# SHOX Deficiency Disorders, Sequencing and Deletion/Duplication

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 (eg, Leri-Weill dyschondrosteosis [LWD] or Langer mesomelic dysplasia [LMD]).

## Disease Overview

### Epidemiology

The prevalence for SHOX deficiency disorders is at least 1/1,000[1]

### Associated Conditions

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

[a]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[1]; Marchini, 2016[2]; John Hopkins University, 2021[3]

## Tests to Consider

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

**Method:** Massively Parallel Sequencing/Multiplex Ligation-dependent Probe Amplification

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

**Related Tests**

### Cytogenomic SNP Microarray 2003414

**Method:** Genomic Microarray (Oligo-SNP Array)

Useful if there is suspicion of a large, contiguous gene deletion/duplication that includes the *SHOX* gene

### Chromosome Analysis, Constitutional Peripheral Blood 2002289

**Method:** Giemsa Band

May be helpful to determine mechanism of *SHOX* deletions (eg, translocations, Turner syndrome, etc.)

### Familial Mutation, Targeted Sequencing 2001961

**Method:** Polymerase Chain Reaction/Sequencing

- Useful to confirm a diagnosis when a pathogenic sequence variant has been previously identified in a family member
- A copy of the family member's test result documenting the familial variant is REQUIRED.

### Deletion/Duplication Analysis by MLPA 3003144

**Method:** Multiplex Ligation-dependent Probe Amplification

- Useful to confirm a diagnosis when a pathogenic deletion/duplication variant has been previously identified in a family member
- A copy of the family member's test result documenting the familial variant is REQUIRED.

# Genetics

## Inheritance

Pseudoautosomal inheritance[1]

- Homologous *SHOX* genes are located on the X chromosome and Y chromosome and follow autosomal inheritance instead of sex-linked inheritance.
- 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[1]

## Etiology

- Deletions account for 80-90% of pathogenic variants[1]
  - 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[1]

# 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[1]
- About 10% of individuals with LWD do not have a demonstrable *SHOX* pathogenic variant[1]

## Analytical Sensitivity/Specificity

For massively parallel sequencing:

| Variant Class | Analytical Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%) | Analytical Specificity (NPA) (%) |
|---|---|---|
| SNVs | >99 (96.9-99.4) | >99.9 |

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

[b]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

| Variant Class | Analytical Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%) | Analytical Specificity (NPA) (%) |
|---|---|---|
| Deletions 1-10 bp[b] | 93.8 (84.3-98.2) | >99.9 |
| Insertions 1-10 bp[b] | 94.8 (86.8-98.5) | >99.9 |

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

[b]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 *SHOX* variant detected | Confirms a diagnosis of LWD or ISS |
| | Two pathogenic *SHOX* variants detected | Confirms diagnosis of LMD if located on opposite chromosomes |
| Negative | No pathogenic *SHOX* variants detected | Decreases likelihood of, but does not exclude, a diagnosis of a SHOX deficiency disorder |
| Inconclusive | Variant of uncertain clinical significance detected | Diagnosis of a SHOX 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
  - 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 (eg, 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, editors. GeneReviews, University of Washington; 1993-2021. [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]

## Additional Resources

Hirschfeldova K, Florianova M, Kebrdlova V, et al. Detection of SHOX gene aberrations in routine diagnostic practice and evaluation of phenotype scoring form effectiveness. *J Hum Genet*. 2017;62(2):253-257.

Niesler B, Röth R, Wilke S, et al. The novel human SHOX allelic variant database. *Hum Mutat*. 2007;28(10):933-938.

SHOX gene (protein coding). GeneCards: Human Gene Database, Weizmann Institute of Science. [Accessed: Dec 2021]

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