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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: Surgical treatment of ocular cataracts using special techniques; cholesterol-lowering drugs if lipid profile is abnormal with statin treatment for those with low-density lipoprotein cholesterol levels >190 mg/dL; lifestyle counseling including tobacco avoidance, regular exercise, and maintenance of healthy weight; treatment of malignancies in a standard fashion; control of type 2 diabetes mellitus; standard treatment of osteoporosis; aggressive treatment of skin ulcers; skin care with trauma avoidance; fertility preservation treatments as needed.

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Surveillance: Annual ophthalmologic examination for cataracts; ten-year atherosclerotic cardiovascular disease risk estimation, annual lipid profile, surveillance for cardiovascular risk factors such as hypertension and diabetes mellitus; physical examination including neurologic assessment with attention to signs and symptoms of malignancies common in Werner syndrome; fasting glucose level, hemoglobin A1c, or oral glucose tolerance test annually; monitoring for osteoporosis, and annual skin examination for ulcers and lentiginous melanoma.

Agents/circumstances to avoid: Smoking and obesity, which increase the risk for atherosclerosis. Smoking and alcohol increase the risk of osteoporosis and cataracts. Avoid falls, trauma to the extremities, and excessive sun exposure.

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 a pregnancy 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** [Oshima et al 2017]:

- 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%)
- Skin ulcers, usually of distal legs (40%)
- Atherosclerosis (30%)

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

Establishing the Diagnosis

The clinical 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 Pathogenic Variants [2] Detectable by Method
WRN	Sequence analysis [3]	~97% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	6 reported [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on 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 [Yokote et al 2017]. Founder variants have been identified in other populations (see Table 6).
5. Deep intronic pathogenic variants that affect splicing [Yokote et al 2017] would not be detected by routine genomic sequence 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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]. Pathogenic variants that occur in an intron and create a new exon as well as multiexon deletions and duplications have also been reported [Yokote et al 2017].

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. Instances where protein analysis may supplement sequence analysis include the following:

- When sequencing identifies only one pathogenic variant known not to 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 diagnosis ranges from late 30s to 40s [Oshima et al 2017, Takemoto et al 2013].

Cataracts. Median age of onset of cataracts is approximately 31 years [Oshima et al 2017]. Bilateral cataracts are universal, and progress rapidly in individuals with Werner syndrome. Complications from surgical treatment are common and include (among others) wound dehiscence, peripheral anterior synechiae, epiretinal membrane formation, and cystoid macular edema [Lyons et al 2019]. Specific intraoperative and postoperative techniques (phacoemulsification, small incision size, use of viscoelastic to protect corneal endothelium, use of a weak topical steroid to avoid suppression of fibroblast proliferation) have been reviewed [Lyons et al 2019] in order to optimize outcome.

Facial features. 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.

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 [Oshima et al 2017]. 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 [Lauper 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 [Lauper et al 2013]. Common types of carcinomas have also been observed.

Osteoporosis. The osteoporosis of individuals with Werner syndrome is unusual in that it preferentially affects the long bones [Mori et al 2021]. In contrast, osteoporosis during normative aging preferentially involves the

vertebral bodies, particularly in women. Characteristic osteolytic lesions of the distal phalanges of the fingers are observed on radiograph.

Skin. Deep, chronic ulcers around the ankles (Achilles tendon, medial malleolus, lateral malleolus) are highly characteristic [Kubota et al 2021].

Neurologic. Controversy exists concerning the degree to which the brain is involved. While individuals with Werner syndrome may have cerebrovascular disease resulting in stroke, they do not appear to be unusually susceptible to Alzheimer disease. 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.

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.

The p.Arg834Cys allele is common in Latino populations, and results in reduced helicase and exonuclease activity in vitro, but multiple Mexican individuals homozygous for the allele have been reported to have no clinical features of Werner syndrome [Kamath-Loeb et al 2017].

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 [Yokote et al 2017]. 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 [Yokote et al 2017].

