Report

Werner Syndrome

M. Bitar[1,*]

[1]Department of Bioinformatics and Computational Biology, TUM, Boltzmanstraße 3 - Garching

1 INTRODUCTION

The Werner Syndrome (WS) is an autosomal recessive disorder, also known as Adult Progeria. The syndrome was described for the first time in 1904 by Otto Werner (and therefore, named after him), in his PhD thesis entitled "Über katarakt in Verbindung mit Sklerodermie" (which can be translated to "About cataracts connected to sclerodermia"). In the first 90 years of research concerning WS, over 1000 patients were reported, 75% of which were Japanese descent (figure 1) [1]. WS is one of the several types of segmental progeroid syndromes, which affect multiple tissues and organs (on the other hand, unimodal syndromes predominantly affect a single organ) [2]. As one can expect, the most notable symptoms of WS mimic the background of the most general condition called Progeria, with a complex phenotype of accelerated aging. The patients prematurely acquire the appearance of someone several decades older, accompanied by loss or graying of hair, scleroderma-like skin and voice alterations, usually around the second or third decade of life [3]. The phenotype of WS was previously summarized as a "caricature of aging" [1].

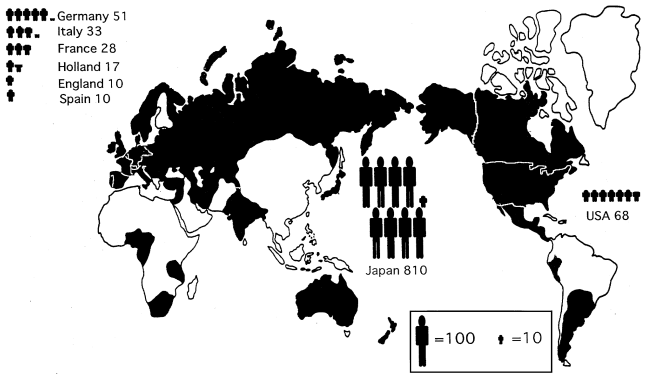

Figure 1: Distribution of Werner Syndrome by nationality as registered from 1904 until 1994 [1]. All countries with at least one patient is shaded.

In general, the subjects develop normally until adolescence, when there is absence of the common growth spurt. The clinical manifestations usually include atherosclerosis, osteoporosis, diabetes, lenticular cataracts, heart failure, cancer and other age-related conditions that appear during early adulthood, following puberty (figure 2) [1, 2]. The typical cause of death is cancer or cardiovascular disease, often occurring between the fourth and fifth decades of life. While in 1966, the median age of death was 47 years [4], in 1997, Makoto Goto reported a surprising median age of death of 54 years [2]. At the cellular level, a reduction in the replicative rate is often observed (cellular senescence) and genomic instability is present in the form of chromosome breaks and translocations, as well as large deletions at the molecular level. A higher occurrence of somatic mutations is also related to the syndrome [1-4].

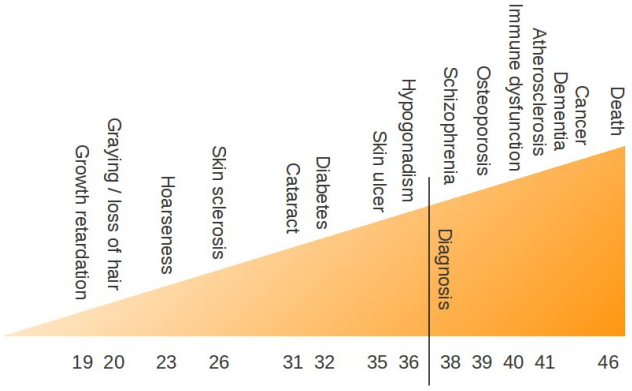

Figure 2: Appearance of symptoms in Werner Syndrome patients. The horizontal axis represents the average age at which each clinical manifestation occurs, according to Makoto Goto in his study from 1997 [1].

The gene related to WS (*WRN*) was identified as located in the chromosome 8p12 and cloned for the first time in 1996 [5] and pointed as homologous to members of the DNA helicase family. Later on, the protein was shown to catalyze DNA unwinding, as expected [5]. The protein was predicted to have 1,432 amino acids and 35 exons, from which 34 are protein coding. At first, four mutations at this gene were identified in WS patients, all correlated to truncated proteins of no more than 1,250 amino acids. The mutated proteins were shorter, but did not present any effects on the helicase domain itself, which is situated between amino acids 569 and 859. Five additional mutations were identified shortly after, being two nonsense mutations, one mutation at a splice-junction site and a deletion leading to a frameshift [3]. The majority of these mutations directly affect the helicase domain, two of those are located within the domain and other two lead to its loss with truncated proteins.

