GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory.

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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Williams Syndrome
[Williams-Beuren Syndrome]

PMID: 20301427
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Summary

Disease characteristics. Williams syndrome (WS) is characterized by cardiovascular disease (elastin arteriopathy, peripheral pulmonary stenosis, supravalvular aortic stenosis, hypertension), distinctive facies, connective tissue abnormalities, mental retardation (usually mild), a specific cognitive profile, unique personality characteristics, growth abnormalities, and endocrine abnormalities (hypercalcemia, hypercalciuria, hypothyroidism, and early puberty). Feeding difficulties often lead to failure to thrive in infancy. Hypotonia and hyperextensible joints can result in delayed attainment of motor milestones.

Diagnosis/testing. Clinical diagnostic criteria are available for Williams syndrome; however, the mainstay for diagnosis is detection of the contiguous gene deletion of the Williams-Beuren syndrome critical region (WBSCR) that encompasses the elastin (ELN) gene. Over 99% of individuals with the clinical diagnosis of WS have this contiguous gene deletion, which can be detected using fluorescent in situ hybridization (FISH) or targeted mutation analysis.

Management. Treatment includes early intervention programs, special education programs, and vocational training to address developmental disabilities, including speech/language, physical, occupational, and sensory integration therapies. Psychologic evaluation, polysomnography, and psychiatric evaluation should guide therapy for the individual. Behavioral counseling and psychotropic medication are often used to manage behavior problems, especially attention deficit disorder and anxiety. Surgery may be required for supravalvular aortic stenosis, mitral valve insufficiency, or renal artery stenosis. Treatment of hypercalcemia may include diet modification, oral corticosteroids, and/or intravenous pamidronate. Referral to a nephrologist is appropriate for management of nephrocalcinosis and persistent hypercalcemia and/or hypercalcuria. Infants often benefit from feeding therapy. Surveillance includes yearly: medical evaluation, vision screening, measurement of blood pressure, calculation of calcium/creatinine ratio in a random spot urine, and urinalysis. Additional periodic evaluations during childhood include: serum concentration of calcium, thyroid function, hearing, and renal and bladder ultrasound examination. Periodic evaluations during adulthood include: glucose tolerance; cardiac evaluation for mitral valve prolapse, aortic insufficiency, and arterial stenosis; and ophthalmologic evaluation for cataracts. Children with WS should not be given multivitamins because all pediatric multivitamin preparations contain vitamin D.
Genetic counseling. Williams syndrome is transmitted in an autosomal dominant manner. Most cases are de novo occurrences, but occasionally, parent-to-child transmission is observed. Prenatal testing is clinically available, but is rarely used because most cases occur in a single family member only and no prenatal indicators exist for low-risk pregnancies.

Diagnosis

Clinical Diagnosis

Clinical diagnostic criteria are available for Williams syndrome (WS) [Preus 1984; Committee on Genetics 2001, 2002]. The WS phenotype is variable, and no single clinical feature is required to establish the diagnosis. Williams syndrome is suspected in individuals with the following findings:

- **Cardiovascular disease (elastin arteriopathy).** Any artery may be narrowed. Supravalvular aortic stenosis (SVAS) is the most clinically significant and most common cardiovascular finding; it occurs in 75% of affected individuals. Peripheral pulmonic stenosis (PPS) is common in infancy.

- **Distinctive facies.** Broad brow, bitemporal narrowness, peri orbital fullness, a stellate/lacy iris pattern, strabismus, short nose, full nasal tip, malar hypoplasia, long philtrum, full lips, wide mouth, malocclusion, small jaw, and prominent earlobes are observed at all ages. Young children have epicantal folds, full cheeks and small, widely spaced teeth, while adults typically have a long face and neck, accentuated by sloping shoulders, resulting in a more gaunt appearance.

- **Connective tissue abnormalities.** Hoarse voice, inguinal/umbilical hernia, bowel/bladder diverticulae, rectal prolapse, joint limitation or laxity, and soft, lax skin are observed.

- **Mental retardation.** Most individuals have some degree of mental retardation, which can range from severe to mild. Some have average intelligence.