Based on the population allele frequency of the most common pathogenic variant, c.1105C>T, 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 germline pathogenic variants in *WRN*.

Differential Diagnosis

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

Table 2. Genetic Disorders in the Differential Diagnosis of Werner Syndrome

Presenting Symptoms	Gene	Disorder	MOI	Other Features / Comments
Progeroid features	*LMNA*	Atypical Werner syndrome [1]	AD	Usually earlier onset (early 20s or earlier) & faster rate of progression of symptoms than in typical Werner syndrome
		Hutchinson-Gilford progeria syndrome (HGPS, progeria of childhood) [2]	AD	Like Werner syndrome, affects multiple organs w/ presentations characterized as accelerated aging. Typically healthy at birth; profound FTT occurs in 1st yr. Death (usually from complications of cardiac or cerebrovascular disease) generally by age 6-20 yrs
		Mandibuloacral dysplasia w/type A lipodystrophy (OMIM 248370)	AR	Characterized by growth deficiency, mandibular hypoplasia, progressive osteolysis of distal phalanges & clavicles, & acral lipodystrophy w/ normal fat in neck & trunk
	POLD1	Mandibular hypoplasia, deafness, progeroid features, & lipodystrophy (MDPL) syndrome (OMIM 615381)	AD	Unlike Werner syndrome, ocular cataracts are not a feature of MDPL syndrome & risk of malignancy does not appear increased.
	ZMPSTE24	Mandibuloacral dysplasia w/type B lipodystrophy (OMIM 608612)	AR	Onset at birth or early childhood of mandibular hypoplasia w/prominent eyes, atrophic skin, acroosteolysis, & lipodystrophy
Young adult-onset cataracts	*CNBP*	Myotonic dystrophy type 2 (DM2)	AD	May be considered w/young-adult onset cataracts, & adults may show muscle wasting, but other manifestations (e.g., myotonia or cardiac conduction abnormalities) are quite different & onset is usually in adulthood.
	DMPK	Myotonic dystrophy type 1	AD	
Cancer	*BLM*	Bloom syndrome	AR	May be considered if cancer is presenting symptom, but RTS & Bloom syndrome are childhood-onset disorders. Also, Werner syndrome cells do not exhibit ↑ sister chromatid exchange typical of Bloom syndrome.
	RECQL4	Rothmund-Thomson syndrome (RTS)	AR	
	TP53	Li-Fraumeni syndrome (LFS)	AD	May present w/multiple cancers, incl non-epithelial cancers similar to those in Werner syndrome, but juvenile-onset cataracts & other manifestations of Werner syndrome are not part of LFS.
Progeria-like facies & lipodystrophy	*PIK3R1*	SHORT syndrome	AD	May incl progeria-like facies & lipodystrophy, type 2 diabetes mellitus, cataracts, & glaucoma
Premature graying in adults	*TFAP2A*	Branchiooculofacial syndrome	AD	Eye findings typically incl strabismus, coloboma, & microphthalmia; dysmorphic facial features are also present.

AD = autosomal dominant; AR = autosomal recessive; FTT = failure to thrive; MOI = mode of inheritance; SHORT = *s*hort stature, *h*yperextensibility, hernia, *o*cular depression, *R*ieger anomaly, & *t*eething delay

1. A small subset of persons in the Werner Syndrome Registry have normal WRN protein and some signs and symptoms that sufficiently overlap with Werner syndrome. Among this group, approximately 15% had novel heterozygous pathogenic missense variants in *LMNA* [Oshima & Hisama 2014].

2. Classic Hutchinson-Gilford progeria syndrome is defined by the presence of the pathogenic variant c.1824C>T.

Early-onset type 2 diabetes with secondary complications of vascular disease and skin complications could mimic some features of Werner syndrome.

