SHOX-Related Disorders

Pathogenic variants in the SHOX gene result in a spectrum of disorders due to haploinsufficiency of the SHOX gene/protein. 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 wrist (Madelung deformity). Variable expressivity results in some individuals affected only with isolated short stature (ISS), while others have short stature and additional findings resulting in syndrome disorders (e.g., Leri-Weill dyschondrosteosis [LWD] or Langer mesomelic dysplasia [LMD]).

TESTS TO CONSIDER

SHOX-Related Disorders, Deletion/Duplication with Reflex to Sequencing 3001401
Method: Multiplex Ligation-dependent Probe Amplification/Polymerase Chain Reaction/Sequencing
Most comprehensive test for molecular confirmation of SHOX-related disorders
Deletion/duplication analysis is performed first; sequencing will then be performed based on clinical information/suspected diagnosis provided and result of deletion/duplication analysis

SHOX-Related Disorders, Deletion/Duplication 3001395
Method: Multiplex Ligation-dependent Probe Amplification
Primary test for molecular confirmation of SHOX-related disorders
Does not detect sequence variants

SHOX-Related Disorders, Sequencing 3001399
Method: Polymerase Chain Reaction/Sequencing
Used when prior SHOX deletion/duplication testing does not explain the clinical phenotype

Cytogenomic SNP Microarray 2003414
Method: Genomic Microarray (Oligo-SNP Array)
Useful if there is suspicion for a large, contiguous gene deletion/duplication that includes the SHOX gene

Chromosome Analysis, Peripheral Blood 2002289
Method: Giemsa Band
May be helpful to determine mechanism of SHOX deletions (e.g., translocations, Turner syndrome)

Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing

DISEASE OVERVIEW

Prevalence
At least 1/1,000 for a SHOX deficiency related disorders
- Isolated/idiopathic short stature (ISS); MIM 300582
  - Stature (below the third percentile)
  - Usually no mesomelia or Madelung deformity
  - 6-15% have one pathogenic SHOX variant
  - Highly variable presentation even within the same family
- Leri-Weill dyschondrosteosis (LWD); MIM 127300
  - Symptoms -- triad of short stature in early childhood, mesomelia, and Madelung deformity
  - Madelung deformity typically develops in mid-late childhood; more common and severe in females
  - Other features may include high-arched palate, bowing of forearm, hypertrophy of calf muscles, short fourth metacarpals, scoliosis
  - 70-90% have one pathogenic SHOX variant
- Langer mesomelic dysplasia (LMD); MIM 249700
  - Symptoms -- more severe than LWD; severe short stature, hypoplasia/aplasia of the ulna and fibula and thickened/curved radius and tibia; very rare
  - Typically do not have Madelung deformity
  - Most patients have two pathogenic SHOX variants on opposite chromosomes leading to complete absence of functional SHOX protein
  - Others: Turner syndrome (45,X) and contiguous gene deletion syndromes containing the SHOX region share some features

GENETICS

Short stature homeobox-containing SHOX gene
- Composed of 6 exons; 35 kb
- Produces a transcription factor for skeletal development, especially growth and maturation of long bones in arms/legs
- Located in pseudoautosomal region 1 (PAR1) on short arms of X and Y chromosomes
- Gene does not undergo X-inactivation; males and females typically have two functional/expressed copies of SHOX gene
- Enhancer elements located upstream and downstream of the gene regulate SHOX expression
Inheritance
Pseudoautosomal inheritance
- 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 SHOX deficiency 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
- Some cases may be caused by a de novo pathogenic variant but the specific proportion of such cases is unknown
- Germline mosaicism is possible, but not reported to date

Penetrance
High
- Variable expressivity
- Increased female: male ratio

Etiology
- Most pathogenic SHOX variants are deletions (80-90%)
  - Range from single exon deletions to >2.5 Mb or larger
  - Intragenic and enhancer elements deletions are reported
- Sequence variants account for 10-20% of pathogenic variants

TEST INTERPRETATION

Clinical Sensitivity
- Deletion/duplication analysis: 80-90%
- Sanger sequencing: 10-20%

Analytical Sensitivity/Specificity
>99%

Results

<table>
<thead>
<tr>
<th>SHOX copy number</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
<td>Homozygous deletion&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>1</td>
<td>Heterozygous deletion&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>Heterozygous duplication&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Homozygous duplication or heterozygous triplication&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
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<sup>a</sup>Typically diagnostic for SHOX-related disorders (ISS, LWD, LMD)
<sup>b</sup>May or may not be associated with SHOX-related disorders; could be associated with chromosomal aneuploidy

Possible Results by Sanger Sequencing
- One pathogenic SHOX variant detected
  - Confirms a diagnosis of LWD or ISS
- Two pathogenic SHOX variants detected
  - Confirms diagnosis of LMD

Negative Result
No pathogenic SHOX variants detected
- Decreases likelihood of, but does not exclude, a diagnosis of a SHOX-related disorder
Inconclusive Result
Variant of uncertain clinical significance detected
- Diagnosis of a SHOX-related disorder can neither be confirmed nor excluded

Limitations
- Not all copy number changes will affect gene function and result in disease
  - Not detected:
    - Breakpoints of deletions
    - Deep intronic and some regulatory variants
    - Most chromosomal inversions or translocations
- Diagnostic errors can occur due to rare sequence variants or repeat element insertions
- MLPA results suggestive of aneuploidy will require further analyses by other methods (chromosome analysis/karyotype, microarray, etc.) for confirmation.

REFERENCES