



Werner Syndrome

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Summary

Clinical characteristics

Werner syndrome is characterized by the premature appearance of features associated with normal aging and cancer predisposition. Individuals with Werner syndrome develop normally until the end of the first decade. The first sign is the lack of a growth spurt during the early teen years. Early findings (usually observed in the 20s) include loss and graying of hair, hoarseness, and scleroderma-like skin changes, followed by bilateral ocular cataracts, type 2 diabetes mellitus, hypogonadism, skin ulcers, and osteoporosis in the 30s. Myocardial infarction and cancer are the most common causes of death; the mean age of death in individuals with Werner syndrome is 54 years.

Diagnosis/testing

The diagnosis of Werner syndrome is established in a proband with the following cardinal signs: bilateral ocular cataracts, premature graying and/or thinning of scalp hair, characteristic dermatologic pathology, and short stature. Identification of biallelic *WRN* pathogenic variants on molecular genetic testing confirms the diagnosis if clinical features are inconclusive.

Management

Treatment of manifestations: Aggressive treatment of skin ulcers; control of type 2 diabetes mellitus (pioglitazone has been successful); cholesterol-lowering drugs if lipid profile is abnormal; surgical treatment of ocular cataracts using special techniques; treatment of malignancies in a standard fashion.

Prevention of secondary complications: Smoking avoidance, regular exercise, weight control to reduce atherosclerosis risk; excellent skin care and avoidance of trauma to the skin.

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Surveillance: Screening for type 2 diabetes mellitus at least annually; annual lipid profile; at least annual physical examination with attention to malignancies common in Werner syndrome; annual ophthalmologic examination for cataracts; attention to symptoms of angina or peripheral cerebrovascular disease.

Agents/circumstances to avoid: Smoking and excess weight, which increase the risk for atherosclerosis; trauma to the extremities.

Genetic counseling

Werner syndrome is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being neither affected nor a carrier. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the pathogenic variants in the family have been identified.

Diagnosis

Suggestive Findings

The diagnosis of Werner syndrome **should be suspected** in individuals who have the following **cardinal signs** [Huang et al 2006]:

- Bilateral ocular cataracts (present in 99%)*
- Premature graying and/or thinning of scalp hair (100%)
- Characteristic dermatologic pathology (96%)
- Short stature (95%)

Approximately 91% of affected individuals have all four cardinal signs.

The clinical diagnosis may be further supported by the presence of the following **additional signs** and symptoms:

- Thin limbs (present in 98%)
- Pinched facial features (96%)
- Osteoporosis (91%)
- Voice change (89%)
- Hypogonadism (80%)
- Type 2 diabetes mellitus (71%)
- Soft tissue calcification (67%)
- Neoplasm(s) (44%)
- Atherosclerosis (30%)

* Note: Percent frequencies are derived from individuals with a diagnosis of Werner syndrome confirmed by molecular testing.

Establishing the Diagnosis

The diagnosis of Werner syndrome **is established** in a proband who has all four cardinal signs and two additional signs (definite) or the first three cardinal signs and two additional signs (probable). Identification of biallelic pathogenic variants in *WRN* on molecular genetic testing confirms the diagnosis if clinical features are inconclusive (See Table 1).

Similar diagnostic criteria have been proposed by Takemoto et al [2013].

Molecular genetic testing

- **Single-gene testing.** Sequence analysis of *WRN* is performed first and followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.
- **A multigene panel** that includes *WRN* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered if single-gene testing (and/or use of a multigene panel that includes *WRN*) fails to confirm a diagnosis in an individual with features of Werner syndrome. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene that results in a similar clinical presentation).

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

Table 1. Molecular Genetic Testing Used in Werner Syndrome

Gene ¹	Method	Proportion of Probands with Pathogenic Variants ² Detectable by Method
<i>WRN</i>	Sequence analysis ³	~97% ^{4, 5}
	Gene-targeted deletion/duplication analysis ⁶	6 individuals ⁷

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on allelic variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Sequence analysis of the *WRN* coding region detects biallelic pathogenic variants in approximately 97% of affected individuals. The most common pathogenic variant, c.1105C>T, accounts for 20%-25% of pathogenic variants in the European and Japanese populations [Matsumoto et al 1997, Friedrich et al 2010]. Founder variants have been identified in other populations (see Table 2).

5. Deep intronic pathogenic variants that affect splicing [Friedrich et al 2010] would not be detected by routine genomic sequencing analysis.

6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

7. Reported pathogenic variants that require deletion/duplication analysis for detection include deletion and duplication of exon(s) [Friedrich et al 2010; Table A, **Locus Specific** and **HGMD**]. Pathogenic variants that occur in an intron and create a new exon as well as multiexon deletions and duplications have also been reported [Huang et al 2006, Uhrhammer et al 2006, Friedrich et al 2010].

Protein analysis. In certain unusual instances, protein analysis may be useful when both pathogenic *WRN* alleles cannot be identified by sequence analysis. Because the majority of *WRN* pathogenic variants are null and do not produce *WRN* protein (or rarely, produce truncated *WRN*), variants that are not detected by sequencing may be detectable by western blot or immunoblot analysis [Muftuoglu et al 2008]. Instances where protein analysis may supplement sequence analysis include the following:

- When sequencing identifies only one pathogenic variant known to not produce WRN. If protein analysis failed to detect any WRN protein, it may be inferred that the second unidentified pathogenic allele produced no or unstable WRN, thereby providing strong evidence for a diagnosis of Werner syndrome.
- When compound heterozygosity is identified, where one pathogenic allele is known to confer WRN absence but a second missense variant is of uncertain clinical significance
- If protein analysis implicates a missense variant of uncertain significance in conferring protein instability, which would suggest that it is a pathogenic allele. Such instances are rare.

Clinical Characteristics

Clinical Description

Werner syndrome is characterized by the premature appearance of features associated with normal aging and cancer predisposition. Individuals with Werner syndrome develop normally until the end of the first decade. The first symptom, often recognized retrospectively, is the lack of a growth spurt during the early teen years.

Symptoms typically start in the 20s. Initial findings include loss and graying of hair, hoarseness, and scleroderma-like skin changes, followed by bilateral ocular cataracts, type 2 diabetes mellitus, hypogonadism, skin ulcers, and osteoporosis in the 30s. Median age of onset of cataracts is approximately 31 years [Huang et al 2006]. A characteristic facial appearance, termed "bird-like" because of the pinched appearance at the bridge of the nose, evolves during the third or fourth decade. Median age of diagnosis ranges from late 30s to 40s [Huang et al 2006, Goto et al 2013, Takemoto et al 2013].

Male to female ratio. The male:female ratio is believed to be 1:1. In the [International Registry of Werner Syndrome](#), women are slightly overrepresented, probably because of ascertainment bias: women are more likely than men to present for medical care and tend to have more concern about a youthful appearance.

Cardiovascular. Affected individuals exhibit several forms of arteriosclerosis; the most serious form, coronary artery atherosclerosis, may lead to myocardial infarction, which, together with cancer, is the most common cause of death. The mean age of death in individuals with Werner syndrome is 54 years [Huang et al 2006]. Similarly, the median life span of Japanese individuals with Werner syndrome is 53 years [Goto et al 2013].

Malignancy. The spectrum of cancers in individuals with Werner syndrome is unusual in that it includes a large number of sarcomas and very rare cancer types in typical locations [Lauer et al 2013]. The most common cancers in Japanese individuals (for whom the most data exist) are soft-tissue sarcomas, osteosarcomas, melanomas, and thyroid carcinomas. Acral lentiginous melanomas (most often observed on the feet and nasal mucosa) are particularly prevalent compared to levels observed in the general population [Lauer et al 2013]. Common types of carcinomas have also been observed.

Osteoporosis. The osteoporosis of individuals with Werner syndrome is unusual in that it especially affects the long bones. In contrast, osteoporosis during normative aging preferentially involves the vertebral bodies, particularly in women. Characteristic osteolytic lesions of the distal joints of the fingers are observed on radiograph.

Skin. Deep, chronic ulcers around the ankles (Achilles tendon, medial malleolus, lateral malleolus) are highly characteristic.

Neurologic. Controversy exists concerning the degree to which the brain is involved. While individuals with Werner syndrome may have central nervous system complications of arteriosclerosis, they do not appear to be unusually susceptible to Alzheimer disease [Martin et al 1999]. Cognitive changes are not typically observed. Diffuse changes observed on brain MRI in some individuals warrant further investigation in research studies [De Stefano et al 2003].

Fertility. Fertility appears to decline soon after sexual maturity. This decline in fertility is associated with testicular atrophy and probable accelerated rate of loss of primordial follicles in the ovaries, although data are sparse. Early menopause is common in women, as are multiple miscarriages, but successful pregnancies have also been reported. Men have fathered children, usually at younger ages than in the general population.

Genotype-Phenotype Correlations

The chronologic order of the onset of signs and symptoms is similar in all individuals with Werner syndrome regardless of the specific *WRN* pathogenic variants [Goto 1997].

The specific cell type in which cancer develops may depend on the type of *WRN* pathogenic variant present. In individuals of Japanese descent, papillary thyroid carcinoma has been associated with an N-terminal variant, whereas follicular thyroid carcinoma is more frequently observed with a C-terminal variant [Ishikawa et al 1999]. This finding clearly contradicts the original assumption that all identified *WRN* pathogenic variants result in truncation of the nuclear localization signal of WRN protein and thereby act as null variants. Further studies may reveal additional genotype-phenotype correlations.

Nomenclature

An older term for Werner syndrome was "progeria of the adult" (to distinguish it from the [Hutchinson-Gilford progeria syndrome](#), which was often referred to as progeria of childhood).

Prevalence

The prevalence of Werner syndrome varies with the level of consanguinity in populations.

Apparent *WRN* founder variants contribute to higher prevalence in some populations. In the Japanese, the frequency ranges from about 1:20,000 to 1:40,000, based on the frequencies of detectable heterozygous pathogenic variants [Sato et al 1999]. This is most likely the result of a founder variant in the Japanese population. Similarly, in the Sardinian population, the frequency is estimated at 1:50,000 [Masala et al 2007].

Based on the population allele frequency of the most common pathogenic variant, c.1105C>T (rs17847577), which accounts for approximately 20% of pathogenic alleles, the prevalence of Werner syndrome is estimated at 1:380,000-1:1,000,000.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *WRN*.

[Bloom syndrome](#) and [Rothmund-Thomson syndrome](#) are caused by pathogenic variants in closely related but distinct genes in the RecQ helicase family.

Atypical Werner syndrome is caused by pathogenic variants in *LMNA* (see [Differential Diagnosis](#)).

Differential Diagnosis

The differential diagnosis depends on the presenting symptoms and age of onset.

- Atypical Werner syndrome characterizes a small subset of individuals in the Werner Syndrome Registry who have normal WRN protein and some signs and symptoms that sufficiently overlap with the Werner syndrome such that clinicians submit their cases to the International Registry. These individuals typically have comparatively early age of onset (early 20s or earlier) and a faster rate of progression of symptoms

than those with typical Werner syndrome. Among this group, approximately 15% had novel heterozygous pathogenic missense variants in *LMNA* [Oshima & Hisama 2014].

- Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome (MDPL) (OMIM 615381) is a systemic disorder characterized by progeroid features, lipodystrophy, characteristic facial features, and sensorineural hearing loss. Unlike Werner syndrome, ocular cataracts are not a feature of MDPL and the risk of malignancy does not appear to be increased. MDPL is caused by *de novo* heterozygous *POLD1* pathogenic variants [Weedon et al 2013, Lessel et al 2015].
- Mandibulo-acral dysplasia (MAD) is a progeroid syndrome characterized by short stature, type A lipodystrophy (OMIM 248370) with loss of fat in the extremities but accumulation of fat in the neck and trunk, thin, hyperpigmented skin, partial alopecia, prominent eyes, convex nasal ridge, tooth loss, micrognathia, retrognathia, and short fingers [Garavelli et al 2009]. Biallelic pathogenic variants in *LMNA* have been reported in MAD type A [Garavelli et al 2009]. MAD with a generalized loss of subcutaneous fat (type B lipodystrophy) and insulin resistance (OMIM 608612) has been attributed to biallelic pathogenic variants in the zinc metalloproteinase *ZMPSTE24* [Barrowman et al 2012].
- **Hutchinson-Gilford progeria syndrome** (HGPS, progeria of childhood), like Werner syndrome, affects multiple organs with presentations characterized as accelerated aging. Newborns with HGPS usually appear normal, but profound failure to thrive occurs during the first year. Characteristic facies, partial alopecia progressing to total alopecia, loss of subcutaneous fat, progressive joint contractures, bone changes, and abnormal tightness and/or small soft outpouchings of the skin over the abdomen and upper thighs usually become apparent during the second to third year. Motor and mental development is normal. Individuals with HGPS develop severe atherosclerosis. Death usually occurs as a result of complications of cardiac or cerebrovascular disease generally between age six and 20 years. Average life span is approximately 14.6 years. Classic Hutchinson-Gilford progeria syndrome is defined by the presence of the *LMNA* pathogenic variant c.1824C>T. Almost all individuals with HGPS have the disorder as the result of a *de novo* autosomal dominant pathogenic variant.
- Early-onset type 2 diabetes with secondary complications of vascular disease and skin complications could mimic some features of Werner syndrome.
- Though bilateral ocular cataracts (probably presenting as posterior subcapsular cataracts) are one of the most commonly observed features of Werner syndrome, the age of onset is typically in the second decade when graying of hair and skin findings would likely be present. Isolated congenital, infantile, or juvenile cataracts are therefore not likely to be a feature of Werner syndrome. **Myotonic dystrophy type 1** or **myotonic dystrophy type 2** could be a consideration with young adult-onset cataracts, and adults may show muscle wasting, although other manifestations (e.g., myotonia or cardiac conduction abnormalities) are quite different and onset is usually in adulthood.
- Scleroderma, mixed connective tissue disorders, and lipodystrophy may have skin features similar to those of Werner syndrome. Distal atrophy and skin ulcerations in the absence of other manifestations characteristic of Werner syndrome could raise the possibility of **Charcot-Marie-Tooth Hereditary Neuropathy** or familial leg ulcers of juvenile onset.
- Other cancer-prone syndromes:
 - **Rothmund-Thomson syndrome** (RTS) (an autosomal recessive disorder caused by pathogenic variants in *RECQL4*) and **Bloom syndrome** (an autosomal recessive disorder caused by pathogenic variants in *BLM*) may be considered if cancer is the presenting symptom. However, RTS and Bloom syndrome are childhood-onset disorders. Werner syndrome cells do not exhibit the increased sister chromatid exchange typical of Bloom syndrome.
 - **Li-Fraumeni syndrome** (an autosomal dominant disorder caused by pathogenic variants in *TP53*) may present with multiple cancers, including non-epithelial cancers similar to those observed in Werner syndrome, but juvenile-onset cataracts and other manifestations of Werner syndrome are not part of Li-Fraumeni syndrome.

The following conditions share at least two features of Werner syndrome, but are less likely to be confused with the condition because they are characterized by onset in childhood and additional characteristic features:

- The Flynn-Aird syndrome includes cataracts combined with skin atrophy and ulceration; neurologic abnormalities are also present [Flynn & Aird 1965] (OMIM 136300).
- **Branchiooculofacial syndrome** is characterized by premature graying in adults. Eye findings typically include strabismus, coloboma, and microphthalmia. Dysmorphic facial features are also present. *TFAP2A* is the only gene in which pathogenic variants are currently known to cause this autosomal dominant condition.
- **SHORT syndrome** (short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly, and teething delay) may include progeria-like facies and lipodystrophy. Type 2 diabetes mellitus, as well as cataracts and glaucoma, has been reported in affected individuals [Avila et al 2016]. SHORT syndrome is an autosomal dominant disorder resulting from pathogenic variants in *PIK3R1*.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Werner syndrome, the following evaluations are recommended:

- Screening for type 2 diabetes mellitus by standard clinical assays including fasting glucose level, hemoglobin A1c, or oral glucose tolerance test
- Lipid profile
- Physical examination for cancers common in Werner syndrome (e.g., thyroid nodules, skin tumors)
- Ophthalmologic examination including slit lamp examination
- Skin examination for common findings, especially early ulcerations of the feet, with special attention to nail beds and soles of feet for lentiginous melanoma
- Head MRI if neurologic symptoms including new-onset seizures, focal neurologic signs such as weakness or visual field defect, or symptoms such as diplopia or headache are present. These can be indicative of meningioma, a common neoplasm in Werner syndrome.
- Assessment of coping and psychological fitness in light of prognosis
- Consultation with a clinical geneticist and/or genetic counselor

Infants with Werner syndrome are unaffected at birth; thus, no special precautions or investigations are recommended in the neonatal period.

Treatment of Manifestations

The following are appropriate:

- Aggressive treatment of skin ulcers with standard or novel techniques [Yeong & Yang 2004]. Bosentan has been reported to be effective in the treatment of digital ulcers in individuals with systemic sclerosis, and its use has been recently reported to be beneficial in people with Werner syndrome [Matucci-Cerinic et al 2011, Noda et al 2011].
- Control of type 2 diabetes mellitus. Favorable results have been reported with use of pioglitazone and sitagliptin [Durbin 2004, Yokote et al 2004, Watanabe et al 2013].
- Use of cholesterol-lowering drugs if lipid profile is abnormal. Muscle atrophy is a potential complication.
- Surgical treatment of ocular cataracts. Complications are common and specific techniques can optimize outcome [Ruprecht 1989, Shintani et al 1993].
- Treatment of malignancies in a standard fashion

Prevention of Secondary Complications

To prevent secondary complications:

- Lifestyle counseling for smoking avoidance, regular exercise, and weight control to reduce atherosclerosis risk
- Excellent skin care, trauma avoidance, and examination to treat problems early

Surveillance

Appropriate surveillance includes the following:

- Screening for type 2 diabetes mellitus at least annually
- Annual lipid profile
- At least annual physical examination for malignancies common in Werner syndrome and other skin manifestations
- Annual ophthalmologic examination for cataracts
- Attention to symptoms of angina, or peripheral or cerebrovascular disease

Agents/Circumstances to Avoid

Smoking and excess weight increase the risk of atherosclerosis.

Trauma to the extremities should be avoided.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger sibs of a proband/at-risk relatives in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

Evaluations can include:

- Molecular genetic testing if the pathogenic variants in the family are known;
- Clinical examination including growth assessment, skin examination, and ophthalmology evaluation including slit lamp examination if the pathogenic variants in the family are not known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

In one study of individuals with Werner syndrome, signs of hypogonadism were reported in 80%; however, approximately half of those had children and showed signs of hypogonadism after age 30 years [Goto 1997]. Reports in the medical literature of pregnancy in individuals with Werner syndrome are rare; however, many of the women in the [International Registry of Werner Syndrome](#) have had offspring. Preterm delivery has been reported in several cases, and has been attributed to cervical incompetence. Preeclampsia is another reported obstetric complication [Murakami et al 2003].

The use of assisted reproductive technologies such as in vitro fertilization and egg donation has not been reported in women with Werner syndrome.

Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Affected individuals may benefit from reproductive advice regarding the rapid decline in fertility.

Although topical PDGF-BB has been shown to provide some improvement of granulation, it failed to heal the ulcer in a person with Werner syndrome [Wollina et al 2004].

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Werner syndrome is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- Parents of a proband are obligate heterozygotes (i.e., carriers of one *WRN* pathogenic variant).
- Although systematic clinical studies have not been reported, heterozygotes (carriers) are asymptomatic and do not appear to be at increased risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- The offspring of an individual with Werner syndrome are obligate heterozygotes (carriers) for a pathogenic variant in *WRN*.
- Due to the very low prevalence in the US population, the risk for Werner syndrome in the offspring of an affected individual is negligible unless the affected individual and his/her reproductive partner are consanguineous.
- In Japan, where heterozygotes may be as common as one in 150, the risk for Werner syndrome in an offspring is still less than 1/500.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *WRN* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *WRN* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *WRN* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for Werner syndrome are possible.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **National Library of Medicine Genetics Home Reference**
[Werner syndrome](#)
- **National Organization for Rare Disorders (NORD)**
[Werner Syndrome](#)
- **NCBI Genes and Disease**
[Werner syndrome](#)
- **International Registry of Werner Syndrome**
University of Washington School of Medicine, Department of Pathology
Box 357470
Seattle WA 98195-7470
Phone: 206-543-5088
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Email: kshih@u.washington.edu
[International Registry of Werner Syndrome](#)

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Werner Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

<i>WRN</i>	8p12	Werner syndrome ATP-dependent helicase	Werner Syndrome Mutational Database WRN database	WRN	WRN
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Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

Table B. OMIM Entries for Werner Syndrome ([View All in OMIM](#))

277700	WERNER SYNDROME; WRN
604611	RECQ PROTEIN-LIKE 2; RECQL2

Molecular Pathogenesis

The mechanism by which *WRN* pathogenic variants cause the Werner syndrome phenotype is not clear. *WRN* encodes a multifunctional nuclear protein of 1,432 amino acids [Yu et al 1996] that is a member of the RecQ family of DNA helicases. The N-terminal region of the protein encoded by *WRN* has exonuclease activity as well.

DNA-type helicases are ATP-dependent 3'→5' helicases that are necessary to maintain genomic integrity in cells. Other human RecQ helicases are encoded by *RECQL*, *BLM* (responsible for the [Bloom syndrome](#)), *RECQL4* (responsible for the [Rothmund-Thomson syndrome](#)), and *RecQL5* (reviewed by Croteau et al [2014]).

The *WRN* helicase preferentially unwinds DNA structures, such as tetraplex DNA, double-strand DNA with mismatch "bubbles," and Holliday junctions. It unwinds DNA-DNA double strands as well as DNA-RNA double strands. *WRN* exonuclease activity also preferentially digests single strands in complex DNA structures, such as double-stranded DNA with mismatched ends or bubbles. *WRN* helicase and exonuclease activities are modified by binding to interacting proteins (e.g., Ku complex, p53, replication protein A) and by phosphorylation [Croteau et al 2014].

Biochemical and cell biologic studies suggest that *WRN* protein is involved in DNA repair, recombination, replication, and transcription as well as combined functions such as DNA repair during replication. *WRN* protein can potentially unwind or digest aberrant DNA structures accidentally generated during various DNA metabolisms and can also regulate DNA recombination and repair processes by unwinding or digesting intermediate DNA structures. *WRN* protein is also involved in the maintenance of telomeres. These findings are consistent with the notion that *WRN* plays a role in maintenance of genomic stability [Croteau et al 2014].

Gene structure. *WRN* has a transcript of 5765 bp and consists of 35 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Variants of uncertain significance. The allelic variant of uncertain significance c.2500C>T was found in Latino populations with a heterozygote frequency of 0.02. This change greatly reduces helicase and exonuclease activities in vitro. Homozygous individuals could exhibit some of the phenotypes of Werner syndrome, but this has not been demonstrated [Kamath-Loeb et al 2004].