Isolated cataracts. Isolated congenital, infantile, or juvenile cataracts are not likely to be a feature of Werner syndrome. (Although bilateral ocular cataracts – more commonly posterior subcapsular rather than nuclear 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.)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Werner syndrome, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Werner Syndrome

System/Concern	Evaluation	Comment
Eyes	Ophthalmologic eval incl slit lamp exam for cataracts; eval for glaucoma & diabetic retinopathy	At diagnosis
Cardiovascular	• Use of a 10-yr risk calculator & assessment of risk factors • Lipid profile • Blood pressure	
Malignancy	Physical exam for cancers common in Werner syndrome (e.g., thyroid nodules, skin tumors)	
Endocrine	• Screening for type 2 diabetes mellitus by standard clinical assays incl fasting glucose level, hemoglobin A1c, or oral glucose tolerance test • Ask about menstrual cycle (women) or sexual dysfunction (men) to screen for hypogonadism.	
Skeletal	• Bone mineral density screening • Encourage adequate intake of calcium, vitamin D. • Counsel on fall prevention & weight-bearing exercise.	Beginning at age 40 yrs
Integument	Skin exam for common findings, esp calluses or early ulcerations of elbows & lower legs; special attn to nail beds & soles of feet for lentiginous melanoma	At diagnosis
Neurologic	Head MRI if neurologic symptoms incl new-onset seizures, focal neurologic signs such as weakness or visual field defect, or symptoms such as diplopia or headache	These signs/symptoms can be indicative of meningioma, a common neoplasm in Werner syndrome.
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of Werner syndrome to facilitate medical & personal decision making
Psychosocial	Assessment of coping & psychological fitness in light of prognosis	At diagnosis

MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Werner Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Cataracts	Surgical treatment of ocular cataracts	Cystic macular edema is a postsurgical complication [Lyons et al 2019].
Atherosclerosis	• Use of cholesterol-lowering drugs if lipid profile is abnormal w/statin treatment for those w/LDL cholesterol levels >190 mg/dL • Primary prevention per current guidelines [Arnett et al 2019] • Evaluate stable angina w/cardiac stress testing per current guidelines.	In persons w/Werner syndrome, >80%-100% achieve target levels on statin therapy [Tsukamoto et al 2021].
Malignancy	Standard treatment of malignancies	
Type 2 diabetes mellitus	Control of type 2 diabetes mellitus; favorable results reported w/use of thiazolidine, metformin, & sitagliptin	Watanabe et al [2013], Takemoto et al [2021]
Osteoporosis	Treat osteoporosis per current guidelines [Cosman et al 2014]. Options incl: bisphosphonates, teriparatide. In women: calcitonin, estrogen/hormone therapy.	Cosman et al [2014]
Skin ulcers	Aggressive treatment of skin ulcers w/debridement, topical medication to promote moist environment & wound healing, negative pressure wound therapy & skin grafting or flap surgery	Kubota et al [2021]
	Bosentan	Matucci-Cerinic et al [2011]
Reduced fertility / Infertility	Fertility preservation may be achieved w/oocyte cryopreservation, sperm banking, or embryo banking.	Affected persons may benefit from consultation w/reproductive endocrinology infertility specialist.

LDL = low-density lipoprotein

Surveillance

Table 5. Recommended Surveillance for Individuals with Werner Syndrome

System/Concern	Evaluation	Frequency
Cataracts	Ophthalmologic exam	Annually
Atherosclerosis	• Use of a 10-yr risk calculator • Lipid profile • Blood pressure • Lifestyle counseling: diet rich in fruits & vegetables, tobacco avoidance, regular exercise, healthy weight • Std clinical assessment for atherosclerosis risk, signs/symptoms of angina, & peripheral or cerebrovascular disease	
Malignancy	• Physical exam for malignancies common in Werner syndrome • Incl neurologic assessment for signs/symptoms of intracranial tumors.	
Type 2 diabetes mellitus	Fasting glucose level, hemoglobin A1c, or oral glucose tolerance test	
Hypogonadism	Ask about menstrual cycle (women) or sexual dysfunction (men).	
Skeletal	Bone mineral density by dual-energy x-ray absorptiometry	Frequency depends on initial Z score.

