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SHOX Deficiency Disorders

Gerhard Binder, MD[1] and Gudrun A Rappold, PhD[2]

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Summary

Clinical characteristics

The phenotypic spectrum of SHOX deficiency disorders, caused by haploinsufficiency of the *s*hort stature *ho*meobo*x*-containing gene (*SHOX*), ranges from Leri-Weill dyschondrosteosis (LWD) at the severe end of the spectrum to nonspecific short stature at the mild end of the spectrum. In adults with SHOX deficiency, the proportion of LWD versus short stature without features of LWD is not well defined. In LWD the classic clinical triad is short stature, mesomelia, and Madelung deformity. Mesomelia, in which the middle portion of a limb is shortened in relation to the proximal portion, can be evident first in school-aged children and increases with age in frequency and severity. Madelung deformity (abnormal alignment of the radius, ulna, and carpal bones at the wrist) typically develops in mid-to-late childhood and is more common and severe in females. The phenotype of short stature caused by SHOX deficiency in the absence of mesomelia and Madelung deformity (called SHOX-deficient short stature in this *GeneReview*) is highly variable, even within the same family.

Diagnosis/testing

The diagnosis of SHOX deficiency is established in a proband with either a pathogenic *SHOX* variant or a deletion, duplication, or insertion that can encompass the *SHOX* coding region and/or the enhancer region regulating *SHOX* expression.

Management

Treatment of manifestations: For prepubertal children with SHOX-deficient short stature, recombinant human growth hormone (rhGH therapy) (dose 50 µg/kg body weight/day) should be offered. The therapeutic effect is a gain in final height of 7 to 10 cm. For individuals with LWD and painful bilateral Madelung deformity (which is uncommon): wrist splints and supports during periods of increased discomfort and the use of ergonomic devices such as ergonomic computer keyboards. Different operative procedures have been attempted to decrease pain and restore wrist function.

Author Affiliations: 1 Pediatric Endocrinology, University Children's Hospital, Tübingen, Germany; Email: gerhard.binder@med.uni-tuebingen.de. 2 Molecular Genetics, University of Heidelberg, Heidelberg, Germany; Email: gudrun.rappold@med.uni-heidelberg.de.

Surveillance: For children with a SHOX deficiency disorder: biannual measurement of growth.

Agents/circumstances to avoid: If Madelung deformity is associated with discomfort, physical activities such as lifting, gripping, writing, typing, and sports that strain the wrist should be limited and ergonomic aids sought.

Evaluation of relatives at risk: Presymptomatic diagnosis and treatment are warranted for sibs at risk for SHOX-deficient short stature in order to identify as early as possible those who would benefit from recombinant human growth hormone (rhGH) treatment.

Genetic counseling

SHOX deficiency disorders are inherited in a pseudoautosomal dominant manner. In pseudoautosomal dominant inheritance, homologous genes located on the short arm of the X chromosome (Xp) and the short arm of the Y chromosome (Yp) follow the rules of autosomal inheritance; thus, a *SHOX* pathogenic variant responsible for SHOX deficiency can be located on either the X or the Y chromosome of an affected male, or on either of the X chromosomes of an affected female.

Each child of an individual with a SHOX deficiency disorder has a 50% chance of inheriting the *SHOX* pathogenic variant. If both parents have SHOX deficiency, the offspring have a 50% chance of having a SHOX deficiency disorder, a 25% chance of having Langer type of mesomelic dwarfism, and a 25% chance of having neither condition. If the *SHOX* pathogenic variant has been identified in one or both parents, prenatal testing for pregnancies at increased risk is possible; however, the phenotype of the SHOX deficiency disorder cannot be accurately predicted on the basis of prenatal molecular genetic testing results.

GeneReview Scope

SHOX Deficiency Disorders: Included Phenotypes [1]
• Leri-Weill dyschondrosteosis (LWD) • SHOX-deficient short stature

1. For other genetic causes of these phenotypes, see Differential Diagnosis.

Diagnosis

The phenotypic spectrum of SHOX deficiency disorders, caused by haploinsufficiency of the *s*hort stature *ho*meobo*x*-containing gene (*SHOX*), ranges from nonspecific short stature with absence of mesomelia and Madelung deformity (called SHOX-deficient short stature in this *GeneRevie*w) at the mild end of the spectrum to Leri-Weill dyschondrosteosis (LWD) at the severe end of the spectrum.

Suggestive Findings

***SHOX*-related Leri-Weill dyschondrosteosis (LWD)** should be suspected in individuals with the following clinical and radiographic findings.

Clinical Findings of LWD

Short stature is defined as height below the third centile of the reference population.

Mesomelia (disproportionate shortening of the middle portion of the limbs) is present in 60%-100% of females and 45%-82% of males with LWD older than age six years [Kosho et al 1999, Schiller et al 2000, Grigelioniene et al 2001, Ross et al 2001, Munns et al 2003b]. In rare cases, rhizomelic limb shortening (disproportionate shortening of the upper portion of the limbs) can be found [Deshwar et al 2018, Ramachandrappa et al 2018].