- **Specific cognitive profile.** Strengths in verbal short-term memory and language and extreme weakness in visuospatial construction are typical. The Williams syndrome cognitive profile is independent of IQ.

- **Unique personality.** Overfriendliness, empathy, generalized anxiety, and attention deficit disorder are commonly observed.

- **Growth abnormalities.** The growth pattern is characterized by: prenatal growth deficiency, failure to thrive in infancy (70%), poor weight gain and linear growth in the first four years; a rate of linear growth that is 75% of normal in childhood; and a brief pubertal growth spurt. The mean adult height is below the third centile.

- **Endocrine abnormalities.** Findings include idiopathic hypercalcemia (15%), hypercalciuria (30%), hypothyroidism (10%), and early (but not precocious) puberty (50%). An increased frequency of subclinical hypothyroidism, abnormal oral glucose tolerance tests, and diabetes mellitus is observed in adults with WS.

Molecular Genetic Testing

**Gene.** Contiguous gene deletions in the Williams-Beuren syndrome critical region (WBSCR) are known to be...
associated with Williams syndrome.

**Clinical uses**

- Confirmatory diagnostic testing
- Prenatal diagnosis

**Clinical testing**

- **FISH.** A commonly used commercially available [FISH probe](#) covers approximately 180 kb of the WBSCR deleted in WS including *ELN, LIMK1,* and the D7S613 locus [Ewart, Morris, Atkinson et al 1993; Lowery et al 1995; Mari et al 1995; Nickerson et al 1995].

- **Targeted mutation analysis.** Non-FISH based methods for the detection of contiguous gene deletions in the WBSCR include:
  - **Real-time quantitative PCR.** Real-time quantitative PCR is used to determine the dosage (copy number) of three genes within the WBSCR: *ELN, LIMK1,* and *GTF2I* [Somerville et al 2002]. The finding of only a single copy of a gene region indicates the presence of a WBSCR deletion.
  - **Genomic microarray analysis.** Use of commercially available array-based [comparative genomic hybridization](#) detects DNA copy number changes in the deletion of the WBSCR. See [graphic element](#) for laboratories offering array CGH.
  - **Heterozygosity testing.** A panel of STRs (short tandem repeats) spanning the WBSCR is tested. The finding of two different STR sizes (heterozygosity) at all of the markers indicates that a deletion is not present. The finding of a single STR size at any or all of the markers indicates the possibility of either a deletion (i.e., an abnormal finding) or homozygosity for the marker(s) (i.e., a normal finding). Quantitative PCR can be used to determine if a deletion is in fact present. STR analysis is used primarily to determine the size of deletions.

**Table 1. Summary of Molecular Genetic Testing Used in Williams Syndrome**

<table>
<thead>
<tr>
<th>Test Methods</th>
<th>Mutations Detected</th>
<th>Mutation Detection Frequency</th>
<th>Test Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>FISH</td>
<td><em>ELN deletion</em></td>
<td>~99%</td>
<td>Clinical graphic element</td>
</tr>
<tr>
<td>Targeted mutation analysis</td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Test Availability refers to availability in the [GeneTests Laboratory Directory](#). [GeneReviews](#) designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.

1. Includes real-time quantitative PCR, genomic microarray analysis, and heterozygosity testing

**Genetically Related (Allelic) Disorders**

**Autosomal dominant cutis laxa** is caused by frameshift *ELN* mutations that have a dominant-negative effect on elastic fiber structure [Tassabehji et al 1998, Zhang et al 1999, Morris & Mervis 2000].
**Autosomal dominant** supravalvular aortic stenosis (SVAS) is caused by mutation or intragenic deletion of the **ELN** gene [Ewart, Morris, Ensing et al 1993; Olson et al 1993; Morris & Mervis 2000]. Individuals with **autosomal dominant** SVAS typically have only connective tissue abnormalities, and thus do not have WS.

**Autosomal dominant** "SVAS plus" is caused by deletion of contiguous genes in the WBSCR that includes **ELN** and other contiguous genes. Members of families with these short deletions have SVAS rather than classic WS; however, they share some phenotypic features with WS, such as difficulty with visuospatial construction [Morris & Mervis 2000, Morris et al 2003].

