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Wolf-Hirschhorn Syndrome – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonyms: 4p- Syndrome, Monosomy 4p

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

Wolf-Hirschhorn syndrome (WHS) is characterized by typical craniofacial features in infancy consisting of "Greek warrior helmet" appearance of the nose (wide bridge of the nose continuing to the forehead), microcephaly, high anterior hairline with prominent glabella, widely spaced eyes, epicanthus, highly arched eyebrows, short philtrum, downturned corners of the mouth, micrognathia, and poorly formed ears with pits/tags. All affected individuals have prenatal-onset growth deficiency followed by postnatal growth retardation and hypotonia with muscle underdevelopment. Developmental delay/intellectual disability of variable degree is present in all. Seizures occur in 90% to 100% of children with WHS. Other findings include skeletal anomalies (60%-70%), congenital heart defects (~50%), hearing loss (mostly conductive) (>40%), urinary tract malformations (25%), and structural brain abnormalities (33%).

Diagnosis/testing

The diagnosis of WHS is established by the finding of a heterozygous deletion of the Wolf-Hirschhorn syndrome critical region (WHSCR) on chromosome 4p16.3 by chromosomal microarray (CMA), conventional G-banded cytogenetic analysis, or fluorescence in situ hybridization (FISH).

Management

Treatment of manifestations: Treatment includes: rehabilitation, speech/communication therapy and sign language; valproic acid for atypical absence seizures; benzodiazepines for status epilepticus; special feeding

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techniques, gavage feeding, and/or gastrostomy for feeding difficulties. Standard care is recommended for skeletal anomalies, ophthalmologic abnormalities, congenital heart defects, hearing loss, sleep disturbance, and hepatic adenomas.

Prevention of secondary complications: Antibiotic prophylaxis for vesicoureteral reflux; IVIG infusions or continuous antibiotics for those with antibody deficiencies.

Surveillance: Systematic follow up to monitor rehabilitation and treatment as needed; annual complete blood count and renal function testing; consideration of routine liver ultrasounds.

Agents/circumstances to avoid: Carbamazepine may worsen atypical absence seizures.

Genetic counseling

WHS is caused by deletion of the WHSCR of chromosome 4p16.3 by one of several genetic mechanisms. About 50%-60% of individuals with WHS have a *de novo* pure deletion of 4p16 and about 40%-45% have an unbalanced translocation with both a deletion of 4p and a partial trisomy of a different chromosome arm. These unbalanced translocations may be *de novo* or inherited from a parent with a balanced rearrangement. The remaining have other complex rearrangements leading to a 4p16.3 deletion (e.g., ring 4). Risks to family members depend on the mechanism of origin of the deletion. Prenatal testing is possible for families in which one parent is known to be a carrier of a chromosome rearrangement involving 4p16.3.

Diagnosis

Suggestive Findings

Wolf-Hirschhorn syndrome (WHS) **should be suspected** in individuals with the following clinical findings.

Typical facial features [Battaglia et al 1999a, Battaglia et al 1999b, Battaglia et al 2000, Battaglia & Carey 2000, Battaglia et al 2008] (see Figure 1):

- "Greek warrior helmet" appearance of the nose (wide bridge of the nose continuing to the forehead)
- Microcephaly
- High anterior hairline with prominent glabella
- Widely spaced eyes
- Epicanthus
- Highly arched eyebrows
- Short philtrum
- Downturned corners of the mouth
- Micrognathia
- Poorly formed ears with pits/tags

Prenatal-onset growth deficiency followed by postnatal growth retardation

Developmental delay/intellectual disability of variable degree

Seizure disorder and/or distinctive EEG abnormalities [Battaglia et al 2009]

