Werner syndrome

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Definition

Werner syndrome (WS) is a rare, autosomal recessive, genetic instability syndrome with a phenotype that mimics premature aging and is caused by inactivation of the *WRN* gene.

MIM No. 277700

Synonyms

Werner syndrome; progeria of the adult

Epidemiology

Patients with WS have been identified worldwide, with the largest number in Japan {1017}. Estimates of the frequency or prevalence of WS, obtained from case-counting and consanguinity data, range from 1 per 22000 to 1 per 10^6 {2464}. The frequency of WS is strongly influenced by the presence of local founder mutations and consanguinity. WS is likely to be under-diagnosed by virtue of its variable, slowly developing and incompletely penetrant clinical phenotype {762,1017, 1967,2464}.

Clinical features and diagnostic criteria

Patients develop a prematurely aged appearance in the second and third decades of life, and are at increased risk of developing age-associated neoplastic and non-neoplastic diseases. The elevated risk of neoplasia in WS is selective, and divided almost equally between epithelial and non-epithelial neoplasms. The most common causes of death are cancer and atherosclerotic cardiovascular disease.

The most consistent clinical findings, seen after age 10 years, include bilateral cataracts; scleroderma-like skin changes; short stature; and premature greying and loss of scalp hair. There may be affected siblings, as well as parental consanguinity (third cousin or closer). Additional, less consistent findings include diabetes mellitus; hypogonadism; osteoporosis; soft tissue calcification, most notably of the Achilles tendon; premature atherosclerotic cardiovascular disease; a high pitched, "squeaky" or hoarse voice; and flat feet {762,1017,1967,2134,2464}. Clinical findings and family history, if scored consistently, allow the reliable identification of definite, probable or possible WS patients {71,2134,2464}. A definitive diagnosis can be established by *WRN* mutation typing in conjunction with demonstration of loss of expression of the WRN protein (see below).

Neoplastic disease spectrum

WS patients are at increased risk of developing both sarcomas and epithelial neoplasms {1018,1932}. The elevated risk of neoplasia in WS is selective. Table 26.05 summarizes a recent, quantitatively rigorous analysis of tumour spectrum and risk in a cohort of 189 WS patients with

Table 27.05 Histopathological spectrum of neoplasia in Werner syndrome

Frequent neoplasms (67% of total)[a]	Less common neoplasms (33% of total)
Thyroid neoplasms (15.8%)	**Non-melanoma skin cancer (4.9%)**
Follicular carcinoma	Squamous cell carcinoma
Papillary thyroid carcinoma	Basal cell carcinoma
Anaplastic thyroid carcinoma	**Gastrointestinal (4.9%)**
Thyroid adenoma	Oesophageal carcinoma
Malignant melanoma (13.0%)	Gastric adenocarcinoma
Acral lentiginous melanoma (ALM)	Pancreatic adenocarcinoma
Malignant mucosal melanoma	**Uterus/ovary (4.0%)**
Malignant melanoma non-ALM	Ovarian cystadenocarcinoma
Meningioma (11.3%)	Uterine carcinoma
Soft tissue sarcomas (9.7%)	Uterine leiomyoma
Undifferentiated pleomorphic sarcoma	**Hepatobiliary (4.0%)**
Leiomyosarcoma	Cholangiocarcinoma
Fibrosarcoma	Hepatocellular carcinoma
Malignant peripheral nerve sheath tumour	**Genito-urinary (3.6%)**
Rhabdomyosarcoma	Ureteral transitional cell carcinoma
Synovial sarcoma	Bladder transitional cell carcinoma
Haematologic/lymphoid (9.3%)	Vulvar carcinoma
Acute myeloid leukaemia (M1–M5, M6, M7)	Prostrate carcinoma
Pre-leukaemic marrow disorders	**Head and neck neoplasms (3.2%)**
Myelofibrosis	Nasal carcinoma NOS
Myelodysplasia	Hard/soft palate squamous cell carcinoma
Refractory anaemia with excess blasts	Tongue squamous cell carcinoma
T-cell leukaemia	Laryngeal carcinoma NOS
Plasmacytoma	**Breast carcinoma (2.8%)**
Osteosarcoma/bone (7.7%)	**Lung (2.0%)**
Conventional osteosarcoma	Squamous cell carcinoma
Extraskeletal osteosarcoma	Adenocarcinoma
Osteochondroma	Bronchioloalveolar carcinoma
	Carcinoid
	CNS (2.0%)
	Astrocytoma
	Spinal cord haemangiolipoma
	Adrenal (1.6%)
	Cortical carcinoma
	Pheochromocytoma