This shortening of the forearm and lower leg can be assessed by two ratios:

- **Extremities-to-trunk ratio.** An extremity-to-trunk ratio (sum of arm span and calculated leg length divided by the sitting height) less than 1.95 + 0.5 x height (metric) is indicative of shortening of arms and legs; it serves as a sensitive auxologic test to detect SHOX deficiency [Binder et al 2003].
- **Sitting height-to-height ratio.** A high sitting height-to-height ratio is indicative of shortening of the legs and can also be used as the first auxologic test when screening for short children with SHOX deficiency [Malaquias et al 2013, Wolters et al 2013].

Madelung wrist deformity, caused by an abnormal radial, ulna, and carpal alignment, is characterized by spontaneous dorsal subluxation of the distal ulna resulting in a lateral "dinner fork" appearance of the wrist first described by Madelung [1878].

Radiographic Findings of LWD

The radiographic criteria for Madelung deformity [Dannerberg et al 1939, Langer 1965, Fagg 1988] include the following main abnormalities:

- **Radius**
  - Triangulation of the distal epiphysis
  - Early fusion of the ulnar half of the distal epiphysis
  - Localized lucency at the distal ulnar border
  - Decreased length
  - Dorsal and ulnar curve
- **Carpal bones.** Pyramidalization of the carpal row becoming wedge-shaped with the os lunatum at its tip
- **Ulna**
  - Decreased length
  - Dorsal subluxation
  - Triangular deformity of the epiphysis

SHOX-deficient short stature should be suspected in children with a first-degree relative with clinical LWD or SHOX deficiency disorder and one of the following [Binder et al 2000, Ezquieta et al 2002, Ogata et al 2002, Rappold et al 2002, Binder et al 2003, Binder 2011]:

- Disproportionate short stature (young school age)
- Madelung deformity (older school age)
- Short stature and specific minor abnormalities (See Clinical Characteristics, Clinical Description.)

The following two testing algorithms have been proposed:

- A scoring system based on various clinical signs including body disproportion, arm span:height ratio <96.5%, sitting height:height ratio >55.5%, body mass index >50th centile, the presence of cubitus valgus, short forearm, bowing of the forearm, appearance of muscular hypertrophy, and/or dislocation of the ulna [Rappold et al 2007]. Items scored and the scoring weight were derived by multivariate analysis in 1,608 individuals with short stature including 68 with molecularly confirmed SHOX deficiency (i.e., presence of pathogenic variants / deletions in the coding region; note that enhancers had not yet been identified). See Rappold et al [2007], Figure 1 and Table 7 (full text).

  While the values for body disproportions in children and adults are useful, they may not apply to very young children [Jorge & Arnhold 2007].

- A diagnostic algorithm (not yet evaluated) based on clinical, auxologic, and radiologic criteria [Binder 2011]. See Figure 1.

Note: The absence of the above signs does not exclude the diagnosis of SHOX deficiency, especially in very young children.

