Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

J Invest Dermatol. Author manuscript; available in PMC 2015 December 01.

Published in final edited form as:

J Invest Dermatol. 2015 June ; 135(6): 1484–1490. doi:10.1038/jid.2015.88.

'…Re-written in the skin' – Clues to skin biology and aging from inherited disease

Raymond J. Monnat Jr., M.D.*

Professor of Pathology and Genome Sciences University of Washington Seattle, WA 91895-7705

Abstract

The growing diversity of heritable skin diseases, a practical challenge to clinicians and dermatonosologists alike, has nonetheless served as a rich source of insight into skin biology and disease mechanisms. I summarize below some key insights from the recent gene-driven phase of research on Werner syndrome, a heritable adult progeroid syndrome with prominent dermatologic features, constitutional genomic instability and an elevated risk of cancer. I also indicate how new insights into skin biology, disease and aging may come from unexpected sources.

INTRODUCTION

Werner syndrome (WS) is an autosomal recessive disease that first captured wide attention due to its prominent premature aging (or progeroid) features. WS is also of considerable biomedical science interest in light of the pairing of these progeroid features with constitutional genomic instability and an elevated risk of many clinically important, age-dependent human diseases.

The progeroid features of WS were first well-described by Otto Werner (Werner, 1985), who described a North German family of four siblings, ages 31 – 40, with short stature, prematurely gray hair, bilateral cataracts, atrophy of the extremities, hyperkeratosis and scleroderma-like changes together with foot and ankle skin ulceration. He noted one of the siblings, a 36 yr old male, gave "…the impression of extreme senility." These observations were published as part of Werner's doctoral thesis prior to his embarking on a career in a small North Sea village. Werner never again returned to study his syndrome (Pehmoeller, 2001).

The term 'Werner's syndrome' was first used in a subsequent report of an additional patient who resembled the family members seen by Werner (Oppenheimer and Kugel, 1934). This case report together with a more comprehensive study by Thannhauser of five additional patients (Thannhauser, 1945) provided a detailed description of WS. Werner syndrome was

Users may view, print, copy, and download text and data-mine the content in such documents, for the purposes of academic research, subject always to the full Conditions of use:http://www.nature.com/authors/editorial_policies/license.html#terms

*Corresponding author: University of Washington, Department of Pathology Box 357705, Seattle, WA 98195-7705. Telephone: 206.616.7392 (office)/206.543.6585 (lab). Fax: 206.543.3967. monnat@u.washington.edu.

Conflicts of Interest

The author has no relevant conflicts of interest to declare.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

next ‘rediscovered’ by colleagues at the University of Washington who described three Japanese-American sisters with WS (one of whom is shown in Figure 1). Their analysis established the autosomal recessive inheritance of WS and delineated key differences between WS and normal aging (Epstein *et al.*, 1966).

Werner syndrome as a clinical entity

The most consistent and earliest noted findings are premature graying and loss of hair together with bilateral cataracts, short stature and progressive, scleroderma-like skin changes (Table 1)(Epstein *et al.*, 1966; Goto, 1997; Tollefsbol and Cohen, 1984). Hair graying and loss begin in the second decade with the scalp and eyebrows, as do bilateral ocular cataracts. The short stature of WS patients reflects the absence of a pubertal growth spurt. Short stature together with progressive limb thinning, atrophy and a stocky trunk give many patients a ‘cushingoid’ appearance (see Figure 2 of (Goto, 2001)).

The scleroderma-like skin changes of WS (Thannhauser, 1945) consist of a mix of atrophic and proliferative changes: epidermal atrophy that includes skin appendages in conjunction with focal hyperkeratosis and basal hypermelanosis. Dermal subcutaneous atrophy is often found with dermal fibrosis underlying atrophic skin (Epstein *et al.*, 1966; Goto, 1997; Hatamochi, 2001; Thannhauser, 1945). These changes give skin a ‘tight, white and shiny’ appearance, with a progressive sharpening of facial features to give a ‘pinched’, ‘beaked’ or ‘bird-like’ appearance (see Figure 3 in (Goto, 2001)). The lower extremities, especially the feet, may be markedly deformed with ulceration and calcification of soft tissue and tendons (Hatamochi, 2001).

Many of these changes are readily apparent in patient photos taken in early adulthood and later in life (Figure 1). The progressive development of phenotype makes the diagnosis of WS challenging, especially in young adults. However cardinal features are often present early, and can be used together with molecular confirmation to confirm or exclude a diagnosis (Table 1)(Hisama *et al.*, 2014).

Related RECQ helicase deficiency syndromes

The positional cloning of the *WRN* locus (Yu *et al.*, 1996) and other members of the *RECQ* helicase gene family led to recognition of deeper links between WS and two additional genodermatoses: Bloom syndrome (BS)(Ellis *et al.*, 1995) and Rothmund-Thomson syndrome (RTS)(Kitao *et al.*, 1999). Bloom syndrome patients display congenital short stature and a characteristic sun-sensitive ‘butterfly’ rash across the bridge of the nose and cheeks that may involve hands and forearms (Bloom, 1954). Many patients display cellular and humoral immune deficits; an elevated risk of otitis media, pneumonia and diabetes mellitus with reduced fertility. Cancer is the leading cause of premature death (Bloom, 1954; German, 1979, 1993, 1997).

