Sotos Syndrome: NSD1 Gene Sequencing

Test Code: SNSD1  
Turnaround time: 6 weeks  
CPT Codes: 81406 x1

**Condition Description**

Sotos syndrome is characterized by the cardinal features of typical facial appearance, overgrowth (height and/or head circumference ≥2 SD above the mean), and learning disability ranging from mild (children attend mainstream schools and are likely to be independent as adults) to severe (lifelong care and support are required). Based on the analysis of more than 500 individuals, these cardinal features were shown to occur in at least 90% of affected individuals. Sotos syndrome is also associated in 15-89% of affected individuals with the major features of behavioral problems, congenital cardiac anomalies, neonatal jaundice, renal anomalies, scoliosis, and seizures.

Typical facial features include malar flushing, sparse frontotemporal hair, high bossed forehead, downslanting palpebral fissures, a long narrow face, and prominent narrow jaw; the head is said to resemble an inverted pear. The facial shape is retained into adulthood, but with time the chin becomes squarer in shape and more prominent. In older children and adults, the facial features, although still typical, can be more subtle. Approximately 90% of children have a height and/or head circumference two or more SD above the mean. Height may normalize in adulthood, but macrocephaly is usually present at all ages. Delay of early developmental milestones is very common and motor skills may appear particularly delayed because of the large size, hypotonia, and poor coordination. Language delay is also usually apparent. The great majority of affected individuals have some degree of intellectual impairment; the extent, however, is highly variable.

The diagnosis of Sotos syndrome is established by a combination of clinical findings and molecular genetic testing. NSD1 (5q35) is the only gene known to be associated with Sotos syndrome. About 80%-90% of individuals with Sotos syndrome have a demonstrable NSD1 abnormality. More than 95% of individuals have a de novo mutation. If neither parent of a proband has Sotos syndrome, the risk to sibs of the proband is low (<1%).

Among those with classic Sotos syndrome, about 50% of individuals of Japanese heritage and 10% of individuals of non-Japanese heritage have a 5q35 microdeletion that encompasses NSD1. Exonic/multiexonic gene deletions (i.e., deletion of one or more exons) are responsible for an estimated 5% of Sotos syndrome. Deletions encompassing exons 1 and 2 are most common, likely reflecting the high density of Alu repeats in the flanking sequences.

Sotos syndrome is inherited in an autosomal dominant manner.

For patients with suspected Sotos syndrome, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

[Click here](#) for the GeneTests summary on this condition.

**Genes**

NSD1

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of Sotos syndrome

**Methodology**

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Detection**

Clinical Sensitivity: About 80%-90% of individuals with Sotos syndrome have a demonstrable NSD1 abnormality. 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 biochemical phenotype.

**Specimen Requirements**

Submit only 1 of the following specimen types
Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) or ACD (yellow 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.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Deletion/duplication analysis of the *NSD1* gene by CGH array is available for those individuals in whom sequence analysis is negative.
- 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 to adults who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.