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Case Report

Partial lipodystrophy, severe dyslipidaemia and insulin resistant diabetes as early signs of Werner syndrome

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KEYWORDS
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Partial lipodystrophy;
Liver steatosis;
Helicase;
Exome

Werner syndrome is a premature ageing disorder caused by biallelic variants in the *WRN* gene. *WRN* encodes a dual DNA helicase/exonuclease enzyme. Molecular diagnosis is commonly only made at a late disease stage in the third or fourth decade, when cardinal features have become apparent. We describe a 28 year-old woman who presented with early onset diabetes associated with partial lipodystrophy, severe dyslipidaemia and rapidly progressive liver fibrosis related to non-alcoholic steatohepatitis in the absence of progeroid features. Werner syndrome was diagnosed by trio exome analysis, which revealed compound heterozygous *WRN* mutations: the known variant c.1290_1293del (p.Asn430Lysfs*7) and the novel intronic splice site variant c.2732+5G>*A*. cDNA analysis demonstrated this to lead to in-frame skipping of exon 22, predicted to delete most of the zinc binding region of the helicase domain. We suggest that including the *WRN* gene in genetic analysis of early onset diabetes, lipodystrophy or dyslipidaemia would allow for the opportunity to diagnose some cases of Werner syndrome long before clinical criteria are met, thereby allowing early implementation of important primary prevention interventions.

Introduction

Lipodystrophy denotes loss of adipose tissue from some or all adipose depots, and may be genetic or acquired. It is characteristically not reversible even given sustained positive energy balance, and it is usually accompanied by metabolic features of "adipose failure" such as insulin resistance, fatty liver, dyslipidaemia and often diabetes. These, in turn, strikingly increase risk of advanced liver disease and accelerate

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atherosclerosis.[1] In cases of partial lipodystrophy, clinical signs are most commonly first noticed peripubertally, especially in girls.

Werner syndrome (WS; OMIM #277,700) is an autosomal recessive disorder characterized by short stature due to absent of the pubertal growth spurt and a wider pattern of premature ageing features with onset on the third decade. These include greying and thinning of the hair, bilateral cataracts, scleroderma-like skin changes, cutaneous calcinosis and ulceration of the extremities, premature atherosclerosis and a propensity to develop early onset cancers. WS patients may also develop partial lipodystrophy affecting subcutaneous fat, and show premature muscle loss from the limbs, or sarcopenia. Diabetes, fatty liver disease and dyslipidaemia are commonly reported amongst those with an established dagnosis.[2] Diagnostic criteria have been developed,[3, 4] but they rely on several of the later onset features of the disease, and so diagnosis is often made only at late stages of the natural history. Delays of many years between appearance of the first clinical manifestation and the molecular diagnosis are thus the norm.[5]

Isolated partial lipodystrophy is not regarded as a classic sign of WS, and its diagnosis in childhood rarely triggers targeted analysis of the *WRN* gene.[6] However genetic diagnosis increasingly commonly relies on sequencing of exomes or panels of relevant genes, and inclusion of the *WRN* gene in these panels presents a key opportunity to accelerate diagnosis and to open up opportunities for early interventions and trials seeking to delay or prevent later complications.

Here, we report a woman first diagnosed with early onset diabetes at 10 years old, later developing anatomical and biochemical features of partial lipodystrophy together with fibrosing steatohepatitis with no overt features of premature ageing. Exome sequencing revealed that she is affected by WS, with compound heterozygous *WRN* mutations including a novel splice variant predicted to produce a WRN protein missing the zinc binding region of the helicase domain.

Materials and methods

Exome sequencing and analysis

Genomic DNA was isolated from leucocytes using Qiaamp DNA mini kit (Thermoscientific™). Exome-enriched genomic DNA (gDNA) libraries were prepared with the Illumina TruSeq Exome Library (FC-150–1002) and sequenced on the NextSeq 550 platform (llumina Inc, #SY-415–1002) with the NextSeq 500/550 Mid-Output v2.5 150 cycle kit (20,024,904; 2 × 75 bp sequencing). Variant calling was performed to GATK best practice standards[7] with Base Quality Score Recalibration, realignment, and HaplotypeCaller variant calling, with bcbio.[8] Sequences were aligned with bwa[9] to the GRCh38/hg38 human reference genome[10] and variant effects were annotated via Ensembl Variant Effect Predictor. Candidate causal variants were identified by applying custom filters to variant tables following GATK guidelines,[7] and were confirmed by Sanger sequencing of trio gDNA. PCR primers were designed with PrimerBlast and Primer3Plus. Amplicons were purified from agarose gel by QIAquick Gel Extraction kit and sequenced in both directions by SourceBioscience. Sequencing traces were assessed by SnapGeneViewer. Splicing effects of the intronic mutation identified mutation were predicted with the Alternative Splice Site Predictor (ASSP) Tool.[11]