Rothmund-Thomson syndrome (RTS) was first described as a familial occurrence of skin changes with bilateral juvenile cataracts (Rothmund, 1868; Taylor, 1957; Thomson, 1936). A characteristic sun-sensitive rash with redness, swelling and blistering appears in the first year of life, and may involve the buttocks and extremities while sparing the chest, back and

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

abdomen. The rash may further develop variable pigmentation, telangiectasia and focal atrophy. Hair, eyelashes and eyebrows are often sparse or absent. Congenital short stature is common, though less severe than in BS. Developmental abnormalities include dysplastic, malformed or absent bones, often in the hand or thumbs; delayed bone formation or bone density loss; and malformed, missing or extra teeth. Cataracts have been documented in only a minority of contemporary RTS patients (Larizza *et al.*, 2010; Wang *et al.*, 2001). Cancer risk is largely limited to osteosarcoma (Siitonen *et al.*, 2009; Wang *et al.*, 2003). Immunologic function appears intact, but fertility may be reduced. Additional diseases associated with *RECQL4* mutations are RAPADILINO and Baller-Gerold (BGS) syndromes. RAPADILINO syndrome patients have joint dislocations and patellar hypoplasia or aplasia, but lack skin changes. BGS patients have craniosynostosis with radial aplasia, and RTS-like skin changes (Siitonen *et al.*, 2003; Siitonen *et al.*, 2009; Van Maldergem *et al.*, 2006). Life expectancy appears normal in the absence of cancer (Larizza *et al.*, 2010; Wang *et al.*, 2001).

Elevated acquired disease risk in Werner syndrome

Many WS patients prematurely develop age-dependent diseases such as myocardial infarction and stroke; cancer; osteoporosis; diabetes mellitus; and hypogonadism. Cardio-vascular disease and cancer are leading causes of premature death (Goto, 1997; Goto *et al.*, 2013). The elevated risk of neoplasia is quite selective: two-thirds of neoplasms in WS patients were of 6, not obviously related, tumor types: thyroid epithelial carcinomas, melanomas, meningiomas, soft tissue sarcomas, hematologic neoplasia, chiefly leukemias, and osteosarcoma (Lauper *et al.*, 2013; Lauper and Monnat Jr, 2013; Monnat Jr, 2013). Multiple neoplasms were common: 22% of 189 patients in our series had 1 to 4 concurrent or sequential neoplasms, often of unusual types or at unusual sites. For example, melanomas were almost exclusively less common variants: acral lentiginous melanomas arising on the palms, soles or in nail beds; and mucosal melanomas arising in the nasal cavity or esophagus. Thyroid neoplasms, in similar fashion, were disproportionately less common follicular carcinomas (Lauper *et al.*, 2013). The excess risk of these specific neoplasms, estimated using a combination of standardized incidence ratio (SIR), proportional incidence ratio (SPIR) analyses, ranged from nearly 60-fold for melanoma to 1.5-fold for leukemia and pre-leukemic disorders (Lauper *et al.*, 2013). This spectrum of neoplasia overlaps with, but is distinct from, the neoplasms observed in BS and RTS (German, 1997; Monnat, 2001; Siitonen *et al.*, 2009). BS is unusual among heritable cancer predispositions as *many* different tumor types are involved (German, 1997; Monnat, 2001). The cancer risk in the RTS-associated *RECQL4* syndromes is, conversely, restricted largely to osteosarcoma and lymphoma (Siitonen *et al.*, 2009; Wang *et al.*, 2003; Wang *et al.*, 2001).

Physiologic roles of RECQ helicases

All of the human RECQ helicases hydrolyze ATP, unwind double-stranded DNA and possess good DNA strand annealing activity. WRN alone possesses an additional, 3' to 5' exonuclease activity. Despite their common biochemical activities, the three disease-associated RECQ helicases have differing substrate preferences and different sets of protein partners (reviewed in (Bachrati and Hickson, 2003; Brosh Jr, 2013; Croteau *et al.*, 2014;

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Sidorova and Monnat Jr, 2015)). These biochemical data together with functional and cellular data begin to indicate how these seemingly similar proteins fill different physiologic 'niches' in human cells and, by extension, how the loss of function of one RECQ protein may lead to distinct cellular and organismal phenotypes.

Functional characterizations have identified distinct roles in specific RECQ helicase proteins in DNA replication. For example, RECQL4 and to a lesser extent RECQL bind replication origins and contribute to DNA replication initiation (Thangavel *et al.*, 2009; Xu *et al.*, 2009). Single molecule DNA replication track analyses we and others have performed revealed roles for BLM, WRN and RECQL in replication fork rate maintenance and fork restart (Berti *et al.*, 2013; Sidorova *et al.*, 2013; Sidorova *et al.*, 2008). RECQL4 has an interesting additional role in mtDNA maintenance: it is co-imported with TP53, and appears to limit mtDNA damage in a replication-dependent manner (Croteau *et al.*, 2012; De *et al.*, 2012; Gupta *et al.*, 2014).

Several RECQ helicases also help maintain telomeres, though again display apparent functional specialization. Telomeric DNA poses a dual challenge to the DNA replication machinery as it is composed of repeated (the human telomeric repeat sequence is TTAGGG), GC-rich DNA organized into a unique chromatin 'cap' at the ends of chromosomes (Sfeir *et al.*, 2009). G-rich lagging strands may form G4 DNA quadruplex structures (Maizels and Gray, 2013) which are a good biochemical substrates for WRN and BLM. Only WRN helicase activity is required for complete replication of telomeric G-rich lagging strands, whereas cells lacking RECQL, RECQL4 or BLM also show telomere breakage and loss. It is unclear whether these effects are via a common mechanism (Barefield and Karlseder, 2012; Crabbe *et al.*, 2007; Crabbe *et al.*, 2004; Ghosh *et al.*, 2012; Popuri *et al.*, 2014). In contrast, WRN and BLM both participate in the recombination-mediated 'alternative lengthening of telomeres' (ALT) pathway used by many tumor cells to gain replicative immortality (Mendez-Bermudez *et al.*, 2012). One phenomenon that is not yet well-understood is the sensitivity of WRN+ cells to telomere-homologous DNA oligonucleotides ('T-oligos'). The ability to respond to T-oligos may depend upon WRN exonuclease activity, and may have therapeutic potential in light of protective or deleterious responses in different cell types (Eller *et al.*, 2006; Gilchrest and Eller, 2009).