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Integument	Prevention of calluses & ulcers w/orthotics, changing limb position, & padding to avoid pressure sores; eval of ulcers for any assoc malignancy	Annually

Agents/Circumstances to Avoid

Smoking and obesity increase the risk of atherosclerosis.

Smoking and alcohol ingestion increase the risk of osteoporosis and cataracts.

Falls resulting in fracture can be prevented or reduced by adding grab bars in the bathroom, eliminating slippery surfaces and tripping hazards, and providing adequate lighting.

Avoid trauma to the extremities and prolonged pressure to the elbows, feet, and ankles, where ulcers commonly form.

Avoidance of excessive sun exposure, use of sunscreen, protective clothing, and UV blocking sunglasses may reduce the risk of skin cancer (including melanoma) and cataracts.

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 [Sołek-Pastuszka et al 2011]. Preeclampsia is another reported obstetric complication.

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 in the US and EU Clinical Trials Register 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.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise 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

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *WRN* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *WRN* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- 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

- If both parents are known to be heterozygous for a *WRN* pathogenic variant, each sib of an affected individual has at conception 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.
- 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.

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 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 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. 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 from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic alteration/s are unknown).

Prenatal Testing and Preimplantation Genetic Testing

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

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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.

- **MedlinePlus**
  Werner syndrome
- **National Organization for Rare Disorders (NORD)**
  Werner Syndrome
- **NCBI Genes and Disease**
  Werner syndrome
- **International Registry of Werner Syndrome**
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  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.

WRN	8p12	Bifunctional 3'-5' exonuclease/ATP-dependent helicase WRN	Werner Syndrome Mutational Database WRN database	WRN	WRN

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

WRN encodes a multifunctional nuclear protein that is a member of the RecQ family of DNA helicases [Yu et al 1996]. DNA-type helicases are ATP-dependent 3'→ 5' helicases that are necessary to maintain genomic integrity in cells. The N-terminal region of the protein encoded by *WRN* has exonuclease activity as well.

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 metabolic processes 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].

More than 90 different *WRN* pathogenic variants have been identified. The majority of pathogenic variants are stop codons, insertions, or deletions that result in a frameshift, or a splice donor or acceptor site variant that results 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 [Yokote et al 2017].

Mechanism of disease causation. Loss of function

Table 6. Notable *WRN* Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000553.6 NP_000544.2	c.2500C>T	p.Arg834Cys	Variant common in Latino population (heterozygote frequency of 0.02); significantly reduces helicase & exonuclease activity in vitro. Homozygotes do not exhibit a Werner syndrome phenotype [Kamath-Loeb et al 2017].
	c.1105C>T	p.Arg369Ter	Most common pathogenic variant worldwide; accounts for 20%-25% of pathogenic variants in the European & Japanese populations [Yokote et al 2017]
	c.2089-3024A>G	See footnote 1.	A founder variant in the Sardinian population [Yokote et al 2017]
	c.2179dupT	p.Cys727LeufsTer5	Potential founder variant in the Moroccan population [Yokote et al 2017]
	c.3139-1G>C	See footnote 2.	Founder variant in the Japanese population; accounts for ~60% of variants in affected persons in this group [Yokote et al 2017]
	c.3460-2A>C	See footnote 3.	Potential founder variant in the Turkish population [Yokote et al 2017]
	c.3590delA	p.Asn1197ThrfsTer2	Potential founder variant in the Dutch population [Yokote et al 2017]

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. Creates a new exon between exons 18 and 19 that introduces a stop codon and alters the length of the protein [Yokote et al 2017]
2. Results in exon 26 skipping
3. Results in exon 30 deletion

Chapter Notes

Author Notes

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Revision History

- 13 May 2021 (sw) Comprehensive update posted live
- 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
- 16 March 2004 (nh) Revision: Normal allelic variants
- 2 December 2002 (me) Review posted live
- 30 July 2002 (nh) Original submission

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