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CLINICAL UTILITY GENE CARD UPDATE

Clinical utility gene card for: Werner Syndrome - Update 2014

Fuki M Hisama*[,1], Christian Kubisch[2], George M Martin[3] and Junko Oshima[3]

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Werner Syndrome, Werner's Syndrome, adult-onset progeria.

1.2 OMIM# of the disease

277700.

1.3 Name of the analysed genes or DNA/chromosome segments

WRN (*RECQL2*, *RECQ3*)

1.4 OMIM# of the gene(s)

604611.

1.5 Variant spectrum

More than 70 disease-causing variants have been reported.[1,2] One or two mutations are identified in the majority of patients who fulfil clinical diagnostic criteria. The majority of disease-causing variants are either stop codon mutations, splice mutations or small ins/del that result in truncations of the protein and/or non-sense-mediated decay of mutant mRNA. Several missense variants that abolish helicase activity or confer protein instability, an intronic mutation that creates a new exon, as well as genomic rearrangements (deletions and duplications) have also been reported.[1–3] The most common mutation in Caucasian patients is a stop codon mutation in exon 9 (c.1105C>T, p.(Arg369Ter), which accounts for approximately 20% of the mutations. There are founder variants reported among Japanese patients (c.3139-2G>C, which result in skipping of exon 26) and in Sardinian patients (c.2089-3024A>G, which creates a new exon between exons 18 and 19).[4,5] Potential founder mutations have been reported for Dutch (c.3590delA, p.(Asn1197fs), Turkish (c.3460-2A>C, exon 30 deletion) and Moroccan (c.2179dupT resulting in p.(Cys727fs)) patients.[2] All of the variants thus far identified in clinically ascertained Werner Syndrome patients result in a null biochemical phenotype that abolishes the catalytic activities of the WRN protein. A database of *WRN* variants is available at http://www.pathology.washington.edu/research/werner/database; the database is accessible through the Human Genome Variation Society (http://www.hgvs.org/dblist/glsdb.html). *WRN* variants are also listed in ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/). Nucleotide and proteins sequences and exon numbers are based on GenBank accession number NG_008870.1.

1.6 Analytical methods

Standard exon sequencing combined with western blot analysis are performed as routine tests.[6]

1.7 Analytical validation

Sequencing results are confirmed by exon sequencing using different sets of primers. RT-PCR sequencing may be performed to confirm potential splicing mutations. For potential missense mutations, enzyme assays and protein stability may be performed on a research basis using recombinant WRN protein containing the mutations.[6] If genomic rearrangements are suspected, high-density array CGH can be performed.

1.8 Estimated frequency of the disease (Incidence at birth ('birth prevalence') or population prevalence)

The population prevalence of Werner Syndrome is unknown. However, it is likely under-diagnosed because of the lack of awareness of this disorder and the relatively nonspecific symptoms (absence of pathognomonic signs).

1.9 If applicable, prevalence in the ethnic group of investigated person

The prevalence of heterozygous carriers in Japan is approximately 1/167 and it is estimated to be approximately 1/120 in Sardinia.[4,5]

1.10 Diagnostic setting

	Yes	No
A. (Differential) diagnostics	☒	☐
B. Predictive testing	☐	☒
C. Risk assessment in relatives	☒	☐
D. Prenatal	☐	☒

Comment: This is an adult-onset disorder. The earliest sign is the lack of growth spurt during adolescence. Onset of a prematurely aged-appearance (grey hair, scleroderma-like skin) typically starts in the 20–30 s followed by the appearance of age-related disorders (cataracts, diabetes mellitus, atherosclerosis, cancers, osteoporosis).