All five of the human RECQ helicases also participate in DNA double strand break repair by non-homologous DNA end joining (NHEJ) or homology-dependent recombination (HDR or HR). WRN and RECQL4 participate in base excision repair, and RECQL5 may play an additional role in ssDNA break repair (reviewed in (Brosh Jr, 2013; Croteau *et al.*, 2014; Sidorova and Monnat Jr, 2015).

'Rewritten in the skin' – RECQ helicases in transcription

Previous analyses had suggested a role for the WRN and BLM RECQ helicases in transcription (Johnson *et al.*, 2010; Kyng *et al.*, 2003). In order to better understand this role, we analyzed gene and miRNA expression in mutation-typed WS and BS primary fibroblasts and in isogenic control primary fibroblasts depleted of the WRN or BLM protein. These analyses identified −3,000 genes and dozens of miRNAs whose expression was significantly

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

altered by the loss of WRN and BLM function. Among the subset (−25%) of genes altered in both WS and BS cells, a surprisingly high fraction (>90%) had expression altered in the same direction (Nguyen *et al.*, 2014)(Tang, Robles et. al., in preparation). Many WRN- and BLM-responsive downregulated genes contained G quadruplex (G4) DNA motifs in their 5' ends, providing strong evidence that G4 DNA structures are physiologic as well as biochemical substrates for WRN and BLM.

The genes and miRNAs altered in WS and/or BS cells play important roles in pathways that drive cell growth, proliferation, death and survival. BS patient cells had gene expression patterns predicted to alter DNA replication recombination and repair, as well as immune function and tumorigenic/DNA damage signaling. These make good sense in light of our understanding of the biochemical, cellular and organismal phenotype of BS (Nguyen *et al.*, 2014)(Tang, Robles et. al., in preparation). WS appears more complex, and thus intriguing. One remarkable—and as yet not fully understood—finding in WS cells was coordinate upregulation of nearly all of the cytoplasmic tRNA synthestase (ARS) and synthetase-associated interacting protein (AIMP) genes (Kim *et al.*, 2011; Park *et al.*, 2010; Wallen and Antonellis, 2013; Yao and Fox, 2013).

The mechanism of ARS/AIMP upregulation is not yet understood but may include MYC, which can alter and in turn be modulated by ARSs (Shi *et al.*, 2014) while driving expression of *WRN* and telomerase (Grandori *et al.*, 2003). ARS and AIMP overexpression in WS could perturb protein homeostasis by altering global protein turnover and/or translational fidelity (Lee *et al.*, 2014; Wolff *et al.*, 2014). Altered tRNA charging could affect the balance between mitochondrial and nuclear protein synthesis to promote mitochondrial dysfunction and oxidative stress (Jovaisaite and Auwerx, 2015). It could also drive disease pathogenesis via the growing list of ARS/AIMP ‘non-canonical’ functions that modulate disease-related metabolic, developmental, angiogenic, tumorigenic, immune and inflammatory pathways (Paul and Schimmel, 2013; Son *et al.*, 2014). All of these areas are ripe for further exploration using a combination of new genomic and proteomic approaches.

The origins of phenotype

The biochemical and cellular specializations of the individual RECQ helicases outlined above begin to indicate how the loss of function of a single RECQ protein may lead to specific RECQ deficiency syndromes and their associated disease risks. As noted above, RECQ-deficient cells display cell proliferation defects in conjunction with genomic instability (Dhillon *et al.*, 2007; Mao *et al.*, 2010; Martin *et al.*, 1970; Sharma *et al.*, 2007; Sidorova *et al.*, 2013; Thangavel *et al.*, 2009; Warren *et al.*, 1981). These cellular defects in turn are likely part of the explanation for why BS and RTS patients are often small though proportionately developed. BLM or RECQL4 loss can both interfere with DNA replication and impair cell production throughout development. Despite this, development appears largely normal in both syndromes and responds by proportionately scaling output (the fetus) to reflect inadequate substrate (cells). This proportional dwarfing is particularly striking in BS, where patients are born and often remain at or below the 5th percentile for height and weight (Keller *et al.*, 1999).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

The progressive development of progeroid features in WS only after development is largely complete may reflect the starkly different outcome of replication arrest, which leads to high levels of cell death in BS though not in WS cells (Mao *et al.*, 2010; Sidorova *et al.*, 2013). WRN loss, in contrast, has a more profound effect on transcription than does BLM loss, and thus may have a correspondingly more prominent role in transcription and tissue maintenance (see above). Disrupted DNA metabolism in WS patient cells could drive the progressive accumulation of mutant and senescent cells in many tissues, with acquisition of a senescence-associated secretory phenotype that could in turn promote the elevated risk of many clinically important age-associated diseases (Campisi, 2013). Cellular senescence in the RECQ helicase syndromes may have one modest silver lining: it is an effective, albeit non-specific, tumor-suppressive mechanism (Adda di Fagagna, 2008; Collado and Serrano, 2010). Altered *RECQ* expression, as opposed to mutation, may be frequent in many tumor types (Lao *et al.*, 2013). However the previous suggestion that these changes may be largely methylation-driven (Agrelo *et al.*, 2006) has not been consistent enough in our hands to serve as a reliable marker for altered *WRN* expression in tumors (Lao *et al.*, 2013)(Bosch, Luo *et al*, in preparation).

