

Sotos Syndrome via *NSDI* Gene Sequencing (Test #132)

Brief Description of Clinical Features: Sotos Syndrome (OMIM 117550) is characterized clinically by cardinal features of craniofacial dysmorphism, childhood overgrowth and learning disability. Variable features include behavioral problems; advanced bone age among childhood-aged patients; congenital heart defects; cranial defects; joint hyperlaxity; structural renal abnormalities; scoliosis; seizures; and jaundice, poor feeding and hypotonia in newborns (Cole, Tatton-Brown and Rahman *GeneReviews*, 2009). Children with Sotos syndrome uniformly have macrocephaly, approximately half of which is acquired in the first year of life. Other craniofacial features include dolicocephaly, sparse hair in the frontopareital region, prominent jaw, down-slanting palpebral fissures, and malar flushing. Mental deficiency is variable ranging from mild to severe. Early signs of delay are apparent and often motor delay is first noticeable because of poor coordination and hypotonia. Overgrowth is prenatal in onset, and length is affected more than weight. Through childhood and adolescence growth remains at or above 97th percentile but final height is often within normal range. An estimated risk of 3.9% for developing benign or malignant tumors has been proposed for Sotos syndrome (Gorlin et al. In: *Syndromes of the Head and Neck*. 3rd Ed. NY, Oxford Univ Press, 1990).

Genetics: Sotos syndrome is a fully penetrant autosomal dominant disorder. Approximately 95% of Sotos syndrome patients have *de novo NSDI* mutations and 5% have an affected parent. Haploinsufficiency for *NSDI*, the most common etiology, results from intragenic point mutations (~80%), 5q35 microdeletions (~10%) or partial *NSDI* gene deletions (~5%), (Douglas et al. *Am J Hum Genet* 72:132-143, 2003; Tatton-Brown et al. *Am J Hum Genet* 77:193-204, 2005). Missense mutations are limited to functional domains of the protein while nonsense mutations occur throughout the protein. Compared to patients with *NSDI* intragenic point mutations, patients with microdeletions have been found to have more severe learning disability and less prominent overgrowth (Tatton-Brown et al. 2005). Some patients with Weaver syndrome (OMIM 277590) have been found to also have mutations in the *NSDI* gene (Douglas et al. 2003).

Description of This Particular Test: Nuclear Receptor SET Domain-Containing Protein 1 is coded by exons 2-23 of the *NSDI* gene on chromosome 5q35. Testing is accomplished by amplifying each coding exon and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. This test will not detect partial *NSDI* gene deletions or 5q35 microdeletions. As indicated, we will also sequence any single exon (Test #100, \$190) in family members of patients with a known mutation or to confirm research results.

Reference Sequences: Genomic: **NC_000005.9** mRNA: **NM_002245.4**
 Protein: **NP_071900.2** mRNA and Protein: **CCDS 4412.1**

Indication for Testing: A child with characteristic facial features, developmental delay and overgrowth.

Sensitivity of test: Clinical sensitivity of *NSDI* sequencing should be high in children with the facial gestalt in conjunction with overgrowth, macrocephaly, and developmental delay (Turkmen et al. *Europ J Hum Genet* 11:858-865, 2003). Among 266 *NSDI* positive patients, Tatton-Brown et al. (2005) found point mutations in 83%. Similarly, Douglas et al. (2003) found *NSDI* point mutations in 76% of a group of subjects characterized as typical Sotos syndrome patients. The same authors found three of seven Weaver syndrome patients to have *NSDI* mutations, all between amino acids 2142 and 2184.

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

Specimen Requirements: See page 4 of the Requisition Form.

Price:	Sequencing of <i>NSDI</i> Gene	Exons 2-23	\$ 1590
CPT Codes:			
Sample Ascertainment	83890 \$ 30	DNA Isolation	83891 \$ 40
Amplification x33	83898 \$ 520	Sequencing x33	83904 \$ 780
Separation	83894 \$ 100	Interpretation/Report	83912 \$ 120

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

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