Severe metabolic disorders coexisting with Werner syndrome: a case report

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Abstract. Werner syndrome, also called adult progeria, is a heritable autosomal recessive human disorder characterized by the premature onset of numerous age-related diseases including juvenile cataracts, dyslipidemia, diabetes mellitus (DM), osteoporosis, atherosclerosis, and cancer. Werner syndrome is a segmental progeroid syndrome whose presentation resembles accelerated aging. The most common causes of death for WS patients are atherosclerosis and cancer. A 40-year-old female presented with short stature, bird-like facies, canities with alopecia, scleroderma-like skin changes, and non-healing foot ulcers. The patient reported a history of delayed puberty, abortion, hypertriglyceridemia, and juvenile cataracts. A clinical diagnosis of WS was made and subsequently confirmed. We discovered two WRN gene mutations in the patient, Variant 1 was the most common WRN mutation, nonsense mutation (c.1105C>T:p.R369Ter) in exon 9, which caused a premature termination codon (PTC) at position 369. Variant 2 was a frameshift mutation (c.1134delA:p.E379KfsTer5) in exon 9, which caused a PTC at position 383 and has no published reports describing. Patients with WS can show a wide variety of clinical and biological manifestations in endocrine-metabolic systems (DM, thyroid dysfunction, and hyperlipidemia). Doctors must be cognizant of early manifestations of WS and treatment options.

Key words: Werner syndrome, WRN gene, Progeroid, Diabetes mellitus

WERNER SYNDROME (WS) is a rare, autosomal recessive condition with multiple progeroid features caused by a mutation in the Werner gene (WRN) that encodes the protein WRN RecQ-like helicase [1, 2]. It was first described by Otto Werner in 1904 [3]. Classic WS is caused by WRN mutation and WS cases without WRN mutations is caused by LMNA mutation. WS patients suffer prematurely from a variety of age-related diseases in one or more of the body’s major systems (nervous, immune, connective tissue, and endocrine-metabolic systems), and die at an average age of 54 years [4]. In this article we report the results of genetic analysis in the diagnosis of a patient with WS.

Case Presentation

A 40-year-old Chinese woman presented with a chief complaint of non-healing foot ulcers. After a thorough examination, the patient was diagnosed as having WS. The patient was healthy at birth and developed normally during childhood. There were sequentially-appearing clinical manifestations of WS in the patient: lack of a pubertal growth spurt (at age 14); canities with alopecia (at age 22); hoarseness (at age 25); skin atrophy (at age 28); cataracts (at age 33); and severe hypertriglyceridemia and DM (at age 34). She married at the age of 21 years and had 3 spontaneous abortions, each at 6 months of pregnancy. The patient had a normal menstrual history until the age of 36, after which the menstrual cycle increased to 2–4 months, the menstrual period remained at 2–4 days, however the menstrual volume was reduced. The patient was being treated with Gansulin 30R® (66 U, 2x daily), but her fasting blood glucose (FPG) level and glycosylated hemoglobin (HbA1c) remained high (11.62 mmol/L and 8.7%, respectively).

A clinical examination included blood pressure (130/70 mm Hg), heart rate (76 bpm), temperature (36.5°C), body weight (32 kg), height (147 cm), waist circumference (72 cm), body mass index (14.81 kg/m²), and assessment of physical features: bird-like facies; skin ulcers on the feet; abdominal obesity and thin limbs (Fig. 1A). The patient’s present father was not her biological father, her mother had lost contact with the patient’s biological father for more than 30 years. Clinical examinations of her mother, two half-brothers, nephews, and nieces revealed that all were in good health.
Laboratory tests revealed a decline in postprandial C-peptide levels and negative beta-cell autoantibodies (GADA, IAA, IA-2A, ICA, and ZnT8A), characteristic of Type 2 DM, poor glycemic control with concomitant severe hyperlipidemia, sub-clinical hypothyroidism with negative antithyroid peroxidase antibodies, and a slight decline in ovarian function. Visceral fat area measured by computed tomography, whole-body fat percentage and lean mass measured by dual-energy X-ray absorptiometry were 68 cm², 27.9% and 21.92 kg. Routine laboratory including blood routine examination, routine urine test, liver function tests, renal function tests were all normal. Cardiovascular assessment including Electrocardiography (ECG) and echocardiography were normal. Ultrasound imaging revealed a fatty liver and hypoplastic uterus. The patient’s thyroid was of normal size with normal blood flow. Dual energy X-ray absorptiometry (DEXA) revealed osteopenia. Laboratory test data are presented in Table 1.