Cell culture and cDNA sequencing

Primary dermal fibroblast cultures were established from a punch skin biopsy from the proband, according to standard procedures. Fibroblasts were maintained in DMEM (41,966–029; LifeTechnologies) supplemented with 10% foetal bovine serum (10,500,064; Gibco) and 1x Penicillin-Streptomycin-Glutamine (10,378,016; LifeTechnologies) at 37 °C in 5% CO_2. For RNA analysis cells were trypsinised, pelleted by centrifugation and snap frozen on dry ice. Total cellular RNA was purified by Direct-zol RNA MiniPrep-Plus (R2072; Zymo). cDNA was prepared by High-Capacity cDNA kit (4,368,814; Applied Biosystems), and selected regions amplified by PCR with custom primers. Sanger sequencing of PCR products was undertaken by Source Bioscience.

Results

Case report

A 28-year-old female was the third child of non-consanguineous parents from Cape Verde. She was born at term (2800 gr) and her growth and developmental milestones were normal. Around age 7, she had acute weight loss. At that time, a postive HBeAg hepatitis B infection was diagnosed and treatment with pegylated interferon was attempted in Cape Verde. When she arrived in Switzerland at age 10, she had short stature with a moon face, a prominent abdomen and thin extremities. Laboratory workup found marked hyperglycaemia and a diagnosis of early onsed diabetes was made. Anti-glutamic acid decarboxylase (GAD) and anti-islet antigen 2 (IA2) antibodies were negative. High doses of insulin were needed to achieve glycaemic control. Recurrent episodes of compulsive hyperphagia were reported which contributed also to the hyperglycaemia. In spite of pubertal development with menarche at age 13, she did not show a growth spurt. In ensuing years she was noticed to have severe dyslipidaemia, with serum triglycerides up to 100 mmol/L and low HDL cholesterol of 0.3 mmol/L. She had been treated, since the age of 19 years, with pegylated alpha-interferon, entecavir, tenofovir and finally, tenofovir alafenamide due to HBeAg positive chronic hepatitis B. Otherwise, she had been treated with levothyroxine for autoimmune hypothyroidism since the age of 28 years.

Physical examination at age 28 years (Fig. 1) revealed height to be 147 cm (−2.5 SD; target height 159.3 ± 8.5 cm),