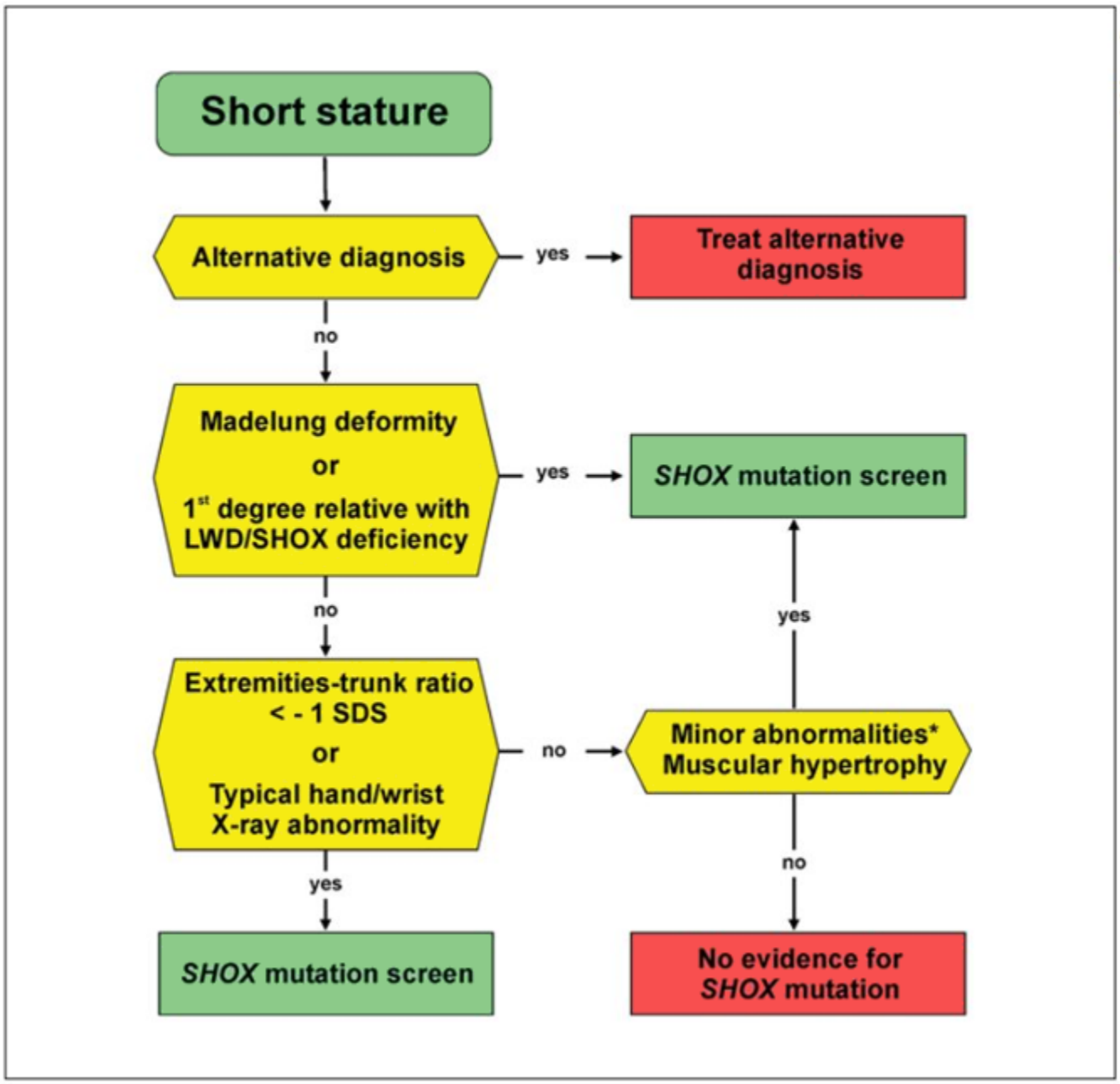

Figure 1. This schema provides an algorithmic approach to *SHOX* pathogenic variant screening in a child with short stature. Minor abnormalities (*) in SHOX deficiency are shortening of the fourth and fifth metacarpals, high-arched palate, increased carrying angle of the elbow, scoliosis, and micrognathia.

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Establishing the Diagnosis

The diagnosis of SHOX deficiency **is established** in a proband who has **either of the following** on molecular genetic testing (see Table 1) [Marchini et al 2016]:

- A heterozygous *SHOX* deletion (80%-90% of affected individuals)
  - *SHOX* is located on the pseudoautosomal region of the X chromosome at Xp22.3 and the pseudoautosomal region of the Y chromosome at Yp11.3; thus, in usual circumstances *SHOX* is present in two identical copies:

        - In females, one copy is present on the short arm of each X chromosome (Xp).
        - In males, one copy is present on the short arm of the X chromosome (Xp) and one copy – sometimes called *SHOX(Y)* – is present on the short arm of the Y chromosome (Yp).
    - Deletions can encompass all or part of *SHOX* or only enhancer sequences, leaving *SHOX* intact [Schneider et al 2005b, Benito-Sanz et al 2006, Huber et al 2006, Chen et al 2009, Rosilio et al 2012].
- A *SHOX* heterozygous pathogenic (or likely pathogenic) variant (10%-20% of affected individuals)

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *SHOX* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **gene-targeted testing** and **comprehensive genomic testing** depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of SHOX deficiency is broad, individuals with the distinctive findings of Leri-Weill dyschondrosteosis (LWD) described in Suggestive Findings are likely to be diagnosed using a combination of chromosomal microarray analysis (CMA) and gene-targeted testing (see Option 1), whereas individuals with SHOX-deficient short stature in which the phenotype may be indistinguishable from many other inherited disorders with short stature –particularly in early childhood – are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of Leri-Weill dyschondrosteosis (LWD) or SHOX-deficient short stature, molecular genetic testing approaches can include **methods to detect large deletions** and **methods to detect intragenic *SHOX* pathogenic variants**.

Methods to detect large deletions. Overall, 80%-90% of individuals with SHOX deficiency have deletions that vary in size from an intragenic single-exon deletion to (more commonly) 10 kb to 2.5 Mb or more. Of note, deletions with the *SHOX* enhancer regions that leave *SHOX* intact have been reported.

- **CMA,** which uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *SHOX)* that cannot be detected by sequence analysis, should be performed first.
- If a large *SHOX* deletion is not detected by CMA, perform **gene-targeted deletion/duplication analysis** next.
- Deletions can also be detected using **SNP array analysis.** Ideally, determining heterozygosity for (a) SNP(s) involves analysis of DNA from the proband and both parents.

Methods to detect intragenic pathogenic variants in the 10%-20% of individuals with SHOX deficiency who have an intragenic *SHOX* variant include the following:

- **Sequence analysis,** which detects small intragenic deletions/insertions and missense, nonsense, and splice site variants
- **A multigene panel** that includes *SHOX* and other genes of interest (see Differential Diagnosis). Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of

uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When SHOX-deficient short stature is indistinguishable from many other inherited disorders characterized by short stature, **comprehensive genomic testing** – which does not require the clinician to determine which gene(s) are likely involved – is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

Exome array (when clinically available) or alternatively CMA – if not previously performed – may be considered if exome sequencing is nondiagnostic.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Cytogenetic testing. If either a contiguous gene syndrome encompassing signs of a SHOX deficiency disorder (in addition to other distinctive features) or an X;Y chromosomal translocation is suspected, a G-banded karyotype should be carried out [Ballabio et al 1989, Shears et al 1998, Shears et al 2002]. Rarely, individuals with LWD may have one of the following:

- Balanced and unbalanced translocations involving X, Y, and other chromosomes [Shears et al 1998, Izumi et al 2007]
- Other complex sex-chromosome abnormalities [Wei et al 2001]

Table 1. Molecular Genetic Testing Used in SHOX Deficiency

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method[3, 4]
SHOX	Sequence analysis [5]	~10%-20%
	Gene-targeted deletion/duplication analysis [6]	Rare
	CMA / SNP array [7]	~80%-90%
	Karyotype	Rare

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Currently, about 10% of individuals with LWD do not have a demonstrable *SHOX* pathogenic variant and may either represent a false-negative result beyond the limits of current technology or represent phenocopies (true negatives).
4. Numbers vary between laboratories using different methodologies. Numbers also differ in patients from different ethnic origins.
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon (e.g., those described by Mitka et al [2016] and Shima et al [2016]) to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Chen et al [2009] and Shima et al [2016]) may not be detected by these methods.
7. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *SHOX* that cannot be detected by sequence analysis). The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the Xp22.32;Yp11.3 region. CMA designs in current clinical use target the Xp22.32;Yp11.3 region.
8. Balanced and unbalanced chromosome rearrangements disrupting *SHOX* have been detected in some individuals with SHOX deficiency [Shears et al 1998, Izumi et al 2007]; thus, chromosome analysis should be considered in those in whom SHOX deficiency is a strong possibility but whose molecular testing gave a normal result.

Clinical Characteristics

Clinical Description

The phenotypic spectrum of SHOX deficiency disorders ranges from Leri-Weill dyschondrosteosis (LWD) at the severe end of the spectrum to SHOX-deficient short stature (without mesomelia or Madelung deformity) at the mild end. In adults with SHOX deficiency, the proportion of LWD versus SHOX-deficient short stature is not well defined. In LWD the classic clinical triad is short stature, mesomelia, and Madelung deformity. Mesomelia, in which the middle portion of a limb is shortened in relation to the proximal portion, can be evident first in school-aged children and increases with age in frequency and severity. Madelung deformity (abnormal alignment of the radius, ulna, and carpal bones at the wrist) typically develops in mid-to-late childhood and is more common and severe in females. The phenotype of SHOX-deficient short stature is highly variable, even within the same family.

Leri-Weill Dyschondrosteosis (LWD)

Short stature. Natural growth in SHOX deficiency is not well studied. In a review of 129 individuals with SHOX deficiency, Munns et al [2003b] reported a progressive decline in the height z score from birth (-1.05), through childhood (female -2.23, male -2.10), and into final adult height (female -2.84, male -2.36).

- Antenatally detected shortening of the long bones attributable to SHOX deficiency was reported in five infants. In four of the five, SHOX deficiency was inherited from a previously undiagnosed parent with

final height z score between -1.2 and -1.9, suggesting that SHOX deficiency can be well tolerated within a favorable genetic context [Ramachandrappa et al 2018].
- Mean birth length is only mildly reduced, at 0.6-0.9 standard deviations (SD) below the mean [Munns et al 2003a, Binder et al 2004].
- Infancy is characterized by significant growth failure resulting in short stature in early childhood with mean heights of 2.1-2.2 SD below the mean [Ross et al 2001, Binder et al 2003, Munns et al 2003b].
- During childhood, there is probably no relevant additional loss of height.
- The pubertal growth spurt, however, appears to be blunted, resulting in an additional height deficit.

Mesomelia. Mesomelic disproportion of the skeleton with shortening of the extremities can be evident first in school-aged children and increase with age in frequency and severity [Ross et al 2001]. In very rare instances rhizomelic limb shortening can also be seen [Deshwar et al 2018, Ramachandrappa et al 2018].

Madelung deformity. Like mesomelia, Madelung deformity evolves with time and is generally more common and more severe in females. During infancy and early childhood, children with LWD may have subtle radiologic signs of Madelung deformity (i.e., lucency of the distal radius), but they are usually asymptomatic and the physical examination is normal.

Madelung deformity typically develops in mid-to-late childhood. The first common sign is a subtle reduction in pronation and supination of the forearm. The complete deformity with distal subluxation of the ulna (dinner fork sign) evolves during puberty and is associated with further restriction of forearm supination and pronation [Vickers & Nielsen 1992, Munns et al 2001].

Rarely, Madelung deformity causes joint pain in adolescence [Schmidt-Rohlfing et al 2001].

Other features of LWD [Rao et al 2001, Ross et al 2001, Munns et al 2003b, Rappold et al 2007, Rosilio et al 2012]:

- Hypertrophy of calf muscles
- Short fourth metacarpals
- Increased carrying angle of the elbow
- High-arched palate
- Scoliosis
- High body mass index (not caused by excess of fat mass)

No other visceral involvement occurs. Intellect is normal.

SHOX-Deficient Short Stature

When SHOX deficiency occurs in the absence of Madelung deformity and mesomelia excludes the diagnosis of LWD; in these instances, the diagnosis is SHOX-deficient short stature. The phenotype is highly variable, even within the same family [Rao et al 2001, Ross et al 2001, Munns et al 2003b, Rappold et al 2007, Rosilio et al 2012].

Genotype-Phenotype Correlations

No correlation has been established between the severity of phenotype and the underlying *SHOX* pathogenic variant [Clement-Jones et al 2000, Schiller et al 2000, Grigelioniene et al 2001, Ross et al 2001].

Based on a limited number of studies, the frequency of LWS is greater than SHOX-deficient short stature caused by a *SHOX* enhancer deletion [Chen et al 2009, Benito-Sanz et al 2012, Bunyan et al 2013], suggesting that enhancer deletions cause a more severe phenotype. In the French population, however, deletions of the downstream enhancer region of *SHOX* appear to be associated with a milder phenotype [Rosilio et al 2012]. Thus, this issue remains unresolved.

Penetrance

While the penetrance of SHOX deficiency is high, its clinical expression is highly variable, becomes more pronounced with age, and is more severe in females.

For reasons unknown, the female-to-male ratio in studied cohorts with SHOX deficiency is increased.

Prevalence

Estimates of the prevalence of SHOX deficiency depend on the inclusion criteria used for the selection of persons tested, the size of the cohort tested, and the genetic tests available for detecting pathogenic variants of *SHOX* and its enhancer regions.

LWD. Estimates of the prevalence of SHOX deficiency in LWD range from 70% to 90% [Binder et al 2004, Jorge & Arnhold 2007, Rappold et al 2007, Rosilio et al 2012].

Children with short stature of unknown cause (often called idiopathic short stature) and no signs of LWD. Taking into account the most recent reports that use MLPA and Sanger sequencing to detect *SHOX* deletions/duplications and *SHOX* enhancer deletions, the frequency of SHOX-deficient short stature in children with short stature of unknown cause and no signs of LWD ranges from 6% to 22% (for a review see Marchini et al [2016]).

Given the results of studies of *SHOX* pathogenic variants in children with short stature of unknown cause and given that not all individuals with a *SHOX* pathogenic variant have short stature, it has been estimated that the prevalence of SHOX deficiency is at least 1:1,000.

Genetically Related (Allelic) Disorders

Turner syndrome (TS). All individuals with Turner syndrome have *SHOX* haploinsufficiency because of numeric or structural aberration of the sex chromosome. TS occurs in 1:2,500 to 1:3,000 live female births [Sybert & McCauley 2004]. TS is diagnosed in the presence of characteristic physical features in combination with complete or partial absence of the second sex chromosome, with or without mosaicism [Ferguson-Smith 1965, Gravholt et al 2017].

Note: In the case of isolated Xp deletions, the diagnosis of TS is reserved for deletions larger than Xp22.3 [Saenger et al 2001]. Smaller distal Xp deletions encompassing *SHOX* and/or its regulatory regions are compatible with the diagnosis of *SHOX* deficiency, but not TS.

Characteristic physical features of TS are nonfamilial short stature with or without skeletal disproportion, pubertal delay because of primary hypogonadism, peripheral lymphedema, nuchal folds, left-sided cardiac anomalies (especially coarctation of the aorta or hypoplastic left heart), low hairline, low-set ears, small mandible, cubitus valgus, nail dysplasia, multiple pigmented nevi, characteristic facies, short fourth metacarpal, and chronic otitis media [Bondy & Turner Syndrome Study Group 2007]. Madelung deformity probably affects fewer than 5% of individuals with TS [Binder et al 2001].

The phenotype is variable and somewhat related to the karyotype; some individuals manifest only short stature or primary amenorrhea. Short stature, the most constant feature, is present in at least 95% of individuals with TS [Batch 2002]. The final adult height of women with TS is reduced by approximately 20 cm (3.0 SD below the mean) [Saenger et al 2001]. See Gravholt et al [2017] for a comprehensive review of TS.

Langer mesomelic dysplasia (LMD) (OMIM 249700) results from biallelic (homozygous or compound heterozygous) *SHOX* pathogenic variants resulting in *SHOX* nullizygosity [Belin et al 1998, Shears et al 1998, Ogata et al 2002, Shears et al 2002, Zinn et al 2002]. Several couples in which both members are affected with LWD have had offspring with LMD [Shears et al 2002, Thomas et al 2004].

LMD is a much more severe skeletal dysplasia than LWD and typically results in severe short stature with final heights ranging from 5.5 to 8.9 SD below the mean (data from case reports reviewed by Fukami et al [2005]). Shortening of the long tubular bones is more marked in the proximal segment of the extremity. LMD is characterized by aplasia or severe hypoplasia of the ulna and fibula, and thickened and curved radius and tibia; it may be associated with mild hypoplasia of the mandible. Typically, Madelung deformity is not part of LMD.

Contiguous gene syndromes on Xp22.3. Deletions of Xp22.3 can result in contiguous gene syndromes in males associated with variable combinations of ichthyosis and chondrodysplasia punctata (see Chondrodysplasia Punctata 2, X-Linked), hypogonadotropic hypogonadism and anosmia (see Isolated Gonadotropin-Releasing Hormone [GnRH] Deficiency), ocular albinism, intellectual disability, and SHOX-deficient short stature [Ballabio et al 1989, Spranger et al 1999, Boycott et al 2003, Doherty et al 2003].