WS can be clinically diagnosed when the presence of

Fig. 1 A: Physical characteristics of the patient. (A1) Bird-like facies. (A2) Skin ulcers on the feet. (A3) Abdominal obesity and thin limbs. B and C: Genetic analysis of the WRN gene of the patient and her mother. The mutated nucleotides are marked with an arrow. B. Patient DNA. B(1) Nonsense mutation c.1105 C>T in exon 9. B(2) Frame shift mutation c.1134delA in exon 9. C. Maternal DNA. C(1) No mutation in exon 9. C(2) Frame shift mutation c.1134delA in exon 9.
multiple metabolic disorders and specific physical characteristics (as described above) are present based on the genetic analysis of the patient and her mother. Genetic testing of the patient’s maternal genome revealed that her mother was a carrier of the exon 9: c.1134delA:p.E379KfsTer5 (Variant 2) mutation in a single allele (Fig. 1C).

**Discussion**

Our patient was a non-obese female, without risk factors of metabolic diseases including type 2 DM and lipid disorders. The patient was noted to have specific physical characteristics (history of cataracts, hair changes, bird-like face, and low body mass index), which in addition to metabolic diseases, met diagnostic criteria for WS [5]. Genetic testing for WRN mutations confirmed our clinical diagnosis.

WS, an autosomal recessive premature ageing syndrome, is considered to be a model of natural human aging [1]. About 1,100 patients with WS have been reported between the first description by Otto Werner in 1904 [3] and 1994 [6]. People of Japanese descent account for 75% of all WS patients and 43% of WS patients are offspring of consanguineous marriages according to a Japanese nationwide epidemiological survey of WS conducted in 2009 [5, 7]. A study of the clinical features of 102 WS patients in Japan, revealed that the male-to-female ratio was 3:2 [8]. As long as the affected individual and his/her reproductive partner are non-consanguineous, offspring with WS is rare.

The clinical identification of WS as a genetic disorder led to the cloning of the responsible gene (WRN) in 1996 [9-11]. The protein defective in WS patients (WRN) is encoded by a member of the human RECQ gene family which contains both DNA exonuclease and helicase domains. WRN has been shown to participate in several DNA metabolic pathways, including DNA replication, recombination, repair, telomere maintenance, and transcription modulation [12]. Monnat RJ et al. have proposed a simple model for the pathogenesis of WS, in this model, lack of WRN protein causes genomic instability, accelerated telomere attrition and cell dysfunction and cell loss in many cell lineages with the accumulation of somatic mutations [13]. To date, a total of 83 different WRN mutations have been summarized, including eight previously unpublished mutations identified by the International Registry of Werner Syndrome (Seattle, WA) and the Japanese Werner Consortium (Chiba, Japan) [14]. WS patients primarily have the following WRN

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**Table 1 Laboratory Data of the Patient**

