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Williams Syndrome

Synonym: Williams-Beuren Syndrome

Colleen A Morris, MD, FACMG, FAAP[1,2]

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Summary

Clinical characteristics

Williams syndrome (WS) is characterized by developmental delay, intellectual disability (usually mild), a specific cognitive profile, unique personality characteristics, cardiovascular disease (supravalvar aortic stenosis, peripheral pulmonary stenosis, hypertension), connective tissue abnormalities, growth deficiency, endocrine abnormalities (early puberty, hypercalcemia, hypercalciuria, hypothyroidism), and distinctive facies. Hypotonia and hyperextensible joints can result in delayed attainment of motor milestones. Feeding difficulties often lead to poor weight gain in infancy.

Diagnosis/testing

The diagnosis of WS is established by identification of a heterozygous 1.5- to 1.8-Mb deletion of the Williams-Beuren syndrome critical region (WBSCR) on chromosome 7q11.23.

Management

Treatment of manifestations: Infants with feeding issues may benefit from feeding therapy. Early intervention programs, special education programs, and vocational training address developmental disabilities; programs include speech-language, physical, occupational, feeding, and sensory integration therapies as well as hippotherapy; phonics methods are recommended to teach reading. Psychological and psychiatric evaluation and treatment provide individualized behavioral counseling and medications, especially for attention-deficit/hyperactivity disorder and anxiety. Surgery may be required for supravalvar aortic or pulmonary artery stenosis, mitral valve insufficiency, and/or renal artery stenosis. Anesthesia consultation and electrocardiogram is recommended prior to sedation and surgical procedures. Orthodontic referral should be considered for malocclusion. Constipation should be aggressively managed at all ages. The lower urinary tract should be evaluated in those with febrile urinary tract infections; refer to a nephrologist for management of nephrocalcinosis, persistent hypercalcemia, and/or hypercalciuria. Range of motion exercises are recommended

Author Affiliations: 1 Professor Emerita, Department of Pediatrics, School of Medicine, University of Nevada, Reno, Reno, Nevada; Email: colleen.morris@unlv.edu. 2 Professor of Pediatrics, Kirk Kerkorian School of Medicine at UNLV, Las Vegas, Nevada; Email: colleen.morris@unlv.edu.

to prevent or ameliorate joint contractures. Treatment of hypercalcemia may include diet modification, oral corticosteroids, and/or intravenous pamidronate. Early puberty may be treated with a gonadotropin-releasing hormone agonist. Treatment of hypertension, sleep disorders, ocular manifestations, recurrent otitis media, hearing loss, dental issues, hypothyroidism, and insulin resistance does not differ from that in the general population.

Surveillance: Children younger than age two years should have serum calcium studies every four to six months. Thyroid function should be checked yearly until age three years and every two years thereafter. Medical evaluation, vision screening, hearing evaluation, measurement of blood pressure in both arms, calcium-to-creatinine ratio in spot urine, and urinalysis should be performed annually. Additional periodic evaluations for all individuals include: measurement of serum concentration of calcium every two years; cardiology evaluation for elastin arteriopathy at least annually until age five years and every two to three years thereafter; and renal and bladder ultrasound examination every ten years. Oral glucose tolerance tests in adults should start at age 20 years.

Agents/circumstances to avoid: Multivitamins for children, because all pediatric multivitamin preparations contain vitamin D.

Genetic counseling

WS is an autosomal dominant disorder. Most individuals diagnosed with WS have the disorder as the result of a *de novo* 1.5- to 1.8-Mb 7q11.23 deletion; rarely, an individual with WS has an affected parent. Recommendations for the parents of a proband with WS include obtaining a medical history to determine if signs or symptoms of WS are present. In the absence of clinical findings of WS in the parents, testing of the parents for the 7q11.23 deletion identified in the proband is not warranted. Each child of an individual with WS has a 50% chance of inheriting the 7q11.23 deletion and being affected. Once the WS-causing 1.5- to 1.8-Mb 7q11.23 deletion has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Williams syndrome (WS) **should be suspected** in individuals with the following findings:

- **Intellectual disability** affects most individuals and is typically mild.
- **Specific cognitive profile** includes strengths in verbal short-term memory and language and extreme weakness in visuospatial construction.
- **Unique personality** includes overfriendliness, empathy, generalized anxiety, specific phobias, and attention-deficit/hyperactivity disorder.
- **Cardiovascular disease (elastin arteriopathy).** Supravalvar aortic stenosis is the most common. Peripheral pulmonic stenosis is common in infancy. Any artery may be narrowed.
- **Distinctive facies.** Broad forehead, bitemporal narrowing, periorbital fullness, a stellate/lacy iris pattern (see Figure 1), strabismus, short nose, broad nasal tip, malar flattening, long philtrum, thick vermilion of the upper and lower lips, wide mouth, malocclusion, small jaw, and large ear lobes are observed at all ages (see Figure 2). Young children have epicanthal folds, full cheeks, and small, widely spaced teeth (see Figure 3); adults have a long face and neck and sloping shoulders (see Figure 4).
- **Connective tissue abnormalities** include hoarse voice, inguinal/umbilical hernia, bowel/bladder diverticulae, rectal prolapse, joint limitation or laxity, and soft, lax skin.
- **Growth abnormalities** include prenatal growth deficiency, postnatal poor weight gain, and decreased linear growth.

- **Endocrine abnormalities** include early puberty, hypercalcemia, hypercalciuria, hypothyroidism, and diabetes mellitus.

Note: See the National Human Genome Research Institute (NHGRI) Atlas of Human Malformation Syndromes (scroll to **ATLAS IMAGES**) for photographs of individuals with WS from diverse ethnic backgrounds.

Establishing the Diagnosis

The diagnosis of WS **is established** by identification of a heterozygous 1.5-to 1.8-Mb deletion at chromosome 7q11.23. For this *GeneReview*, WS is defined as the presence of a recurrent 1.5- to 1.8-Mb deletion at the approximate position of chr7:73,330,452-74,728,172 in the reference genome (NCBI Build 38).

Note: The phenotype of significantly larger or smaller deletions within this region may be clinically distinct from WS (see Genetically Related Disorders).

Although several genes of interest (e.g., *ELN*) are within the 1.5- to 1.8-Mb recurrent deletion, no single gene in which pathogenic variants are causative of WS has been identified (see Molecular Genetics for genes of interest in the deleted region).

Genomic testing methods that determine the copy number of sequences can include **chromosomal microarray (CMA)** or **targeted deletion analysis** by **fluorescence in situ hybridization (FISH).** Note: The 7q11.23 recurrent deletion cannot be identified by routine analysis of G-banded chromosomes or other conventional cytogenetic banding techniques.

- **Chromosomal microarray (CMA)** using oligonucleotide arrays or SNP genotyping arrays can detect the recurrent deletion in a proband. The ability to size the deletion depends on the type of microarray used and the density of probes in the 7q11.23 region.

  Note: (1) Most individuals with WS are identified by CMA performed in the context of evaluation for developmental delay, intellectual disability, or autism spectrum disorders. (2) The recurrent deletion was detected by early arrays (e.g., BAC arrays).

- **Targeted deletion analysis.** A FISH probe targeted to the 7q11.23 region can be reliably used for diagnosis in situations where CMA is not available. FISH analysis may be used to test at-risk relatives of a proband known to have WS.

  Note: (1) Targeted deletion testing by FISH is not appropriate for the relative of an individual suspected of having WS in whom a deletion was not detected by FISH or by CMA designed to target 7q11.23. By definition, such individuals do not have WS. (2) It is not possible to routinely size the deletion by use of FISH.

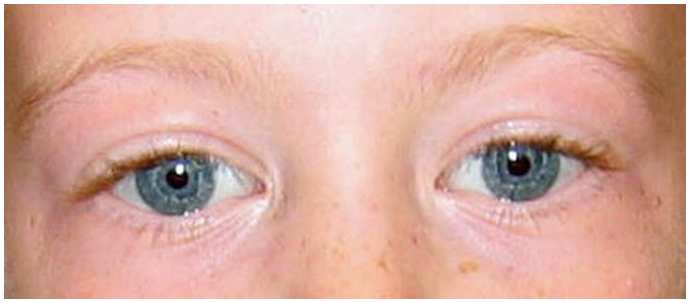

Figure 1. Note the stellate iris pattern in an individual with Williams syndrome

Figure 2. A broad forehead, bitemporal narrowing, periorbital fullness, strabismus, short nose, broad nasal tip, malar flattening, long philtrum, thick vermilion of the upper and lower lips, wide mouth, malocclusion, small jaw, and large earlobes are observed at all ages and in all ethnic groups. The ages of the children shown here are as follows:

A and B. 3 years

C. 4 years

D. 7 years

E. 8 years

F, G, and H. 12 years

I and J. 16 years

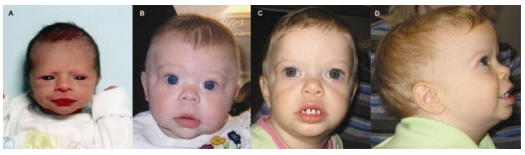

Figure 3. Young children with Williams syndrome typically have epicanthal folds, full cheeks, and small, widely spaced teeth, as seen in these children at the following ages:

A. Newborn

B. 10 months

C and D. 21 months

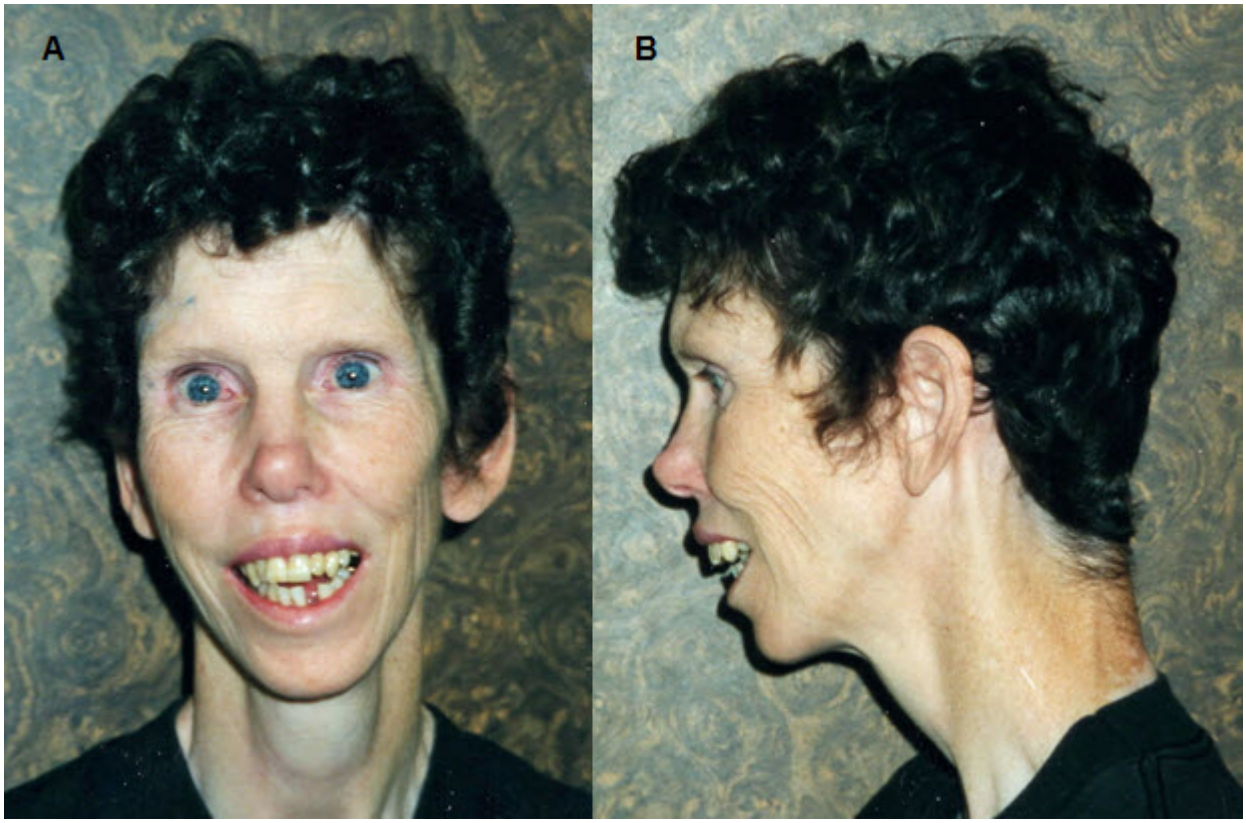

Figure 4. Adults typically have a long face and neck, accentuated by sloping shoulders, resulting in a gaunt appearance, as seen in this affected individual, age 43 years.

Table 1. Genomic Testing Used in Williams Syndrome

Deletion [1]	Method	Sensitivity	
		Proband	At-risk family members
1.5- to 1.8-Mb heterozygous deletion at 7q11.23 ISCN: seq[GRCh38] del(7)(q11.23) chr7:73,330,452-74,728,172 [2] ISCA-37392	CMA [3]	100%	100%
	FISH	100%	100% [4]

1. See Molecular Genetics for details of the deletion and genes of interest.
2. Standardized ISCN annotation and interpretation for genomic variants from the Clinical Genome Resource (ClinGen) project (formerly the International Standards for Cytogenomic Arrays [ISCA] Consortium). Genomic coordinates represent the minimum deletion size associated with the 7q11.23 recurrent deletion as designated by ClinGen. Deletion coordinates may vary slightly based on array design used by the testing laboratory. Note: The size of the deletion as calculated from these genomic positions may differ from the expected deletion size due to the presence of segmental duplications near breakpoints. The phenotype of significantly larger or smaller deletions within this region may be clinically distinct from the recurrent 7q11.23 deletion (see Genetically Related Disorders).
3. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use target the 7q11.23 region.
4. FISH is not appropriate as a diagnostic method for the relative of an affected individual in whom Williams syndrome was not detected by FISH or by CMA designed to target this region.

Clinical Characteristics

Clinical Description

Williams syndrome (WS) is a multisystem disorder characterized by cardiovascular disease (elastin arteriopathy, most often manifesting as supravalvar aortic stenosis), developmental delay, usually mild intellectual disability, a specific cognitive profile, unique personality characteristics, connective tissue abnormalities, growth abnormalities, other endocrine manifestations, and distinctive facies. Additional manifestations can include sleep problems, ocular issues, hearing loss, dental problems, gastrointestinal difficulties, urinary tract abnormalities, and musculoskeletal issues.

Table 2. Williams Syndrome: Frequency of Select Features

System	Feature	% of Persons w/Feature	Comment
Neurodevelopment	Developmental delay	100%	Average age for walking & talking is 21 mos.
	Hypotonia	80%	
	Intellectual disability	75%	Typically mild
	Characteristic cognitive profile	95%	Severe impairment of visuospatial construction, relative strength in language
Neurobehavioral	Unique personality	95%	Overfriendliness, difficulty w/emotional regulation
	Anxiety (non-social)	80%	Specific phobia most common
	ADHD	65%	
	Sleep disorders	65%	
	Autism spectrum disorder	10%-20%	
Cardiovascular	Any arterial stenosis	80%	Elastin arteriopathy
	SVAS	75%	
	PPS	40%-60%	Typically improves w/time
	Hypertension	50%	Renal artery stenosis may contribute
	Mitral valve prolapse	15%	
	QTc prolongation	13%	
Ocular/visual	Esotropia	50%	
	Hyperopia	60%	
Auditory	Recurrent otitis media	50%	
	Hypersensitivity to sound	90%	
	Sensorineural hearing loss	>60%	Present in >90% of adults
Dental	Microdontia	95%	
	Malocclusion	85%	

Table 2. continued from previous page.

System	Feature	% of Persons w/Feature	Comment
Gastrointestinal	Feeding difficulties	70%	
	Constipation	50%	
	Umbilical hernia	50%	
	Inguinal hernia	40%	
	Colon diverticula	30%	
	Rectal prolapse	15%	
Urinary tract	Urinary frequency	70%	
	Enuresis	50%	
	Bladder diverticula	50%	
Musculoskeletal	Joint hypermobility	90%	Most common in young children
	Joint contractures	50%	
	Scoliosis	20%-35%	
Integument / connective tissue	Hoarse voice	90%	
	Soft, lax skin	90%	
Endocrine	Short stature	50%	Mean adult height is <3rd centile
	Early puberty	50%	
	Hypercalcemia	20%-40%	Clinically significant hypercalcemia typically occurs at age <2 yrs
	Hypercalciuria	30%	Nephrocalcinosis in 5%
	Hypothyroidism	10%	Subclinical in 30%
	Diabetes mellitus	20%	More common in adults
Craniofacial	Characteristic facial features	100%	See Figures 1, 2, 3, and 4.
	Microcephaly	30%	

ADHD = attention-deficit/hyperactivity disorder; PPS = peripheral pulmonic stenosis; SVAS = supravalvar aortic stenosis

Infancy. Infants with WS are often born post-term, and 50% of infants are small for gestational age [Li et al 2022]. Feeding difficulties leading to poor weight gain are common, including gastroesophageal reflux, disordered suck and swallow, textural aversion, and vomiting. Prolonged colic (lasting longer than four months) may be related to gastroesophageal reflux, chronic constipation, and/or idiopathic hypercalcemia.

Developmental delay. Infants with WS are hypotonic and typically have hyperextensible joints, resulting in delayed attainment of motor milestones [Morris & Mervis 2021]. Walking usually occurs by age 24 months. Speech is also delayed but later becomes a relative strength [Kozel et al 2021]. Fine motor difficulties are present at all ages.

Cognitive abilities. Intellectual disability, 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 [Mervis & Greiner de Magalhães 2022]. No difference in IQ between males and females is reported, and IQ is stable throughout childhood [Mervis et al 2012].

Academically, individuals with WS perform relatively well in reading, and adults may read at a high school level, though the range of achievement is wide. Reading skills correlate with method of reading instruction rather than IQ, with the highest reading skills following systemic phonics instruction [Mervis & Greiner de Magalhães 2022]. Difficulty with writing, drawing, and mathematics is significant, although many adults with WS are able to perform simple addition.

Unique personality/behavior. The characteristic personality profile of WS includes overfriendliness, social disinhibition, excessive empathy, attention problems, and non-social anxiety. Other common behavior problems include difficulty with sensory modulation/processing, emotional regulation, and perseveration. Some individuals have overlapping symptoms with autism spectrum disorder, such as restricted interests and repetitive behavior. Children with WS who meet diagnostic criteria for autism spectrum disorder (ASD; 10%-20%) fit in the active-but-odd subtype rather than the aloof subtype of ASD [Klein-Tasman et al 2018]. In children, attention-deficit/hyperactivity disorder occurs in 65% of individuals and anxiety disorder in 57% (usually specific phobias) [Leyfer et al 2006]. Anxiety is common across the life span; longitudinal studies of anxiety indicate a prevalence of 80% [Woodruff-Borden et al 2010]. Pharmacotherapy for psychiatric disorders in WS should take into account the medical comorbidities associated with WS [Thom et al 2021]. For instance, use of stimulants (which can increase blood pressure and heart rate) to treat ADHD should be discussed with the individual's cardiologist; atomoxetine is a non-stimulant alternative [Thom et al 2021].

Adaptive behavior is less than expected for IQ in both children and adults [Howlin & Udwin 2006, Mervis & Pitts 2015], and adversely affects the ability of adults with WS to function independently (less than 10% live independently). There is typically a relative strength in socialization and communication skills, with significant weakness in motor skills and daily living skills. Executive function deficits occur in 70% of children and adolescents with WS. Difficulties with behavioral and emotional regulation are associated with behavior issues and poor adaptive behavior; difficulty with inhibition is associated with attention problems; and difficulty with flexibility in shifting focus is associated with anxiety [Greiner de Magalhães et al 2022].

Sleep disorders occur in 65% of affected individuals and include increased sleep latency and decreased sleep efficiency [Goldman et al 2009, Mason et al 2011]. Abnormal or absent nocturnal melatonin peak has been documented [Sniecinska-Cooper et al 2015, Santoro et al 2016]; melatonin treatment may be helpful [Martens et al 2017, Morris & Mervis 2021]. Sleep-related breathing disorder (reported in 15%) and excessive daytime sleepiness (reported in 30%) were associated with more externalizing behavior problems in toddlers with WS at age two years [Greiner de Magalhães et al 2020].

Cardiovascular disease occurs in 80% of individuals with WS [Collins 2018, Honjo et al 2022]. Elastin arteriopathy is the major cause of morbidity and mortality. Any artery may be narrowed, but supravalvar aortic stenosis (SVAS) is most common and may worsen over time, especially in the first five years of life [Collins et al 2010b]. SVAS can be either a discrete hourglass stenosis or diffuse aortic stenosis. If untreated, the resultant increase in arterial resistance leads to elevated left heart pressure, cardiac hypertrophy, and cardiac failure. Progression is more likely if the stenosis is moderate or severe and presents in infancy or early childhood. Mild SVAS is less likely to progress. Approximately one third of children with SVAS will require surgical correction.