Hypotonia and muscle underdevelopment, mainly of the lower limbs

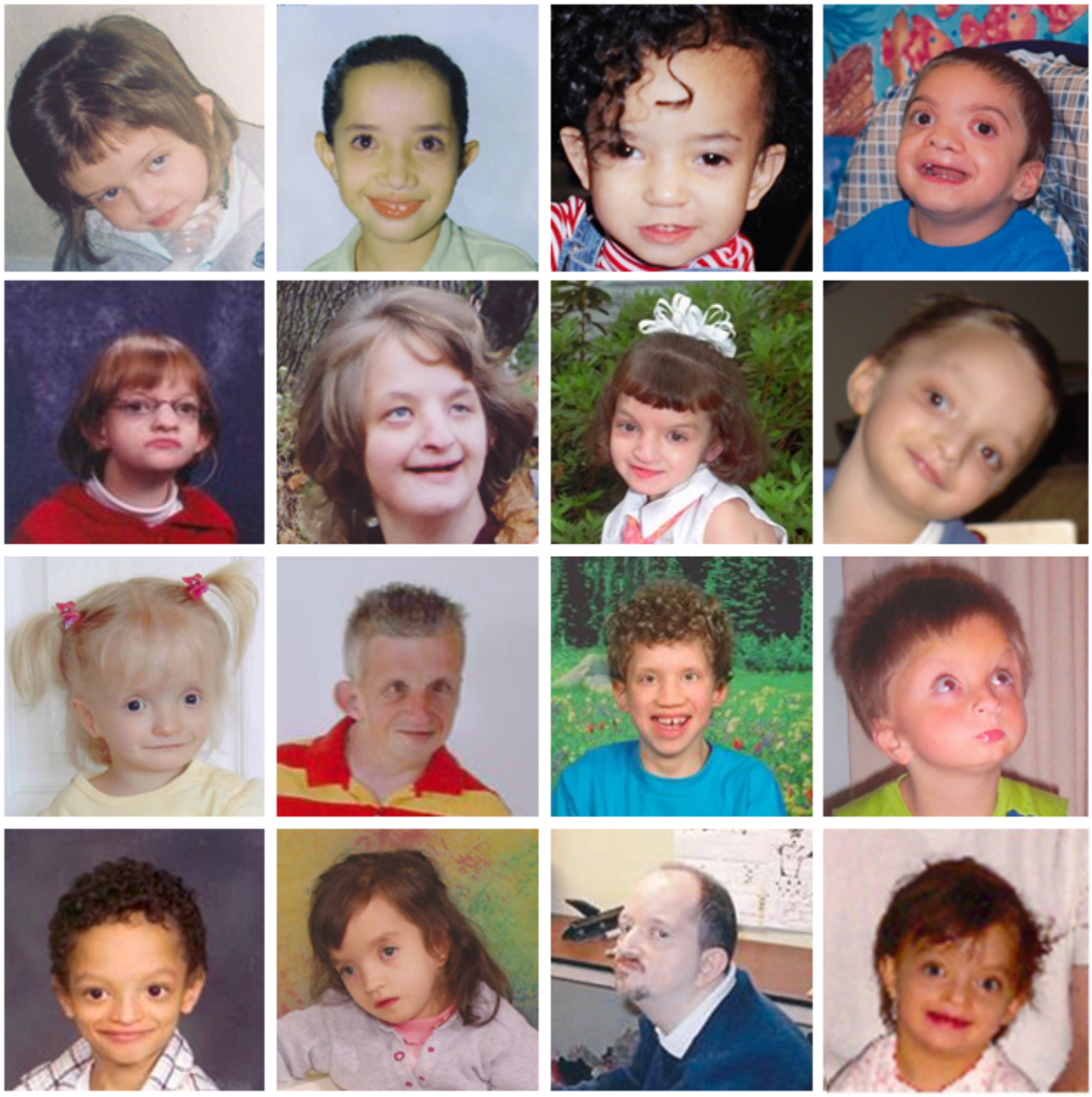

Figure 1. Facial appearance of 16 individuals with WHS at different ages

Reprinted from South et al [2008c]

Establishing the Diagnosis

The diagnosis of Wolf-Hirschhorn syndrome **is established** in a proband by detection of a heterozygous deletion of the Wolf-Hirschhorn syndrome critical region (WHSCR) within 4p16.3 at ~1.4-1.9 Mb from the terminus (see Table 1).

The WHSCR on 4p16.3 is defined as the presence of a deletion at the approximate position of chr4: 419,224-2,010,962 in the reference genome (NCBI BuildGRCh37/hg19).

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

Genomic testing methods that determine the copy number of sequences can include chromosomal microarray (CMA), conventional G-banded cytogenetic studies, or targeted deletion analysis by fluorescence in situ hybridization (FISH).

- **Chromosomal microarray (CMA)** using oligonucleotide arrays or SNP genotyping arrays can detect the WHSCR deletion in more than 95% of probands. The ability to size the deletion depends on the type of microarray used and the density of probes in the 4p16.3 region.

  Note: CMA testing may be appropriate in a proband who previously had a normal conventional G-band cytogenetic study.

- **Conventional G-banded cytogenetic studies** detect a deletion in the distal portion of the short arm of one chromosome 4 involving band 4p16.3 in approximately 50%-60% of individuals with WHS.
  - Many individuals (~55%) have a deletion with no other cytogenetic abnormality (a so-called "pure deletion").
  - About 40%-45% of affected individuals have an unbalanced translocation with both a deletion of 4p and a partial trisomy of a different chromosome arm.
  - The remaining individuals have other complex rearrangements leading to a 4p16.3 deletion (e.g., ring 4) [South et al 2008a].

- **Targeted deletion analysis.** FISH analysis may be used in individuals with clinical features that suggest a diagnosis of WHS. It is not possible to size the deletion routinely by use of FISH.

Table 1. Genomic Testing Used in Wolf-Hirschhorn syndrome

Deletion [1]	ISCA ID [2]	Region Location [3]	Method	Test Sensitivity	
				Proband	At-risk family members
0.5-2.0-Mb heterozygous deletion at 4p16.3	ISCA-37429	GRCh37/hg19 chr4: 419,224-2,010,962	CMA [4]	>95%	>95%
			Cytogenetic analysis	~50%-60%	>95% [5]
			FISH [6]	>95%	>95%

1. See Molecular Genetics for details of the deletion.
2. Standardized clinical annotation and interpretation for genomic variants from the Clinical Genome Resource project (ClinGen; formerly the International Standards for Cytogenomic Arrays [ISCA] Consortium)
3. See Molecular Genetics, Molecular Pathogenesis for genes of interest included in this region.
4. Chromosome microarray analysis (CMA) using oligonucleotide arrays or SNP genotyping arrays. CMA designs in current clinical use target the WHSCR. A combination of CMA, FISH, and/or G-banded cytogenetic studies may be necessary for complete characterization of the chromosome rearrangement.
5. This number applies only to the situation in which the deletion can be detected by cytogenetic analysis in the proband.
6. FISH is not appropriate for an individual in whom a WHSCR deletion was not detected by CMA designed to target 4p16.3.