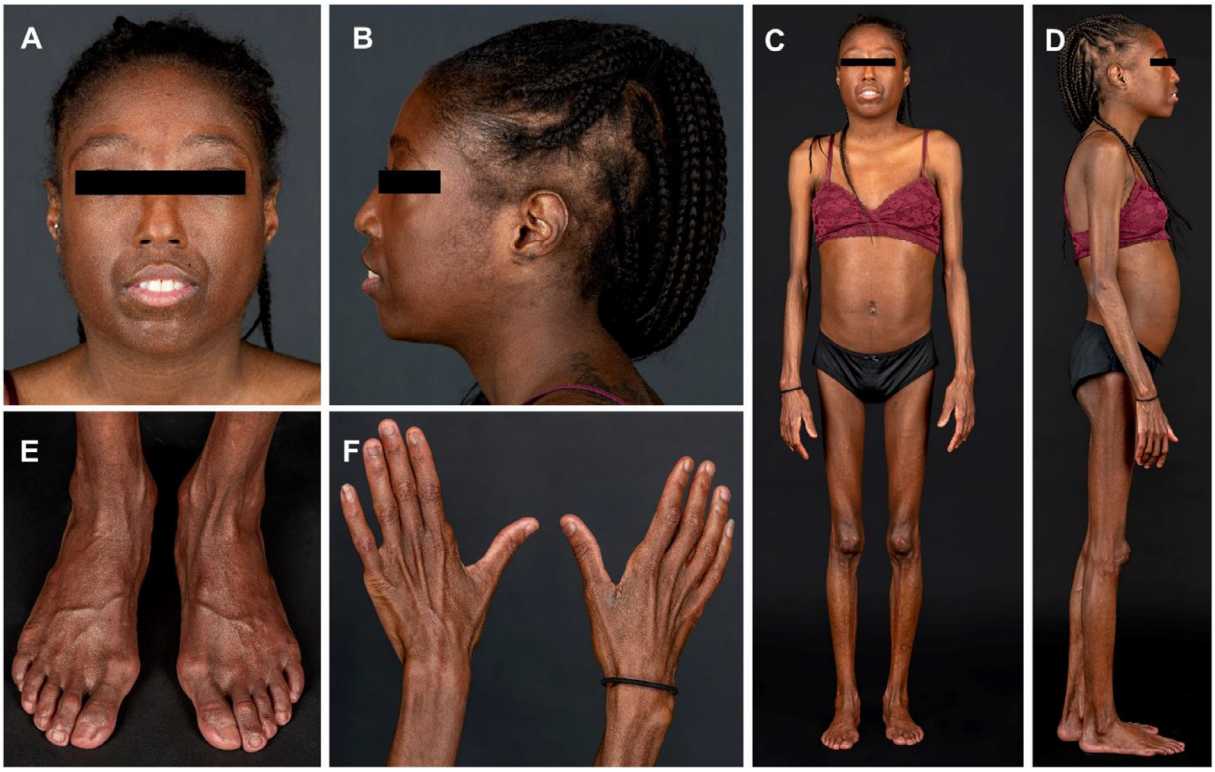


Fig. 1 Appearance of the proband at 28 years old. A,B) Round, youthfull face with mild preauricular hypertrichosis and hypoplastic ear lobes C, D) Severe loss of sub-cutaneous adipose tissue and muscle from the limbs with mild abdominal protrusion E,F) Note the mild acrogeria with distal fat loss around the hand and feet and proeminent veins.

weight 32.25 kg (−3.8 SD) and body mass index (BMI) 14.9 kg/m^2 (−3.96 SD).[12] The abdomen was prominent without palpable hepatomegaly or clinical signs of chronic liver disease. Limbs appeared thin due to loss of both subcutaneous adipose tissue and muscle, with no evidence of the calf hypertrophy seen in some commoner forms of familial partial lipodystrophy (FPLD) such as FPLD2 or FPLD3. The skin on the extremities appeared tight. The thin limbs contrasted with her round face that gave her a youthful appearance (Fig. 1). Mild facial hirsutism was observed. There was no greying or thinning of the hair, nor any evidence of cataracts. Her voice was hoarse.

Biochemical investigation revealed elevated glycated haemoglobin at 10.1% (4–6) and mixed dyslipidaemia, with total serum cholesterol 6.4 mmol/l (<5.0 mmol/l), triglycerides 11.9 mmol/L (<2.2 mmol/l), and HDL cholesterol 0.6 mmol/L (>1 mmol/L). Serum leptin was at 4.1 μg/L (1.8–28 μg/L).[13] Liver function indices were mildly disturbed: LDH 261 U/L (135–214 U/L), ASAT 59 U/L (9–32), ALAT 66 U/L (9–36), phosphatase alkaline 72 U/L (36–108 U/L), GGT 135 U/L (6–42). Abdominal magnetic resonance imaging (MRI) showed liver steatosis without hepatomegaly and identified one focal lesion of 1.1 cm in segment VI. A percutaneous biopsy was performed both in the non tumoral liver and in the lesion. The non tumoral liver parenchyma showed features of non alcoholic steatohepatitis, with macrovesicular steatosis (25%), numerous ballooned hepatocytes and glycogenated nuclei, and a few foci of lobular inflammation. Inflammation without interface hepatitis was also found in the some of the portal tracts. Fibrosis was present both in portal tracts with incomplete septa, and in lobules where it exhibited a typical pericellular "chicken wire" pattern of distribution. Of note, in the liver biopsy performed 10 years before, some steatohepatitic features were already present but without fibrosis (Fig. 2). The focal lesion corresponded to an inflammatory hepatocellular adenoma and there was no sign of malignancy. HBs and HBc antigens were found by immunostaining in some hepatocyte cytoplasms and nuclei, respectively. The steatohepatitis and fibrosis progression, despite successful antiviral treatment, could not be explained by hepatitis B.