**Williams syndrome region duplication syndrome** is caused by duplication of the contiguous genes in the WBSCR. The first child reported with the duplication syndrome had dolichocephaly, high and narrow forehead, long eyelashes, high and broad nose, short philtrum, high arched palate, anterior open bite, retrognathia, and asymmetric crying facies. He also had mild difficulty with tandem gait and unipedal stance, and mild dysmetria. The most significant finding was severe impairment in expressive language in contrast to the relative strength in language exhibited by individuals with WS [Somerville et al 2005].

**Clinical Description**

**Natural History**

**Infancy.** The infant with WS is often born post-term, and is small for the family background. Feeding difficulties leading to failure to thrive are common, including gastro-esophageal (G-E) reflux, disordered suck and swallow, textural aversion, and vomiting. Prolonged colic (>4 months) may be related to G-E reflux, chronic constipation, and/or idiopathic hypercalcemia, which occurs in 15% of individuals with WS. Other medical problems that often occur in the first year include strabismus, chronic otitis media, rectal prolapse, inguinal hernia, and cardiovascular disease [Morris et al 1988]. Infants with WS are hypotonic and typically have hyperextensible joints, resulting in delayed attainment of motor milestones. Walking usually occurs by 24 months. Speech is also delayed, but later becomes a relative strength. Fine motor difficulties are present at all ages.

**Cognitive abilities.** Mental retardation, usually mild, occurs in 75% of individuals with WS. The cognitive profile is distinctive, consisting of strengths in verbal short-term memory and language, but extreme weakness in visuospatial constructive cognition. As a result, children with WS usually score higher on verbal subtests than on tests measuring visuospatial construction [Greer et al 1997, Mervis et al 1998].

Academically, individuals with WS perform relatively well in reading, and adults may read at the high school level, though the range of achievement is wide. Reading skills correlate with cognitive ability rather than language-related skills [Levy et al 2003]. Difficulty with writing, drawing, and mathematics is significant; however, many adults with WS are able to perform simple addition.

Adaptive behavior is commensurate with IQ in children [Mervis et al 2001], but adaptive behavior is less than expected for IQ in adults [Davies et al 1997], adversely affecting the ability of adults with WS to function independently.

**Unique personality.** The characteristic personality profile of WS includes overfriendliness, excessive empathy, attention problems, and anxiety [Einfeld et al 2001, Cassidy & Morris 2002, Doyle et al 2004]. Other common behavior problems include sensory defensiveness, perseveration, unusual or restricted interests, sleep difficulties, and specific phobias (80%) [Dykenes 2003, Laws & Bishop 2004]. Compared to other children with disabilities, children with WS rate high on measures of the following: empathy, gregariousness, people-orientation, tenseness, sensitivity, and "visibility" (easily noticed) [Klein-Tasmin & Mervis 2003]. Anxiety is common in adults with WS (80%).
Cardiovascular disease. Elastin arteriopathy is present in about 75% of affected individuals and may affect any artery. Males are more likely to have severe cardiovascular disease than females [Sadler et al 2001].

Peripheral pulmonic stenosis (PPS) is common in infancy but usually improves over time. The most common arteriopathy is supravalvular aortic stenosis (SVAS), which may worsen over time. The greatest morbidity results from this aortic narrowing, which can be either a discrete hourglass stenosis or diffuse aortic hypoplasia. If untreated, the resultant increase in arterial resistance leads to elevated left heart pressure, cardiac hypertrophy, and cardiac failure.

Individuals with combined SVAS and PPS (biventricular outflow tract obstruction) may develop biventricular hypertrophy and hypertension, increasing the risk for myocardial ischemia, dysrhythmias, and sudden death [Lacro & Smoot 2006]. Coronary artery stenosis has been implicated in some cases of sudden death in WS [Bird et al 1996]. The incidence of sudden death in one WS cohort of 293 was 1/1000 patient years, which is 25 to 100 times higher than the age matched population [Wessel et al 2004].

Hypertension is common in adolescents and adults [Broder et al 1999, Giordano et al 2001, Eronen et al 2002], and may be secondary to renal artery stenosis in some cases [Deal et al 1992].

Mitral valve prolapse and aortic insufficiency have been reported in adults [Morris et al 1990, Kececioglu et al 1993].

Stenosis of the mesenteric arteries may contribute to abdominal pain.

Neurovascular abnormalities are rarely reported but may result in stroke [Ardinger et al 1994, Soper et al 1995, Cherniske et al 2004].

Eye, ear, nose, and throat. Hyperopia is found in 50% of individuals with WS and strabismus in 50% [Kapp et al 1995]. Cataracts have been reported in adults [Cherniske et al 2004].

Chronic otitis media is seen in 50% of affected individuals. Increased sensitivity to sound is common (90%) and individuals with WS report discomfort at 20 decibels (db) lower than controls [Gothelf et al 2006]. Many report specific phobias for certain sounds [Levitin et al 2005].

Progressive sensorineural hearing loss has been demonstrated [Marler et al 2005, Gothelf et al 2006]. Mild to moderate high-frequency sensorineural hearing loss is common in adults, as is excessive build-up of ear wax [Cherniske et al 2004].

Most individuals have a hoarse or low-pitched voice; vocal cord abnormalities secondary to elastin deficiency are likely causative [Vaux et al 2003].

Dental problems include microdontia, enamel hypoplasia, and malocclusion [Hertzberg et al 1994]. One or more permanent teeth are missing in 40% of individuals with WS [Axelsson et al 2003].

Gastrointestinal difficulties. Individuals with WS have sensory defensiveness, both auditory [Van Borsel et al 1997] and tactile. The difficulty with food textures leads to problems in transitioning from breast milk or formula to solid foods in infancy.

Chronic abdominal pain is a common complaint of children and adults with WS; possible causes include G-E reflux, hiatal hernia, peptic ulcer disease, cholelithiasis, diverticulitis, ischemic bowel disease, chronic constipation, and somatization of anxiety. The prevalence of diverticulitis is increased in adults with WS [Partsch et al 2005].
Hypercalcemia may contribute to irritability, vomiting, constipation, and muscle cramps; it is more common in infancy but may recur in adults [Morris et al 1990, Pober et al 1993].

In one study, the incidence of celiac disease was increased in children with WS (9.6% vs 0.5% in the general population) [Giannotti et al 2001].

**Urinary tract abnormalities.** Urinary frequency and enuresis (50%) are common in children with WS. Structural abnormalities of the urinary tract are found in 35-50%, renal artery stenosis in 50%, bladder diverticulae in 40%, chronic urinary tract infections in 30% of adults, and nephrocalcinosis in fewer than 5% [Pober et al 1993, Pankau et al 1996, Sforzini et al 2002, Sammour et al 2006]. Bladder capacity is reduced and detrusor overactivity is observed in 60% [Sammour et al 2006].

**Musculoskeletal/neurologic problems.** The hypotonia and lax joints of the young child lead to abnormal compensatory postures to achieve stability. Older children and adults with WS typically have hypertonia and hyperactive deep-tendon reflexes. Gradual tightening of the heel cords and hamstrings occurs, resulting in a stiff and awkward gait, kyphosis, and lordosis by adolescence [Morris et al 1988, Kaplan et al 1989]. Fine motor function is impaired, leading to difficulty with tool use and handwriting at all ages. Cerebellar signs in adults include ataxia and tremor [Pober & Szekely 1999].

**Growth.** Individuals with WS are short for their family background. Specific growth curves for WS are available [Morris et al 1988, Saul et al 1988]. Failure to thrive is observed in 70% of infants. The growth pattern is characterized by prenatal growth deficiency, poor weight gain and poor linear growth in the first four years, a rate of linear growth that is 75% of normal in childhood, and a brief pubertal growth spurt. The mean adult height is below the third centile.

Puberty usually occurs early [Partsch et al 2002], but true precocious puberty is rare.

**Endocrine problems.** Endocrine abnormalities include idiopathic hypercalcemia (15%), hypercalciuria (30%), hypothyroidism (10%), and early (though not precocious) puberty (50%). An increased frequency of subclinical hypothyroidism, abnormal oral glucose tolerance tests, and diabetes mellitus is observed in adults with WS [Cherniske et al 2004].

