Ageing Research Reviews xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Werner syndrome: Clinical features, pathogenesis and potential therapeutic interventions

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ARTICLE INFO

Article history:
Received 23 November 2015
Received in revised form 9 February 2016
Accepted 11 March 2016
Available online xxx

Keywords:
Werner syndrome
Progeroid syndrome
Genomic instability
Human

ABSTRACT

Werner syndrome (WS) is a prototypical segmental progeroid syndrome characterized by multiple features consistent with accelerated aging. It is caused by null mutations of the *WRN* gene, which encodes a member of the RECQ family of DNA helicases. A unique feature of the WRN helicase is the presence of an exonuclease domain in its N-terminal region. Biochemical and cell biological studies during the past decade have demonstrated involvements of the WRN protein in multiple DNA transactions, including DNA repair, recombination, replication and transcription. A role of the WRN protein in telomere maintenance could explain many of the WS phenotypes. Recent discoveries of new progeroid loci found in atypical Werner cases continue to support the concept of genomic instability as a major mechanism of biological aging. Based on these biological insights, efforts are underway to develop therapeutic interventions for WS and related progeroid syndromes.

Contents

1. Introduction

Werner syndrome (WS; OMIM# 277700) is a rare genetic disorder that displays clinical features suggestive of accelerated aging. WS was originally described by a German medical student, Otto Werner, in 1904 (Werner, 1985). Werner reported a family of four siblings, ages 31–40, who presented with "Cataracts in Connection with Scleroderma" as well as short stature and premature graying of hair. The term, "Werner's syndrome" was first used in 1934 by Oppenheimer and Kugel who described a new case of WS (Oppenheimer and Kugel, 1934) and subsequently by Thannhauser in 1945, who provided a comprehensive review of "Werner's syndrome (Progeria of the Adults)" (Thannhauser, 1945). The gene responsible for WS was discovered in 1996 through then-ground breaking positional cloning method (Yu et al., 1996). This review summarizes our current understandings of clinical phenotypes, normal functions of the *WRN* gene product and potential therapeutic approaches.

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http://dx.doi.org/10.1016/j.arr.2016.03.002
1568-1637/

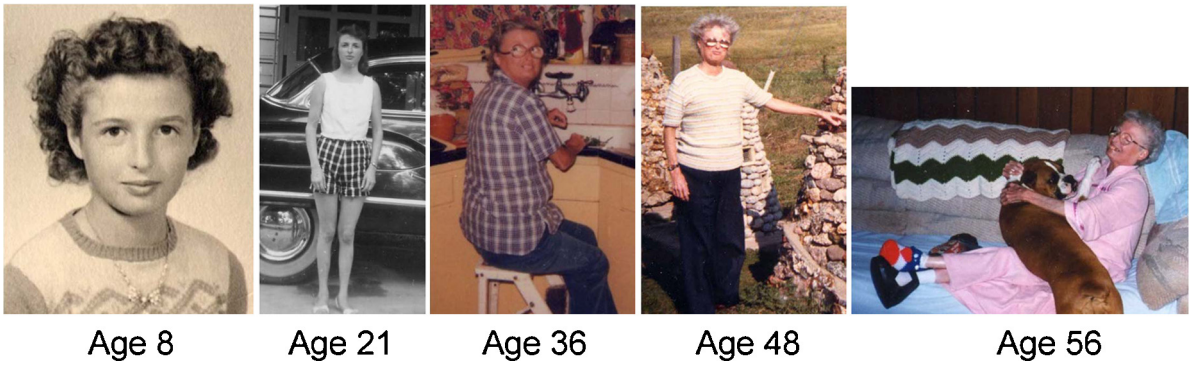

Fig. 1. Werner syndrome patient with homozygous null WRN mutations. Although apparently normal at age 8, cataracts were removed at age 36 and severe ankle ulcerations were recorded at age 56. (Registry# SANAN1010) (Hisama et al., 2006).

2. Classical aspects of the Werner syndrome

WS is a rare autosomal recessive disorder characterized by an array of features consistent with accelerated aging (Fig. 1) (Oshima et al., 2014; Takemoto et al., 2013). This is one of the few adult-onset syndromes of accelerated aging in which patients generally develop normally until they reach adolescence. The first sign, often recognized retrospectively, is a lack of a growth spurt and a relatively short stature as adults. Beginning in the early third decade of life patients begin to develop an aged appearance that includes skin atrophy, loss of subcutaneous fat and graying and loss of hair. Bilateral cataracts requiring surgery are seen in virtually all cases by the late 20s or early 30s (Huang et al., 2006; Takemoto et al., 2013). This is accompanied by a series of common age-related diseases that appear during middle age. These disorders include type 2 diabetes mellitus, hypogonadism, osteoporosis, atherosclerosis and malignancies. Several studies report that 30–40% of WS cases had children before gonadal atrophy leading to early loss of fertility in their 30s (Goto, 1997; Takemoto et al., 2013). Indolent deep ulcerations around Achilles tendons and, less frequently, at elbows, are almost pathognomonic to WS. These are associated with extensive subcutaneous calcifications and often lead to amputation of feet or lower extremities (Takemoto et al., 2013). Other features frequently seen in WS include a high pitched hoarse voice (recognizable over the phone), characteristic facial features (a "pinched" facial appearance), thin limbs, truncal obesity, and flat feet. The most common causes of death are cancer and myocardial infarction, at a median age of 54 (Huang et al., 2006). This is 7 years older than the median age of death reported in 1996 (Epstein et al., 1966), likely owing to improvements of medical care, as the median age for the extraction of cataracts (at age 31) were comparable in both eras.