Loss of adipose tissue from the limbs allied to fatty liver, dyslipidaemia and insulin resistant diabetes led to a clinical diagnosis of partial lipodystrophy. A genetic aetiology was favoured given the difference in the adipose distribution to the stereotyped pattern of acquired partial lipodystrophy, which usually starts in the face and extends caudally to around the umbilicus.[14] Diagnostic sequencing of a panel of 61 genes involved in lipodystrophies, glycogen storage disorder and MODY (maturity onset of diabetes of the young) was undertaken (Supplementary Table 1), however no pathogenic variant was found and the diagnostic search was therefore opened to exome sequencing (see below).

Exome and cDNA studies

Initial exome analysis of the proband and her parents failed to reveal any plausible genetic aetiology for

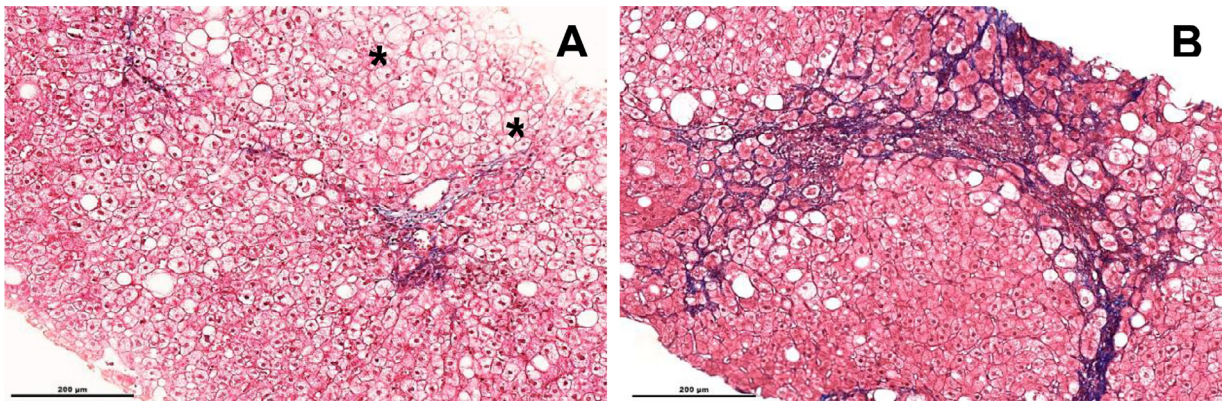


Fig. 2 A) Liver biopsy taken at the age of 18 years old showing mild macrovacuolar steatosis, rare ballooned hepatocytes (*) and no significant portal or lobular fibrosis and B) Liver biopsy at 29 years old revealed numerous ballooned hepatocytes and extensive portal and lobular pericellular fibrosis (Masson's Trichrome, scale bar: 200μm).