More systematic collection of patient data, longitudinal study of patients, and the collection and distribution of well-characterized clinical samples should all aid our understanding of the RECQ deficiency syndromes. We also have a growing range of options to capture and analyze patient-derived cells and cell lines, including improved short term primary culture, organoid culture and the generation of cell lines and iPS cells (Cheung *et al.*, 2014; Martin *et al.*, 1970; Shimamoto *et al.*, 2014; Wyllie *et al.*, 2000). These analyses and materials have the potential to identify genetic and environmental modifiers of disease progression and acquired disease risk.

New clues to skin biology, disease and therapy

The above analyses emphasize the complexity of disease pathogenesis in even ‘simple’ monogenic genetic diseases such as Werner syndrome. They also emphasize how new insights into disease pathogenesis from rare heritable diseases may improve our understanding of skin biology while identifying potential new therapies. One example comes from another skin disease, recessive dystrophic epidemolysis bullosa (RDEB). RDEB results from *COL7A1* mutations leading to loss of Type VII collagen, a marked reduction in anchoring fibrils and extreme skin fragility with loss and scaring (Tolar and Wagner).

The potential for genetic therapies of EB and a handful of other heritable diseases was emphasized over two decades ago by the identification of patients who had undergone spontaneous reversion of causative mutations with partial or full correction of disease-specific defects in skin, blood, lymphoid or liver (Hirschhorn 2003). A deeper understanding of the role of Type VII collagen in skin (Tolar and Wagner) had led to a diversity of therapeutic approaches: complementation (GENEGRAFT 2014) or targeted correction of causative *COL7A1* mutations in epidermal cells (Sebastiano *et al.*, 2014); use of patient-derived, mutation-reverted keratinocytes (Tolar *et al.*, 2014); and the repair *in trans* of anchoring fibrils using allogeneic fibroblasts (Venugopal *et al.*, 2013), mutation-corrected, iPS-derived fibroblasts (Wenzel *et al.*, 2014) or bone marrow transplantation (Tolar and

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Wagner; Wagner *et al.*, 2010). Repair *in trans* may be a viable option for dealing with the scleroderma-like skin changes seen in WS, as might aminoglycoside suppression of *WRN* missense mutations, a strategy that has been used in RDEB (Cogan *et al.*, 2014).

Another unusual example of where we may find new clues to treating heritable or acquired skin disease as well as age-associated changes comes from comparative genetics, more specifically the African spiny mice *Acomys kempi* and *Acomys percivali*. *Acomys* mice have the remarkable ability to shed–and then regenerate without scaring–large segments of skin, and may have evolved this ability to escape predators (Seifert *et al.*, 2012). While scarless wound healing also occurs in humans, it is largely restricted to the fetus (Yates *et al.*, 2012). *Acomys* mice, in contrast, are able to continuously regenerate skin without scaring in the face of injury, inflammation and infection. Understanding the mechanistic basis for this remarkable example of epimorphic regeneration may identify new ways to maintain or rejuvenate skin, and to help individuals with injuries that lead to disfiguring scaring. Nature undoubtedly holds more examples of remarkable cutaneous biology. Finding these and turning them to good use will require imagination, together with a willingness to look—and think—a bit beyond our usual comfort zone.

Acknowledgments

Work in the author's lab has been supported by the US National Institutes on Aging, Cancer and Environmental Health Sciences and by the Nippon Boehringer Ingelheim Virtual Research Institute of Aging. The author thanks the many individuals who have contributed to the basic science of RECQ helicases, and patients, families and clinicians for their friendship, generosity and support. The preparation of this manuscript was supported in part by US NIH NCI Award CA77852 to the author, and Montagna Symposium on the Biology of Skin NIAMS/NIA award R13-AR009431-48 to M. Kulesz-Martin.

References

Adda di Fagagna F. Living on a break: cellular senescence as a DNA-damage response. Nat Rev Cancer. 2008; 8:512–522. [PubMed: 18574463]

Agrelo R, Cheng WH, Setien F, et al. Epigenetic inactivation of the premature aging Werner syndrome gene in human cancer. Proceedings of the National Academy of Sciences. 2006; 103:8822–8827.

Bachrati CZ, Hickson ID. RecQ helicases: suppressors of tumorigenesis and premature aging. Biochemical Journal. 2003; 374:577–606. [PubMed: 12803543]

Barefield C, Karlseder J. The BLM helicase contributes to telomere maintenance through processing of late-replicating intermediate structures. Nucleic Acids Res. 2012; 40:7358–7367. [PubMed: 22576367]

Berti M, Chaudhuri AR, Thangavel S, et al. Human RECQ1 promotes restart of replication forks reversed by DNA topoisomerase I inhibition. Nat Struct Mol Biol. 2013; 20:347–354. [PubMed: 23396353]

Bloom D. Congenital telangiectatic erythema resembling lupus erythematosus in dwarfs. American Journal of Diseases of Children. 1954; 88:754–758. [PubMed: 13206391]

Brosh RM Jr. DNA helicases involved in DNA repair and their roles in cancer. Nat Rev Cancer. 2013; 13:542–558. [PubMed: 23842644]

Campisi J. Aging, cellular senescence, and cancer. Annual Review of Physiology. 2013; 75:685–705.