| Index                          | Results | Reference Range   |
|-------------------------------|---------|-------------------|
| Fasting plasma glucose (mmol/L)| 11.62   | 3.9–6.1           |
| Glycosylated hemoglobin (%)    | 8.70    | 4.27–6.07         |
| Fasting serum C-peptide (ng/mL)| 1.77    | 0.5–3.8           |
| 1h postprandial serum C-peptide (ng/mL) | 1.98   | 5.38–6.67         |
| 2h postprandial serum C-peptide (ng/mL) | 1.69   | 4.10–5.56         |
| TG (mmol/L)                   | 24.56   | 0.56–1.71         |
| TC (mmol/L)                   | 6.28    | 2.90–5.17         |
| HDL-C (mmol/L)                | 0.64    | 0.90–1.68         |
| LDL-C (mmol/L)                | 1.16    | 2.70–3.40         |
| LH (mIU/mL)                   | 8.98    | 1.9–12.5          |
| FSH (mIU/mL)                  | 17.52   | 2.5–10.2          |
| PRL (ng/mL)                   | 43.35   | 2.8–29.2          |
| E2 (pg/mL)                    | 24.95   | 18.9–246.7        |
| PG (ng/mL)                    | 0.45    | 0.15–1.4          |
| T (ng/dL)                     | 8.76    | 9.01–47.94        |
| TT3 (nmol/L)                  | 1.92    | 0.92–2.79         |
| TT4 (nmol/L)                  | 91.7    | 58.1–140.6        |
| FT3 (pmol/L)                  | 4.34    | 3.5–6.5           |
| FT4 (pmol/L)                  | 10.27   | 11.5–22.7         |
| TSH (mU/L)                    | 7.445   | 0.55–4.78         |
| TPOAb (U/mL)                  | 35.1    | 0–60              |
| Tg (ng/mL)                    | 38.9    | 1.6–55            |
| TgAb (U/mL)                   | 28      | 0–60              |

TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LH, luteinizing hormone; FSH, follicle-stimulating hormone; PRL, prolactin; E2, estradiol; PG, progesterone; T, testosterone; TSH, thyrotropin hormone; TPOAb, antithyroid peroxidase antibodies; Tg, thyroglobulin; TgAb, thyroglobulin antibody.
mutations; (a) nonsense mutations, which change amino acid codons to premature termination codons (PTCs), causing the premature termination of protein translation; (b) insertions and/or deletions, which lead to reading frameshift and premature termination of protein translation; (c) substitutions at splice junctions, which cause the skipping of exons and a subsequent frameshift; and (d) missense mutations, which cause amino acid change in the protein sequence [4]. The most frequent WS mutation is the Variant 1 nonsense mutation, c.1105C>T:p.R369Ter, in exon 9, which caused the mutation of codon 379 from a glutamate to a lysine and resulted in a PTC at position 383. There are no published reports describing Variant 2. We have not confirmed the presence of a Variant 2 protein but a possible mechanism that may eliminate its protein expression is nonsense-mediated decay (NMD) of mRNAs containing premature termination codons. NMD is a cellular surveillance system that prevents errors in gene expression. If generation of PTC mRNA is not eliminated through NMD, the abnormal proteins produced can be toxic to cells through dominant-negative or gain-of-function effects. There are three major ways that NMD can effect clinical outcomes: (1) changing the pattern of heredity, (2) causing different traits to be expressed from the same gene mutations, and (3) modifying the specific clinical phenotype [16].

WS patients usually develop normally in their childhood, but typically stop growing due to a lack of the pubertal growth spurt during the teen years. Most WS patients are reported to have short stature [4]. Median age of diagnosis ranges from late 30s to 40s [4, 5, 17]. The overall medical statistics (age, SD) for WS include: onset of growth delay (18.9, 7.7); canities (20.1, 10.4); sclerosis (26.4, 10.1); cataracts (31.2, 8.5); DM (31.5, 9.0); skin ulcers (34.7, 9.6); hypogonadism (35.6, 8.4); and osteoporosis (39.5, 7.5) [3]. Predictable subsequent events (age, SD) include: immune dysfunction (40.0, 10.5); atherosclerosis (40.6, 9.0); brain atrophy (40.7, 9.1); dementia (41.1, 7.7); malignancy (41.3, 9.2); and age at death (46.0, 11.6) [15]. We used “Werner syndrome” and “WRN mutation”, “Werner syndrome” and “LMNA mutation”, “Werner syndrome” or “progeria” to search in English database (Pubmed), and Chinese database (China National Knowledge Infrastructure (CNKI) up to 15th August 2020, and found 16 Chinese patients with WS reported [18-33]. Demographic (i.e., age, sex) and clinical characteristics of individual patients were summarized in Table 2.