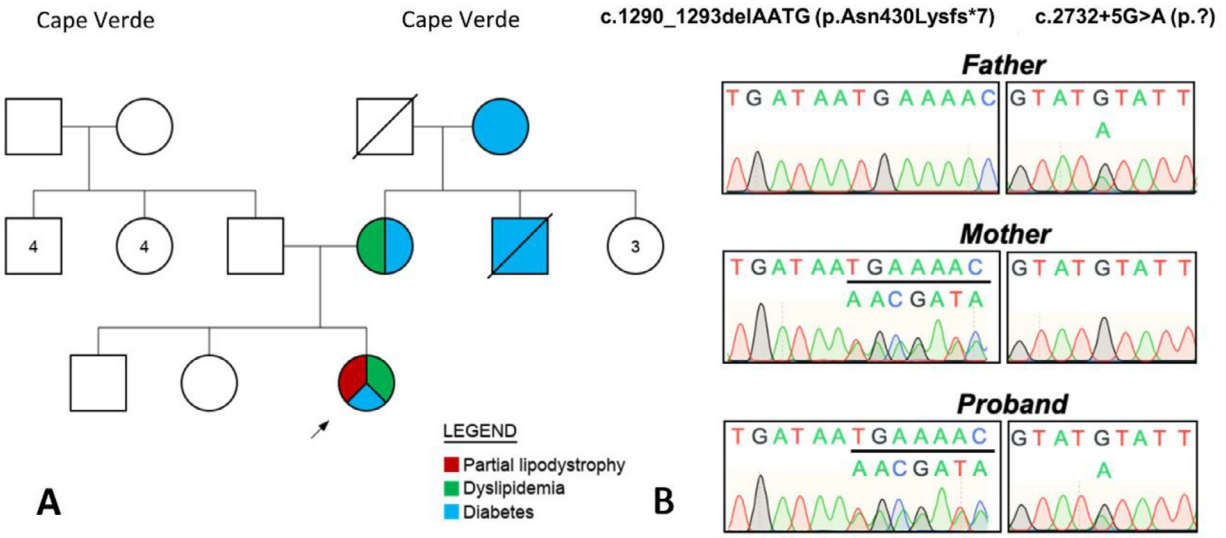
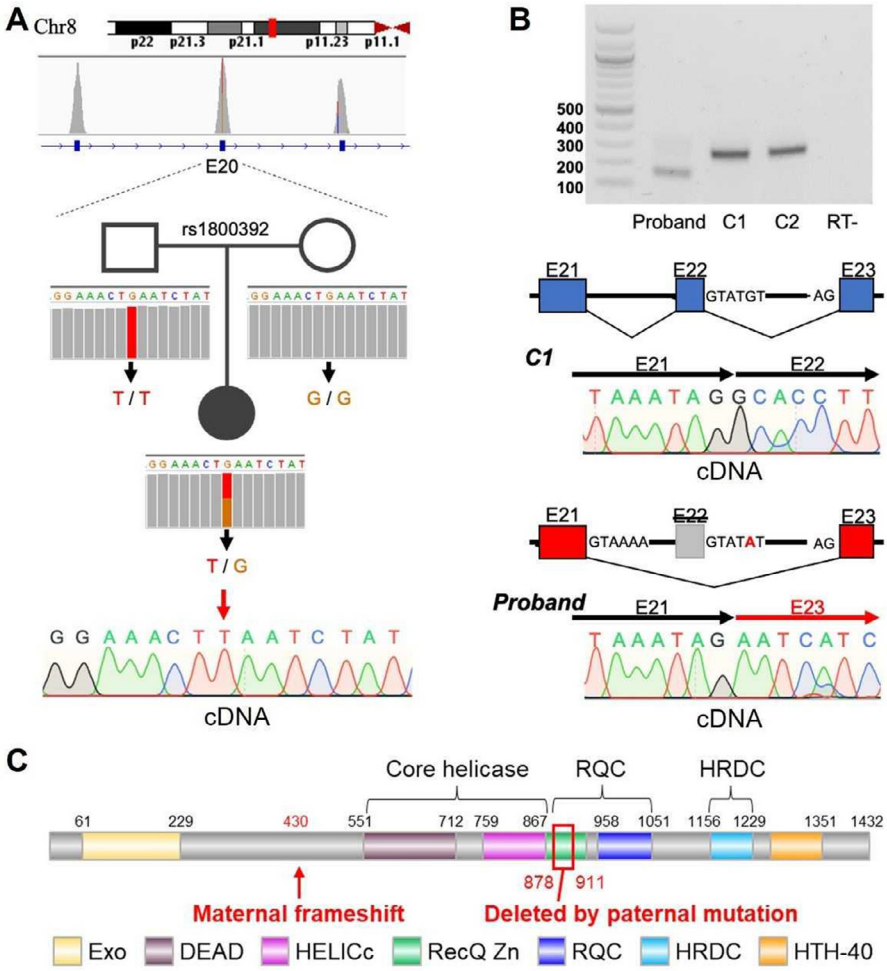


