



NSD1 analysis for Sotos Syndrome

Clinical Features:

Sotos syndrome is characterized by characteristic facial features, developmental delay, and increased height and head circumference. Other features may include: neonatal jaundice, scoliosis, seizures, strabismus, conductive hearing loss, congenital heart defects, renal anomalies, and behavioral problems (1).

Inheritance:

Sotos syndrome is an autosomal dominant condition that occurs in 1 in 14,000 live births (1). More than 95% of cases appear to be *de novo*. Recurrence risk for unaffected parents of an isolated case is <1%. However, due to the variability in expression, parents of affected individuals may be carriers. Recurrence risk for affected individuals and carrier parents is 50%.

Molecular Genetics:

Microdeletions and mutations of the *NSD1* gene have been identified in approximately 80% of patients with a clinical diagnosis of Sotos syndrome (2, 3). Recently, intragenic deletions of one or more exons of *NSD1* have been reported in approximately 5% of patients with a clinical diagnosis of Sotos syndrome (4). These intragenic deletions/duplications will not be detected by FISH or CGH analysis.

Additional Resources:

Sotos Syndrome Support Association

P.O. Box 4626

Wheaton IL 60187

Phone: 888-246-7772

Email: info@sotossyndrome.org

www.sotossyndrome.org

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *NSD1* gene is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. We also offer deletion/duplication analysis of the *NSD1* gene by MLPA or oligonucleotide array-CGH to identify deletions/duplications of one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

NSD1 sequencing

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|------------------------|--|
| Sample specifications: | 3 to10 cc of blood in a purple top (EDTA) tube |
| Cost: | \$1,000 |
| CPT codes: | 81406 |
| Turn-around time: | 4 weeks |

NSD1 deletion/duplication analysis

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|------------------------|--|
| Sample specifications: | 3 to10 cc of blood in a purple top (EDTA) tube |
| Cost: | \$1000 |
| CPT codes: | 81405 |
| Turn-around time: | 4 weeks |

NSD1 mutation analysis (sequencing and del/dup analysis)

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|------------------------|---|
| Sample specifications: | 3 to 10 cc of blood in a purple top (EDTA) tube |
| Cost: | \$1700 |
| CPT codes: | 81405, 81406 |
| Turn-around time: | 4 weeks |

Note: The sensitivity of our assay may be reduced when DNA is extracted by an outside laboratory.

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone or email.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Tatton-Brown K, Cole T, Rahman N. Sotos Syndrome. In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washington, 2004.
2. Douglas J, Hanks S, Temple IK et al. NSD1 mutations are the major cause of Sotos syndrome and occur in some cases of Weaver syndrome but are rare in other overgrowth phenotypes. *Am J Hum Genet* 2003; 72: 132-143.
3. Kurotaki N, Imaizumi K, Harada N et al. Haploinsufficiency of NSD1 causes Sotos syndrome. *Nat Genet* 2002; 30: 365-366.
4. Douglas J, Tatton-Brown K, Coleman K et al. Partial NSD1 deletions cause 5% of Sotos syndrome and are readily identifiable by multiplex ligation dependent probe amplification. *J Med Genet* 2005; 42: e56.

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