Evaluating at-risk relatives. FISH can be used to identify a deletion encompassing the WHSCR on 4p16.3 in at-risk relatives of the proband. Testing parental samples is important in determining recurrence risk (see Genetic Counseling).

Clinical Characteristics

Clinical Description

Classic WHS. Table 2 summarizes the frequency of clinical findings associated with WHS.

Table 2. Frequency of Clinical Findings in Wolf-Hirschhorn Syndrome

Findings [1]	Frequency
• **Typical facial features** (see Suggestive Findings) • **Intrauterine/postnatal growth retardation** • **Intellectual disability** • Hypotonia • Decreased muscle bulk • **Seizures** and/or distinctive EEG abnormalities • Feeding difficulties	>75%
• Skin changes (hemangioma; marble/dry skin) • Skeletal anomalies • Craniofacial asymmetry • Ptosis • Abnormal teeth • Antibody deficiency	50%-75%
• Hearing loss • Heart defects • Eye/optic nerve anomalies • Cleft lip/palate • Genitourinary tract anomalies • Structural brain anomalies • Stereotypies (hand washing/flapping, rocking)	25%-50%
Anomalies of the following: • Liver • Gallbladder • Gut • Diaphragm • Esophagus • Lung • Aorta	<25%

From Battaglia & Carey [2000], Battaglia et al [2001], Battaglia et al [2008]
1. **Bolded** features represent the core phenotype of WHS.

Facial features. The "Greek warrior helmet" appearance of the nose (wide bridge of the nose continuing to the forehead) is recognizable in all individuals from birth to childhood but becomes less evident at puberty.

Postnatal growth retardation. Most individuals with WHS have marked intrauterine growth retardation, short stature, and slow weight gain later in life despite adequate energy and protein intake [Battaglia et al 1999a, Battaglia et al 1999b, Battaglia & Carey 2000, Battaglia et al 2008]. Specific growth charts have been produced for children from birth to age four years [Antonius et al 2008]. In all affected individuals, except those with certain cryptic unbalanced translocations, head circumference is less than the second centile [South et al 2008c].

Intellectual disability. Although it is commonly stated that individuals with WHS have severe/profound intellectual disability, do not develop speech, and have minimal communication skills, a broad range of intellectual abilities has been observed in individuals with WHS. Battaglia et al [2008] found that the degree of intellectual disability was mild in 10%, moderate in 25%, and severe/profound in 65%. Thus, one third of affected individuals had mild to moderate disability. Expressive language, although limited to guttural or disyllabic sounds in most individuals, was at the level of simple sentences in 6%. Comprehension appears to be limited to a specific context. Intent to communicate appears to be present in most individuals with WHS and improves over time with extension of the gesture repertoire. Recently, Fisch et al [2010] studied 19 affected

children who had expressive speech and language skills and observed relative strengths in the socialization domain.

About 10% of affected individuals achieve sphincter control by day, usually between ages eight and 14 years. By age two to 12 years, approximately 45% of affected individuals walk, either independently (25%) or with support (20%) [Battaglia & Carey 2000, Battaglia et al 2008]. About 30% of children reach some autonomy with eating (10% self-feed), dressing and undressing (20%), and simple household tasks. Slow but constant improvement has been observed over time in all individuals with WHS; these individuals reach more advanced milestones than previously suggested.

Seizures occur in 90%-100% of children with WHS [Battaglia et al 1999a, Battaglia et al 1999b, Battaglia & Carey 2000, Battaglia et al 2009]. Age at onset varies between three and 23 months with a peak incidence around six to 12 months. Seizures are either unilateral clonic or tonic, with or without secondary generalization, or generalized tonic-clonic from the onset; they are frequently triggered by fever and can occur in clusters and last over 15 minutes.

Other seizure types described in a few individuals include tonic spasms, myoclonic seizures, and complex partial seizures [Battaglia & Carey 2005]. Status epilepticus occurs in as many as 50% of individuals. Atypical absences develop between ages one and six years in one third of children [Battaglia et al 2009].

Seizures can be difficult to control in some individuals during the early years, but if properly treated tend to disappear with age. Seizures stop by age two to 13 years in up to 55% of individuals [Battaglia et al 2009].

Distinctive electroencephalographic (EEG) abnormalities have been found in 90% of individuals with WHS, including diffuse ill-defined sharp element spike/wave complexes at 2-3.5 Hz, occurring in long bursts, activated by sleep; and high amplitude spikes-polyspike/wave complexes at 4-6 Hz, over the posterior third of the head, often triggered by eye closure [Battaglia et al 2009].