[1]Division of Medical Genetics, Department of Medicine, University of Washington, Seattle, WA, USA; [2]Institute of Human Genetics, University of Ulm, Ulm, Germany; [3]Department of Pathology, University of Washington, Seattle, WA, USA
*Correspondence: Dr FM Hisama, Division of Medical Genetics, Department of Medicine, University of Washington, Box 357720, 1959 NE Pacific St, Seattle, WA 98195, USA. Tel: +1 206 598 4030; Fax: +1 206 598 3269; E-mail: fmh2@u.washington.edu
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2. TEST CHARACTERISTICS

	Genotype or disease		A: True positives B: False positives	C: False negative D: True negative
	Present	Absent		
Test				
Positive	A	B	Sensitivity:	A/(A + C)
			Specificity:	D/(D + B)
Negative	C	D	Positive predictive value:	A/(A + B)
			Negative predictive value:	D/(C + D)

2.1 Analytical sensitivity
(proportion of positive tests if the genotype is present)
Undefined.

To date, 146 cases were molecularly diagnosed by exon sequencing and western blot analysis by the International Registry of Werner Syndrome.

2.2 Analytical specificity
(proportion of negative tests if the genotype is not present)
Undefined.

2.3 Clinical sensitivity
(proportion of positive tests if the disease is present)
The clinical sensitivity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.

Approximately 20% of patients referred to the International Registry of Werner Syndrome have no detectable disease-causing *WRN* variants and normal western blot analysis results. If the clinical criteria for clinically definite WS are met, 97% (146 out of 151 patients) have two *WRN* variants.

2.4 Clinical specificity
(proportion of negative tests if the disease is not present)
The clinical specificity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.
Undefined.

2.5 Positive clinical predictive value
(lifetime risk to develop the disease if the test is positive)
Undefined. Based on the studies of large pedigrees, most, if not all patients appear to develop symptoms in time.

2.6 Negative clinical predictive value
(Probability not to develop the disease if the test is negative)
Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.
Index case in that family had been tested
Undefined.
Index case in that family had not been tested
Undefined.

3. CLINICAL UTILITY

3.1 (Differential) diagnosis: The tested person is clinically affected
(To be answered if in 1.10 'A' was marked)

3.1.1 Can a diagnosis be made other than through a genetic test?

No	☐ (continue with 3.1.4)	
Yes	☒	
	Clinically	☒
	Imaging	☐
	Endoscopy	☐
	Biochemistry	☐
	Electrophysiology	☐
	Other (please describe):	Highly experienced clinicians may be able to diagnose clinically

3.1.2 Describe the burden of alternative diagnostic methods to the patient
Werner Syndrome can be diagnosed clinically, but not solely, using the criteria established by the International Registry of Werner Syndrome (http://www.wernersyndrome.org), which divides clinical signs and symptoms into 'cardinal' and 'further' with onset of symptoms after the age of 10 years. Clinical diagnosis may include: ophthalmologic exam for cataracts, testing for diabetes mellitus, taking a family pedigree and clinical assessment by a clinical geneticist or other physician familiar with Werner Syndrome.

An increase in structural chromosomal aberrations (termed variegated translocation mosaicism) in lymphocyte and fibroblast cultures from individuals with Werner Syndrome is characteristically observed, but is not diagnostic for the condition.[7,8]

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
Either genetic testing or clinical criteria can miss some individuals with Werner Syndrome. Gene testing that identifies pathogenic *WRN* mutations in patients can be used to help confirm both a clinical diagnosis of Werner Syndrome, and the subsequent low risk of this recessive disease in offspring. Atypical Werner Syndrome is a heterogeneous group of conditions with progeroid features often lacking cataracts with earlier onset during 1st or 2nd decades of life, and in which *WRN* mutations are absent. The most commonly identified cause of atypical Werner Syndrome is a *LMNA* mutation, where offspring are at 50% risk.[9] Other possible phenocopies include: Aicardi-Goutieres syndrome or lipodystrophy with mandibuloacral dysplasia caused by a *POLD1* mutation.

3.1.4 Will disease management be influenced by the result of a genetic test?

No	☐	
Yes	☒	
	Therapy (please describe)	There is symptomatic and supportive care for Werner Syndrome patients, though no definitive therapy that addresses the underlying molecular defect. Symptomatic care differs according to the clinical manifestations, but many of the signs of Werner Syndrome (cataracts, diabetes, atherosclerosis, skin ulcers) are treatable with standard therapies. Identification and treatment of cataracts in the teens or twenties can improve prognosis for vision. There are no reports of treatment of the short stature of Werner Syndrome with growth hormone. Platelet-derived growth factor-BB has reported to result in some improvement in chronic leg ulcers in a WS patient.[10] Bosentan has been reported to

