

Spondylocostal Dysostosis Testing via Sequential *DLL3*, *MESP2*, and *LFNG* Gene Sequencing

Brief Description of Disorder: Spondylocostal Dysostosis (SCD) (OMIM 277300, 608681, 609813) is characterized by abnormal segmentation of the vertebral column. Patients have short trunks with multiple vertebral defects and rib anomalies (Turnpenny et al. J Med Genet 40:333-339, 2003). An autosomal dominant and three autosomal recessive forms (Types 1-3) of SCD are known. The most common recessive type (Type 1) is caused by mutations in the *DLL3* gene. Types 2 and 3 are caused by mutations in the *MESP2* and *LFNG* genes, respectively.

Genetics: All three types of SCD that have been characterized genetically are autosomal recessive. About 25 causative mutations have been reported in the *DLL3* gene (Bulman et al. Nature Genet 24:438-441, 2000). Mutations are located throughout the length of the *DLL3* gene. No mutations are predominant. Although some missense mutations have been reported, the great majority of causative mutations have been nonsense, splicing, and particularly, frameshift. To date, only one carefully documented causative mutation has been reported in each of the *MESP2* (Whitlock et al. Am J Hum Genet 74:1249-1254, 2004) and *LFNG* (Sparrow et al. Am J Hum Genet 78:28-37, 2006) genes. Insufficient cases have yet been studied to draw firm conclusions about phenotypic differences among the three types. See the PreventionGenetics Test Descriptions for the individual *DLL3*, *MESP2* and *LFNG* tests for more information.

Description of This Particular Test: This test has two sequential tiers. Tier 1 involves bidirectional DNA sequencing of the coding regions of all 8 exons of *DLL3*. If two likely causative mutations are found in *DLL3*, testing stops. Otherwise, testing continues with full sequencing of all coding exons of both *MESP2* and *LFNG*.

Indications for Test: All SCD patients are candidates for this test. We offer sequencing of one or two exons in parents and other family members of patients with known mutations. We also offer clinical confirmation of mutations that have been identified in research labs.

Sensitivity of Test: Sparrow et al. (Am J Hum Genet 78:28-37, 2006) reported that 20-25% of SCD patients have mutations in *DLL3*. *DLL3* mutations appear to be by far the most common, known cause of SCD. Causative mutations in *MESP2* and *LFNG* are each probably responsible for < 5% of SCD patients.

Turn Around Time: Maximum of 40 days, although many tests are completed in 2-3 weeks. A 10 day STAT option for an additional \$250 is also available.

SPECIMEN REQUIREMENTS: See page 4 of the Requisition Form.

Prices:	Tier 1 alone	\$540	Tier 2 alone	\$790
	Tiers 1 and 2	\$1290		
Ascertainment	83890	\$ 30	DNA Isolation	83891 \$ 40
Amplification X18	83898	\$ 410	Mutation Ident by Sequencing X19	83904 \$ 620
Separation	83894	\$ 60	Interpretation and Report	83912 \$ 130

Single exon sequencing for the presence of previously identified mutations in any gene that we test is available for \$190, or two exon sequencing for \$340.

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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