Cancer Prone Disease Section
Mini Review

Werner syndrome
Mounira Amor-Guéret
Institut Curie - Section de Recherche, UMR 2027 CNRS, Batiment 110, Centre Universitaire, F-91405 Orsay Cedex, France (MAG)

Published in Atlas Database: October 2000
Online updated version : http://AtlasGeneticsOncology.org/Kprones/WernerID10017.html
DOI: 10.4267/2042/37681

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2000 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Inheritance
Autosomal recessive; prevalence of carriers is as high as 1 in 150 to 1 in 200; frequency is about 0.3/10^5 newborns in Japanese.

Clinics

Note
Uncommon disorder characterized by early onset of geriatric diseases and described as a "caricature of aging" or "progeria of adults".

Phenotype and clinics
Early onset of atherosclerosis, osteoporosis, diabetes mellitus, scleroderma-like skin changes, especially in the extremities, cataract, graying of the hair, subcutaneous calcification, slender limbs, stocky trunk, beaked nose and cancers of non-epithelial cell origin.

Neoplastic risk
Malignancy is found in approximately 10% of WRN patients.
Excess of soft-tissue sarcomas, osteosarcomas, myeloid disorders and benign meningiomas. In addition, the Japanese have an excess of melanomas and follicular, and anaplastic thyroid carcinomas.

Evolution
During the first decade of life, WS patients appear normal: the first manifestation is lack of the adolescent growth spurt.
In the twenties, WS patients develop bilateral ocular cataract and premature graying of the hair.
In the thirties and forties, osteoporosis, type II diabetes mellitus, accelerated atherosclerosis, and cancer occur.
In the fourth and fifth decades, WS patients often succumb to cardiovascular disease or cancer.

Cytogenetics

Inborn conditions
'Variegated translocation mosaicism': skin fibroblast cell lines from WRN patients are usually composed of one or several clones, each marked by a distinctive, apparently balanced translocation.

Other findings

Note
WS cells express constitutively high levels of collagenase in vitro.
WS cells exhibit a mutator phenotype characterized by extensive deletions: 8-fold higher average frequency of 6-thioguanine-resistant lymphocytes in Werner syndrome patients than in sex- and age-matched normal controls.
WS cells usually achieve only about 20 population doublings versus approximately 60 in normal cells in culture (WRN gene could be a 'counting' gene controlling the number of times that human cells are able to divide before terminal differentiation). Forced expression of telomerase in Werner syndrome fibroblasts confers extended cellular life span and probable immortality.

Genes involved and proteins

Complementation groups
No complementation group.

WRN
Location
8p12
Protein
Description: 1432 amino acids; contains one ATP binding site, one DEXH helicase box, one exonuclease
domain unique among known RecQ helicases in the N-terminal region, a nuclear localization signal in the C-terminus and a direct repeat of 27 amino acids between the exonuclease and helicase domains.

Localisation: Nuclear, predominant nucleolar localization.

Function: 3'-5' DNA helicase; 3'-5' exonuclease; functionally interacts with DNA polymerase delta (POLD1), which is required for DNA replication and DNA repair; functionally interacts with Ku, involved in double strand DNA break repair by non-homologous DNA end joining.

Homology: With the RecQ helicases.

Mutations

Germinal: All of the WRN mutations found to date either create a stop codon or cause frameshifts that lead to premature termination: not a single missense mutation had been identified.

References


Faragher RG, Kill IR, Hunter JA, Pope FM, Tannock C, Shall S. The gene responsible for Werner syndrome may be a cell division "counting" gene. Proc Natl Acad Sci U S A. 1993 Dec 15;90(24):12030-4


This article should be referenced as such: