

# SHOX Deficiency Disorders, Sequencing and Deletion/Duplication

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Pathogenic variants in the *SHOX* gene result in a spectrum of disorders due to haploinsufficiency of the *SHOX* gene. Clinical features often include short stature, mesomelia (shortening of the lower portion of arm and leg), and abnormal alignment of the radius, ulna, and carpal bones at the wrist (Madelung deformity). Variable expressivity results in some individuals only affected with isolated short stature (ISS), whereas others have short stature and additional findings resulting in syndrome disorders (e.g., Leri-Weill dyschondrosteosis [LWD] or Langer mesomelic dysplasia [LMD]).

## Disease Overview

## Epidemiology

The prevalence for SHOX deficiency disorders is at least 1/1,000<sup>1</sup>

## Associated Conditions

Condition <sup>a</sup>	MIM Number	Clinical Information
Isolated/idiopathic short stature	300582	Short stature (below the third percentile) of unknown cause Usually no mesomelia or Madelung deformity Highly variable presentation even within the same family 6-22% have one pathogenic <i>SHOX</i> variant <sup>2</sup>
Leri-Weill dyschondrosteosis	127300	Triad of short stature in early childhood, mesomelia, and Madelung deformity Madelung deformity typically develops in mid-late childhood Other features may include high-arched palate, bowing of forearm, hypertrophy of calf muscles, short fourth metacarpals, scoliosis More common and severe in females 70-90% have one pathogenic <i>SHOX</i> variant <sup>2</sup>
Langer mesomelic dysplasia	249700	Severe short stature, hypoplasia/aplasia of the ulna and fibula, and thickened/curved radius and tibia More severe than LWD Very rare

<sup>a</sup>In addition to the conditions listed, Turner syndrome (45,X) and contiguous gene deletion syndromes containing the *SHOX* region share some features.

Sources: Binder, 2018<sup>1</sup>; Marchini, 2016<sup>2</sup>; John Hopkins University, 2021<sup>3</sup>

## Genetics

## Inheritance

Pseudoautosomal inheritance<sup>1</sup>

- Homologous *SHOX* genes are located on the X chromosome and Y chromosome and follow autosomal inheritance instead of sex-linked inheritance.

## Featured ARUP Testing

### SHOX Deficiency Disorders, Sequencing and Deletion/Duplication 3004603

**Method:** Massively Parallel Sequencing/Multiplex Ligation-Dependent Probe Amplification (MLPA)

Use to detect pathogenic variants in the *SHOX* gene which cause SHOX deficiency disorders (e.g., ISS, LWD, or LMD)

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the [Laboratory Test Directory](#) for additional information.

- A *SHOX* pathogenic variant causing a SHOX deficiency disorder can be located on either of the X chromosomes in a female or on either the X or Y chromosome in a male.
  - Pseudoautosomal dominant for LWD and ISS; haploinsufficiency caused by only one functional/expressed copy of *SHOX* gene
  - Pseudoautosomal recessive for LMD; complete loss of *SHOX* function/expression due to biallelic inactivation

## Penetrance

High, with variable expressivity and an increased female:male ratio<sup>1</sup>

## Etiology

- Deletions account for 80-90% of pathogenic variants<sup>1</sup>
  - Range from single exon deletions to >2.5 Mb or larger
  - Intragenic deletions and deletions involving enhancer elements are reported
- Sequence variants account for 10-20% of pathogenic variants<sup>1</sup>

## Test Interpretation

### Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as NGS) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Multiplex ligation-dependent probe amplification (MLPA) is performed to call exon-level deletions and duplications.

### Clinical Sensitivity

- At least 90% for SHOX deficiency disorders<sup>1</sup>
- About 10% of individuals with LWD do not have a demonstrable *SHOX* pathogenic variant<sup>1</sup>

### Analytic Sensitivity/Specificity

For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate <sup>a</sup> (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp <sup>b</sup>	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp <sup>b</sup>	94.8 (86.8-98.5)	>99.9

<sup>a</sup>Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

<sup>b</sup>Variants greater than 10 bp may be detected, but the analytical sensitivity may be reduced.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

### MLPA

>99%

### Results

Result	Variant(s) Detected	Clinical Significance
Positive	One pathogenic <i>SHOX</i> variant detected	Confirms a diagnosis of LWD or ISS

Result	Variant(s) Detected	Clinical Significance
	Two pathogenic <i>SHOX</i> variants detected	Confirms diagnosis of LMD if located on opposite chromosomes
Negative	No pathogenic <i>SHOX</i> variants detected	Decreases likelihood of, but does not exclude, a diagnosis of a <i>SHOX</i> deficiency disorder
Inconclusive	Variant of uncertain clinical significance detected	Diagnosis of a <i>SHOX</i> deficiency disorder can neither be confirmed nor excluded

## Limitations

- A negative result does not exclude a diagnosis of a *SHOX* deficiency disorder.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- *SHOX* (NM\_006883) exon 6, also known as exon 6b, is not sequenced due to technical limitations of the assay.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted gene(s)
  - Regulatory region and deep intronic variants
  - Breakpoints of large deletions/duplications
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Single exon deletions/duplications based on the breakpoints of the rearrangement
  - Noncoding transcripts
  - Low-level somatic variants
  - Certain other variants due to technical limitations in the presence of pseudogenes and repetitive/homologous regions
- MLPA results suggestive of aneuploidy will require further analyses by other methods (e.g., chromosome analysis/karyotype, microarray, etc.) for confirmation.

## References

1. Binder G, Rappold GA. [SHOX deficiency disorders](#). In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews*. University of Washington, Seattle. Last update Jun 2018; accessed Dec 2021.
2. Marchini A, Ogata T, Rappold GA. [A track record on SHOX: from basic research to complex models and therapy](#). *Endocr Rev*. 2016;37(4):417-448.
3. [Online Mendelian inheritance in man](#). John Hopkins University. Updated Dec 2021; accessed Dec 2021.

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