Differential Diagnosis

The differential diagnosis of isolated SHOX-deficient short stature includes the following:

- Turner syndrome in females (See Genetically Related Disorders.)
- Children of both sexes with short stature of unknown cause (often called idiopathic short stature [ISS]). ISS is defined as height below the third centile in an individual for whom no skeletal, hormonal, chromosomal, or genetic etiology [Attie 2000]. With the recent use of methods to detect *SHOX* deletions/duplications and *SHOX* enhancer deletions, SHOX-deficient short stature appears to comprise 10% to 20% of children with apparent ISS [Hirschfeldova et al 2012, Rosilio et al 2012, Sandoval et al 2014, van Duyvenvoorde et al 2014, Poggi et al 2015]. (Using less sensitive molecular genetic testing methods, the prevalence of SHOX-deficient short stature in children who had been identified as having ISS was estimated at 2%-10% [Ezquieta et al 2002, Rappold et al 2002, Binder et al 2003, Stuppia et al 2003, Schneider et al 2005b, Huber et al 2006, Rappold et al 2007].)

The differential diagnosis of LWD caused by SHOX deficiency includes the following:

- Turner syndrome (See Genetically Related Disorders.)
- LWD caused by pathogenic variants at an unidentified alternate locus or in gene(s) outside the *SHOX* locus
- Trauma to, infection of, or tumors in the distal radial growth plate

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with SHOX deficiency, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended [Rappold et al 2007, Binder 2011]:

- **Growth parameters.** Height, arm span, and sitting height. Calculate extremities-to-trunk ratio or sitting height-to-height ratio (see Diagnosis).
- **Assessment of pubertal stage** in preadolescents to determine if use of recombinant human growth hormone (rhGH) is appropriate
- **Madelung deformity.** Prominence of distal ulna, limitation of forearm pronation and supination, and wrist pain
- **Scoliosis**
- **Body mass index.** Frequently above the mean; mainly because of shortening of the legs
- **Other.** Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Short Stature

For prepubertal children with short stature, recombinant human growth hormone (rhGH therapy) (dose 50 µg/kg body weight/day) should be offered. The therapeutic effect is a gain in final height of 7 to 10 cm. Hand/wrist radiographs for bone age determination should be taken at the initial visit and annually during rhGH therapy to assess maturation tempo.

Treatment with high-dose rhGH augments the growth of children with SHOX deficiency to the same extent as in Turner syndrome according to a two-year randomized controlled trial [Blum et al 2007]. This effect caused a similar gain in final height as well [Blum et al 2013]. No adverse radiologic effects were noted in those who were treated [Child et al 2015].

Painful Bilateral Madelung Deformity (uncommon)

Conservative management consists of wrist splints and supports during periods of increased discomfort and the use of ergonomic devices such as ergonomic computer keyboards. These measures may reduce wrist discomfort but do not alter the natural history of the deformity [Fagg 1988, Schmidt-Rohlfing et al 2001].

Different operative procedures have been attempted to decrease pain and restore wrist function [Anton et al 1938]. Although Anton et al did not recommend operating until skeletal maturity because of concern that surgery at an early age may result in further deformity, Vickers & Nielsen [1992] and Schmidt-Rohlfing et al [2001] reported encouraging results from prophylactic physiolysis of the ulnar (lateral) aspect of the distal radius and excision of the Vickers ligament (an abnormal fibroelastic ligament that runs from the lunate to the ulna aspect of the distal radius) during mid-to-late childhood. Their rationale for early intervention is to alter the natural history of the deformity by excising the area of dyschondrosteosis in the distal radius, thus restoring growth in the distal radius [Vickers & Nielsen 1992]. They reported decreased pain, increased function, and a reduction in wrist deformity following surgery over a period of 15 months to 12 years of follow up. They also speculate that MRI may allow for the early detection and subsequent removal of the Vickers ligament, which may play a central role in the development of Madelung deformity [Vickers & Nielsen 1992]. Similar results have been reported by Carter & Ezaki [2000] when a dome osteotomy of the radial metaphysis is combined with release of the Vickers ligament [Carter & Ezaki 2000].

Surveillance

The growth of a child with SHOX deficiency should be monitored every six months.

In case of growth failure or short stature, treatment with recombinant human growth hormone is an option to increase growth rate and adult height; consultation with a pediatric endocrinologist is recommended.

Agents/Circumstances to Avoid

If Madelung deformity is associated with discomfort, physical activities such as lifting, gripping, writing, typing, and sports that strain the wrist should be limited and ergonomic aids sought [Fagg 1988].

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of the sibs of an affected individual in order to identify as early as possible those who would also benefit from recombinant human growth hormone (rhGH) treatment.

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

SHOX deficiency disorders are inherited in a pseudoautosomal dominant manner. In pseudoautosomal dominant inheritance, homologous genes located on the short arm of the X chromosome (Xp) and the short arm of the Y chromosome (Yp) follow the rules of autosomal inheritance; thus, a *SHOX* pathogenic variant responsible for SHOX deficiency can be located on either the X or Y chromosome of an affected male, or on either of the X chromosomes of an affected female.

