Werner syndrome

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Definition

Werner syndrome (WS) is a rare, autosomal recessive genetic instability syndrome and is caused by mutations in the *WRN* gene. Affected patients develop a prematurely aged appearance in the second and third decades of life, and are at increased risk of developing both neoplastic and non-neoplastic diseases. Tumours include soft tissue sarcomas, thyroid carcinoma, malignant melanoma, meningioma, haematological neoplasms, and osteosarcoma. The most common causes of death are cancer and atherosclerotic cardiovascular disease.

OMIM number

277700

Synonym

Progeria of the adult.

Incidence

WS patients have been identified worldwide {819}. Estimates of the frequency or prevalence of WS, obtained by case counting and from consanguinity data, range from 1/22,000 to 1/10^6 (reviewed in {1883}). The frequency of WS in different countries is strongly influenced by the presence of founder mutations and the frequency of consanguinity or inbreeding. The range of frequency estimates also undoubtedly reflects the variable and delayed development of the WS clinical phenotype {604, 819}, with consequent underdiagnosis.

Clinical features and diagnostic criteria

The most consistent clinical findings develop after age 10. These include bilateral cataracts, dermatological pathology resembling scleroderma, short stature and premature greying and loss of scalp hair {604,819}. There may be affected siblings as well as evidence of parental consanguinity (3rd cousin or closer). Additional, less consistent findings include diabetes mellitus, hypogonadism, osteoporosis, soft tissue calcification, premature atherosclerotic cardiovascular disease, high pitched, 'squeeky', or hoarse voice and flat feet.

A definite diagnosis can be established on clinical grounds when all of the consistent features and at least two additional findings are present. Additional diagnostic aids include evidence of elevated 24 hr urinary hyaluronic acid secretion; loss of WRN protein from fibroblasts or peripheral blood lymphocytes; and mutations in the *WRN* gene on chromosome arm 8p.

A clinical scoring system has been devised to identify more reliably definite, probable or possible WS patients. Additional information on this scoring system and the clinical diagnosis of WS can be found on the International Registry of Werner Syndrome Web site:
www.pathology.washington.edu/research/werner/registry/diagnostic.html

Table 21.05
Histopathological spectrum of neoplasia in Werner syndrome.
A wide spectrum of neoplasms has been identified in Werner syndrome (WS) patients, who are clearly at elevated risk of developing one or more of the neoplasms listed in the left column ('frequent'). These neoplasms represent 71% of all neoplasms reported in WS patients. WS patients may be at elevated risk of developing neoplasms listed in the right column, although the number of affected patients is too small in most cases to firmly establish this suspicion. A total of 257 neoplasms were represented in this analysis {820, 1494} (Y. Ishikawa, personal communication). The percentage of neoplasms from this analysis in each column or tumour type is indicated in parentheses.

Frequent (71%)	Less common (29%)
Soft tissue sarcomas (15.5% of cases) malignant fibrous histiocytoma leiomyosarcoma fibrosarcoma malignant schwannoma synovial sarcoma rhabdomyosarcoma	**Non-melanoma skin cancer (5.8%)**
Thyroid carcinomas (14%) follicular papillary anaplastic	**Hepatobiliary carcinomas (5.3%)** hepatocellular cholangiocarcinoma gallbladder
Malignant melanoma (12.6%) acral lentigenous melanoma mucosal malignant melanoma	**Genito-urinary (4.8%)** bladder carcinoma uterine/ovarian carcinoma renal cell carcinoma prostate carcinoma seminoma
Meningioma (11.1%) benign multiple / malignant	**Gastro-intestinal carcinoma (4.3%)** gastric oesophagus pancreas colon
Haematological (11.1%) acute myelogenous leukaemias (M1-5) erythroleukaemia (M6) megakaryocytic leukaemia (M7) myelofibrosis/myelodysplasia aplastic anaemia	**Breast carcinoma (3.9%)**
Osteosarcoma (6.3%)	**Oro-pharyngeal carcinoma (2.4%)**

Neoplastic disease spectrum

WS patients are at increased risk of developing both sarcomas and epithelial neoplasms {820, 1494}. The elevated risk of neoplasia is selective, and includes the following neoplasms in order of decreasing frequency: soft tissue sarcomas, thyroid carcinoma, meningioma, malignant melanoma, malignant or pre-neoplastic haematological disease and osteosarcoma. Many other neoplasms, including common adult epithelial malignancies, have been observed in WS patients. However, it is not clear whether the risk of developing these neoplasms is elevated above population controls. This histo-pathological spectrum of neoplasms overlaps with, though is distinct from, that observed in patients with two other RecQ helicase deficiency syndromes, Bloom syndrome and Rothmund-Thomson syndrome {1494}.