Peripheral pulmonic stenosis (PPS) is common in infancy but usually improves over time without intervention. However, 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 [Pham et al 2009]. The overall 30-year survival rate for children undergoing interventions for obstructive lesions is 90% in North America [Zinyandu et al 2023]. Individuals with either isolated left heart obstructive lesions or isolated right heart obstructive lesions have better survival rates than those with combined disease (96% vs 83%). In-hospital mortality was 2.5%, and 9% required reoperation (mostly for recurrent SVAS) [Zinyandu et al 2023].

Coronary artery stenosis has been implicated as a cause of sudden death in individuals with WS [Bird et al 1996]. Coronary artery stenosis or dilatation are found in 10%-30% of individuals with WS, and coronary blood flow may be restricted at the sinuses of Valsalva in the setting of narrowed sinotubular junction [Brown et al 2018]. The incidence of sudden death in one cohort of 293 individuals with WS was one in 1,000 patient years, which is 25 to 100 times higher than the age-matched population [Wessel et al 2004].

The prevalence of hypertension in individuals with WS is 40%-50%. Hypertension may present at any age [Bouchireb et al 2010] and may be secondary to renal artery stenosis in some instances [Honjo et al 2022]. Increased vascular stiffness has been documented in individuals with WS and responds to antihypertensive medication [Kozel et al 2014].

Mitral valve prolapse and aortic insufficiency have been reported in adults [Morris et al 1990, Collins et al 2010a].

Prolonged QTc has been reported in 13.6% of individuals with WS; screening for repolarization abnormalities is recommended [Collins et al 2010a, Brink et al 2022].

Anesthesia and sedation are associated with an increased risk for adverse events, including cardiac arrest, in individuals with WS [Olsen et al 2014]. Sedation and anesthesia risk assessment and management guidelines have been developed [Schmidt et al 2021, Staudt & Eagle 2021] with the goal of maintaining intravascular volume and a stable blood pressure to optimize coronary perfusion [Schmidt et al 2021]. In centers using these strategies specifically for individuals with WS, morbidity and mortality is decreased. Brown et al [2018] reported no adverse events in 90% of individuals undergoing cardiac procedures, and no adverse events in 95% of individuals undergoing noncardiac procedures. Schmidt et al [2021] compared a historical group with an intervention group after new anesthesia guidelines were adopted for WS and found that incidence of adverse cardiac events in the intervention group was 2% compared to 6% in the historical group.

Stenosis of additional arteries has been reported. Neurovascular abnormalities are rarely reported but may result in stroke [Cherniske et al 2004]. Stenosis of the mesenteric arteries may contribute to abdominal pain.

Ocular manifestations. Lacrimal duct obstruction, hyperopia (67%), and esotropia (50%) are common in individuals with WS [Weber et al 2014]. Cataracts have been reported in adults [Cherniske et al 2004].

Ears and hearing. 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 lower than controls [Gothelf et al 2006]. Many affected individuals report specific phobias for certain sounds [Levitin et al 2005]. Hyperacusis occurs in 35% and is associated with absence of contralateral acoustic reflexes [Silva et al 2021].

Progressive sensorineural hearing loss has been observed; mild-to-moderate hearing loss is detected in 63% of children and 92% of adults [Gothelf et al 2006, Marler et al 2010]. Mild-to-moderate high-frequency sensorineural hearing loss is common in adults, as is excessive buildup of ear wax [Cherniske et al 2004].

Dental findings include generalized diastemas (70%), hypodontia (50%), microdontia, enamel hypoplasia, and malocclusion (angle class II and III) [Castro et al 2019].

Gastrointestinal manifestations. Individuals with WS have sensory defensiveness; difficulty with food textures leads to problems in transitioning from breast milk or formula to solid foods in infancy.

Chronic abdominal pain is common in children and adults with WS; possible causes include gastroesophageal reflux, hiatal hernia, peptic ulcer disease, cholelithiasis, diverticulitis, ischemic bowel disease, chronic constipation, and somatization of anxiety. The prevalence of diverticulitis is increased in adolescents [Stagi et al 2010] and adults with WS [Partsch et al 2005]. Complications of constipation may include rectal prolapse, hemorrhoids, or intestinal perforation.

Hypercalcemia may contribute to irritability, vomiting, constipation, and muscle cramps. Hypercalcemia is more common in infancy but may recur in adults [Morris et al 1990, Pober et al 1993].

Urinary tract abnormalities. Urinary frequency and enuresis are common in children with WS. Renal artery stenosis is found in 50% of individuals with WS, structural abnormalities of the urinary tract in 10%, bladder diverticulae in 50%, and nephrocalcinosis in fewer than 5% [Pober et al 1993, Pankau et al 1996, Sforzini et al 2002, Sammour et al 2006, Sammour et al 2014]. Bladder capacity is reduced, and detrusor overactivity is observed in 60% of affected individuals [Sammour et al 2006]. Average age of daytime urinary continence is four years; nocturnal continence occurs in 50% by age ten years. Nocturnal enuresis occurs in an estimated 3% of adults [von Gontard et al 2016].

Musculoskeletal and additional neurologic manifestations. 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, Copes et al 2016]. Scoliosis is common [Damasceno et al 2014]. Ten percent of individuals with WS have radioulnar synostosis [Morris & Carey 1990]. Fine motor function is impaired, leading to difficulty with tool use and handwriting at all ages. Cerebellar signs in adults include ataxia, dysmetria, and tremor [Pober & Morris 2007].

Neuroimaging. Reduced brain size, reduced gray matter volume (especially in the parietal and occipital regions), and increased gyral complexity are seen on brain MRI [Jackowski et al 2009, Eisenberg et al 2010]. Reduced posterior fossa size coupled with preserved cerebellar size may contribute to Chiari I malformation found in some affected individuals [Pober & Filiano 1995, Mercuri et al 1997].

Integument and additional connective tissue manifestations. Most individuals have a hoarse or low-pitched voice; vocal cord abnormalities secondary to elastin deficiency are likely causative [Vaux et al 2003]. Soft, lax skin is typical. The hair grays prematurely [Morris et al 1988].

Growth deficiency. Poor weight gain 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. Individuals with WS are shorter than predicted by midparental height [Levy-Shraga et al 2018]. The mean adult height is below the third centile. Specific growth curves for WS are available [Saul et al 1988, Martin et al 2007, Morris et al 2020]. For a systematic review of growth studies in WS cohorts, see de Sousa Lima Strafacci et al [2020]. Obesity or overweight is seen in 50% of older children and adults [Cherniske et al 2004, Stanley et al 2021]. A lipedema phenotype of the lower extremities in seen in 25% of adults [Shaikh et al 2018].

Puberty may occur early, and central precocious puberty is present in 18% of individuals with WS [Partsch et al 2002, Kim et al 2016]. Hormonal suppression with gonadotropin-releasing hormone agonist is well tolerated by girls with either early or precocious puberty, and treated girls are taller than WS controls [Spielmann et al 2015].

Hypercalcemia is most often symptomatic (irritability, vomiting, constipation) in the first two years of life [Martin et al 1984, Morris et al 1988, Kim et al 2016]. Hypercalcemia is associated with dehydration, hypercalciuria, and nephrocalcinosis. Compared to controls, higher median serum calcium levels are found in all age groups [Sindhar et al 2016]. The etiology of hypercalcemia in WS is unknown [Stagi et al 2016].