Risk to Family Members

Parents of a proband

- Many individuals diagnosed with SHOX deficiency have an affected parent.
- A proband with SHOX deficiency may have the disorder as the result of a *de novo* pathogenic variant. The exact proportion of cases caused by a *de novo* pathogenic variant is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include physical examination, radiographs of the wrists, and molecular genetic testing.
- In males an obligatory crossover during meiosis I results in transfer of genes located within pseudoautosomal region 1 from the Y chromosome to the X chromosome and vice versa. Because of the high recombination frequency in pseudoautosomal region 1 on Xp and Yp, males produce a mixture of sperm in which some harbor a Y-linked *SHOX* deletion and some an X-linked *SHOX* deletion. Because segregation of these sperm is identical to autosomal dominant inheritance, in some families such recombination results in [Flanagan et al 2002, Sabherwal et al 2004a, Kant et al 2011]:
  - The LWD phenotype (e.g., a father bearing a Y-linked *SHOX* deletion has a daughter with an X-linked *SHOX* deletion); and
  - Father-to-son transmission.
- The family history of some individuals diagnosed with SHOX deficiency may appear to be negative because of failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed unless appropriate evaluations and molecular genetic testing have been performed on the parents of the proband.
- Note: If the parent is the individual in whom the *SHOX* pathogenic variant first occurred, the parent may have somatic mosaicism for the pathogenic variant and may be mildly/minimally affected.

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

- If a parent of the proband is affected and/or is known to have the *SHOX* pathogenic variant identified in the proband, the risk to the sibs is 50%; intrafamilial clinical expression can be highly variable.

- If the *SHOX* pathogenic variant cannot be detected in the DNA of either parent, the recurrence risk to sibs is low, but greater than that of the general population because of the possibility of germline mosaicism. Germline mosaicism has not been reported to date.
- If the parents have not been tested for the *SHOX* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for SHOX deficiency because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism [Ramachandrappa et al 2018].

Offspring of a proband

- Each child of an individual with SHOX deficiency has a 50% chance of inheriting the *SHOX* pathogenic variant.
- If both parents have SHOX deficiency, the offspring have a 50% chance of inheriting one pathogenic variant and having SHOX deficiency, a 25% chance of inheriting two pathogenic variants and having Langer type of mesomelic dwarfism (see Genetically Related Disorders), and a 25% chance of having neither condition.
- Because many individuals with short stature select reproductive partners with short stature, offspring of individuals with SHOX deficiency may be at risk of having double heterozygosity for two dominantly inherited bone growth disorders. The phenotypes of these individuals are usually distinct from those of the parents [Ross et al 2003].

  If both parents have a dominantly inherited bone growth disorder, the offspring have a 25% chance of having the maternal bone growth disorder, a 25% chance of having the paternal bone growth disorder, a 25% chance of having normal stature and bone growth, and a 25% chance of having double heterozygosity for both disorders.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *SHOX* pathogenic variant, the parent's family members are at risk.

Related Genetic Counseling Issues

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

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with SHOX deficiency has the *SHOX* pathogenic variant or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *SHOX* pathogenic variant has been identified in one or both parents, prenatal and preimplantation genetic testing are possible. However, the phenotypic spectrum of SHOX deficiency disorders is broad and the phenotype cannot be accurately predicted on the basis of prenatal molecular genetic testing results.

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.

- **Bundesverband Kleinwüchsige Menschen (BKMF)**
  Leinestrasse 2
  28199 Bremen
  Germany
  Phone: 49-421-336169-0
  Email: info@bkmf.de
  www.bkmf.de
- **Human Growth Foundation**
  www.hgfound.org
- **Little People of America**
  Phone: 888-LPA-2001; 714-368-3689
  Fax: 707-721-1896
  Email: info@lpaonline.org
  lpaonline.org
- **MAGIC Foundation**
  Phone: 800-362-4423
  Email: contactus@magicfoundation.org
  www.magicfoundation.org
- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  Phone: 310-825-8998
  International Skeletal Dysplasia Registry

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. SHOX Deficiency Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SHOX	Xp22.33	Short stature homeobox protein	SHOX @ LOVD	SHOX	SHOX

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 SHOX Deficiency Disorders (View All in OMIM)

127300	LERI-WEILL DYSCHONDROSTEOSIS; LWD
312865	SHORT STATURE HOMEOBOX; SHOX
400020	SHORT STATURE HOMEOBOX, Y-LINKED; SHOXY

Molecular Pathogenesis

The short stature homeobox-containing gene *(SHOX)* is located within the pseudoautosomal region of the X (Xp22.3) and Y (Yp11.3) chromosomes. Although *SHOX* on the Y chromosome has been referred to as *SHOXY*, the official gene name, *SHOX*, does not refer to the chromosome on which it is located. Of note, *SHOX* escapes X-chromosome inactivation. The frequency with which pathogenic variants in *SHOX* occur on the X or Y chromosome is not known but is irrelevant, as this gene, located at the tip of the pseudoautosomal region, has an exchange rate of 50% in male meiosis [Kant et al 2011].

