**SHOX-related Haploinsufficiency Disorders: SHOX Gene Sequencing**

**Condition Description**

SHOX-related haploinsufficiency disorders are a spectrum of disorders that range from Leri-Weill dyschondrosteosis (LWD) (severe) to SHOX-related short stature (mild). LWD is characterized by three features; mesomelia (the middle portion of the limb is shortened in relation to the proximal portion), Madelung deformity (abnormal alignment of the radius, ulna, and carpal bones at the wrist), and short stature. Individuals with SHOX-related short stature have disproportionate short stature and/or wrist abnormalities.

Mutations in the SHOX gene, located on the pseudoautosomal regions of the X and Y chromosomes (Xp22.3 and Yp11.3), cause SHOX-related haploinsufficiency disorders. Mutations/deletions can be identified in ~70% of individuals with LWD. SHOX-related haploinsufficiency disorders are inherited in a pseudoautosomal dominant manner.

Individuals who have mutations in two copies of the SHOX gene have Langer mesomelic dysplasia (LMD). LMD is much more severe than LWD and is characterized by severe short stature and severe skeletal dysplasia.

**References:**

- GeneReviews
- OMIM #312865: SHOX gene
- OMIM #127300: LWD
- OMIM #249700: LMD
- OMIM #300582: SHOX-related short stature

**Genes**

**SHOX**

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of SHOX-related haploinsufficiency disorders.
- Carrier testing in adults with a family history of SHOX-related haploinsufficiency disorders.

**Methodology**

PCR amplification of 5 exons contained in the SHOX gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

**Detection**

Clinical Sensitivity: Mutations/deletions can be identified in ~70% of individuals with LWD. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Analytical Sensitivity: ~99%

**Specimen Requirements**

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.
Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Related Tests**

- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.