Cheung H-H, Liu X, Canterel-Thouennon L, et al. Telomerase protects Werner syndrome lineage-specific stem cells from premature aging. Stem Cell Reports. 2014; 2:534–546. [PubMed: 24749076]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Cogan J, Weinstein J, Wang X, et al. Aminoglycosides restore full-length Type VII collagen by overcoming premature termination codons: therapeutic implications for dystrophic epidermolysis bullosa. Mol Ther. 2014; 22:1741–1752. [PubMed: 25155989]

Collado M, Serrano M. Senescence in tumours: evidence from mice and humans. Nat Rev Cancer. 2010; 10:51–57. [PubMed: 20029423]

Crabbe L, Jauch A, Naeger CM, et al. Telomere dysfunction as a cause of genomic instability in Werner syndrome. Proceedings of the National Academy of Sciences. 2007; 104:2205–2210.

Crabbe L, Verdun RE, Haggblom CI, et al. Defective telomere lagging strand synthesis in cells lacking WRN helicase activity. Science. 2004; 306:1951–1953. [PubMed: 15591207]

Croteau DL, Popuri V, Opresko PL, et al. Human RecQ helicases in DNA repair, recombination, and replication. Annu Rev Biochem. 2014; 83:519–552. [PubMed: 24606147]

Croteau DL, Rossi ML, Canugovi C, et al. RECQL4 localizes to mitochondria and preserves mitochondrial DNA integrity. Aging Cell. 2012; 11:456–466. [PubMed: 22296597]

De S, Kumari J, Mudgal R, et al. RECQL4 is essential for the transport of p53 to mitochondria in normal human cells in the absence of exogenous stress. Journal of Cell Science. 2012; 125:2509–2522. [PubMed: 22357944]

Dhillon KK, Sidorova J, Saintigny Y, et al. Functional role of the Werner syndrome RecQ helicase in human fibroblasts. Aging Cell. 2007; 6:53–61. [PubMed: 17266675]

Eller MS, Liao X, Liu S, et al. A role for WRN in telomere-based DNA damage responses. Proceedings of the National Academy of Sciences. 2006; 103:15073–15078.

Ellis NA, Groden J, Ye TZ, et al. The Bloom's syndrome gene product is homologous to RecQ helicases. Cell. 1995; 83:655–666. [PubMed: 7585968]

Epstein CJ, Martin GM, Schultz AL, et al. Werner's syndrome: A review of its symptomatology, natural history, pathologic features, genetics and relationship to the natural aging process. Medicine. 1966; 45:177–221. [PubMed: 5327241]

GENEGRAFT. Phase I/II ex vivo gene therapy clinical trial for recessive dystrophic epidermolysis bullosa using skin equivalent grafts genetically corrected with a COL7A1-encoding SIN retroviral vector (GENEGRAFT). Human Gene Therapy Clinical Development. 2014; 25:65–66. [PubMed: 24933565]

German, J. Bloom's syndrome. VIII. Review of clinical and genetic aspects. In: Goodman, RM.; Motulsky, AG., editors. Genetic Diseases Among Askenazi Jews. Vol. 1. New York: Raven Press; 1979. p. 121-139.

German J. Bloom syndrome: a Mendelian prototype of somatic mutational disease. Medicine. 1993; 72:393–406. [PubMed: 8231788]

German J. Bloom's syndrome: XX. The first 100 cancers. Cytogenetics and Cell Genetics. 1997; 93:100–106.

Ghosh AK, Rossi ML, Singh DK, et al. RECQL4, the protein mutated in Rothmund-Thomson syndrome, functions in telomere maintenance. J Biol Chem. 2012; 287:196–209. [PubMed: 22039056]

Gilchrest BA, Eller MS. Cancer therapeutics: smart and smarter. Drugs of the Future. 2009; 34:205–216.

Goto M. Hierarchical deterioration of body systems in Werner's syndrome: implications for normal ageing. Mechanisms of Ageing and Development. 1997; 98:239–254. [PubMed: 9352493]

Goto M. Clinical characteristics of Werner syndrome and other premature aging syndromes: pattern of aging in progeroid syndromes. Gann Monograph Cancer Res. 2001; 49:27–39.

Goto M, Ishikawa Y, Sugimoto M, et al. Werner syndrome: A changing pattern of clinical manifestations in Japan (1917−2008). BioScience Trends. 2013; 7:13–22. [PubMed: 23524889]

Grandori C, Wu KJ, Fernandez P, et al. Werner syndrome protein limits MYC-induced cellular senescence. Genes and Development. 2003; 17:1569–1574. [PubMed: 12842909]

Gupta S, De S, Srivastava V, et al. RECQL4 and p53 potentiate the activity of polymerase γ and maintain the integrity of the human mitochondrial genome. Carcinogenesis. 2014; 35:34–45. [PubMed: 24067899]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Hatamochi, A. Dermatological features and collagen metabolism in Werner syndrome. In: Goto, M.; Miller, RW., editors. From Premature Gray Hair to Helicase-Werner Syndrome: Implications for Aging and Cancer. Tokyo: Japan Scientific Societies Press; 2001. p. 51-59.