Additional endocrine problems. Endocrine abnormalities include hypothyroidism, including subclinical hypothyroidism (thyroid-stimulating hormone elevation with normal T3/T4 levels) [Palacios-Verdú et al 2015]. Prevalence of impaired glucose tolerance is 42%, and incidence of diabetes mellitus is increased in adolescents and adults with WS [Stanley et al 2021]. Low bone mineral density has been reported in 50% of adults with WS [Cherniske et al 2004] and is associated with low serum phosphate [Palmieri et al 2019].

Distinctive facial features including broad forehead, bitemporal narrowing, periorbital fullness, a stellate/lacy iris pattern (see Figure 1), strabismus, short nose, broad nasal tip, malar flattening, long philtrum, thick vermilion of the upper and lower lips, wide mouth, malocclusion, small jaw, and large ear lobes are observed at all ages (see Figure 2). Young children have epicanthal folds, full cheeks, and small, widely spaced teeth (see Figure 3), while adults typically have a long face and neck, accentuated by sloping shoulders (see Figure 4).

Genotype-Phenotype Correlations

The 7q11.23 recurrent deletions of the Williams-Beuren syndrome critical region (WBSCR) comprise either 1.55 Mb (90%-95% of individuals with WS) or 1.84 Mb (5%-10% of individuals with WS) [Palacios-Verdú et al 2015].

- *ELN* deletion results in elastin arteriopathy.
- Hypertension is less prevalent in individuals with WS whose deletion includes *NCF1*, 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 large deletions (>2-4 Mb) that include the WBSCR than in individuals with a typical 1.5- to 1.8-Mb WBSCR deletion [Stock et al 2003, Marshall et al 2008, Ramocki et al 2010, Lugo et al 2020].

Deletions within the WBSCR smaller than the recurrent deletions associated with WS are rare and are associated with a variable phenotype. Genotype-phenotype correlations are limited for genes other than *ELN* [Kozel et al 2021, Serrano-Juárez et al 2022].

- Individuals with partial WBSCR deletions that include the usual telomeric breakpoint (including *GTF2I*) have classic manifestations of WS, including intellectual disability [Botta et al 1999, Heller et al 2003]. Individuals with deletions of the WBSCR that include distal genes in the region (especially *GTF2IRD1* and *GTF2I*) are more likely to have intellectual disability and facial features characteristic of WS [Alesi et al 2021]. One individual with a partial deletion of the WBSCR that included *GTF2I* had borderline adaptive and language development [Zhou et al 2022].
- Individuals with partial deletions that include *ELN* have SVAS.
- Individuals with partial WBSCR deletions that include *ELN* but do not include deletion of *GTF2I* do not have intellectual disability but often demonstrate the WS cognitive profile [Morris et al 2003]. In two families, deletion of *ELN* and *LIMK1* was associated with the WS cognitive profile but not with intellectual disability or other characteristics of WS [Frangiskakis et al 1996]. Another family with a similar deletion did not have the WS cognitive profile [Tassabehji et al 2005].

Deletions within the WBSCR may be of maternal or paternal origin [Ewart et al 1993, Urbán 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%.

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" and cardiologists reported "supravalvular aortic stenosis syndrome."

Early reports also noted dysmorphic facial features that were thought to resemble elves of legend: 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 US and Williams-Beuren syndrome in Europe.

Prevalence

A study of WS in Norway reported a prevalence of 1:7,500 [Strømme et al 2002].

Genetically Related (Allelic) Disorders

Atypical deletions involving the WBSCR

- **Larger deletions** that include the WBSCR typically result in a more severe phenotype. Individuals whose deletion includes *AUTS2* are more likely to have microcephaly [Lugo et al 2020]. Individuals with larger deletions including *YWHAG* and/or *MAGI2* may have a seizure disorder [Marshall et al 2008, Ramocki et al 2010]. Individuals with deletions including *HIP1* are reported to have severe intellectual disability and autism [Stock et al 2003, Serrano-Juárez et al 2022].
- **Smaller deletions.** In individuals with a smaller deletion including *ELN*, elastin arteriopathy is observed. Deletion of *LIMK1* is associated with difficulty with visuospatial construction, part of the WS cognitive profile [Morris et al 2003]. Deletions that include *GTF2I* and *GTF2IRD1* are associated with the cognitive and behavioral features of the WS phenotype. *GTF2I* deletion is associated with intellectual disability, and *GTF2IRD1* deletion is associated with the behavioral phenotype.

7q11.23 duplication syndrome is caused a recurrent 1.5- to 1.8-Mb heterozygous duplication of the WBSCR. The most significant clinical finding is severe impairment in expressive language, including a phonologic disorder, in contrast to the relative strength in language exhibited by individuals with Williams syndrome. Other characteristic features are delayed motor and social skills in early childhood; neurologic abnormalities; behavior issues including anxiety disorders (especially social anxiety disorder [social phobia]), selective mutism, attention-deficit/hyperactivity disorder, oppositional disorders, physical aggression, and autism spectrum disorder; and intellectual disability in some individuals. Distinctive facial features are common. Cardiovascular disease includes dilatation of the ascending aorta.

Disorders associated with germline intragenic *ELN*, *GTF2IRD1*, and *NCF1* pathogenic variants are summarized in Table 3.

Table 3. Disorders Associated with Germline Intragenic *ELN*, *GTF2IRD1*, and *NCF1* Pathogenic Variants

Gene	Disorder	Comment
ELN	Autosomal dominant cutis laxa type 1 (ADCL1) (OMIM 123700)	Generalized cutis laxa of variable severity. Aortic root dilatation & emphysema may occur. (See *LTBP4*-Related Cutis Laxa.)
	Autosomal dominant supravalvuar aortic stenosis (SVAS) (OMIM 185500)	Persons w/SVAS should be evaluated to determine if WS or autosomal dominant SVAS is the appropriate diagnosis. Persons w/autosomal dominant SVAS typically have only connective tissue abnormalities, & thus do not have WS.
GTF2IRD1	*GTF2IRD1*-related neurodevelopmental disorder	Reported in 1 family to date. Biallelic *GTF2IRD1* variants were reported in 2 brothers w/autism, severe neurodevelopmental delay (incl seizures), & dysmorphic facial features (different from those in WS); heterozygous parents & sibs did not exhibit signs or symptoms of the presumably autosomal recessive syndrome [Cummings & Starr 2023].
NCF1	Chronic granulomatous disease (CGD)	Biallelic pathogenic variants cause autosomal recessive CGD, a primary immunodeficiency disorder of phagocytes resulting from impaired killing of bacteria & fungi.

WS = Williams syndrome

Differential Diagnosis

Williams syndrome (WS) should be distinguished from other chromosomal (see Table 4a) and single-gene disorders (see Table 4b) characterized by developmental delay, attention-deficit/hyperactivity disorder, short stature, distinctive facies, and/or congenital heart disease.

