

What is the SHOX-DNA-Dx™ test?

SHOX-DNA-Dx™ is a genetic test that detects sequence variants, including whole gene deletions, in the SHOX gene. This test can be used to confirm a diagnosis of Léri-Weill syndrome, establish a genetic etiology for idiopathic short stature, determine carrier status of individuals in families with a previously identified SHOX gene mutation, and may be useful for identifying individuals appropriate for specific therapies.

What is the SHOX gene?

Discovered in 1997, SHOX is an acronym for the Short-stature Homeobox gene, which is located on the short arms of the X and Y chromosomes in the pseudoautosomal region. A deficiency in one copy of the SHOX gene is believed to be the basis for short stature in Turner syndrome. In addition, deficiency in one copy of the SHOX gene is detected in the majority of individuals with Léri-Weill syndrome and in some individuals with idiopathic short stature. Deficiency of both copies of the SHOX gene is usually detected in individuals with Langer syndrome.

What are the types of genetic defects that have been found in the SHOX gene?

About two-thirds of the variants described in the SHOX gene are large deletions of the entire gene. A gene deletion is virtually certain to result in SHOX deficiency. The other variants detected are smaller changes including small insertions and deletions and single-site changes. These smaller genetic changes can have varying influence on the function of the SHOX gene.

How is the SHOX gene analyzed and what are the possible results that can be obtained by the SHOX-DNA-Dx™ test?

SHOX-DNA-Dx™ uses molecular methods that detect whole SHOX gene deletions and smaller gene variants. Whole gene deletions are detected by analyzing single nucleotide polymorphisms (SNPs) spanning the SHOX gene. The absence of heterozygosity for all the SNPs is compelling evidence of a SHOX gene deletion. The smaller gene variants are detected by denaturing high performance liquid chromatography (DHPLC). Any variants detected by DHPLC are characterized by DNA sequencing. From the DNA sequence, the predicted effect of the variant on SHOX gene function is determined. It is also possible that no variant will be detected.

How are the results of the SHOX-DNA-Dx™ test interpreted?

The test report describes whether or not a variant(s) has been detected, and if detected, explains the predicted effect of the variant(s) on gene function. In some cases, the clinical significance of a variant will not be known. Some general guidelines for interpretation of different types of genetic variants can be found in the published guidelines of the American College of Medical Genetics Laboratory Practice Committee Working Group (Reference 1).

What are the specimen and submission requirements for SHOX-DNA-Dx™ testing?

Specimen type: 3 mL whole blood collected in an EDTA (lavender-top) plastic tube.

Shipping details: Complete the Test Request Form (test code 504005), and include with each sample. Call Esoterix for sample pick-up. When direct shipping is required, follow the basic IATA guidelines as summarized here. Submit the sample in a sealed plastic tube like the lavender-top vacutainer tube or other closed plastic tube. Wrap each tube submitted and place the tube and forms within a secondary leak-proof package* and place this secondary container inside a rigid outer package like a fibreboard box**. Label the outer box with a diamond-shaped square label sign displaying UN3373. Next to the diamond-shaped label mark the box with the words "Diagnostic Specimens". Note the same description should be included on any air waybill. *See IATA regulations for more detail. Leak-proof means able to withstand without leaking an internal pressure of 95 kPa at -40°C-55°C.

**To meet regulations the final sealed package must withstand a drop from 1.2 meters without damage to the contents.

What is the sample stability for SHOX-DNA-Dx™ testing and what are the sample rejection criteria?

Stability: Four days at ambient temperature, Seven days refrigerated. Do not freeze or freeze and thaw.

Sample rejection criteria. Frozen samples will be rejected. Samples older than seven days may be rejected. Alternate sample types like purified DNA or swabs may not be suitable. Consult the laboratory directly prior to submitting alternate sample types.

When will you get the laboratory report?

Test turnaround time: Usually a report will be available within two weeks after the sample is received.

How are questions about the report managed? How do I contact the laboratory?

Contact us at 800-444-9111 to arrange a technical consultation with the laboratory, or by E Mail using the address: CLBMolecularBiology@esoterix.com.

How much is the testing fee?

Testing list fee: third party \$700, client \$400. Esoterix can accept credit card payment, or payment from private insurance or governmental providers. Esoterix can invoice the appropriate insurance or governmental provider. Please be sure to provide payor information.

Do you have references for SHOX testing?

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4. Binder G., Schwarze C.P. & Ranke M.B. Identification of short stature caused by SHOX defects and therapeutic effect of recombinant human growth hormone. *J. Clin. Endocrinol. Metab.* 85, 245-249 (2000).
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Ellison J.W. et al. PHOG, a candidate gene for involvement in the short stature of Turner syndrome. *Hum. Mol. Genet.* 6, 1341-1347 (1997).
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9. Ogata et al. SHOX haploinsufficiency and overdosage: impact of gonadal function status (Review). *J. Med. Genet.* 38, 1-6 (2001).
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11. Sabherwal N., et al. A novel point mutation A170P in the SHOX gene defines impaired nuclear translocation as a molecular cause for Léri-Weill dyschondrosteosis and Langer dysplasia. *J. Med. Genet.* 41, e83 (2004).
12. Schiller S. et al. Phenotypic variation and genetic heterogeneity in Léri-Weill syndrome. *Eur. J. Hum. Genet.* 8, 54-62 (2000).
13. Shears D.J. et al. Mutation and deletion of the pseudoautosomal gene SHOX cause Leri-Weill dyschondrosteosis. *Nature Genet.* 19, 70-73 (1998).
14. Rappold, G et al. Screening for Short Stature Homeobox (SHOX) Gene Defects. Abstract Pediatric Academic Societies 2006.

Online SHOX gene variant databases and resources

1. Human short stature gene allelic variant database: <http://www.shox.uni-hd.de/>
2. Human gene mutation database: <http://www.hgmd.cf.ac.uk/>
3. GeneTests GeneReview on SHOX-related haploinsufficiency disorders:
<http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=O2NO3KwC2NFep&gry=&fcn=y&fw=TBKE&filename=/profiles/lwd/index.html>



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