

Spondylocostal Dysostosis and Spondylothoracic Dysostosis via *MESP2* Gene Sequencing (Test #423)

Brief Description of Disorder: Spondylocostal Dysostosis (SCD) (OMIM 277300, 608681, 609813) is characterized by asymmetry of rib fusions as well as fused, block and hemi vertebra. Patients have short trunks with multiple vertebral defects and rib anomalies (Turnpenny et al. *J Med Genet* 40:333-339, 2003). SCD have a high rate of mild congenital scoliosis. An autosomal dominant and three autosomal recessive forms (Types 1-3) of SCD are known. Spondylothoracic Dysostosis (STD; also known as Lavy-Moseley syndrome) is characterized by markedly shortened thorax (the thoracic spine is fused and the ribs are fused posteriorly creating a fan-like or “crab” configuration). Mild scoliosis may be present, but is uncommon. There has been confusion regarding the distinction between these two phenotypically similar syndromes that cause thoracic insufficiency. In general, SCD causes mild to moderate respiratory insufficiency and is panethnic, while STD results in more severe respiratory compromise and is largely linked to Puerto Rican cohorts (Berdon et al. *Pediatr Radiol* 41:384-388, 2011).

Genetics: SCD and STD are both inherited in an autosomal recessive manner. SCD Type 2 is caused by mutations in the *MESP2* gene. The same gene is also known to be causative for STD. *MESP2* mutations have been reported in a number of Puerto Rican families with STD (Cornier et al. *Am J Med Genet* 128A:120-126, 2004; Cornier et al. *Am J Hum Genet* 82:1334-1341, 2008) as well as one Lebanese family with SCD (Whitlock et al. *Am J Hum Genet* 74:1249-1254, 2004). Most of patients with Puerto Rican origin carry a homozygous nonsense mutation p.Glu103Stop, likely indicating a founder effect. Affected children from the reported Lebanese family were homozygous for a frameshift mutation (c.500_503dupACCG). Other nonsense and missense mutations in *MESP2* have also been reported.

Description of This Particular Test: This test involves bidirectional DNA sequencing of the coding regions of all exons of the *MESP2* gene plus ~50 bp of flanking non-coding DNA on each side. As indicated, we will also sequence any single exon (Test #100, \$190) or pair of exons (Test #200, \$340) in family members of patients with known mutations, or to confirm research results.

Reference Sequences: Genomic: NC_000015.8 mRNA: NM_001039958.1 Protein: NP_001035047.1

Indications for Test: Candidates for this test are patients with clinical and radiographic findings consistent with STD, and family members of patients who have a known *MESP2* mutation. SCD patients that do not carry *DLL3* mutations are also candidates for this test.

Sensitivity of Test: Sensitivity should be high (>90%) among STD patients with Puerto Rican ancestry (Cornier et al. 2008). The percent of STD caused by mutations in *MESP2* may vary by ethnic background. Probably <5% of SCD patients have causative mutations in *MESP2* (Sparrow et al. *Am J Hum Genet* 78:28-37, 2006).

Turnaround Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of Requisition Form.

Price: Sequencing of the *MESP2* Gene: \$ 440

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x13	83898 \$ 90	Sequencing x13	83904 \$ 130
Separation x1	83894 \$ 30	Interpretation/Report x1	83912 \$ 120

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

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