Table 4a. Selected Chromosomal Disorders in the Differential Diagnosis of Williams Syndrome

Genetic Mechanism	Disorder	Clinical Characteristics	Comment
2.54-Mb heterozygous deletion at 22q11.2	22q11.2 deletion syndrome	Wide range of highly variable features. Major clinical manifestations incl CHD (particularly conotruncal malformations), palatal abnormalities, immune deficiency, characteristic facial features (e.g., hooded eyelids, ear anomalies, prominent nasal bridge, bulbous nose, asymmetric crying facies), learning difficulties, & hearing loss.	CHD in WS is typically SVAS.
17p11.2 deletion or intragenic *RAI1* pathogenic variant	Smith-Magenis syndrome (SMS)	Distinctive physical features, DD, ID, behavioral abnormalities, sleep disturbance, & childhood-onset abdominal obesity. Behavioral phenotype, incl significant sleep disturbance, stereotypies, & maladaptive & self-injurious behaviors, is generally not recognized until age ≥18 mos & continues to change until adulthood. Significant anxiety & problems w/executive functioning are common.	Phenotypic overlap between SMS & WS incl short stature, hoarse voice, & CHD, w/SVAS being rarely reported in SMS but common in WS. The facial gestalt is quite different.

CHD = congenital heart disease; DD = developmental delay; ID = intellectual disability; SVAS = supravalvar aortic stenosis

Table 4b. Selected Single-Gene Disorders with Short Stature and Congenital Heart Disease in the Differential Diagnosis of Williams Syndrome

Gene(s)	Disorder	MOI	Clinical Characteristics	Comment
BRAF *KRAS* *LZTR1* *MAP2K1* *MRAS* *NRAS* *PTPN11* *RAF1* *RASA2* *RIT1* *RRAS2* *SOS1* *SOS2*	Noonan syndrome (NS)	AD AR [1]	Characteristic facies, short stature, DD of variable degree, & CHD (most commonly pulmonary valve stenosis, often w/dysplasia). Hypertrophic cardiomyopathy may be present at birth or develop in infancy or childhood.	The facial features of NS & WS are similar in infancy but are more easily distinguished in older children & adults. CHD in WS is typically supravalvar or peripheral pulmonic stenosis & in NS is commonly valvar stenosis.

Table 4b. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Characteristics	Comment
KDM6A *KMT2D*	Kabuki syndrome (KS)	AD XL [2]	Typical facial features, minor skeletal anomalies, persistence of fetal fingertip pads, mild-to-moderate ID, & postnatal growth deficiency. ~70% of affected persons have CHD (most commonly left-sided obstructive lesions, esp coarctation of aorta).	KS is assoc w/long palpebral fissures w/ everted lower lid, leading to different facial gestalt than WS. The left-sided cardiac lesion in KS is typically aortic coarctation, while SVAS is most common CHD in WS.

AD = autosomal dominant; AR = autosomal recessive; CHD = congenital heart disease; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; SVAS = supravalvar aortic stenosis; WS = Williams syndrome; XL = X-linked
1. Noonan syndrome (NS) is most often inherited in an autosomal dominant manner. NS caused by pathogenic variants in *LZTR1* can be inherited in either an autosomal dominant or an autosomal recessive manner.
2. KMT2D-related Kabuki syndrome is inherited in an autosomal dominant manner; *KDM6A*-related Kabuki syndrome is inherited in an X-linked manner.

Fetal alcohol spectrum disorders associated with characteristic facial features (short palpebral fissures, flat philtrum, thin vermilion of the upper lip), growth deficiency, cognitive impairment, and disinhibited behavior can also be considered in the differential diagnosis of WS. Septal defects are the most common congenital heart defect in infants with fetal alcohol spectrum disorders, whereas supravalvar aortic stenosis is most common in WS.

Management

Clinical practice guidelines for Williams syndrome (WS) have been published [Morris et al 2020].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with WS, and to guide medical management, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to diagnosis) are recommended [Morris et al 2020].

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Williams Syndrome

System/Concern	Evaluation	Comment
General	• Plotting of growth parameters on WS growth charts • Complete physical & neurologic exam	WS growth charts are available. [1]
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl attention, anxiety, adaptive skills, & sleep disturbances
Cardiovascular	• Eval by cardiologist w/experience in WS • Measurement of blood pressure in all four limbs • Echocardiogram, incl doppler flow studies • Electrocardiogram	Additional cardiovascular imaging studies (CT, MRA, or cardiac catheterization) may be required in persons w/ diminished pulses, bruits, or signs of diffuse thoracic aortic stenosis.
Eyes	Ophthalmologic eval	To assess for reduced vision, abnormal ocular movement, best corrected visual acuity, refractive errors, strabismus, & lacrimal duct stenosis

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Hearing	Audiologic eval	To assess for hearing loss
Dental	Dental eval	To assess for microdontia, malocclusion, & missing teeth
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	To incl eval for nutritional status, gastroesophageal reflux, constipation, hernias, & rectal prolapse
Genitourinary	• Ultrasound exam of bladder & kidneys • Serum concentration of BUN & creatinine • Urinalysis	
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures & kyphoscoliosis • Mobility, ADL • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Hypercalcemia	• Serum concentration of calcium or ionized calcium • Urine calcium-to-creatinine on spot urine sample	See Sargent et al [1993] for normal values.
Endocrine	Thyroid function tests	
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of WS to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

= activities of daily living; BUN = blood urea nitrogen; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; WS = Williams syndrome

1. Martin et al [2007], Morris et al [2020]

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

Treatment of Manifestations

Table 6. Treatment of Manifestations in Individuals with Williams Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Poor weight gain	Feeding therapy	The treatment of feeding issues in infancy & childhood depends on the cause (e.g., disordered suck & swallow, textural aversion, gastroesophageal reflux, hypercalcemia).

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	• Developmental disabilities should be addressed by early intervention programs, special education programs, & vocational training. • Recommended therapies include speech-language therapy, PT, & OT. • Consider hippotherapy (use of equine movement during speech-language therapy, PT, &/or OT). • Verbal strengths can be used to assist in learning spatial tasks. • Phonics methods are recommended to teach reading. [1] • Mastery of ADL contributes to adult well-being & should be encouraged.	See also Developmental Delay / Intellectual Disability Management Issues.
Behavioral & psychiatric manifestations	• Treatment per psychologist &/or psychiatrist • Behavior in young children may be addressed using techniques based on applied behavior analysis. [1] • Behavioral counseling & psychotropic medication are often used to manage behavior issues, esp ADHD & anxiety, which require pharmacologic treatment in ~50%. [2, 3] • Self-calming techniques can help manage anxiety.	See also Developmental Delay / Intellectual Disability Management Issues.
Sleep disturbance	Mgmt per sleep specialist	Consider melatonin therapy. [4]
Cardiovascular	Mgmt of SVAS & other cardiovascular disease per cardiologist	• Surgical correction of SVAS is performed in 30%. • Surgical treatment of mitral valve insufficiency or renal artery stenosis may be required.
	Hypertension is usually treated medically. [5]	
Risk of adverse events w/ sedation or anesthesia	• Anesthesia consultation for surgical procedures • Electrocardiogram prior to surgery • Use of a center equipped for cardiopulmonary resuscitation	• Guidelines for sedation & anesthesia risk assessment & anesthetic mgmt for WS have been published. [6] • There is ↑ risk for myocardial insufficiency & cardiac arrest in persons w/biventricular outflow tract obstruction, esp during induction of anesthesia.
Eyes	• Hyperopia is treated w/corrective lenses. • Strabismus is treated w/patching of 1 eye or surgery. • Standard treatments for lacrimal duct abnormalities	
Hearing	• Recurrent otitis media may be treated w/ tympanotomy tubes. • Hypersensitivity to sounds may be treated w/ear protection when ↑ noise levels can be predicted. • Hearing aids may be helpful per otolaryngologist.	Community hearing services through early intervention or school district
Dental issues	• Dental care may require assistance w/daily brushing & flossing. • Dental cleaning frequency should be ↑ to every 4 mos in adolescents & adults. • Orthodontic referral for treatment of malocclusion.	