WS was accurately diagnosed in the patient through the collection of a detailed medical history, a careful physical examination, and obtaining extensive laboratory test results. The diagnosis of WS was based on the diagnostic criteria recommended by Takemoto et al. [5]. The treatment for the patient was comprehensive, including: lowering blood glucose and reducing insulin resistance (pioglitazone, 30 mg, once per day), lowering lipid levels (fenofibrate, 200 mg, once per day), antioxidant therapy (thioctic acid injection, 600 mg, once per day), neuroprotection (mecobalamin, 0.5 mg, 3 times per day), and proper care and dressing of foot ulcers and scleroderma.

Over the course of a 7-day treatment, FPG decreased to 8.0–9.0 mmol/L, the 2-hour postprandial glucose decreased to 6.0–11.0 mmol/L, the serum triglyceride level decreased from 24.56 to 19.85 mmol/L; the total serum cholesterol level decreased from 11.68 to 9.45 mmol/L, and the daily insulin requirement decreased from 66 to 38 U/day. Treatment after discharge included: Gansulin 30R® (38 U, 2x daily); pioglitazone (30 mg, once daily); fenofibrate (200 mg, once daily); and mecobalamin, (0.5 mg, 3x daily). The follow-up results after 6 months were: FPG (5.0–9.0 mmol/L); 2 hour postprandial glucose (7.0–13.0 mmol/L); serum triglyceride level (6.61 mmol/L); and total serum cholesterol level (4.37 mmol/L); The patient’s foot ulcers improved and the cooling sensation decreased.

When WS is diagnosed in patients, annual screening is important for early detection of tumors and cataracts. In addition, physicians should monitor any development of arteriosclerosis-related diseases. Treatments for the symptoms of WS include: surgery for refractory ulcers [34] and cataracts [31], anti-aging treatment such as vitamin C [35], or rapamycin [36], either with or without a farnesyltransferase inhibitor [37], and pluripotent stem cell therapy [38, 39]. With an increasing awareness of WS, the availability of genetic testing, and the variety of available investigative tools (genomics, epigenomics, transcriptomics, proteomics, and metabonomics), it is hoped that new approaches for the treatment of WS symptoms will also provide for the early recognition and treatment of age-related disorders [39].

Conclusions

We reported on a 40-year-old Chinese woman who presented with multiple metabolic disorders and progeria. She was clinically diagnosed with WS which was subsequently found to be caused by a WRN gene mutation in each allele. We discovered that the two WRN gene mutations included the Variant 1 nonsense mutation (c.1105C>T:p.R369Ter) in exon 9 (the most common WRN mutation) and a unique frameshift mutation (c.1134delA:p.E379KfsTer5) also in exon 9. Because there is currently no cure for WS, early diagnosis and
Table 2  The Features of Reported Patients with WS