Pathogenic variants. More than 70 different *WRN* pathogenic variants have been identified. The majority of pathogenic variants are stop codons, insertions, or deletions that result in a frame shift or splice donor or acceptor site variant that result in exon skipping. Several missense variants that abolish helicase activity or confer protein instability have been reported.

Pathogenic variants that occur in an intron and result in creation of a new exon as well as multiexon deletions and duplications have also been reported [Huang et al 2006, Uhrhammer et al 2006, Friedrich et al 2010].

The most common pathogenic variant is c.1105C>T, which accounts for 20%-25% of pathogenic variants in the European and Japanese populations [Matsumoto et al 1997, Friedrich et al 2010].

Founder variants have been reported in some populations (see Table 2).

While protein analysis does not distinguish different types of pathogenic variants, it provides important supportive evidence. For example, the Sardinian founder variant, c.2089-3024A>G, is an intronic variant that creates a new exon resulting in a protein of altered length.

Table 2. Selected *WRN* Variants

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
Uncertain significance	c.2500C>T ¹	p.Arg834Cys	
Pathogenic	c.1105C>T	p.Arg369Ter	
	c.2089-3024A>G ²	See footnote 3	NM_000553.4
	c.2179dupT ⁴	p.Cys727LeufsTer5	NP_000544.2
	c.3139-1G>C ⁵	See footnote 6	
	c.3460-2A>C ⁷	See footnote 8	
	c.3590delA ⁹	p.Asn1197ThrfsTer2	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See [Quick Reference](#) for an explanation of nomenclature.

1. Kamath-Loeb et al [2004]; [rs3087425](#). For allele frequencies in different populations, see [Exome Aggregation Consortium](#).

2. A founder variant in the Sardinian population [Masala et al 2007]

3. Creates a new exon between exons 18 and 19 that introduces a stop codon and alters the length of the protein [Masala et al 2007]

4. Potential founder variant in the Moroccan population [Friedrich et al 2010]

5. Founder variant in the Japanese population accounts for approximately 60% of variants in affected individuals of this group [Sato et al 1999]

6. Results in exon 26 skipping

7. Potential founder variant in the Turkish population [Friedrich et al 2010]

8. Results in exon 30 deletion

9. Potential founder variant in the Dutch population [Friedrich et al 2010]

Normal gene product. The normal gene product has 1,432 amino acids. The central region of the WRN ATP-dependent helicase contains the consensus domains of RecQ type helicases [Gray et al 1997] and the N-terminal region contains exonuclease domains [Huang et al 1998]. A nuclear localization signal is at the C-terminal end of the protein [Suzuki et al 2001]. A highly acidic transactivation sequence is present between exonuclease and helicase domains [Balajee et al 1999]. There are two consensus domains in the C-terminal region whose functions have not been completely elucidated: a RecQ C-terminal conserved (RCQ) region and a helicase RNaseD C-terminal (HRDC) conserved region. The RCQ region, which contains a zinc finger motif and a winged helix motif (WH) may be involved in the regulation of helicase enzymatic activity by modulating DNA binding as well as protein folding of WRN helicase [Kitano et al 2010]. The HDRC region is speculated to mediate protein-protein interactions.

Abnormal gene product. A majority of pathogenic variants result in the truncation of the protein. In addition to the loss of the nuclear localization signal in WRN mutated proteins [Huang et al 2006], the mutated mRNAs and the resulting mutated proteins exhibit shorter half-lives than do the wild-type mRNA and WRN protein [Yamabe et al 1997].

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Revision History

- 29 September 2016 (sw) Comprehensive update posted live
- 27 March 2014 (me) Comprehensive update posted live
- 13 December 2012 (cd) Revision: prenatal testing available clinically
- 1 November 2012 (cd) Revision: deletion/duplication analysis available clinically
- 9 February 2012 (cd) Revision: protein analysis clinically available
- 29 December 2011 (cd) Revision: sequence analysis and carrier testing available clinically
- 17 November 2011 (me) Comprehensive update posted live
- 8 March 2007 (me) Comprehensive update posted live
- 13 January 2005 (me) Comprehensive update posted live
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