**Other.** The hair grays prematurely [Morris et al 1988], but there is not yet sufficient evidence to suggest that WS is a premature aging syndrome [Pober 2006].


**Genotype-Phenotype Correlations**

The WBSCR deletion comprises 1.55 megabases (Mb) in 95% of individuals in 1.84 Mb in 5% [Bayes et al 2003].

- Hypertension is less prevalent in those individuals with WS who are hemizygous for the NCF1 gene, located in one of the blocks of low copy repeats that flank the WBSCR [Del Campo et al 2006].

- A more severe phenotype with lower cognitive ability is observed in Individuals with very long deletions (> 2-4 Mb) that include the WBSCR than in individuals with the typical WBSCR deletion [Stock et al 2003].
Shorter deletions within the WBSCR have a variable phenotype depending on the extent of the deletion.

- Individuals with WBSCR deletions that include the usual telomeric breakpoint (including GTF2I) have classic WS features, including mental retardation [Botta et al 1999, Heller et al 2003].

- Those with short WBSCR deletions that do not have deletion of GTF2I, including some individuals with de novo short deletions and families with "SVAS plus," do not have mental retardation but often demonstrate the WS cognitive profile [Morris et al 2003]. In two families, deletion of ELN and an additional gene, LIMK1, was associated with the WS cognitive profile, but not mental retardation or other characteristics of Williams syndrome [Frangiskakis et al 1996]. Another family with a similar deletion did not have the WS cognitive profile [Tassabehji et al 1998].

The WBSCR deletion may be of maternal or paternal origin [Ewart, Morris, Atkinson et al 1993; Dutly & Schinzel 1996; Urban et al 1996]. No phenotypic differences have been related to the parent of origin in some series [Wu et al 1998], while microcephaly has been correlated with maternal origin of the WBSCR deletion in others [Del Campo et al 2006].

**Penetrance**

Penetrance is 100%; expression of the phenotypic features is variable.

**Nomenclature**

The first descriptions of WS were incomplete in that they reflected the chief complaint of the individual or the medical specialty of the observer. Thus, nephrologists and endocrinologists described "idiopathic infantile hypercalcemia" (IHC) and cardiologists reported "supravalvular aortic stenosis syndrome" (SASS).

Early reports also noted dysmorphic facial features which were thought to resemble elves of legend, and for a time, the term "Williams elfin facies syndrome" was used.

After the reports of Williams et al (1961) and Beuren et al (1962), the condition was called Williams syndrome in the United States and Williams-Beuren syndrome in Europe.

**Prevalence**

A recent study of WS in Norway reported a prevalence of 1/7500 [Stromme et al 2002].

**Differential Diagnosis**

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory.

WS should be distinguished from other syndromes that include developmental delay, short stature, distinctive facies, and congenital heart disease. These include Noonan syndrome, deletion 22q11 (DiGeorge syndrome), Smith-Magenis syndrome, Kabuki syndrome, and fetal alcohol syndrome (FAS).

Individuals with SVAS should be evaluated to determine if WS or autosomal dominant SVAS is the appropriate diagnosis.

**Management**
Evaluations Following Initial Diagnosis

To establish the extent of disease and guide medical management the following evaluations are recommended [Morris et al 1999; Committee on Genetics 2001, 2002].

- Complete physical and neurologic examination
- Plotting of growth parameters on Williams syndrome growth charts
- Cardiology evaluation
  - Full clinical evaluation by a cardiologist, with measurement of blood pressure in all four limbs
  - Echocardiogram, including Doppler flow studies
- Urinary system evaluation
  - Ultrasound examination of the bladder and kidneys
  - Serum concentration of BUN and creatinine
  - Urinalysis
- Calcium determinations
  - Serum concentration of calcium or ionized calcium
  - Calcium/creatinine determination on a spot urine sample (See Sargent et al 1993 for normal values.)
- Thyroid function tests
- Ophthalmologic evaluation
- Baseline audiologic evaluation
- Genetics evaluation/consultation for individualized assessment/recommendations and discussion of clinical manifestations, natural history, and recurrence risks
- Multidisciplinary developmental evaluation, including assessment of motor, speech, language, personal-social, general cognitive, and vocational skills
- Assessment of behavior including attention, anxiety, and adaptive skills