Fig. 3 A) Pedigree diagram of the proband (family tree tool from Invitae) **and B) Compound heterozygous *WRN* mutations in the proband.**

the lipodystrophy syndrome, with no *de novo* or biallelic pathogenic mutations in either coding exons or essential splice sites found. A previously described[15] heterozygous pathogenic frameshift variant in the *WRN* gene (NM_000553.6) - hg38; chr.8: g.31083716, TAATG>*T*; c.1290_1293delAATG, p.Asn430Lysfs*7 - inherited from the mother, was identified (Fig. 3). Biallelic mutations in the *WRN* gene cause WS, the coding mutation identified is predicted to truncate the WRN protein before the helicase domain, and the pattern of adipose and muscle loss in the proband was reminiscent of Werner's syndrome. A second candidate pathogenic mutation was thus sought in the non-coding sequence at the *WRN* locus. Such a variant was identified. Specifically, a novel intronic splice site variant – g.31124628: *G*>*A*; c.2732+5G>*A* (p.?) - located at the +5 position of intron 22 was found, and shown to be inherited from the father (Fig. 3).

The intron 22 splice donor site is the 8th most common consensus sequence in humans[16] and the *G*>*A* mutation changes the sequence to such the extent that it is no longer a recognised human consensus donor sequence. Loss of the donor site is predicted to result in loss of exon 22 due to interaction between the constitutive splice donor site in intron 21 with the acceptor before exon 23. Sequencing of cDNA from dermal fibroblasts from the proband revealed exclusive expression at the mRNA level of the paternal allele, consistent with nonsense mediated decay triggered by the maternal frameshift allele (Fig. 4A). It also confirmed skipping of exon 22 in the expressed paternal allele (Fig. 4B). It was not determined whether the truncated protein is expressed, but if it is, then it is predicted to lead to in-frame deletion of a large part of the zinc binding motif that abuts the DNA helicase domain of WRN (p.(His878_Gln911del))(Fig 4C). Taken together, the identification of compound heterozygous loss-of-function mutations in the *WRN* gene confirmed the diagnosis of WS. After genetic counselling, the patient's siblings were clinically assessed but not genetically tested. They did not showed any clinical or biological feature of WS.



Figs. 4 cDNA analysis in the proband. A. Sequencing of an informative SNP in genomic DNA from the family trio (illustrated as IGV traces) and in complementary DNA (cDNA) from the proband's blood-derived RNA (illustrated as chromatogram), showing monoallelic mRNA expression from the paternal allele **B.** cDNA sequencing across exon 22 in control (C1,C2) and proband, demonstrating skipping of exon 22 in proband, evidenced by agarose gel showing PCR products above and Sanger sequencing traces below.**C.** Domain structure of WRN indicating predicted in-frame deletion from RQC domain caused by exon skipping. Exo = 3′–5′ exonuclease domain; DEAD = DEAD/DEAH box helicase; HELICc = Helicase C-terminal domain; RecQ Zn = RecQ Zn^{2+} binding domain; RQC = RecQ DNA binding domain; HRDC = Helicase and RNase D C-terminal domain; HTH-40 = Helix-turn-helix domain; IGV = Integrative Genomics Viewer.

Further clinical course

Following the diagnosis of WS, further care and screening was guided by knowledge of its clinical features and natural history. No ulcers nor cutaneous calcinosis were present. Cardiac exercise stress test was negative and ophthalmic exam did not find cataracts or diabetic retinopathy. Bone densitometry determination revealed osteoporosis (Z-score −2.6), treated by vitamin D supplementation given sustained low serum vitamin D levels (9.2 to 21.9 ug/L; target 30–40 g/l). The BMI was 14.0 kg/m^2, and DEXA showed an android/gynoid ratio of 2.2, and total fat of 20.5% with the following distribution: troncular fat 25.5%, upper limb 14.0%, lower limb 10.7%. The fat mass ratio (FMR) was 2.72 (10–31%).

Glycemic control improved on gliclazide 60 mg, metformin 1000 mg, dapagliflozin 5 mg and 30 UI of long acting insulin given once daily. Glycated haemoglobin decreased to 8.6% (4–6%). A glucagon-like-peptide 1 inhibitor had an initial positive effect on insulin resistance but was stopped due to weight loss, which was regarded as unhealthy given the low baseline body mass index (BMI). In spite of treatment with simvastatin and fibrates, triglycerides exceeded 100 mmol/l at peak, believed likely due to therapeutic non-adherence. Following better therapeutic adherence, triglycerides levels still varied from to 11 to > 100 mmol/l (<2.2 mmol/l) and total cholesterol levels from to 5.4 to 14 mmol/l (<5.0 mmol/l). Serum leptin concentration fell to 1.2 μg/l (1.8–28 μg/l), consistent with inadequate adipose storage. This has raised the possibility that recombinant human leptin therapy (metreleptin) may be used to address the metabolic derangements in this patient. Metreleptin (Myalepta®) was approved by the European Medicines Agency in 2018 as a replacement therapy