Feeding difficulties may be caused by hypotonia and/or oral facial clefts with related difficulty in sucking, poorly coordinated swallow with consequent aspiration, and/or gastroesophageal reflux. Gastroesophageal reflux, though transitory in healthy infants, usually persists in infants with WHS and results in failure to thrive and respiratory diseases.

Skeletal anomalies found in 60%-70% of individuals with WHS [Battaglia et al 1999a, Battaglia et al 1999b, Battaglia & Carey 2000, Battaglia et al 2008] include kyphosis/scoliosis with malformed vertebral bodies, accessory or fused ribs, clubfeet, and split hand [Shanske et al 2010].

Ophthalmologic abnormalities. Exodeviation, nasolacrimal obstruction, eye or optic nerve coloboma, and foveal hypoplasia are the most common ophthalmic manifestations of WHS [Battaglia et al 2001, Wu-Chen et al 2004, Battaglia et al 2008]. Eyelid hypoplasia, requiring skin grafting, has occasionally been observed [Battaglia et al 2001]. Glaucoma can be difficult to treat.

Dental abnormalities. Delayed dental eruption with persistence of deciduous teeth, taurodontism in the primary dentition, peg-shaped teeth, and agenesis of some dental elements are seen in more than 50% of individuals [Battaglia & Carey 2000, Battaglia et al 2001, Battaglia et al 2008].

Congenital heart defects are noted in about 50% of individuals and are usually not complex. The most frequent is atrial septal defect (27%), followed by pulmonary stenosis, ventricular septal defect, patent ductus arteriosus, aortic insufficiency, and tetralogy of Fallot [Battaglia et al 1999a, Battaglia et al 1999b, Battaglia & Carey 2000, Battaglia et al 2008].

Antibody deficiencies (IgA/IgG2 subclass deficiency; isolated IgA deficiency; impaired polysaccharide responsiveness) found in 69% of children studied by Hanley-Lopez et al [1998] appear to be responsible for recurrent respiratory tract infections and otitis media.

Hearing loss, mostly of the conductive type, are detected in more than 40% of individuals with WHS. Sensorineural hearing loss has been reported in 15% of individuals [Battaglia & Carey 2000, Battaglia et al 2008]. Congenital abnormalities of the middle and inner ear appear to contribute to the hearing impairment [Ulualp et al 2004].

Urinary tract malformations are seen in more than 30% of affected individuals and include renal agenesis, cystic dysplasia/hypoplasia, oligomeganephroma (defined as renal hypoplasia characterized by decreased numbers of nephrons and hypertrophy of all nephric elements), horseshoe kidney, renal malrotation, bladder exstrophy, and obstructive uropathy. Oligomeganephroma is associated with chronic renal failure. Some of these anomalies are associated with vesicoureteral reflux [Battaglia & Carey 2000, Grisaru et al 2000, Battaglia et al 2008].

Hypospadias and cryptorchidism are seen in 50% of males [Battaglia & Carey 2000].

Absent uterus, streak gonads, and clitoral aplasia/hyperplasia have been reported in females [Battaglia et al 2008].

Structural central nervous system malformations have been reported in up to 80% of affected individuals [Battaglia et al 2008]. These anomalies mainly include thinning of the corpus callosum associated, in a few cases, with diffusely decreased white matter volume, enlargement of the lateral ventricles, cortical/subcortical atrophy, or marked hypoplasia/agenesis of the posterior lobes of both cerebellar hemispheres. Other reported anomalies are hypoplastic brain with narrow gyri, arhinencephaly, shortening of the H2 area of Ammon's horn, and dystopic dysplastic gyri in the cerebellum [Battaglia & Carey 2000].

Sleep problems, common in early years, can be easily resolved [Battaglia et al 2001], if not caused by clinical problems (e.g., otitis media, gastroesophageal reflux, eczema, obstructive sleep apnea).

Other. A wide variety of congenital anomalies have been reported in a minority of individuals with WHS [Battaglia et al 2001].

- **Hematopoietic dysfunction** has been reported in two children with WHS; dysfunction progressed to refractory cytopenia in one and to acute lymphoblastic leukemia in the other [Sharathkumar et al 2003].
- **Hepatic adenomas** have recently been reported in three individuals with WHS, evolving to hepatocellular carcinoma in one [Calhoun et al 2013, Prunotto et al 2013]. Further studies are under way to better define the occurrence of such medical complications in WHS.

Genotype-Phenotype Correlations

In order to explain the wide phenotypic variability of WHS, investigators have searched for correlations between the size of the 4p deletion and the severity of the clinical manifestations.

Although Wieczorek et al [2000], Zollino et al [2000], and Zollino et al [2008] have respectively suggested a partial or a complete genotype-phenotype correlation, some investigators have concluded that no such correlation exists [Battaglia et al 1999a, Battaglia et al 1999b]. Meloni et al [2000] observed individuals with the "classic syndrome" with severe intellectual disability and a submicroscopic deletion detected only by FISH, as well as individuals with mild to moderate intellectual disability and no major malformations with large deletions detected by routine cytogenetic analysis. These observations suggest that the size of the deletion does not correlate with severity of the clinical findings. Some of the associated structural defects, including cleft palate and heart defects, occur more frequently in individuals who have deletions greater than 3 megabases (Mb) [Zollino et al 2008].