| Patient | Patient | Patient | Patient | Patient | Patient | Patient | Patient | Patient | Patient | Patient | Patient | Patient |
|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
|         | 1       | 2       | 3       | 4       | 5       | 6       | 7       | 8       | 9       | 10      | 11      | 12      | 13      |
| Sex     | F       | F       | M       | F       | F       | M       | M       | F       | M       | F       | M       | M       | M       |
| Age at diagnosis | 46      | 26      | 45      | 18      | 43      | 31      | 30      | 45      | 39      | 18      | 41      | 19      | 26      |
| Age of initial symptoms | 24      | 18      | Early   | Early   | Early   | Early   | NM      | 13      | 13      | 13      | 8       | NM      | 14      |
| Chief complaint | Foot    | Alopecia | Foot    | Alopecia | Hyperglycaemia | Foot    | Alopecia | Loss of binocular vision | Atroventricular block | Nerve deafness | Hyperglycaemia | Arthralgia | Irregular menstruation, hyperglycaemia | Loss of binocular vision | Foot ulcers | Foot ulcers | Foot ulcers |
| Initial presenting symptoms | Alopecia | Alopecia | Short stature | Dark skin | Short stature | Short stature | Short stature | Short stature | Short stature | Short stature | Short stature | Short stature | NM | Short stature | NM |
| Cataracts | Yes     | Yes     | Yes     | No      | Yes     | Yes     | Yes     | No      | Yes     | Yes     | No      | Yes     | Yes     | No |
| DM      | No      | No      | Yes     | Yes     | No      | No      | No      | Yes     | Yes     | No      | Yes     | No      | No     | No |
| Hyperlipidemia | NM     | No      | NM      | NM      | Yes     | NM      | NM      | NM      | No      | NM      | Yes     | NM      | NM      | NM |
| Osteoporosis | Yes    | No      | Yes     | NM      | Yes     | NM      | NM      | Yes     | NM      | Yes     | NM      | NM      | Yes     | NM |
| Cancer   | No      | No      | No      | No      | Yes     | No      | No      | No      | No      | No      | No      | No      | No     | No |
| Arteriosclerosis | NM    | No      | Yes     | NM      | Yes     | NM      | NM      | No      | NM      | NM      | NM      | Yes     | NM     | NM |
| Hypophrenia | No    | Yes     | No      | No      | No      | Yes     | Yes     | No      | No      | No      | No      | No      | NM     | NM |
| Parental consanguinity | NM    | No      | Yes     | No      | NM      | NM      | NM      | Yes     | No      | NM      | Yes     | NM      | Yes     | NM |
| Affered sibling | NM    | No      | Yes     | No      | NM      | NM      | NM      | Yes     | No      | NM      | NM      | NM      | NM     | NM |
| Short stature | Yes    | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | NM |
| Bird-like face | NM    | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | NM |
| Hypogonadism | NM     | Yes     | NM      | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | NM |
| Sensillum | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | NM |
| Voice change | NM    | No      | Yes     | NM      | Yes     | NM      | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | NM |
| Gray hair or alopecia | Yes    | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes |
| Sclerodema | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     | Yes |
| Flat feet | NM      | No      | Yes     | NM      | NM      | NM      | NM      | NM      | NM      | NM      | NM      | NM      | NM     | NM |
| Gene testing | No     | No      | No      | No      | No      | No      | No      | No      | 2967+237A>G | 3309+26C>T | c.2361G>T in exon20 | c.3237G>A in exon27 | L.512R- (Leu512Arg) in the LMNA gene | c.2229A>G | c.3460_3461insTTG (c.IVS28+2C) | p.L140Q (c.410G>A) in the LMNA gene | c.3460_3461insTTG (c.IVS28+2C) | p.L140Q (c.410G>A) in the LMNA gene | c.3460_3461insTTG (c.IVS28+2C) | p.L140Q (c.410G>A) in the LMNA gene |

NM, not mentioned. Of the 16 patients listed, 8 were diagnosed as Werner syndrome by genetic testing, including 2 patients with atypical Werner syndrome (Patient 10 and Patient 12).
treatment of WS will reduce, or eliminate, age-related disorders in WS patients. We hope that this case report will contribute to the clinical awareness and investigations of this rare disease.

**Declaration of Conflicts of Interests**

The authors have nothing to disclose.

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**Ethic Approval and Consent to Participate**

This study involving Human Participants was approved by the ethical review committee of The Second Hospital of Jilin University (2020-014). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

**Consent for Publication**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**Authors Contributions**

HL communicated with the patient and her family, acquired the clinical data, and drafted the initial manuscript. MY assisted with the writing and editing of the manuscript. HS assisted in evaluating the condition of the patient and performed literature searches to assist in the diagnosis of the disease. SW collected blood samples from the patient and her parents. HC designed and supervised the study and assisted in the revision and completion of the manuscript.

