
P10	This article

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