Treatment of Manifestations

- Developmental disabilities should be addressed by early intervention programs, special education programs, and vocational training. Recommended therapies include speech/language, physical, and occupational, especially sensory integration.
  - Verbal strengths can be used to assist in learning spatial tasks.
  - Mastery of daily living skills contributes to adult well-being and should be encouraged.
Psychologic evaluation, polysomnography, and psychiatric evaluation should guide therapy for the individual. Behavioral counseling and psychotropic medication are often used to manage behavior problems, especially attention deficit disorder and anxiety, which requires pharmacologic treatment in approximately 50% [Cherniske et al 2004]. Self-calming techniques can help manage anxiety.

Surgical correction of SVAS is required in 30% [Kececioglu et al 1993, Bruno et al 2003]. Surgical treatment of mitral valve insufficiency or renal artery stenosis may be required.

Hypertension is usually treated medically.

Management of hypercalcemia involves the following:

- The diet should be adjusted with the help of a nutritionist so that the calcium intake is not higher than 100% of the recommended daily allowance (RDA). If the serum concentration of calcium remains elevated, dietary calcium should be reduced, but the serum concentration of calcium must be monitored.

- Refractory hypercalcemia may be treated with oral steroids.

- Intravenous pamidronate has been used successfully to treat infants with severe symptomatic hypercalcemia [Cagle et al 2004, Oliveri et al 2004].

- Referral to a nephrologist is recommended for treatment of nephrocalcinosis or persistent hypercalcemia and/or hypercalciuria.

Hyperopia is treated with corrective lenses; strabismus is treated with patching of one eye or surgery.

Recurrent otitis media may be treated with tympanotomy tubes.

Hypersensitivity to sounds may be treated with ear protection when increased noise levels can be predicted.

Dental care may require assistance with daily brushing and flossing. Dental cleanings should be done every three months. Orthodontic referral should be considered for treatment of malocclusion.

The treatment of feeding problems in infancy and abdominal pain in children and adults depends upon the cause (e.g., G-E reflux, hypercalcemia, hiatal hernia, diverticulitis). Infants often benefit from feeding therapy. Constipation should be aggressively managed at all ages. Severe abdominal pain may indicate diverticulitis which may occur at a young age in WS.

Prevention of Secondary Complications

- Exercise and a balanced diet to avoid insulin resistance/diabetes mellitus

- Range of motion exercises to prevent or ameliorate joint contractures

- Because of the increased risk for myocardial insufficiency in individuals with biventricular outflow tract obstruction, especially during induction of anesthesia [Horowitz et al 2002], anesthesia consultation for surgical procedures

- Awareness of the risk of myocardial insufficiency; for surgical procedures, use of a center equipped for cardiopulmonary resuscitation
Surveillance

See Table 2.

Table 2. Surveillance for Williams Syndrome

<table>
<thead>
<tr>
<th>Interval/Age</th>
<th>Test/Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annual</strong></td>
<td>• Medical evaluation</td>
</tr>
<tr>
<td></td>
<td>• Vision screening to monitor for refractive errors and strabismus</td>
</tr>
<tr>
<td></td>
<td>• Monitoring of blood pressure in both arms</td>
</tr>
<tr>
<td></td>
<td>• Measurement of calcium/creatinine ratio in a random spot urine and urinalysis</td>
</tr>
<tr>
<td><strong>Every 2 years</strong></td>
<td>• Serum concentration of calcium</td>
</tr>
<tr>
<td><strong>Every 3 years</strong></td>
<td>• Thyroid function and TSH level</td>
</tr>
<tr>
<td><strong>Every 5 years</strong></td>
<td>• Audiologic examination</td>
</tr>
<tr>
<td><strong>Every 10 years</strong></td>
<td>• Renal and bladder ultrasound examination</td>
</tr>
<tr>
<td></td>
<td>• Oral glucose tolerance test (OGTT) starting at age 30 years to evaluate for</td>
</tr>
<tr>
<td></td>
<td>diabetes mellitus 1</td>
</tr>
<tr>
<td><strong>In adults</strong></td>
<td>• Evaluation for mitral valve prolapse, aortic insufficiency, and arterial stenoses</td>
</tr>
<tr>
<td></td>
<td>• Evaluation for cataracts</td>
</tr>
</tbody>
</table>