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Gastrointestinal manifestations	Constipation treatment usually incl dietary ↑ in water & fiber followed by osmotic laxative treatment.	Constipation must be aggressively managed at all ages due to ↑ risk for early-onset diverticulosis/diverticulitis.
	The treatment of abdominal pain in children & adults depends on cause (e.g., gastroesophageal reflux, hypercalcemia, hiatal hernia, &/or diverticulitis).	Severe abdominal pain may indicate diverticulitis &/or intestinal perforation, which may occur at a young age in WS.
Urinary tract abnormalities	• Investigation of lower urinary tract (voiding cystourethrogram) in those w/febrile urinary tract infections to direct treatment • Mgmt of nephrocalcinosis, persistent hypercalcemia, &/or hypercalciuria per nephrologist	
Musculoskeletal manifestations	• Range of motion exercises to prevent or ameliorate joint contractures • Orthopedics / physical medicine & rehab / PT & OT as needed for contractures & kyphoscoliosis	
Hypercalcemia	• Avoid vitamin supplements w/vitamin D, esp in young children. • Assess hydration status & ↑ water intake as indicated. • Adjust diet w/nutritionist to maintain calcium intake no higher than 100% of RDI. [7] If serum calcium remains ↑, dietary calcium should be ↓, but serum calcium must be monitored. • Parents should be counseled not to restrict dietary intake of calcium w/o medical supervision. • Refractory hypercalcemia may be treated w/oral steroids. • Referral to endocrinologist &/or nephrologist for treatment of persistent hypercalcemia, hypercalciuria, &/or nephrocalcinosis	• If vitamin D deficiency is suspected, check vitamin D levels prior to initiating therapy, & monitor calcium levels during treatment. Absorption of calcium from the gut is ↑ in WS (cause unknown) & vitamin D promotes calcium absorption. • Intravenous pamidronate has been used successfully to treat infants w/ severe symptomatic hypercalcemia. [8]
Early puberty	Treatment w/gonadotropin-releasing hormone agonist [8]	
Hypothyroidism	Oral thyroxine therapy	Subclinical hypothyroidism typically is monitored but does not require treatment.
Insulin resistance / Diabetes mellitus	• Exercise & balanced diet • Mgmt per endocrinologist	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; OT = occupational therapy; PT = physical therapy; RDI = recommended daily intake; SVAS = supravalvar aortic stenosis

1. Mervis & Greiner de Magalhães [2022]
2. Cherniske et al [2004]
3. See Thom et al [2021] for a discussion of psychopharmacology in WS.
4. Morris & Mervis [2021]
5. For discussion of antihypertensive therapy, see Collins [2018] and Kozel et al [2021].
6. Schmidt et al [2021], Staudt & Eagle [2021]
7. Ross et al [2011]
8. Stanley et al [2021]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the US; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, and special educators. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis).

- Consider hippotherapy (use of equine movement during speech-language therapy, physical therapy, and/or occupational therapy).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder or anxiety.

Surveillance

Table 7. Surveillance for Williams Syndrome

Interval/Age	Test/Measurement
In infants & toddlers	• Serum calcium measurement every 4-6 mos until age 2 yrs • Thyroid function test annually until age 3 yrs
Annually in all ages [1]	• Medical eval • Vision screening to monitor for refractive errors & strabismus (& cataracts in adults) • Hearing eval • Assessment of blood pressure in both arms • Measurement of calcium-to-creatinine ratio in random spot urine & urinalysis • Cardiology eval at least annually until age 5 yrs, every 2-3 yrs thereafter for life
Every 2 yrs in all ages	• Serum concentration of calcium • Thyroid function & TSH level
Every 10 yrs in all ages	• Renal & bladder ultrasound
In adults	• Oral glucose tolerance test starting at age 20 yrs to evaluate for diabetes mellitus [2] • Eval for mitral valve prolapse, aortic insufficiency, hypertension, long QT interval, arterial stenoses

TSH = thyroid-stimulating hormone
1. Except as noted
2. If normal, oral glucose tolerance test should be repeated every five years.

Agents/Circumstances to Avoid

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

Evaluation of Relatives at Risk

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

Pregnancy Management

Pregnancies in women with WS are high risk. They should be monitored for the development of pregnancy-induced hypertension, arrhythmias, and heart failure. Regular urinalyses should be performed in late gestation due to the increased risk for urinary tract infection. Ultrasound monitoring of the fetus is suggested [Lin et al 2008].

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

Williams syndrome (WS) is an autosomal dominant disorder typically caused by a *de novo* genetic alteration.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with WS have the disorder as the result of a *de novo* 1.5- to 1.8-Mb 7q11.23 deletion.
- Rarely, an individual with WS has an affected parent [Morris et al 1993, Sadler et al 1993, Mulik et al 2004].
- Studies have shown that, in approximately 25% of families, the unaffected parent in whom the deletion originated has an inversion on chromosome 7 involving 7q11.23 [Osborne et al 2001, Bayés et al 2003, Hobart et al 2010]. Individuals with an inversion have a 1:1,750 chance of having a child with WS [Hobart et al 2010]. (Note: Approximately 6% of the general population also has this inversion polymorphism [Hobart et al 2010]; the inversion does not cause clinical symptoms [Tam et al 2008]. Because the presence of the inversion does not alter clinical management of the affected individual or the family, testing for the inversion is not recommended.)
- Recommendations for the parents of a proband with WS include obtaining a medical history to determine if signs or symptoms of WS are present. In the absence of clinical findings of WS in the parents, testing of the parents for the 7q11.23 deletion identified in the proband is not warranted.

Sibs of a proband. The risk to the sibs of a proband depends on the genetic status of the parents:

- If one of the parents has the 7q11.23 deletion identified in the proband, the risk to each sib of inheriting the deletion and being affected is 50%. It is not possible to reliably predict the phenotype in a sib who inherits a 7q11.23 deletion because manifestations of WS may vary in affected family members.
- There have been two reports of sib recurrence: in one family, the deletions occurred on the paternal chromosome that had an inversion involving 7q11.23; in the other, the deletions were likely the result of maternal germline mosaicism because no inversion involving 7q11.23 was found [Scherer et al 2005].

- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low (<1%) because few familial cases have been reported. However, the risk to sibs is greater than that of the general population because of the possibility of parental germline mosaicism or an inversion polymorphism in a parent.