Hirschhorn R. In vivo reversion to normal of inherited mutations in humans. Journal of Medical Genetics. 2003; 40:721–728. [PubMed: 14569115]

Hisama FM, Kubisch C, Martin GM, et al. Clinical utility gene card for: Werner Syndrome. Eur J Hum Genet. 2014

Johnson JE, Cao K, Ryvkin P, et al. Altered gene expression in the Werner and Bloom syndromes is associated with sequences having G-quadruplex forming potential. Nucleic Acids Research. 2010; 38:1114–1122. [PubMed: 19966276]

Jovaisaite V, Auwerx J. The mitochondrial unfolded protein response-synchronizing genomes. Current Opinion in Cell Biology. 2015; 33:74–81. [PubMed: 25543897]

Keller C, Keller KR, Shew SB, et al. Growth deficiency and malnutrition in Bloom syndrome. The Journal of Pediatrics. 1999; 134:472–479. [PubMed: 10190923]

Kim S, You S, Hwang D. Aminoacyl-tRNA synthetases and tumorigenesis: more than housekeeping. Nat Rev Cancer. 2011; 11:708–718. [PubMed: 21941282]

Kitao S, Shimamoto A, Goto M, et al. Mutations in RECQ4L cause a subset of cases of Rothmund-Thomson syndrome. Nature Genetics. 1999; 22:82–84. [PubMed: 10319867]

Kyng KJ, May A, Kolvraa S, et al. Gene expression profiling in Werner syndrome closely resembles that of normal aging. Proceedings of the National Academy of Sciences. 2003; 100:12259–12264.

Lao VV, Welcsh P, Luo Y, et al. Altered RECQ helicase expression in sporadic primary colorectal cancers. Translational Oncology. 2013; 6:458–469. [PubMed: 23908689]

Larizza L, Roversi G, Volpi L. Rothmund-Thomson syndrome. Orphanet Journal of Rare Diseases. 2010; 5:2. [PubMed: 20113479]

Lauper JM, Krause A, Vaughan TL, et al. Spectrum and risk of neoplasia in Werner syndrome: A systematic review. PLoS ONE. 2013; 8:e59709. [PubMed: 23573208]

Lauper JM, Monnat RJ Jr. Diabetes mellitus and cancer in Werner syndrome. Acta Diabetologica. 2013; 51:159–161. [PubMed: 23386316]

Lee JY, Kim DG, Kim B-G, et al. Promiscuous methionyl-tRNA synthetase mediates adaptive mistranslation to protect cells against oxidative stress. Journal of Cell Science. 2014; 127:4234–4245. [PubMed: 25097229]

Maizels N, Gray LT. The G4 genome. PLoS Genet. 2013; 9:e1003468. [PubMed: 23637633]

Mao FJ, Sidorova JM, Lauper JM, et al. The human WRN and BLM RecQ helicases differentially regulate cell proliferation and survival after chemotherapeutic DNA damage. Cancer Research. 2010; 70:6548–6555. [PubMed: 20663905]

Martin GM, Sprague CA, Epstein CJ. Replicative life-span of cultivated human cells. Effects of donor's age, tissue, and genotype. Laboratory Investigation. 1970; 23:86–92. [PubMed: 5431223]

Mendez-Bermudez A, Hidalgo-Bravo A, Cotton VE, et al. The roles of WRN and BLM RecQ helicases in the alternative lengthening of telomeres. Nucleic Acids Res. 2012; 40:10809–10820. [PubMed: 22989712]

Monnat, RJ, Jr. Werner syndrome. In: Fletcher, CDM.; Bridge, JA.; Hogendoorn, PCW.; Mertens, F., editors. WHO/IARC Monograph on Pathology and Genetics of Tumours of Soft Tissue and Bone. Lyon: IARC Press; 2013. p. 393-394.

Monnat RJ Jr. Cancer pathogenesis in the human RecQ helicase deficiency syndromes. Gann Monograph Cancer Res. 2001; 49:83–94.

Nguyen GH, Tang W, Robles AI, et al. Regulation of gene expression by the BLM helicase correlates with the presence of G-quadruplex DNA motifs. Proceedings of the National Academy of Sciences. 2014; 111:9905–9910.

Oppenheimer BS, Kugel VH. Werner's syndrome - a heredo-familial disorder with scleroderma, bilateral juvenile cataract, precocious graying of hair and endocrine stigmatization. Trans Assoc Am Physician. 1934; 49:358.

Park SG, Choi E-C, Kim S. Aminoacyl-tRNA synthetase–interacting multifunctional proteins (AIMPs): A triad for cellular homeostasis. IUBMB Life. 2010; 62:296–302. [PubMed: 20306515]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Paul M, Schimmel P. Essential nontranslational functions of tRNA synthetases. Nat Chem Biol. 2013; 9:145–153. [PubMed: 23416400]

Pehmoeller G. Memory of my father, Otto Werner. Gann Monograph Cancer Res. 2001; 49:vii–viii.

Popuri V, Hsu J, Khadka P, et al. Human RECQL1 participates in telomere maintenance. Nucleic Acids Res. 2014; 42:5671–5688. [PubMed: 24623817]

Rothmund A. Ueber cataracten in verbindung mit einer eigent mlichen hautdegeneration. Arch Klin Exp Ophtal. 1868; 14:159–182.

Sebastiano V, Zhen HH, Haddad B, et al. Human COL7A1-corrected induced pluripotent stem cells for the treatment of recessive dystrophic epidermolysis bullosa. Science Translational Medicine. 2014; 6:264ra163.