There are clinical discordances in the presentation of age-related disorders between WS and normal aging. For example, systematic reviews of cancer in WS patients revealed a much higher incidence of sarcomas than expected for an age-matched control cohort (Goto et al., 1996; Lauper et al., 2013). The most common neoplasms in WS are thyroid follicular carcinomas, followed by malignant melanoma, meningioma, soft tissue sarcomas, primary bone tumors and leukemia/myelodysplasia. The elevated risk of these neoplasms ranges from 2 to 60-fold higher than population controls (Goto et al., 1996; Lauper et al., 2013). The arteriosclerosis of WS patients includes premature and severe forms of atherosclerosis, arteriolosclerosis and medial calcinosis. Hypertension, however, is not a common feature of WS. The cataracts seen in WS are almost always posterior sub-capsular, in contrast to those seen in normal aged people, which are typically nuclear cataracts. Osteoporosis in WS is more severe in distal limb bones than in the vertebral column, the opposite of what is seen in normal aged individuals. In addition, osteosclerosis of distal phalanges is highly characteristic of WS, though rarely observed during normal aging. There is no evidence for increased deposition of a variety of amyloids in WS, and dementias of the Alzheimer type are not a common feature of WS (Martin et al., 1999). Mental retardation, dysmorphology, skeletal anomalies and other developmental abnormalities are not features of WS; when present, they are likely due to co-existing disorders. The discordances above may be attributed to a number of factors, such as differential expressions and regulations of the WRN protein in various cell types and tissues, rates of cell turnover, and variations in the replicative potentials of various types of stem cells. The presence or absence of the compensatory enzymes or signal transduction pathways among various tissues may also play important roles. It is clear, however, that further studies are needed to explain the characteristic distributions of phenotypes.

Clinical criteria can be used to facilitate a diagnosis of WS. These are detailed at the International Registry of Werner Syndrome (Table 1) (www.wernersyndrome.org) (Oshima et al., 2014). Cardinal signs include bilateral cataracts (present in 99% of WS cases), premature graying and/or thinning of scalp hair (100%), characteristic dermatologic changes (96%) and short stature (95%) (Huang et al., 2006). Over 91% of affected individuals had all four cardinal signs (Huang et al., 2006). A related set of diagnostic criteria based on a national survey of 146 clinically diagnosed Japanese patients with WS lists progeroid changes of hair, cataracts, scleroderma-like changes of skin, intractable skin ulcers, soft-tissue calcifications, bird-like facies, and abnormal voice can serve as cardinal signs (Takemoto et al., 2013). Confirmation of a clinical diagnosis requires *WRN* gene testing.

3. *WRN* gene product and *WRN* mutations

Classical WS is caused by homozygous or compound heterozygous loss of function mutations in the *WRN* gene (Fig. 2) (Yu et al., 1996). *WRN* is the only known gene in which mutations cause classical WS, and WS is the only known genetic disorder caused by null mutations of the *WRN* gene. The *WRN* locus is located on human chromosome 8p12, and consists of 34 coding exons spanning 140 kb (Yu et al., 1996). The encoded WRN protein is a 1432-amino acid, 160 kDa multifunctional nuclear protein with a $3' \rightarrow 5'$ exonuclease domain in its N-terminal region (Huang et al., 1998), an ATP-dependent $3' \rightarrow 5'$ helicase in its central region (Gray et al., 1997) and a nuclear localization signal in its C-terminal region (Matsumoto et al., 1997; Suzuki et al., 2001). There are two other consensus domains: the RecQ helicase conserved region (RQC) and the "helicase, RNaseD, C-terminal conserved region" (HRDC). Structural analysis and biochemical studies demonstrated that RQC, with its winged-helix (WH) domain, is critical for substrate-specific DNA binding to initiate unwinding (Kitano et al., 2010; Tadokoro et al., 2012; von Kobbe et al., 2003).

Please cite this article in press as: Oshima, J., et al., Werner syndrome: Clinical features, pathogenesis and potential therapeutic interventions. Ageing Res. Rev. (2016), http://dx.doi.org/10.1016/j.arr.2016.03.002