The *WRN* gene can be divided into three distinct regions. The N-terminal portion, comprising codons 1-539 is mainly acid and first it was described as presenting no homology to known genes. Currently, this region is known to contain an exonuclease domain, an unusual feature among members of this protein family

[6]. Similar high concentration of acidic residues are also observed in other DNA repair-deficiency disorders. The median portion of the gene, from codon 540 to 963 is closely related to other helicases from several organisms, presenting all seven conserved motifs that characterize the protein. The C-terminal end of the WRN gene enclosures a nuclear localization signal (NLS) [7]. Two additional domains are found between the helicase domain and the NLS, namely a RecQ helicase conserved region (RQC) and a helicase RNaseD C-terminal conserved region (HDRC, figure 3) [2]. The WRN protein is likely to act on DNA repair, recombination and replication as well as in the maintenance of telomeres.

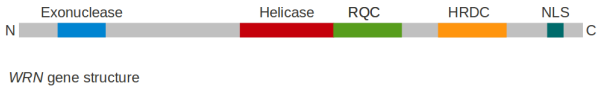

Figure 3: Basic structure of the WRN gene, with known domains highlighted according to description made by Friedrich et al. [2].

The majority of the 60 first described mutations associated to the occurrence of WS are related to the loss of the NLS, causing the protein to accumulate outside the nucleus and therefore be incapable of performing its function [2]. Nevertheless, in the past year, 18 new mutations were reported, yielding a total of 71 *WRN* disease associated mutations identified in clinically diagnosed patients (table 1) [2].

Mutation Class	Total Number of Known Mutations
Small deletions / insertions	25
Stop codon mutations	21
Splicing mutations	17
Missense mutations	5
Genomic rearrangements beyond the WRN locus	2
Intragenic large deletion	1

Table 1: Mutations of the WRN gene associated to the Werner Syndrome, according to the mutation report by Friedrick et al., 2010. The total number of known mutations by class is given [2].

REFERENCES

1. Goto M (1997). Hierarchical deterioration of body systems in Werner's syndrome: Implications for normal ageing. *Mechanisms of Ageing and Development* 98:239–254
2. Friedrich K, Lee L, Leistritz DF, Nurnberg G, Saha B, Hisama FM, Eyman DK, Lessel D, Nurnberg P, Li C, Garcia FVMJ, Kets CM, Schmidtke J, Cruz VT, Van den Akker PC, Boak J, Peter D, Compoginis G, Cefle K, Ozturk S, Lopez N, Wessel T, Poot M, Ippel PF, Groff-Kellermann B, Hoehn H, Martin GM, Kubisch C and Oshima J (2010). WRN mutations in Werner syndrome patients: genomic rearrangements, unusual intronic mutations and ethnic-specific alterations. *Human Genetics* 128:103-11
3. Yu CE, Oshima J, Wijsman EM, Nakura J, Miki T, Piussan C, Matthews S, Fu YH, Mulligan J, Martin GM, Schellenberg GD and the Werner's Syndrome Collaborative Group (1997). Mutations in the consensus helicase domains of the Werner Syndrome gene. *The American Society of Human Genetics* 60:330-341
4. Epstein CJ, Martin GM, Schultz AL, Motulsky AG (1966). Werner's syndrome: a review of its symptomatology, natural history, pathologic features, genetics and relationship to the natural aging process. *Medicine* 45:177-221
5. Yu CE, Oshima J, Fu YH, Wijsman EM, Hisama F, Alisch R, Matthews S, Nakura J, Miki T, Ouais S, Martin GM, Mulligan J, Schellenberg GD (1996). Positional cloning of the Werner's syndrome gene. *Science* 272:258–262
6. Huang S, Li B, Gray MD, Oshima J, Mian IS, Campisi J (1998) The premature ageing syndrome protein, WRN, is a 3' → 5' exonuclease. Nature Genetics 20:114–116
7. Suzuki T, Shiratori M, Furuichi Y, Matsumoto T (2001). Diverged nuclear localization of Werner helicase in human and mouse cells. *Oncogene* 20:2551-2558

A. Huang S, Lee L, Hanson NB, Lenaerts C, Hoehn H, Poot M, Rubin CD, Chen DF, Yang CC, Juch H, Dorn T, Spiegel R, Oral EA, Abid M, Battisti C, Lucci-Cordisco E, Neri G, Steed EH, Kidd A, Isley W, Showalter D, Vittone JL, Konstantinow A, Ring J, Meyer P, Wenger SL, von Herbay A, Wollina U, Schuelke M, Huizenga CR, Leistritz DF, Martin GM, Mian IS and Oshima J (2006). The spectrum of WRN mutations in Werner syndrome patients. *Human Mutation* 27:558-567