Seifert AW, Kiama SG, Seifert MG, et al. Skin shedding and tissue regeneration in African spiny mice (Acomys). Nature. 2012; 489:561–565. [PubMed: 23018966]

Sfeir A, Kosiyatrakul ST, Hockemeyer D, et al. Mammalian telomeres resemble fragile sites and require TRF1 for efficient replication. Cell. 2009; 138:90–103. [PubMed: 19596237]

Sharma S, Stumpo DJ, Balajee AS, et al. RECQL, a Member of the RecQ Family of DNA Helicases, Suppresses Chromosomal Instability. Molecular and Cellular Biology. 2007; 27:1784–1794. [PubMed: 17158923]

Shi Y, Xu X, Zhang Q, et al. tRNA synthetase counteracts c-Myc to develop functional vasculature. eLife. 2014; 3:e02349. [PubMed: 24940000]

Shimamoto A, Kagawa H, Zensho K, et al. Reprogramming suppresses premature senescence phenotypes of Werner syndrome cells and maintains chromosomal stability over long-term culture. PLoS ONE. 2014; 9:e112900. [PubMed: 25390333]

Sidorova JM, Kehrli K, Mao F, et al. Distinct functions of human RECQ helicases WRN and BLM in replication fork recovery and progression after hydroxyurea-induced stalling. DNA Repair. 2013; 12:128–139. [PubMed: 23253856]

Sidorova JM, Li N, Folch A, et al. The RecQ helicase WRN is required for normal replication fork progression after DNA damage or replication fork arrest. Cell Cycle. 2008; 7:796–807. PMID: 18250621. [PubMed: 18250621]

Sidorova JM, Monnat RJ Jr. Human RECQ helicases: roles in cancer, aging, and inherited disease. Advances in Genomics and Genetics. 2015; 5:19–33.

Siitonen HA, Kopra O, Kaariainen H, et al. Molecular defect of RAPADILINO syndrome expands the phenotype spectrum of RECQL diseases. Human Molecular Genetics. 2003; 12:2837–2844. [PubMed: 12952869]

Siitonen HA, Sotkasiira J, Biervliet M, et al. The mutation spectrum in RECQL4 diseases. Eur J Hum Genet. 2009; 17:151–158. [PubMed: 18716613]

Son, S.; Park, M.; Kim, S. Extracellular activities of aminoacyl-tRNA synthetases: new mediators for cell–cell communication. In: Kim, S., editor. Aminoacyl-tRNA Synthetases in Biology and Medicine. Vol. 344. Netherlands: Springer; 2014. p. 145-166.

Taylor WB. Rothmund's syndrome–Thomson's syndrome: Congenital poikiloderma with and without juvenile cataracts. A review of the literature,report of a case, and discussion of the relationship of the two syndromes. AMA Archives of Dermatology. 1957; 75:236–244. [PubMed: 13393794]

Thangavel S, Mendoza-Maldonado R, Tissino E, et al. The human RECQ1 and RECQ4 helicases play distinct roles in DNA replication initiation. Molecular and Cellular Biology. 2009; 30:1382–1396. [PubMed: 20065033]

Thannhauser SJ. Werner's syndrome (progeria of the adult) and Rothmund's syndrome: two types of closely related hederofamilial atrophic dermatoses with juvenile cataracts and endocrine features; a critical study of five new cases. Annals of Internal Medicine. 1945; 23:559–626.

Thomson MS. Poikiloderma congenitale. British Journal of Dermatology. 1936; 48:221–234.

Tolar J, McGrath JA, Xia L, et al. Patient-specific naturally gene-reverted induced pluripotent stem cells in recessive dystrophic epidermolysis bullosa. J Invest Dermatol. 2014; 134:1246–1254. [PubMed: 24317394]

Tolar J, Wagner JE. Allogeneic blood and bone marrow cells for the treatment of severe epidermolysis bullosa: repair of the extracellular matrix. The Lancet. 382:1214–1223.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Tollefsbol TO, Cohen HJ. Werner's sydrome: an underdiagnosed disorder resembling premature aging. Age. 1984; 7:75–88.

Van Maldergem L, Siitonen HA, Jalkh N, et al. Revisiting the craniosynostosis-radial ray hypoplasia association: Baller-Gerold syndrome caused by mutations in the RECQL4 gene. Journal of Medical Genetics. 2006; 43:148–152. [PubMed: 15964893]

Venugopal SS, Yan W, Frew JW, et al. A phase II randomized vehicle-controlled trial of intradermal allogeneic fibroblasts for recessive dystrophic epidermolysis bullosa. Journal of the American Academy of Dermatology. 2013; 69:898–908.e7. [PubMed: 24075228]

Wagner JE, Ishida-Yamamoto A, McGrath JA, et al. Bone marrow transplantation for recessive dystrophic epidermolysis bullosa. New England Journal of Medicine. 2010; 363:629–639. [PubMed: 20818854]

Wallen RC, Antonellis A. To charge or not to charge: mechanistic insights into neuropathy-associated tRNA synthetase mutations. Current Opinion in Genetics & Development. 2013; 23:302–309. [PubMed: 23465884]

Wang LL, Gannavarapu A, Kozinetz CA, et al. Association between osteosarcoma and deleterious mutations in the RECQL4 gene in Rothmund-Thomson syndrome. J Natl Cancer Inst. 2003; 95:669–674. [PubMed: 12734318]

Wang LL, Levy ML, Lewis RA, et al. Clinical manifestations in a cohort of 41 Rothmund- Thomson syndrome patients. American Journal of Human Genetics. 2001; 102:11–17.

Warren ST, Schultz RA, Chang Cc, et al. Elevated spontaneous mutation rate in Bloom syndrome fibroblasts. Proceedings of the National Academy of Sciences of the United States of America. 1981; 78:3133–3137. [PubMed: 6942420]

Wenzel D, Bayerl J, Nyström A, et al. Genetically corrected iPSCs as cell therapy for recessive dystrophic epidermolysis bullosa. Science Translational Medicine. 2014; 6:264ra165.

Werner, O. On cataract in conjunction with scleroderma (translated by H. Hoehn). In: Salk, D.; Fujiwara, Y.; Martin, GM., editors. Werner's Syndrome and Human Aging. Vol. 1st. New York: Plenum Press; 1985. p. 1-14.