to treat the complications of leptin deficiency in lipodystrophy patients. Thereby becoming the first specific treatment for this condition in Europe. It was started in our patient at 0.06 mg/kg (1.8 mg) by subcutaneous daily injection. Three months later she reported a reduction of hyperphagia. The insulin requirement fell by 20%, glycated haemoglobin dropped from 8.3 to 7.5%, serum triglycerides from 85.4 to 4.5 mmol/l and total cholesterol from 13.3 to 4.3 mmol/l.

Annual ophthalmological and dermatological evaluation, lipid profiling, cardiovascular surveillance, clinical assessment for malignancy, monitoring of osteoporosis and liver surveillance are planned in follow up.

Discussion

WS is rare, with enrichment of cases in Japan, however it has attracted considerable interest and research. This is because it imposes a large burden of early morbidity and mortality on affected people, and also because it manifests several key features of ageing in accelerated form. This suggests that it may be a paradigm for understanding mechanisms of normal ageing.[17]

The product of the *WRN* gene is a large nuclear protein with the dual ability to unwind double stranded DNA using a helicase domain, and to remove single nucleotides from ends of "broken" DNA in which the 3′ strand is recessed, using an exonuclease domain.[18] It plays a role in maintaining genome stability, particularly aiding accurate and timely replication of "difficult" parts of the genome such as telomeres, regions harbouring ribosomal rRNA-encoding genes, or regions with long runs of di- or tri-nucleotide repeats.[19] These sequences are all prone to form complex structures such as DNA hairpins or four stranded quadruplexes[20,21] The WRN protein resolves these to prevent blocks to DNA replication or conflicts between replication and transcription. Impaired telomere maintenance is one of the phenomena most widely implicated in the progeroid features and cancer predisposition of WS in prior studies[22,23,24]

To date, 190 pathogenic or probably pathogenic variants in *WRN* have been described (ClinvarMiner). Most give rise to stop codons that lead to loss of the nuclear localization signal at the C-terminus of the WRN protein and/or promote nonsense-mediated mRNA decay,[25] so are essentially null alleles. No clear genotype-phenotype correlations have been reported.[15] In the case we describe the pathogenic frameshift *WRN* mutation was not expressed at the mRNA level, while the other mutation leads to expression of mRNA in which exon 22 is deleted. We have not established whether the corresponding mutant WRN protein is expressed, but if so, this protein would have a deletion of much of a zinc-binding subdomain which abuts the core helicase domain, and plays a role in interacting with DNA during WRN action.[26] However, both the core helicase domain (amino acids 551–859) and the exonuclease domain (amino acids 60–288), are intact. It is interesting to speculate that selective loss of only one aspect of the functionality of the WRN protein may explain the lack of some cardinal features of WS in the proband we described, at least to the current age of 32 years. However, confirmation of expression of the mutant protein, biochemical studies of the protein, and further follow up of the proband or others with similar mutations will be required to test this.

A major barrier to improving clinical outcomes in WS comes from late diagnosis in many cases. Clinical diagnostic criteria have been developed in both the USA[4] and Japan,[3] however confident diagnosis relies on cardinal features of WS that do not usually appear until the third or fourth decade. These include bilateral cataracts, or thinning and greying of hair. Indeed, a registry-based Japanese study suggested a mean age of onset of symptoms of WS of 26 years, but a mean age at diagnosis of 42.5 years.[5] Even at the age of 28 years, the patient we describe did not meet criteria for WS clinically, and indeed a youthful appearance of her face was specifically commented on at initial evaluation. The mean age of death in WS has been reported to be 54 years,[25] due often to early onset cancer (especially sarcomas, meningiomas, and thyroid follicular carcinomas)[27] or complications of atherosclerosis such as myocardial infarction. It would be highly desirable to identify people with WS early in order to implement appropriate screening and primary prevention strategies.