Gene structure. *SHOX* encodes two major transcripts, *SHOXa* (NM_000451.3) and *SHOXb* (NM_006883.2), each containing five coding exons and differing only in their 3'UTR and a small region of the coding sequence [Rao et al 1997]. Meanwhile, further transcript variants have been described, suggesting that alternative splicing contributes to the regulation of SHOX expression [Durand et al 2011]. For a summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 1,200 unique DNA variants and more than 180 pathogenic variants in *SHOX* have been described. An up-to-date list of these can be found on the Human Short Stature Gene Allelic Variant Database website (grenada.lumc.nl/LSDB_list/lsdbs/SHOX). (For more information, see Table A.)

The majority of *SHOX* pathogenic variants are large deletions encompassing the entire gene as well as adjacent genes.

Partial and complete duplications of *SHOX* have also been described [Benito-Sanz et al 2012, Sandoval et al 2014, van Duyvenvoorde et al 2014, Wit & Oostdijk 2015, Bunyan et al 2016, Benito-Sanz et al 2017, Hirschfeldova & Solc 2017, Upners et al 2017].

Normal gene product

- SHOXa, a 292-amino-acid protein [Rao et al 1997], is expressed in skeletal muscle, placenta, heart, bone marrow fibroblasts, and growth plate chondrocytes [Marchini et al 2004, Munns et al 2004].
- SHOXb, a 225-amino-acid protein [Rao et al 1997], is isolated to fetal kidney, placenta, and bone marrow fibroblasts [Rao et al 1997].

Because there is no *SHOX* mouse ortholog, use of a mouse knockout model has not been possible [Clement-Jones et al 2000]. However, expression of human SHOXa cDNA under the control of a murine *Col2a1* promoter and enhancer has been analyzed in transgenic mice [Beiser et al 2014]. Chicken *SHOX* models have also been a valuable model for limb development [Tiecke et al 2006, Sabherwal et al 2007, Durand et al 2010].

In human embryos *SHOX* is most strongly expressed in the mid-portion of limbs (especially the elbow and knee) and also in the distal ulna/radius and wrist [Clement-Jones et al 2000]. This expression pattern provides an explanation for the short stature, bowing, and shortening of the forearms and lower legs, the Madelung deformity, and the shortening of the fourth metacarpals seen in LWD and Turner syndrome [Clement-Jones et al 2000]. SHOX protein was also identified in human growth plate hypertrophic chondrocytes, further supporting a role for *SHOX* in bone development [Marchini et al 2004, Munns et al 2004].

SHOX is expressed in the first and second pharyngeal arches, suggesting that it may play a role in the development of the palatine maxillary sleeves, mandible, auricular ossicles, and the external auditory meatus [Clement-Jones et al 2000]. As such, haploinsufficiency of *SHOX* may cause the high-arched palate, micrognathia, and sensorineural deafness of Turner syndrome [Clement-Jones et al 2000].

SHOX acts as a nuclear transcription factor that inhibits cellular growth and apoptosis, possibly through the upregulation of p53 [Rao et al 2001, Blaschke et al 2003, Marchini et al 2004, Sabherwal et al 2004a, Sabherwal et

al 2004b]. In the absence of normal SHOX, chondrocytes may undergo atypical proliferation and differentiation [Marchini et al 2004, Marchini et al 2007, Marchini et al 2016].

Direct and indirect targets of the SHOX transcription factor have been described. The targets *BNP*, *FGFR3*, and *Ctgf* are directly regulated by SHOX, whereas the regulation of *Agc1* is indirect [Marchini et al 2007, Aza-Carmona et al 2011, Decker et al 2011, Beiser et al 2014].

An influence of SHOX as a regulator on FGFR3 signaling, CNP/Npr2 signaling and Bmp4 signaling and RUNX activity have been described (for a review see Marchini et al [2016]).

Abnormal gene product. The homeodomain of SHOX mediates several key functions including nuclear localization, DNA binding, and protein-protein interaction [Schneider et al 2005a]. Pathogenic variants within the homeodomain interfere with these processes and result in the skeletal defects. Pathogenic variants outside the homeodomain and deletions may lead to a reduced level of SHOX protein, thereby affecting growth and skeletal development.

Schneider et al [2005a] have shown that single missense pathogenic variants in *SHOX*, which were present in individuals with LWD or children with short stature of unknown cause (often called idiopathic short stature), alter the biologic function of SHOX with loss of DNA binding, dimerization, and/or nuclear localization [Schneider et al 2005a].

Recently, the first genetic modifier of SHOX deficiency, *CYP26C1* (which is associated with a more severe phenotype), was described [Montalbano et al 2016]. Subsequently, pathogenic variants in *CYP26C1* in the absence of pathogenic variants in *SHOX* have been associated with short stature [Montalbano et al 2018].

Chapter Notes

Author History

Gerhard Binder, MD (2015-present)
Ian Glass, MBChB, MD, FRCP, FACMG; University of Washington (2005-2015)
Craig Munns, MBBS, PhD, FRACP; The Children's Hospital at Westmead (2005-2015)
Gudrun A Rappold, PhD (2015-present)

Revision History

- 28 June 2018 (bp) Comprehensive update posted live
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- 4 October 2007 (cd) Revision: sequence analysis and prenatal diagnosis available clinically
- 22 January 2007 (cd) Revision: sequence analysis no longer clinically available
- 12 December 2005 (me) Review posted live
- 25 October 2004 (cm) Original submission

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