	be effective in the treatment of digital ulcers in patients with systemic sclerosis, and its use has been recently reported in Werner Syndrome patients.[11,12] Earlier identification and treatment, for example, of cancers, may improve prognosis. There is no accepted cancer screening protocol recommended for Werner Syndrome patients, but an awareness of the increased risk for the spectrum of malignancies in Werner Syndrome (soft tissue sarcomas, osteosarcomas, melanoma, thyroid cancer, neoplastic and non-neoplastic haematologic diseases) may lead to earlier recognition.[13]
Prognosis (please describe)	A positive genetic test will alert care providers to the diagnosis of Werner Syndrome. Median lifespan of the patients is 54 years,[3] 7 years older than in the report in 1966.[14] Similarly, the median lifespan of Japanese Werner patients was 53 years.[15] The most frequent causes of deaths are cancers and myocardial infarction.
Management (please describe)	The results of genetic testing can provide a rational basis for regular medical screening for known, common medical conditions seen in Werner Syndrome patients, and increase awareness of potential challenges in treatment. There are case reports of special challenges in, for example, the surgical management of leg ulcers and revascularization procedures in patients with Werner Syndrome.[16,17] Cells from Werner Syndrome patients, and presumably the patients themselves, are selectively hypersensitive to some types of DNA damage, including damage mediated by cancer chemotherapy agents such as cis-Pt, mitomycin-C and camptothecin and its derivatives. There is anecdotal evidence suggesting patients may be hypersensitive to the same agents, and thus at elevated risk of treatment-related toxicity.[18]

3.2 Predictive setting: The tested person is clinically unaffected but carries an increased risk based on family history
(To be answered if in 1.10 'B' was marked)

3.2.1 Will the result of a genetic test influence lifestyle and prevention?
If the test result is **positive** (please describe)

If the result is positive, this confirms the diagnosis of Werner Syndrome, and as the manifestations occur over many years, lifestyle changes and preventative measures may be instituted. These include smoking avoidance, maintaining a healthy weight, treatment of hyperlipidaemia if present and regular exercise to reduce risk of atherosclerosis and type 2 diabetes. Skin care, with avoidance of trauma, and early, aggressive treatment of skin ulcers helps to reduce morbidity from this complication. Annual ophthalmologic exam for cataracts, lipid profile, diabetes and hypertension screening are recommended when the diagnosis if confirmed.

If the test result is **negative** (please describe)

If the test result is negative, this reduces the likelihood of Werner Syndrome, but should lead to consideration of other diagnoses such as atypical Werner Syndrome resulting from a *LMNA* mutation. Symptomatic treatment of clinically significant conditions (diabetes, hyperlipidaemia, cataracts) is still indicated.

3.2.2 Which options in view of lifestyle and prevention does a person at-risk have if no genetic test has been done (please describe)?
A person at risk for Werner Syndrome in the absence of genetic testing can be monitored and treated for the clinical manifestations associated with the condition.

3.3 Genetic risk assessment in family members of a diseased person
(To be answered if in 1.10 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?
If the test is positive and diagnostic, then the unaffected sibs have a 2/3 chance to be a carrier. As in other rare autosomal recessive diseases, they could be tested to determine their carrier status and their partners could be tested to obtain a more accurate recurrence risk. The parents of an index patient with Werner Syndrome are obligate carriers, and their sibs or other relatives may also wish to undergo genetic testing to determine their carrier status. Children of a person affected by Werner Syndrome are obligate carriers, their partners could be offered genetic testing to obtain a more accurate recurrence risk.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Yes, if the result is negative or uncertain, testing of family members is not recommended.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
Yes, if the index patient has Werner Syndrome, then younger family members could undergo predictive genetic testing prior to the onset of clinical signs and symptoms. As with other predictive genetic testing situations, genetic counselling is strongly recommended prior to undergoing testing.

3.4 Prenatal diagnosis
(To be answered if in 1.10 'D' was marked)

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnosis?
Yes. However, because of the adult-onset of the condition, prenatal testing is rarely indicated as subsequent sibs likely have already been born. Because of the autosomal recessive nature of the condition, children of an affected index patient are obligate carriers, but unlikely to be affected.

