Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Cancer Prone Disease Section

Mini Review

Werner syndrome

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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 diabete 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

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(5):282-98

Fukuchi K, Martin GM, Monnat RJ Jr. Mutator phenotype of Werner syndrome is characterized by extensive deletions. Proc Natl Acad Sci U S A. 1989 Aug;86(15):5893-7

Fukuchi K, Tanaka K, Kumahara Y, Marumo K, Pride MB, Martin GM, Monnat RJ Jr. Increased frequency of 6-thioguanine-resistant peripheral blood lymphocytes in Werner syndrome patients. Hum Genet. 1990 Feb;84(3):249-52

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

Thweatt R, Goldstein S. Werner syndrome and biological ageing: a molecular genetic hypothesis. Bioessays. 1993 Jun;15(6):421-6

Oshima J, Yu CE, Piussan C, Klein G, Jabkowski J, Balci S, Miki T, Nakura J, Ogihara T, Ells J, Smith M, Melaragno MI, Fraccaro M, Scappaticci S, Matthews J, Ouais S, Jarzebowicz A, Schellenberg GD, Martin GM. Homozygous and compound heterozygous mutations at the Werner syndrome locus. Hum Mol Genet. 1996 Dec;5(12):1909-13

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. Positional cloning of the Werner's syndrome gene. Science. 1996 Apr 12;272(5259):258-62

Ogburn CE, Oshima J, Poot M, Chen R, Hunt KE, Gollahon KA, Rabinovitch PS, Martin GM. An apoptosis-inducing genotoxin differentiates heterozygotic carriers for Werner helicase mutations from wild-type and homozygous mutants. Hum Genet. 1997 Dec;101(2):121-5

Marciniak RA, Lombard DB, Johnson FB, Guarente L. Nucleolar localization of the Werner syndrome protein in human cells. Proc Natl Acad Sci U S A. 1998 Jun 9;95(12):6887-92

Ishikawa Y, Sugano H, Matsumoto T, Furuichi Y, Miller RW, Goto M. Unusual features of thyroid carcinomas in Japanese patients with Werner syndrome and possible genotype-phenotype relations to cell type and race. Cancer. 1999 Mar 15;85(6):1345-52

Moser MJ, Oshima J, Monnat RJ Jr. WRN mutations in Werner syndrome. Hum Mutat. 1999;13(4):271-9

Cooper MP, Machwe A, Orren DK, Brosh RM, Ramsden D, Bohr VA. Ku complex interacts with and stimulates the Werner protein. Genes Dev. 2000 Apr 15;14(8):907-12

Kamath-Loeb AS, Johansson E, Burgers PM, Loeb LA. Functional interaction between the Werner Syndrome protein and DNA polymerase delta. Proc Natl Acad Sci U S A. 2000 Apr 25;97(9):4603-8

Li B, Comai L. Functional interaction between Ku and the werner syndrome protein in DNA end processing. J Biol Chem. 2000 Sep 15;275(37):28349-52

Wyllie FS, Jones CJ, Skinner JW, Haughton MF, Wallis C, Wynford-Thomas D, Faragher RG, Kipling D. Telomerase prevents the accelerated cell ageing of Werner syndrome fibroblasts. Nat Genet. 2000 Jan;24(1):16-7

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