1. If normal, OGTT should be repeated every 5 years.

Agents/Circumstances to Avoid

Children with WS should not be given multivitamins because all pediatric multivitamin preparations contain vitamin D.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

The microdeletion of the WBSCR critical region that causes WS is transmitted in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- In most instances, the parents of an individual with WS are not affected.
- In the absence of clinical findings of WS in the parents, FISH testing of the parents is not warranted.
- Recent studies have shown that in approximately 25-30% of cases, the unaffected parent in whom the chromosome deletion originated has an inversion on chromosome 7 involving the WBSCR [Osborne et al 2001, Bayes et al 2003]. Approximately 6% of the general population also have this inversion polymorphism [Hobart et al 2004]. Testing for such inversions is available on a research basis only. There have been two reports of siblings with WS; in one family the deletions occurred on the paternal chromosome that had an inversion involving the WBSCR, and in the other the deletions were likely the result of maternal germline mosaicism since no inversion involving the WBSCR was found [Scherer et al 2005].

Sibs of a proband

- The risk to the sibs of the proband depends upon the status of the parents.
- If a parent is affected, the risk is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low because few familial cases have been reported.

Offspring of a proband. Individuals who have the WBSCR critical region deletion have a 50% chance of transmitting the deletion to each child. Parent-to-child transmission has been reported [Morris et al 1993, Sadler et al 1993].

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

Prenatal Testing
For pregnancies at 50% risk of WS, **FISH** testing may be used to detect the microdeletion of the **WBSCR critical region** in fetal cells obtained by chorionic villus sampling (CVS) at about 10-12 weeks' gestation or amniocentesis usually performed at about 15-18 weeks' gestation.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Prenatal testing may also be offered to **unaffected** parents who have had a child with WS because of the **recurrence risk** associated with the possibility of **germline mosaicism** or **inversion polymorphism** or in cases of parental anxiety.

Prenatal testing for pregnancies not known to be at increased risk for WS is available, but is rarely used because most cases are a single occurrence in a family.

**Molecular Genetics**

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

Table A. Williams Syndrome: Genes and Databases

<table>
<thead>
<tr>
<th>Critical Region Gene Symbol</th>
<th>Chromosomal Locus</th>
<th>Protein Name</th>
<th>HGMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBSCR</td>
<td>Unknown</td>
<td>7q11.2</td>
<td>Elastin ElN</td>
</tr>
<tr>
<td>ELN</td>
<td>7q11.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are compiled from the following standard references: gene symbol from **HGNC**; chromosomal locus, locus name, critical region, complementation group from **OMIM**; protein name from **UniProt**. For a description of databases (Locus Specific, HGMD) linked to, click **here**.

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

- **130160** ELASTIN; ELN
- **194050** WILLIAMS-BEUREN SYNDROME; WBS
- **605678** MLX-INTERACTING PROTEIN-LIKE; MLXIPL

**Molecular Genetic Pathogenesis**

Both the **deletion** of the WBSCR that causes WS and the **duplication** of the WBSCR are mediated by the genomic structure of the region. The WBSCR is flanked by low copy repeats that predispose to nonallelic homologous **recombination**. The WS **deletion** comprises 1.55 Mb in 95% of individuals and 1.84 Mb in 5% [Bayes et al 2003]; the **deletion** is mediated by nonallelic homologous **recombination** between blocks of low copy repeats (LCRs) and the size of **deletion** reflects which blocks are involved.

Three **genes**, **GTF2I, GTF2IRD1**, and **GTF2IRD2**, have been identified in the telomeric region of the WBSCR and adjacent LCR. These members of the TFII-I **gene** family are likely to play an important role in the WS **phenotype** because they can bind at both basal and upstream regulatory sites in various promoters. These **transcription factor** proteins are involved in complex protein interactions and have a role in signal transduction. Each of the proteins in the family has **isoforms** that have different expression patterns in different tissues, raising the possibility that hemizygosity of these **genes** could contribute to many different aspects of the WS **phenotype** [Hinsley et al 2004, Jackson et al 2005].
Normal allelic variants: A number of genes have been mapped within the region:

- **ELN** (elastin). Deletion of ELN is responsible for the connective tissue abnormalities, including the cardiovascular disease in WS [Ewart, Morris, Atkinson et al 1993].