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or his/her relatives? (Please describe)

Although there is no cure for Werner Syndrome, the diagnosis helps to guide appropriate medical management and screening for diseases common in persons with Werner Syndrome (regular exams for cataracts, screening for diabetes, atherosclerosis). Treatment in general is similar to the general population. An affected person could learn that his or her children are unlikely to be affected by Werner Syndrome.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1 Uhrhammer NA, Lafarge L, Dos Santos L *et al*: Werner syndrome and mutations of the WRN and LMNA genes in France. *Hum Mutat* 2006; **27**: 718–719.
2 Friedrich K, Lee L, Leistritz DF *et al*: WRN mutations in Werner syndrome patients: genomic rearrangements, unusual intronic mutations and ethnic-specific alterations. *Hum Genet* 2010; **128**: 103–111.
3 Huang S, Lee L, Hanson NB *et al*: The spectrum of WRN mutations in Werner syndrome patients. *Hum Mutat* 2006; **27**: 558–567.
4 Satoh M, Imai M, Sugimoto M, Goto M, Furuichi Y: Prevalence of Werner's syndrome heterozygotes in Japan. *Lancet* 1999; **353**: 1766.
5 Masala MV, Scapaticci S, Olivieri C *et al*: Epidemiology and clinical aspects of Werner's syndrome in North Sardinia: description of a cluster. *Eur J Dermatol* 2007; **17**: 213–216.
6 Muftuoglu M, Oshima J, von Kobbe C, Cheng WH, Leistritz DF, Bohr VA: The clinical characteristics of Werner syndrome: molecular and biochemical diagnosis. *Hum Genet* 2008; **124**: 369–377.
7 Grigorova M, Balajee AS, Natarajan AT: Spontaneous and X-ray-induced chromosomal aberrations in Werner syndrome cells detected by FISH using chromosome-specific painting probes. *Mutagenesis* 2000; **15**: 303–310.
8 Hoehn H, Bryant EM, Au K, Norwood TH, Boman H, Martin GM: Variegated translocation mosaicism in human skin fibroblast cultures. *Cytogenet Cell Genet* 1975; **15**: 282–298.
9 Chen L, Lee L, Kudlow BA *et al*: LMNA mutations in atypical Werner's syndrome. *Lancet* 2003; **362**: 440–445.
10 Wollina U, Gruner M, Koch A *et al*: Topical PDGF-BB results in limited healing in a patient with Werner's syndrome and chronic leg ulcers. *J Wound Care* 2004; **13**: 415–416.
11 Matucci-Cerinic M, Denton CP, Furst DE *et al*: Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2011; **70**: 32–38.
12 Noda S, Asano Y, Masuda S *et al*: Bosentan: a novel therapy for leg ulcers in Werner syndrome. *J Am Acad Dermatol* 2011; **65**: e54–e55.
13 Lauper JM, Krause A, Vaughan TL, Monnat RJ Jr: Spectrum and risk of neoplasia in Werner syndrome: a systematic review. *PLoS One* 2013; **8**: e59709.
14 Epstein CJ, Martin GM, Schultz AL, Motulsky AG: Werner's syndrome a review of its symptomatology, natural history, pathologic features, genetics and relationship to the natural aging process. *Medicine (Baltimore)* 1966; **45**: 177–221.
15 Goto M, Matsuura M: Secular trends towards delayed onsets of pathologies and prolonged longevities in Japanese patients with Werner syndrome. *Biosci Trends* 2008; **2**: 81–87.
16 Akiyama K, Takazawa A, Taniyasu N, Sato H: Revascularization of femoropopliteal artery occlusion in Werner's syndrome. Report of a case and review of surgical literature in cardiovascular lesions. *J Cardiovasc Surg (Torino)* 2000; **41**: 303–306.
17 Yeong EK, Yang CC: Chronic leg ulcers in Werner's syndrome. *Br J Plast Surg* 2004; **57**: 86–88.
18 Seiter K, Qureshi A, Liu D *et al*: Severe toxicity following induction chemotherapy for acute myelogenous leukemia in a patient with Werner's syndrome. *Leuk Lymphoma* 2005; **46**: 1091–1095.