The earliest feature of WS generally reported is the absence of a pubertal growth surge, leading to reduced adult height, although this is not specific to WS. Indeed, according to the American diagnostic criteria, the onset of the disease before the age of 10 is considered, in a series of diagnostic criteria, as excluding WS.[4] On the other hand insulin resistance, diabetes, dyslipidaemia and fatty liver are documented as highly prevalent components of WS.[3] In this case diabetes was diagnosed at 10 years old, while we have documented onset of severe insulin resistance as early as 7 years old in a previously reported case of WS.[3] In both cases a genetic diagnosis was based on exome sequencing.

The profile of metabolic abnormalities seen in WS closely that of partial lipodystrophy, in keeping with the progressive loss of subcutaneous adipose tissue from the limbs. Such anatomical evidence of lipodystrophy may not be present at the time of identification of metabolic abnormalities, however when lipodystrophy does develop, it is usually associated with loss of muscle mass that meets criteria for age-related sarcopenia.[3] This is unlike the muscular hypertrophy commonly seen in other more common lipodystrophies.[28] Centripetal redistribution of adipose tissue may confer a cushingoid appearance, as described previously in lipodystrophic presentations of WS.[6]

Genetic diagnosis increasingly relies on sequencing of panel of genes related to a condition of interest simultaneously using next generation sequencing. Adding new genes to such panels is cost efficient and simple, and we suggest that including *WRN* in panels dedicated to early-onset diabetes, hypertrigyceridaemia, or lipodystrophy would accelerate diagnosis of WS in some cases. This would permit en-

gagement of a multidisciplinary team including ophthalmologists, endocrinologists, cardiologists and dermatologists at an early stage. Despite 25 years of research into the mechanistic basis of WS since discovery of *WRN* mutations, no clinical trials in WS are currently recorded as being active, and identification of patients at a disease stage when candidate disease-modifying therapy may have a higher chance of success may moreover give impetus to translational efforts.

Trying to modify the underlying disease process is only one facet of clinical management of WS. As in other patients with lipodystrophy, it is crucial to appreciate that WS patients have "adipose failure".[29] Their physiologic subcutaneous adipose tissue has a limited capacities for adipocyte hypertrophy and hyperplasia. This results in a decreased anabolic capacities of the adipose tissue and an ectopic deposition of fat at the visceral level wich increase oxidative stress and exerce a "lipotoxic" effect at the liver, muscle and pancreas leading to metabolic inflammation and major insulin resistance. The severe and rapidly progressing fibrosis on steatohepatitis observed in our patient together with the development of one of its complication, an hepatocellular adenoma, clearly represents the consequence of liver lipotoxicity of lipodystrophy, which may be increased in Werner patients. Thus, despite low BMI, those patients should benefit of insulin sensitisers and "obesity therapies" that offload adipose tissue. Metformin, sodium-glucose cotransporter SGLT2, glucagon-like peptide 1 receptor (GLP-1) agonists, and pioglitazone are all rational choices of treatment with some anecdotal supporting evidence.[30-32] Metreleptin (a recombinant leptin analogue) has been shown to improve the metabolic profile in patients with generalized and partial lipodystrophy.[33,34] Our patient has recently started metreleptin (Myalepta®) which was followed by metabolic improvement.

Conclusion

WS is a multisystem premature ageing syndrome that reduces life-expectancy and life quality. Prompt diagnosis permits implementation of therapeutic and preventive measures and facilitates clinical trials, however current diagnostic criteria lead to late diagnosis in most cases. Screening for *WRN* mutations in early-onset insulin resistant diabetes, dyslipidaemia and/or lipodystrophy presents the opportunity for diagnosis based on these non-specific sentinel metabolic features long before appearance of the full repertoire of WS-related disorders.

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Credit authorship contribution statement

IA, JMG, MB, MF, CS, ASF and CT acquired and interpreted clinical data. DM and RS performed genetic analysis and interpreted results. CS interpreted liver biopsy histolopathology results. IA, DM, CT and RS wrote the initial manuscript. All authors critically reviewed and edited the manuscript and approved the submitted version.

Ethics statement

Molecular studies were undertaken on a clinical diagnostic basis, in full compliance with national and local regulations. The patient and her parents provided written consent for genetic testing. A written consent was also obtained for photograph publication.

Declaration of interest

Authors have no conflict of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2022.06.004.

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