- **LIMK1** (lim kinase 1), expressed in the brain. Deletion of LIMK1 has been implicated in the abnormality of visuospatial constructive cognition in WS [Frangiskakis et al 1996, Morris et al 2003, Hoogenraad et al 2004].

- **GTF2I** (general transcription factor II, I) [OMIM 601679]. GTF2I encodes transcription factor TFII-I [Perez Jurado et al 1998, Danoff et al 2004]. Deletion mapping of "SVAS plus" families has suggested that deletion of this gene has a negative affect on IQ [Morris et al 2003].

- **STX1A** (syntaxin 1A) [OMIM 186590], involved in neurotransmitter release and insulin secretion. STX1A may have a role in diabetes in WS [Osborne et al 1997, Lam et al 2005].

- **BAZ1B** (bromodomain adjacent to a leucine zipper 1B). Because BAZ1B binds the vitamin D receptor, it has been theorized that it may have a role in hypercalcemia in WS [Meng, Lu, Li et al 1998, Kitagawa et al 2003].

- **CYLN2** (cytoplasmic linker 2). Strongly expressed in the brain, CYLN2 is postulated to be involved in cerebellar abnormalities in WS [Hoogenraad et al 1998, Hoogenraad et al 2004] [OMIM 603432].

- **GTF2IRD1**. Part of the TFII-1 transcription family, GTF2IRD1 has been implicated in the craniofacial features of WS [Osborne et al 1999, Tassabehji et al 2005].

- **NCF1** (neutrophil cytosolic factor 1). NCF1 encodes a component of the NADPH oxidase system. Hemizygosity for NCF1 is associated with a decreased risk for hypertension in WS. It is deleted in approximately 40% of individuals with WS [Del Campo et al 2006].

For the remaining genes, the relationship to the WS phenotype is unknown:

- **RFC2** (replication factor C, subunit 2) [OMIM 600404], involved in DNA elongation [Peoples et al 1996]

- **FZD9** (frizzled 9) [OMIM 601766], homologous to *Drosophila* frizzled gene [Wang et al 1997]

- **FKBP6**, homologous to FK-506 binding protein class of immunophilins [Meng, Lu, Morris et al 1998]

- **TBL2** [Meng, Lu, Li et al 1998]

- **WSbHLH** (WS-basic helix-loop-helix leucine zipper) [Meng, Lu, Li et al 1998]

- **BCL7B** [Meng, Lu, Li et al 1998]

- **CLDN4** [Paperna et al 1998] [OMIM 602909]

- **CLDN3** [Paperna et al 1998] [OMIM 602910]

- **EIF4H** [Osborne et al 1996, Richter-Cook et al 1998] [OMIM 603431]

- **LAT2** [Brdicka et al 2002]
Pathologic allelic variants: Mutations of \( ELN \) typically result in autosomal dominant SVAS [Li et al 1997]. \( ELN \) mutations have also been reported in congenital cutis laxa [Tassabehji et al 1998, Zhang et al 1999].

Normal gene product:

- The \( ELN \) gene product is the structural protein elastin, a major component of elastic fibers found in many tissues.
- Lim kinase 1 has two LIM motifs and a protein kinase domain that may be involved in intracellular signaling.
- \( RFC\ 2\) is a primer recognition protein involved in DNA elongation.
- Syntaxin 1A mediates neurotransmitter release through protein-protein interactions.
- Frizzled is a member of a family of domain receptors.
- \( GTF2I\) encodes a transcription factor, TFII-I.
- \( CYLN2\) encodes CLIP-115, a cytoplasmic linker protein.

Abnormal gene product: Unknown

Resources

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. GeneTests provides information about selected organizations and resources for the benefit of the reader; GeneTests is not responsible for information provided by other organizations.

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page.

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Published Statements and Policies Regarding Genetic Testing


Suggested Readings


Chapter Notes

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