The classic phenotype may include less typical anomalies in persons with WHS and partial trisomy of another chromosome resulting from an unbalanced translocation.

It has been shown that double cryptic chromosome imbalances, initially mistaken as microdeletions, but caused by large deletions associated with an unbalanced translocation, can be an important factor in explaining phenotypic variability in Wolf-Hirschhorn syndrome [Zollino et al 2004]. The deletion size has a partial correlation to severity but some individuals are either more or less severely affected than would be expected based on deletion size.

Nomenclature

Previously thought to be separate disorders, WHS and Pitt-Rogers-Danks syndrome (PRDS) are now recognized as the clinical spectrum associated with a single syndrome due to heterozygous deletion of the WHSCR on 4p16.3 [Battaglia et al 2001].

Prevalence

The prevalence of WHS is estimated at approximately 1:50,000 births, with a 2:1 female/male ratio. However, this is likely an underestimate because of misdiagnosis and under-recognition of affected individuals [Battaglia et al 2001].

Genetically Related (Allelic) Disorders

Deletions from the 4p terminus larger than 22 to 25 Mb in length are associated with a severe phenotype that is said to differ from the spectrum observed in WHS [Zollino et al 2008].

Deletions within just the distal portion of the WHSCR may be either benign or associated with mild developmental delay, growth delay, and possible seizures, but without the diagnostic features of WHS [South et al 2008c].

Differential Diagnosis

Proximal 4p deletion. Several individuals with an interstitial deletion of 4p have been described. This deletion usually involves bands 4p12-p16, which are proximal to and exclude the WHS critical region. This disorder is a discrete syndrome, distinct from WHS [Bailey et al 2010].

WHS phenotype. The clinical phenotype and particularly the facial gestalt of WHS are characteristic; however, some individuals may still be misdiagnosed because of features that overlap with the following disorders:

- **Seckel syndrome** (OMIM PS210600), characterized by pre- and postnatal growth deficiency, microcephaly, and a convex nasal ridge/prominent nose. Seckel syndrome is inherited in an autosomal recessive manner and is caused by biallelic pathogenic variants in one of the following genes: *ATR*, *NIN*, *ATRIP*, *RBBP8*, *CEP152*, *CENPJ*, or *CEP63*.
- **CHARGE syndrome** is characterized by *c*oloboma, *h*eart defects, choanal *a*tresia, *r*etarded growth and development, *g*enital abnormalities, and *e*ar anomalies/deafness. About 65% of individuals with a clinical diagnosis of CHARGE syndrome have an identifiable heterozygous pathogenic variant *CHD7*. CHARGE syndrome is inherited in an autosomal dominant manner; however, most individuals diagnosed with CHARGE syndrome represent simplex cases.
- **Smith-Lemli-Opitz syndrome (SLOS)** is characterized by pre- and postnatal growth retardation, microcephaly, moderate-to-severe intellectual disability, and multiple major and minor malformations. The malformations include distinctive facial features, cleft palate, cardiac defects, underdeveloped external genitalia in males, postaxial polydactyly, and 2-3 syndactyly of the toes. SLOS is caused by an abnormality in cholesterol metabolism resulting from deficiency of the enzyme 7-dehydrocholesterol reductase. SLOS is inherited in an autosomal recessive manner and is caused by biallelic pathogenic variants in *DHCR7*.