Several features of neoplasia in WS patients indicates that this human RecQ helicase deficiency syndrome is a heritable cancer predisposition: patients develop neoplasms at a comparatively early age; often have unusual sites of presentation (e.g., osteosarcoma of the patella) or less common histopathologic subtypes (e.g., follicular as opposed to papillary thyroid carcinoma); and can have multiple concurrent or sequential neoplasms, e.g., thyroid carcinoma and osteosarcoma. Estimates of the increased risk of neoplasia in WS patients range from 30-fold elevated overall lifetime risk across all tumour types to 1000-fold elevated risk for acral lentigenous melanoma.

Soft tissue sarcomas that have been identified in WS patients include malignant fibrous histiocytoma, malignant peripheral nerve sheath tumour, fibrosarcoma, rhabdomyosarcoma, lipo-sarcoma, and synovial sarcoma. Three histological subtypes of thyroid carcinoma have been reported in WS patients (follicular, papillary and anaplastic), with a predominance of the less common follicular variant. There has been no reported case of medullary thyroid carcinoma in a WS patient. The risk of malignant melanoma is confined almost exclusively to the relatively rare variants that arise on the palms and soles (acral lentigenous melanoma) or in mucosa of the nasal cavity or esophagus. Melanoma risk is most clearly elevated in Japanese WS patients {820}.

The spectrum of haematological disease in WS includes acute myelogenous leukaemia (M1-5), erythroleukaemia (M6) and megakaryocytic leukaemia (M7); atypical leukemia arising in the context of myelodysplasia; and the pre-malignant conditions myelodysplasia, myelofibrosis, and aplastic anaemia. The elevated risk of developing marrow-associated pre-malignant or malignant disease may be related to the progressive accumulation of genetic damage in bone marrow cell lineages {1509}.

Genetics

WS is an autosomal recessive disease: no cases are known to have been acquired or to have been caused by other agents. WS constitutes, together with Bloom syndrome and Rothmund-Thomson syndrome, a group of inherited human genetic instability / cancer predisposition syndromes that result from loss of function of a human RecQ helicase protein.

Gene structure and expression

The *WRN* gene consists of 35 exons in a 165 kb region of chromosome region 8p11-12 {2331}.

Two stable RNAs are encoded by the *WRN* gene, and the shorter, of 5.8 kb, is ubiquitously expressed at varying levels in many cell types, tissues and organs {2331}. The 162 kDa WRN protein is readily detectable in cell lines and tissue samples from normal individuals and heterozygous carriers of single mutant copies of the *WRN* gene by Western blot analysis {1510}. No systematic study of the level of expression of WRN protein as a function of cell type or of development has as yet been published. The WRN protein encodes both DNA helicase and exonuclease activities {1931}, and is likely to play an important physiologic role in homologous recombinational repair in human somatic cells {1728}.

Mutations

WS is an autosomal recessive disease, and thus patients have mutations in both *WRN* alleles. Virtually all of the *WRN* patient mutations thus far identified truncate the *WRN* open reading frame, lead to protein reduction or loss from patient cells and thus can be detected by Western blot analysis {821,1510}. Further mutation characterization can be performed by a combination of mutation-specific allele identification and / or DNA sequencing. Mutation analysis can be especially helpful in the diagnosis of WS in young patients, where the diagnosis is suspected but the clinical phenotype may be incompletely developed. A HUGO Locus-Specific *WRN* Mutational Database summarizes patient mutation data and mutation designations, polymorphism data, and related clinical data and cross-references these to the primary literature (www.pathology.washington.edu/research/werner/ws_wrn.html) {1511}. Additional information on *WRN* mutation analysis for the purpose of confirming a diagnosis of Werner syndrome can be obtained through the International Registry of Werner Syndrome Web site (www.pathology.washington.edu/research/werner/registry/diagnostic.html).