Offspring of a proband. Each child of an individual with WS has a 50% chance of inheriting the 7q11.23 deletion and being affected.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, the parent's 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/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 at risk of having a child with WS.

Prenatal Testing and Preimplantation Genetic Testing

Once the WS-causing 1.5- to 1.8-Mb 7q11.23 deletion has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Note: Prenatal test results cannot reliably predict phenotype.

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.

- **Canadian Association for Williams Syndrome**
  Canada
  Phone: 204-256-6594
  Email: contact@williamssyndrome.ca
  www.williamssyndrome.ca
- **MedlinePlus**
  Williams syndrome
- **NCBI Genes and Disease**
  Williams syndrome
- **Williams Syndrome Association**
  Phone: 800-806-1871; 248-244-2229
  Fax: 248-244-2230
  Email: info@williams-syndrome.org
  www.williams-syndrome.org
- **Williams Syndrome Foundation**

United Kingdom
Phone: 0208 5671374
Email: enquiries@williams-syndrome.org.uk
www.williams-syndrome.org.uk

- **Williams Syndrome Registry**
  The Registry - Registration

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. Williams Syndrome: Genes and Databases

Critical Region	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
WBSCR	*Not applicable*	7q11.23	Not applicable			
	ELN	7q11.23	Elastin	ELN database	ELN	ELN
	GTF2I	7q11.23	General transcription factor II-I	GTF2I database	GTF2I	GTF2I
	GTF2IRD1	7q11.23	General transcription factor II-I repeat domain-containing protein 1	GTF2IRD1 database	GTF2IRD1	GTF2IRD1
	LIMK1	7q11.23	LIM domain kinase 1			LIMK1
	NCF1	7q11.23	Neutrophil cytosol factor 1	NCF1 database NCF1base: Mutation registry for autosomal recessive chronic granulomatous disease (CGD), deficiency of p47phox	NCF1	NCF1

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 Williams Syndrome (View All in OMIM)

130160	ELASTIN; ELN
194050	WILLIAMS-BEUREN SYNDROME; WBS
601329	LIM DOMAIN KINASE 1; LIMK1
601679	GENERAL TRANSCRIPTION FACTOR II-I; GTF2I
604318	GTF2I REPEAT DOMAIN-CONTAINING PROTEIN 1; GTF2IRD1
608512	NEUTROPHIL CYTOSOLIC FACTOR 1; NCF1

Molecular Pathogenesis

Both the 7q11.23 deletion that causes Williams syndrome (WS) and the reciprocal 7q11.23 duplication are mediated by the genomic structure of the region. The 7q11.23 region is flanked by low copy repeats that predispose to nonallelic homologous recombination. In 95% of individuals with WS the deletion comprises 1.55

Mb and includes 25 genes; in 5% it comprises 1.84 Mb and includes 27 genes [Bayés 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 that encode transcription factors, *GTF2I*, *GTF2IRD1*, and *GTF2IRD2*, have been identified in the telomeric end of the 7q11.23 region 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 factors 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 heterozygous deletion of these genes could contribute to many different aspects of the WS phenotype [Kozel et al 2021].

Genes of interest in this region

- ***ELN*** encodes the structural protein elastin, a major component of elastic fibers found in many tissues. Deletion of *ELN* is responsible for the connective tissue abnormalities, including the cardiovascular disease associated with WS [Ewart et al 1993]. Pathogenic variants of *ELN* typically result in autosomal dominant SVAS [Li et al 1997]. *ELN* pathogenic variants have also been reported in congenital cutis laxa [Tassabehji et al 1998, Zhang et al 1999].
- ***LIMK1*** encodes LIM domain kinase 1, a protein expressed in the brain that regulates neuronal migration. Deletion of *LIMK1* has been implicated in the abnormal visuospatial constructive cognition in individuals with WS [Frangiskakis et al 1996, Morris et al 2003, Hoogenraad et al 2004]. Variation in *LIMK1* in the general population affects the dorsal processing visual stream mediated through the intraparietal sulcus, which is structurally and functionally altered in WS [Gregory et al 2019]. Lim domain kinase 1 has two LIM motifs and a protein kinase domain that may be involved in intracellular signaling.
- ***GTF2I*** encodes general transcription factor II-I (GTFII-I), which acts as an inducible multifunctional transcription factor in the nucleus [Roy 2012] and as a regulator of agonist-induced calcium entry in the cytoplasm [Caraveo et al 2006]. GTFII-I is involved in embryonic development, actin cytoskeleton, axon outgrowth, and epigenetic regulation [Kozel et al 2021]. Deletion mapping of families with atypical small deletions in the WBSCR has suggested that deletion of this gene has a negative effect on IQ [Morris et al 2003]. *GTF2I* polymorphisms have been associated with severity of manifestations in autism spectrum disorders [Malenfant et al 2012], level of social anxiety, and social communication abilities in the general population [Crespi & Hurd 2014], and with influencing the relation between trait anxiety and brain response to aversive social cues [Jabbi et al 2015].
- ***GTF2IRD1*** encodes general transcription factor II-I repeat domain-containing protein 1 (GTF2IRD1), which has been implicated in craniofacial features [Tassabehji et al 2005] and social communication difficulties [Kozel et al 2021] based on studies of individuals with atypical small deletions in the WBSCR.
- ***NCF1*** encodes neutrophil cytosol factor 1, a component of the NADPH oxidase system. Individuals with deletions of the WBSCR that include *NCF1* have a lower risk for hypertension. *NCF1* is located at the telomeric region of the WBSCR and is deleted in approximately 40% of individuals with WS [Del Campo et al 2006, Kozel et al 2014].

The following genes may be involved in the WS phenotype, but to date the contribution of each these genes has not been confirmed.

- ***STX1A*** encodes syntaxin-1A, which is involved in neurotransmitter release and insulin secretion. *STX1A* may have a role in diabetes in WS [Kozel et al 2021]. Syntaxin-1A mediates neurotransmitter release through protein-protein interactions and may play a role in psychiatric disorders in WS [Kozel et al 2021].
- ***MLXIPL*** encodes carbohydrate-responsive element-binding protein, a ChREBP transcription factor that regulates glucose and lipid metabolism. Deletion of this gene may be involved in metabolic abnormalities common in individuals with WS such as diabetes, obesity, and lipedema [Kozel et al 2021].

- ***BAZ1B*** encodes tyrosine-protein kinase BAZ1B. BAZ1B is part of a chromatin remodeling complex. Because it binds the vitamin D receptor, it has been theorized that it may have a role in hypercalcemia in WS [Meng et al 1998]. Because the gene is involved in neural crest cell migration, it has been proposed that it may be involved in both craniofacial differences and gastrointestinal manifestations in WS [Kozel et al 2021].
- ***CLIP2*** encodes CAP-Gly domain-containing linker protein 2 (CLIP2). Strongly expressed in the brain, CLIP2 interacts with membrane microtubules and is postulated to be involved in cerebellar abnormalities in WS [Hoogenraad et al 2004].

For the remaining genes in the 7q11.23 deletion, the relationship to the WS phenotype is unknown.

Chapter Notes

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