**References**

1. Epstein CJ, Martin GM, Schultz AL, Motulsky AG (1966) Werner’s syndrome: a review of its symptomatology, natural history, pathologic features, genetics and relationship to the natural aging process. Medicine (Baltimore) 45: 177–221.
2. Tollefsbol TO, Cohen HJ (1984) The effect of age on the accumulation of labile triosephosphate isomerase and thymidine incorporation in pokeweed mitogen stimulated human lymphocytes. J Gerontol 39: 398–405.
3. (1985) On cataract in conjunction with scleroderma. Otto Werner, doctoral dissertation, 1904, Royal Ophthalmology Clinic, Royal Christian Albrecht University of Kiel. Adv Exp Med Biol 190: 1–14.
4. Huang S, Lee L, Hanson NB, Lenarths C, Hoehn H, et al. (2006) The spectrum of WRN mutations in Werner syndrome patients. Hum Mutat 27: 558–567.
5. Takemoto M, Moris S, Kuzuya M, Yoshimoto S, Shimamoto A, et al. (2013) Diagnostic criteria for Werner syndrome based on Japanese nationwide epidemiological survey. Geriatr Gerontol Int 13: 475–481.
6. Goto M, Miller RW, Ishikawa Y, Sugano H (1996) Excess of rare cancers in Werner’s syndrome (adult progeria). Cancer Epidemiol Biomarkers Prev 5: 239–246.
7. Goto M, Tanimoto K, Horiiuchi Y, Sasazuki T (1981) Family analysis of Werner’s syndrome: a survey of 42 Japanese families with a review of the literature. Clin Genet 19: 8–15.
8. Imura H, Nakao Y, Kuzuya H, Okamoto M, Okamoto M, et al. (1985) Clinical, endocrine and metabolic aspects of the Werner syndrome compared with those of normal aging. Adv Exp Med Biol 190: 171–185.
9. Goto M, Rubenstein M, Weber J, Woods K, Drayna D, et al. (1992) Genetic linkage of Werner’s syndrome to five markers on chromosome 8. Nature 355: 735–738.
10. Yu CE, Oshima J, Fu YH, Wijsman EM, Hisama F, et al. (1996) Schellenberg, Positional cloning of the Werner’s syndrome gene. Science 272: 258–262.
11. Goto M, Imamura O, Kuromitsu J, Matsumoto T, Yamabe Y, et al. (1997) Analysis of helicase gene mutations in Japanese Werner’s syndrome patients. Hum Genet 99: 191–193.
12. Lebel M, Monnat RJ Jr (2018) Werner syndrome (WRN) gene variants and their association with altered function and age-associated diseases. Ageing Res Rev 41: 82–97.
13. Oshima J, Sidorova JM, Monnat RJ Jr (2017) Werner syndrome: clinical features, pathogenesis and potential therapeutic interventions. Ageing Res Rev 33: 105–114.
14. Masala MV, Scapaticci S, Olivieri C, Pirroda C, Montesu MA, et al. (2007) Epidemiology and clinical aspects of Werner’s syndrome in North Sardinia: description of a cluster. Eur J Dermatol 17: 213–216.
15. Goto M (1997) Hierarchical deterioration of body systems in Werner’s syndrome: implications for normal ageing. Mech Ageing Dev 98: 239–254.
16. Khajiavi M, Inoue K, Lupski JR (2006) Nonsense-mediated mRNA decay modulates clinical outcome of genetic disease. Eur J Hum Genet 14: 1074–1081.
17. Goto M, Ishikawa Y, Sugimoto M, Furuichi Y (2013) Werner syndrome: a changing pattern of clinical manifestations in Japan (1917–2008). Biosci Trends 7: 13–22.
18. Ren J, Liu XK, Li XS, Wang XH, Wang GQ (2012) Mutation analysis in WRN gene in a patient with Werner syndrome accompanied by nerve deafness. *Diagnosis and Treatment of Dermatology J* 19: 339–342 (In Chinese).

19. Liang D, Zhuang EX (1983) A report on Werner syndrome. *New Developments in Ophthalmology J* 04: 278–280 (In Chinese).

20. Shi YD, Zhang XJ, Wu SN, Qi FZ (2003) A report on Werner’s syndrome with chronic right heel ulcer. *Chinese Plastic Surgery J* 01: 77 (In Chinese).

21. Zhu J, Zhu GD, Shi WM (2012) A report on Werner syndrome. *Chinese Society for Integrated Chinese and Western Medicine C*: 112 (In Chinese).

