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

Disease Overview

Prevalence

At least 1/1,000 for a *SHOX* deficiency-related disorder

- 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

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

Related Tests

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, Constitutional Peripheral Blood 2002289

Method: Giemsa Band

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

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

- Useful for confirming a diagnosis when a pathogenic sequence variant has been identified in family member
- A copy of the family member's lab report documenting the familial variant is REQUIRED

Deletion/Duplication Analysis by MLPA 3003144

Method: Multiplex Ligation-dependent Probe Amplification

- Useful for confirming a diagnosis when a pathogenic deletion/duplication variant has been identified in family member
- A copy of the family member's lab report documenting the familial variant is REQUIRED

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

Possible Results by Deletion/Duplication Analysis	
***SHOX* copy number**	**Interpretation**
0	Homozygous deletion[a]
1	Heterozygous deletion[a]
2	Normal
3	Heterozygous duplication[b]

[a]Typically diagnostic for *SHOX*-related disorders (ISS, LWD, LMD)

[b]May or may not be associated with *SHOX*-related disorders; could be associated with chromosomal aneuploidy

SHOX copy number	Interpretation
4	Homozygous duplication or heterozygous triplication[b]

[a]Typically diagnostic for *SHOX*-related disorders (ISS, LWD, LMD)

[b]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.

Additional Resources

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