[a] Table data are from a recent, quantitatively rigorous analysis of tumour spectrum and risk that included 189 WS patients with 247 neoplasms reported between 1939 and 2011, where 139 patients were resident in Japan and the remaining 50 were from a diversity of locations outside of Japan {1565A}. WS patients are at a substantially elevated risk of developing all of the frequent neoplasms listed in the left column of the table.

NOS, not otherwise specified.

247 neoplasms reported between 1939 and 2011 {1565A}. This cohort included 139 resident in Japan WS patients and 50 patients from a diversity of locations outside Japan. The most frequent neoplasms in WS patients, representing two thirds of all reports, were, in order of decreasing frequency: thyroid neoplasms, malignant melanoma, meningioma, soft tissue sarcomas, leukaemia and pre-leukaemic conditions, and osteosarcoma. These frequent neoplasms occur at significantly elevated risk in Japanese WS patients compared with population controls {1565A}. Thyroid neoplasms and melanoma are significantly under-represented in WS patients outside Japan for unknown reasons. Many other neoplasms, including common adult epithelial malignancies, have been observed in WS patients (Table 27.05). However, it is not clear whether these neoplasms are significantly more frequent in WS patients compared with population controls. Multiple neoplasia is common: 21.7% of patients (41 of 189) had one to four additional, concurrent or sequential neoplasms, and these were often at different sites {1018, 1565A}.

Several features of neoplasia in WS are of diagnostic or pathogenetic interest. The risk of malignant melanoma is confined almost exclusively to relatively rare variants that arise on the palms and soles (acral lentigenous melanoma, ALM), or in mucosa (e.g. the nasal cavity or oesophagus). Thyroid neoplasms include frequent follicular and less frequent papillary and anaplastic neoplasms. Leukaemias cover the full spectrum of acute myelogenous leukaemia. Atypical leukaemias have been reported, as have many cases of preleukaemic marrow disorders such as myelodysplasia, myelofibrosis and refractory anaemia with an excess of blasts (RAEB). Rare lymphoid neoplasms (T-cell leukaemia, plasmacytoma) have also been reported. The elevated risk of developing marrow-associated premalignant or malignant disease in WS, may be related to the progressive accumulation of genetic damage in bone marrow {1956}. The histopathological spectrum of neoplasia in WS overlaps with, although distinct from, two other RecQ helicase deficiency syndromes, Bloom syndrome and Rothmund-Thomson syndrome {1932}.

Tumours of soft tissue and bone

Soft tissue sarcomas in WS include, in order of decreasing frequency: undifferentiated pleomorphic sarcoma, leiomyosarcoma, fibrosarcoma, malignant and benign nerve sheath tumours, pleomorphic rhabdomyosarcoma and synovial sarcoma. Osteosarcomas, the only well-documented malignant bone tumour in WS, display osteoblastic or fibroblastic differentiation and may be extraskeletal.

Genetics

The *WRN* (*RECQL2*) gene consists of 35 exons in a 165 kb region at 8p11–12 {3041}. The WRN protein has DNA helicase and exonuclease activities that play important physiological roles in DNA metabolism {1933}. Werner syndrome patients have pathogenic null mutations in both *WRN* alleles, which result in loss of the WRN protein {914,1019,1957,1967, 2813}. Molecular confirmation can be especially helpful in the diagnosis of WS in young patients, or where the diagnosis is suspected but inconclusive on clinical grounds alone. Pathogenic *WRN* mutations and polymorphisms have been summarized in the WRN Mutational Database {69}. Additional information on WS diagnosis and molecular testing can be obtained from the International Registry of Werner Syndrome {71} and from GeneTests {70}.

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