22. Zhu P, Yan L, Zhou ZY (2009) A report on Werner syndrome. *Guangdong Med J* 30: 831 (In Chinese).

23. Sun HY, Zhao L, Ding XY, Gu MY, Huang YH, et al. (2016) Clinical study of LMNA gene mutation leading to atypical Werner syndrome with diabetes mellitus. *Shanghai Med J* 113: 795–797.

24. Hao S, Feng J, Zhang L, Tang J, Wu Z, et al. (2011) Rapid recurrence of petroclival meningioma in Werner syndrome: case report. *Clin Neurol Neurosurg* 113: 795–797.

25. Li RX (1984) Werner syndrome with atrioventricular conduction disorder: a case report. *Bethune Medical University J* 01: 15 (In Chinese).

26. Wang CX, Zhang WE (1998) A report on adults progeria. *Chinese Medical Imaging J* 03: 3–5 (In Chinese).

27. Cao YF, Zhao HM, Wang Y, Shen Y, Zheng MX, et al. (2012) A report of rare Werner syndrome. *Clin Misdiagnosis and Misdiagnosis J* 25: 23–24 (In Chinese).

28. Li SS, Fei JP, Xiang SK, He JW, Fu WZ, et al. (2016) Middle-aged male: premature aging - hypogonadism - cataract. *Chinese Osteoporosis and Bone Mineral Disease J* 9: 308–313 (In Chinese).

29. He G, Yan Z, Sun L, Lv Y, Guo WY, et al. (2019) Rapid recurrence of petroclival meningioma in Werner syndrome: case report. *Clin Neurol Neurosurg* 113: 795–797.

30. Chen CL, Yang JS, Zhang X, Tian T, Zeng R, et al. (2018) A case report of Werner’s syndrome with bilateral juvenile cataracts. *BMC Ophthalmol* 18: 199.

31. He J, Pan D, Wu P, Tang J (2018) Recurrent skin ulcer cross-repair and sensory reconstruction in a WRN gene mutational patient. *An Bras Dermatol* 93: 443–446.

32. Zhao N, Hao F, Qu T, Zuo YG, Wang BX (2008) A novel mutation of the WRN gene in a Chinese patient with Werner syndrome. *Clin Exp Dermatol* 33: 278–281.

33. Wu PF, Jin JY, Li JJ, He JQ, Fan LL, et al. (2017) A novel splice-site mutation of WRN (c.1259+1C>G) identified in a consanguineous family with Werner syndrome. *Mol Med Rep* 15: 3735–3738.

34. Lautrup S, Caponio D, Cheung HH, Piccoli C, Stevnsner T, et al. (2019) Studying Werner syndrome to elucidate mechanisms and therapeutics of human aging and age-related diseases. *Biogerontology* 20: 255–269.

35. Hui CW, St-Pierre MK, Detuncq J, Aumailley L, Dubois MJ, et al. (2018) Nonfunctional mutant Wrn protein leads to neurological deficits, neuronal stress, microglial alteration, and immune imbalance in a mouse model of Werner syndrome. *Brain Behav Immun* 73: 450–469.

36. Oshima J, Sidorova JM, Mommat RJ Jr (2017) Werner syndrome: clinical features, pathogenesis and potential therapeutic interventions. *Ageing Res Rev* 33: 105–114.

37. Bikkul MU, Clements CS, Godwin LS, Goldberg MW, Kill IR, et al. (2018) Farnesyltransferase inhibitor and rapamycin correct aberrant genome organisation and decrease DNA damage respectively, in Hutchinson-Gilford progeria syndrome fibroblasts. *Biogerontology* 19: 579–602.

38. Shimamoto A, Yokote K, Tahara H (2015) Werner syndrome-specific induced pluripotent stem cells: recovery of telomere function by reprogramming. *Front Genet* 6: 10.

39. Wu Z, Zhang W, Song M, Wang W, Wei G, et al. (2018) Differential stem cell aging kinetics in Hutchinson-Gilford progeria syndrome and Werner syndrome. *Protein Cell* 9: 333–350.