- **Opitz G/BBB syndrome** is characterized by facial anomalies (widely spaced eyes, prominent forehead, widow's peak, wide nasal bridge, and anteverted nares), laryngotracheoesophageal anomalies, and genitourinary abnormalities (hypospadias, cryptorchidism, and hypoplastic/bifid scrotum). Developmental delay/intellectual disability and cleft lip and/or palate are present in approximately 50%. Genetic heterogeneity has been demonstrated: an X-linked form is caused by either a hemizygous pathogenic variant in *MID1* in males or a heterozygous pathogenic variant in *MID1* in females; an autosomal dominant form is caused by a heterozygous pathogenic variant in *SPECC1L*.
- **Malpuech syndrome** (OMIM 248340) is characterized by growth retardation, widely spaced eyes, broad forehead, highly arched eyebrows, urogenital anomalies, and hearing problems. Malpuech syndrome is inherited in an autosomal recessive manner.
- **Lowry-MacLean syndrome** (OMIM 600252) is characterized by growth failure, intellectual disability, cleft palate, congenital heart defect, and glaucoma.
- **Williams syndrome (WS)** is characterized by cardiovascular disease, distinctive facial features, connective tissue abnormalities, intellectual disability (usually mild), a specific cognitive profile, unique personality characteristics, growth abnormalities, and endocrine abnormalities. Feeding difficulties often lead to failure to thrive in infancy. Hypotonia and hyperextensible joints can result in delayed attainment of motor milestones. WS is caused by a contiguous gene deletion involving the WS critical region (at 7q11.23) encompassing the elastin gene (*ELN*). It is inherited in an autosomal dominant manner; however, most individuals diagnosed with WS represent simplex cases.
- **Classic Rett syndrome,** a progressive neurodevelopmental disorder primarily affecting girls, is characterized by normal birth and apparently normal psychomotor development during the first six to 18 months of life followed by a short period of developmental stagnation then by rapid regression in language and motor skills. The hallmark of the disease is the loss of purposeful hand use and its replacement with repetitive stereotyped hand movements. Fits of screaming and inconsolable crying, autistic features, panic-like attacks, bruxism, episodic apnea and/or hyperpnea, gait ataxia and apraxia, tremors, and acquired microcephaly also occur. Seizures are reported in up to 90% of females with Rett syndrome. Rett syndrome, caused by a heterozygous pathogenic variant in *MECP2,* is inherited in an X-linked manner; however, more than 99% of girls diagnosed with Rett syndrome represent simplex cases.
- **Angelman syndrome (AS)** is characterized by severe developmental delay or intellectual disability, severe speech impairment, gait ataxia and/or tremulousness of the limbs, and a unique behavior with an inappropriate happy demeanor that includes frequent laughing, smiling, and excitability. Microcephaly and seizures are common. Developmental delays are first noted at around age six months; however, the unique clinical features of AS do not become manifest until after age one year, and it can take several years before the correct clinical diagnosis is obvious. AS is caused by disruption of maternally imprinted *UBE3A* located within the 15q11.2-q13 Angelman syndrome/Prader-Willi syndrome (AS/PWS) region.
- **Smith-Magenis syndrome (SMS)** is characterized by distinctive facial features (particularly facial features that progress with age), developmental delay, cognitive impairment, and behavioral abnormalities. Infants have feeding difficulties, failure to thrive, hypotonia, hyporeflexia, prolonged napping or need to be awakened for feeds, and generalized lethargy. Cognitive and adaptive abilities are in the mild to moderate range of intellectual disability. The behavioral phenotype, including significant sleep disturbance, stereotypies, and maladaptive and self-injurious behaviors, is generally not recognized until age 18 months or older and continues to change until adulthood. Smith-Magenis syndrome (SMS) is caused by deletion of or a heterozygous pathogenic variant in *RAI1* on chromosome 17p11.2. Virtually all individuals diagnosed with SMS represent simplex cases.

Management

Evaluations Following Initial Diagnosis

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

- Measurement of growth parameters and plotting on growth charts
- Evaluation of cognitive, language, and motor development and social skills
- Waking/sleeping video-EEG-polygraphic studies in childhood (mainly ages 1-6 years) to detect atypical absence seizures that may be subtle [Battaglia & Carey 2000, Battaglia et al 2009]
- Evaluation for feeding problems and gastroesophageal reflux with referral to a dysphagia team
- Physical examination for skeletal anomalies (e.g., clubfoot, scoliosis, kyphosis); if anomalies are present, referral for orthopedic and physical therapy evaluation (including full biomechanical assessment)
- Ophthalmology consultation in infancy even in the absence of overt anomalies
- Examination of the heart (auscultation, electrocardiogram, echocardiography) in infancy
- Testing for immunodeficiency (particularly plasma Ig levels, lymphocyte subsets, and polysaccharide responsiveness); although limited data on immunodeficiency in individuals with WHS are available, such testing should be considered when clinically appropriate.
- Complete blood count to evaluate for hematopoietic dysfunction
- Comprehensive evaluation by an otolaryngologist and comprehensive audiologic screening (brain stem auditory evoked responses) as early as possible to allow appropriate interventions
- Renal function testing and renal ultrasonography in infancy to detect structural renal anomalies and/or vesicoureteral reflux [Grisaru et al 2000]
- Baseline liver ultrasound to evaluate for hepatic adenoma
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Intellectual disability. Enrollment in a personalized rehabilitation program with attention to motor development, cognition, communication, and social skills is appropriate [Battaglia & Carey 2000, Battaglia et al 2008]. Use of sign language enhances communication skills and does not inhibit the appearance of speech. Early intervention and, later, appropriate school placement are essential.

Seizures. Because almost 95% of individuals with Wolf-Hirschhorn syndrome have multiple seizures, most often triggered by fever, and almost one third later develop valproic acid-responsive atypical absence seizures, it is appropriate to start treatment with valproic acid soon after the first seizure. Atypical absence seizures are well controlled on valproic acid alone or in association with ethosuccimide [Battaglia & Carey 2000, Battaglia et al 2009].

Sodium bromide has recently been proposed as the initial treatment for the prevention of the development of status epilepticus [Kagitani-Shimono et al 2005].

Clonic, tonic-clonic, absence, or myoclonic status epilepticus can be well controlled by intravenous benzodiazepines (Diazepam) [Battaglia & Carey 2005, Kagitani-Shimono et al 2005].

Because individuals with WHS have distinctive EEG abnormalities not necessarily associated with seizures [Battaglia et al 2009], it seems appropriate to withdraw antiepileptic drugs in individuals who have not experienced seizures for five years.

Feeding difficulties. Feeding therapy with attention to oral motor skills is also appropriate. Special feeding techniques or devices such as the "Haberman feeder" can be used for feeding a hypotonic infant/child without a cleft palate or those with a cleft palate prior to surgical repair.

Gavage feeding may be indicated in individuals with poorly coordinated swallow.

Gastroesophageal reflux should be addressed in a standard manner.

In one study, almost 44% of individuals with WHS were managed with gastrostomy and, occasionally, gastroesophageal fundoplication [Battaglia & Carey 2000].

Skeletal abnormalities (e.g., clubfoot, scoliosis, kyphosis) need to be addressed on an individual basis. Early treatment (both physical therapy and surgery) is suggested.

Ophthalmologic abnormalities are treated in the standard manner.

Congenital heart defects are usually not complex and are amenable to repair.

Hearing loss is treated with a trial of hearing aids.

Sleeping problems. If no medical factors (e.g., otitis media, gastroesophageal reflux, eczema, obstructive sleep apnea) are involved and if sleeping problems are reinforced by parental attention, the "extinction of parental attention" is an effective behavioral treatment [Curfs et al 1999].

Hepatic adenomas. Medical treatment (either surgery or chemotherapy) varies in relation to the number and size of the adenomas.

Other structural anomalies (e.g., diaphragmatic, gastrointestinal, dental) should be addressed in a standard manner.

Prevention of Secondary Complications

Antibiotic prophylaxis is indicated for vesicoureteral reflux.

Intravenous Ig infusions or continuous antibiotics may be indicated for those with antibody deficiencies.

Surveillance

Systematic follow up allows for adjustment of rehabilitation and treatment as skills improve or deteriorate and medical needs change [Ferrarini et al 2003, Battaglia et al 2008, Battaglia 2010].

- Complete blood count annually to evaluate for hematopoietic dysfunction
- Annual renal function testing, including serum BUN, creatinine, and cystatin C; urinalysis; and creatinine clearance test
- Consideration of routine liver ultrasonography to evaluate for liver adenomas

Agents/Circumstances to Avoid

Carbamazepine may worsen atypical absence seizures [Battaglia & Carey 2005].

Evaluation of Relatives at Risk

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

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

Wolf-Hirschhorn syndrome (WHS) is caused by deletion of the Wolf-Hirschhorn critical region (WHSCR) within chromosome 4p16.3 by one of several genetic mechanisms.

Risk to Family Members

Risk to family members depends on the mechanism of origin of the deletion.

Parents of a proband

- The parents of a proband are unaffected.
- About 55% of individuals with WHS have a *de novo* simple deletion of 4p16.3.
- About 40%-45% of individuals with WHS have an unbalanced translocation with both a deletion of 4p and a partial trisomy of a different chromosome arm. These unbalanced translocations may be *de novo* or inherited from a parent with a balanced rearrangement.
- Parental testing for a balanced rearrangement involving 4p16.3 is always recommended.

Sibs of a proband

- The risk to the sibs of a proband depends on the genetic status of the parents.
- If the deletion in the proband is *de novo*, the risk to the sibs of a proband is negligible.
- If a parent is a balanced translocation carrier, the risk to sibs of being affected with 4p monosomy (i.e., WHS) or 4p trisomy is increased.
- Asymptomatic sibs may inherit a balanced translocation from a parent and have reproductive risks themselves.

Offspring of a proband. No individual with WHS is known to have reproduced.

Other family members of a proband. If a parent carries a chromosome rearrangement, his or her family members are also at risk of carrying the rearrangement.

Related Genetic Counseling Issues

Specific empiric risks for translocations involving 4p and another chromosome are unavailable. However, 4p subtelomere FISH analysis of both parents may be considered to rule out this possibility. Genetic counseling is appropriate for families interested in risk of recurrence.

Studies suggest that terminal deletions may vary in size between generations. This has been described for both 4p and 18q [Faravelli et al 2007, South et al 2008b]. The risk for such a finding in a clinically unaffected parent is unknown at present.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal 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 carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Diagnosis

High-risk pregnancy. If one parent is known to be a carrier of a 4p chromosome rearrangement, prenatal testing for a pregnancy at risk and preimplantation genetic diagnosis for WHS are possible.

Low-risk pregnancy. Three-dimensional (3D) ultrasound may reveal facial features resembling the Greek warrior helmet in fetuses with IUGR [Chen et al 2004].

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.

- **4P-Support Group, Inc**
  2159 128th Street
  New Richmond WI 54017
  Phone: 715-248-3937
  www.4p-supportgroup.org

- **Associazione Italiana Sindrome di Wolf-Hirschhorn (AISiWH)**
  Via Bologna 65
  Montecosaro 62010
  Italy
  Phone: 0733 864275
  Fax: 0733 864275
  Email: segreteria.aisiwh@gmail.com
  www.aisiwh.it

- **My46 Trait Profile**
  Wolf-Hirschhorn Syndrome

- **Wolf Hirschhorn Syndrome Trust (WHST)**
  United Kingdom
  Phone: 0845 603 5338
  Email: enquiries@whs4pminus.co.uk
  www.whs4pminus.co.uk

- **Chromosome Disorder Outreach (CDO)**
  PO Box 724
  Boca Raton FL 33429-0724
  Phone: 561-395-4252 (Family Helpline)