Wolff S, Weissman Jonathan S, Dillin A. Differential scales of protein quality control. Cell. 2014; 157:52–64. [PubMed: 24679526]

Wyllie FS, Jones CJ, Skinner JW, et al. Telomerase prevents the accelerated cell ageing of Werner syndrome fibroblasts. Nature Genetics. 2000; 24:16–17. [PubMed: 10615119]

Xu X, Rochette PJ, Feyissa EA, et al. MCM10 mediates RECQ4 association with MCM2-7 helicase complex during DNA replication. EMBO J. 2009; 28:3005–3014. [PubMed: 19696745]

Yao P, Fox PL. Aminoacyl-tRNA synthetases in medicine and disease. EMBO Molecular Medicine. 2013; 5:332–343. [PubMed: 23427196]

Yates CC, Hebda P, Wells A. Skin wound healing and scarring: fetal wounds and regenerative restitution. Birth Defects Research Part C: Embryo Today: Reviews. 2012; 96:325–333.

Yu CE, Oshima J, Fu YH, et al. Positional cloning of the Werner's syndrome gene. Science. 1996; 272:258–262. [PubMed: 8602509]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

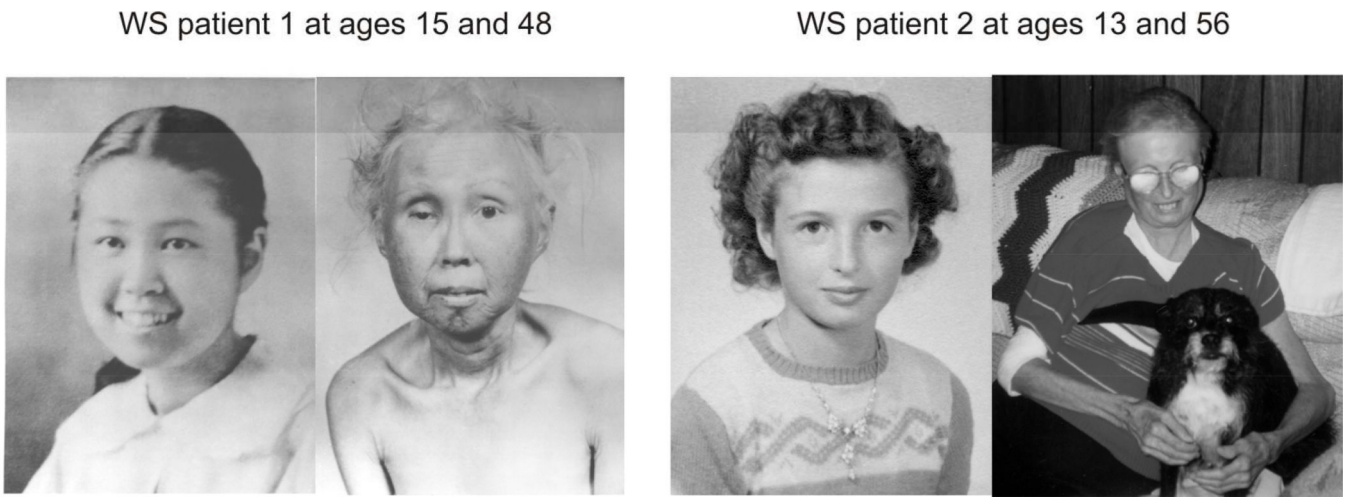

Figure 1.

Clinical features and progression of Werner syndrome. Left photo panels are of Case 1, a Japanese-American WS patient reported by Epstein et al., 1966, at ages 15 (left) and 48 (right). Right photo panels are of a second Caucasian WS patient at ages ~13 (left) and 56 (right). Key clinical features of WS are present in both sets of photos, including the rounded face; sharp facial features; graying, thinning and loss of scalp and eyebrow hair; and in Patient 2 right panel thin, atrophic forearms and right elbow ulceration. Patient 1 archival photos, kindly provided by Drs. George Martin and Nancy Hanson of the International Registry of Werner Syndrome, were digitized and restored by Alden Hackmann. They are used courtesy of Lippincott Williams & Wilkins. Patient 2 photos were provided by Dr. George Martin, and are used here courtesy of the patient's spouse with informed consent of the patient, and of Elsevier Press where they were originally published in different form (Martin, GM (2005) Genetic modulation of senescent phenotypes in Homo sapiens. Cell 120:523–532).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1

Werner syndrome diagnostic criteria

Category	WS signs and symptoms*
*Cardinal***	1. cataracts (bilateral)
	2. sclerodermalike skin changes
	3. short stature
	4. parental consanguinity
	5. premature greying and/or thinning of scalp hair
Additional	1. diabetes mellitus
	2. hypogonadism
	3. osteoporosis
	4. osteosclerosis (distal phalanges/fingers and/or toes)
	5. soft tissue calcification
	6. premature atherosclerosis
	7. neoplasia
	8. thin, highpitched voice

Category	Diagnostic confidence	Diagnostic criteria
Definite	*High confidence*	all cardinal signs + two additional signs ***OR*** confirmed pathogenic *WRN* mutations in both alleles
Probable	*High confidence*	first 3 cardinal signs + any 2 others
Possible	*Low confidence*	either cataracts or dermatological changes + any 4 additional signs
*Exclusion***	*Exclude*	signs or symptoms before adolescence (except stature)

notes:

*WS signs and symptoms are from the diagnostic criteria established by the International Registry of Werner Syndrome: www.wernersyndrome.org/registry/diagnostic.html, with additional discussion and application provided in Lauper *et al.* (2013).