Email: info@chromodisorder.org
www.chromodisorder.org

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. Wolf-Hirschhorn Syndrome: Genes and Databases

Critical Region	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
WHCR	*Not applicable*	4p16.3	Not applicable			
	CPLX1	4p16.3	Complexin-1		CPLX1	CPLX1
	CTBP1	4p16.3	C-terminal-binding protein 1		CTBP1	CTBP1
	FGFRL1	4p16	Fibroblast growth factor receptor-like 1			FGFRL1
	LETM1	4p16.3	Mitochondrial proton/ calcium exchanger protein		LETM1	LETM1
	NELFA	4p16.3	Negative elongation factor A		NELFA	NELFA
	NSD2	4p16.3	Histone-lysine N-methyltransferase NSD2	WHSC1 database	NSD2	NSD2
	PIGG	4p16.3	GPI ethanolamine phosphate transferase 2		PIGG	PIGG

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 Wolf-Hirschhorn Syndrome (View All in OMIM)

194190	WOLF-HIRSCHHORN SYNDROME; WHS
602618	C-TERMINAL-BINDING PROTEIN 1; CTBP1
602952	NUCLEAR RECEPTOR-BINDING SET DOMAIN PROTEIN 2; NSD2
604407	LEUCINE ZIPPER/EF-HAND-CONTAINING TRANSMEMBRANE PROTEIN 1; LETM1
605032	COMPLEXIN 1; CPLX1
605830	FIBROBLAST GROWTH FACTOR RECEPTOR-LIKE 1; FGFRL1
606026	WHS CANDIDATE 2 GENE; WHSC2

Molecular Pathogenesis

The proximal boundary of the WHSCR was defined by the identification of two individuals with the WHS phenotype and a 1.9-Mb terminal deletion of 4p16.3 that includes the candidate genes *LETM1* and *WHSC1* [Zollino et al 2003, Rodríguez et al 2005]. The distal boundary of the WHSCR was established through the analysis of persons with an interstitial 4p16 deletion and a WHS phenotype [Wright et al 1997] and persons with a terminal 4p deletion without a WHS phenotype [South et al 2008a]. However, due to the identification of patients with components of the core phenotype with more distal deletions (seizures or growth delay or craniofacial features) the current hypothesis is that WHS represents a true contiguous gene syndrome with

contribution of genes within a 1.6-Mb region spanning from approximately genomic coordinates chr4: 419,224-2,010,962.

WHSC1 is a novel gene that spans a 90-kb genomic region, two thirds of which maps in the telomeric end of the WHSCR. The temporal and spatial expression of *WHSC1* in early development and the protein domain identities suggest that *WHSC1* may play a significant role in normal development. Its deletion is likely to contribute to the WHS phenotype. However, the variation in severity and phenotype of WHS suggests possible roles for genes that lie proximally and distally to the WHSCR, including *NELFA* (*WHSC2*) and *LETM1* [Zollino et al 2003, Bergemann et al 2005, Rodríguez et al 2005, South et al 2007].

NELFA (previously known as *WHSC2*) is involved in multiple aspects of mRNA processing and the cell cycle. This gene may play a role in the more global aspects of Wolf-Hirschhorn syndrome [Kerzendorfer et al 2012].

LETM1 is a proposed candidate gene for seizures that is deleted in almost all affected individuals. The LETM1 protein functions in ion exchange with potential roles in cell signaling and energy production [Nowikovsky et al 2004, Schlickum et al 2004, Hasegawa & van der Bliek 2007, Dimmer et al 2008, Jiang et al 2009, Kuum et al 2012]. However, individuals with 4p deletions including *LETM1* who do not have seizures have been described, and seizures have been described in individuals with a 4p deletion excluding *LETM1* [Van Buggenhout et al 2004, Faravelli et al 2007, Maas et al 2008, Misceo et al 2012, Bayindir et al 2013, Andersen et al 2014]. Therefore, it is likely that *LETM1* is not the only gene involved in the occurrence of seizures.

Much work is still needed to identify the function of *WHSC1* and *LETM1* in individuals with normal development and in individuals with WHS, and to characterize additional genes in and around the WHSCR that contribute to clinical outcome. In addition, deletion of these two genes alone is not sufficient to result in the WHS phenotype [Andersen et al 2014]. Additional genes within this interval that have been proposed for specific involvement in the WHS phenotype, including ***CTBP1***, ***CPLX1*** and ***PIGG*** for seizures [Misceo et al 2012, Bayindir et al 2013, Zollino et al 2014] and ***FGFRL1*** for contribution to the craniofacial features and potentially other skeletal features [Engbers et al 2009, Catela et al 2009, Hammond et al 2012].

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Chapter Notes

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Revision History

- 18 April 2019 (ma) Chapter retired: non-recurrent deletions or duplications; refers to deletions/duplications of varying size – in contrast to a recurrent deletion/duplication, defined as a deletion/duplication of a specific size (usually mediated by nonallelic homologous recombination) occurring multiple times in the general population
- 20 August 2015 (me) Comprehensive update posted live
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