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Sotos Syndrome

Katrina Tatton-Brown, BM BCh, MD,[1] Trevor RP Cole, MB ChB,[2] and Nazneen Rahman, BM BCh, PhD[3]

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Summary

Clinical characteristics

Sotos syndrome is characterized by a distinctive facial appearance (broad and prominent forehead with a dolichocephalic head shape, sparse frontotemporal hair, downslanting palpebral fissures, malar flushing, long and narrow face, long chin); learning disability (early developmental delay, mild-to-severe intellectual impairment); and overgrowth (height and/or head circumference ≥2 SD above the mean). These three clinical features are considered the cardinal features of Sotos syndrome. Major features of Sotos syndrome include behavioral findings (most notably autistic spectrum disorder), advanced bone age, cardiac anomalies, cranial MRI/CT abnormalities, joint hyperlaxity with or without pes planus, maternal preeclampsia, neonatal complications, renal anomalies, scoliosis, and seizures.

Diagnosis/testing

The diagnosis of Sotos syndrome is established in a proband by identification of a heterozygous *NSD1* pathogenic variant or a deletion encompassing *NSD1* on molecular genetic testing.

Management

Treatment of manifestations: Referral to appropriate specialists for management of learning disability / speech delays, behavioral findings, cardiac abnormalities, renal anomalies, scoliosis, seizures; intervention is not recommended if the brain MRI shows ventricular dilatation without raised intracranial pressure.

Surveillance: Regular review by a general pediatrician for younger children, individuals with many medical complications, and families requiring more support than average; less frequent review of older children / teenagers and those individuals without many medical complications.

Author Affiliations: 1 Consultant in Clinical Genetics, South West Thames Regional Genetics Service, Professor in Clinical Genetics and Genomic Education, St George's University of London, London, United Kingdom; Email: ktatton@sgul.ac.uk. 2 Consultant and Honorary Reader in Clinical Genetics, Clinical Genetics Unit, Birmingham Women's Hospital, Birmingham, United Kingdom; Email: trevor.cole@bham-womens.thenhs.com. 3 Professor and Honorary Consultant in Medical Genetics, Cancer Genetics Section, Institute of Cancer Research, Sutton, Surrey, United Kingdom; Email: nazneen.rahman@icr.ac.uk.

Genetic counseling

Sotos syndrome is inherited in an autosomal dominant manner. More than 95% of individuals have a *de novo* pathogenic variant. If neither parent of a proband has Sotos syndrome, the risk to sibs of the proband is low (<1%). The risk to offspring of affected individuals is 50%. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible if the *NSD1* pathogenic variant has been identified in an affected family member.

Diagnosis

Suggestive Findings

No formal clinical diagnostic criteria are published for Sotos syndrome; the clinical diagnosis **should be suspected** in individuals with the following features.

Characteristic facial appearance (most easily recognizable between ages 1 and 6 years):

- Broad, prominent forehead with a dolichocephalic head shape
- Sparse frontotemporal hair
- Downslanting palpebral fissures
- Malar flushing
- Long narrow face (particularly bitemporal narrowing)
- Long chin

  Note: Facial shape is retained into adulthood; with time the chin becomes broader (squarer in shape).

Learning disability

- Early developmental delay
- Mild-to-severe intellectual impairment

Overgrowth

- Height and/or head circumference ≥2 SD above the mean (i.e., ~98th centile)

  Note: Height may normalize in adulthood.
- Macrocephaly usually present at all ages

Note: Based on the analysis of more than 266 individuals with an *NSD1* pathogenic variant, the three cardinal features (facial appearance, learning disability, and overgrowth) were shown to occur in at least 90% of affected individuals [Tatton-Brown et al 2005b].

Establishing the Diagnosis

The diagnosis of Sotos syndrome **is established** in a proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in *NSD1* or a deletion encompassing *NSD1* on molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview*

is understood to include likely pathogenic variants. (2) Identification of a heterozygous *NSD1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of Sotos syndrome is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with atypical features in whom the diagnosis of Sotos syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of Sotos syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *NSD1* detects missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

  Note: Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *NSD1*) that cannot be detected by sequence analysis. Many individuals with developmental delay will have had CMA as part of their evaluation, sometimes prior to the consideration of Sotos syndrome as a possibility. CMA designs in current clinical use target the *NSD1* region. Gene-targeted deletion/duplication assays may have higher resolution than CMA; however, testing is unlikely to detect a deletion or duplication in cases where sequence analysis and CMA of *NSD1* was not diagnostic.

- **A multigene panel** that includes *NSD1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of Sotos syndrome is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

Exome array (when clinically available) may be considered if exome sequencing is not diagnostic.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Sotos Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
NSD1	Sequence analysis [3]	45%-80%
	CMA [4]	15%-50% [5, 6]
	Gene-targeted deletion/duplication analysis [7]	20%-55% [7, 8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *NSD1*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 5q35 region. Typically, single-exon deletions or duplications are below the resolution of CMA detection. CMA designs in current clinical use target the 5q35 region and *NSD1*.
5. ClinGen-ISCA-37425. Standardized clinical annotation and interpretation for genomic variants from the Clinical Genome Resource (ClinGen) project (formerly the International Standards for Cytogenomic Arrays [ISCA] Consortium).
6. The incidence of the common 1.9-Mb deletion varies by population [Kurotaki et al 2003, Tatton-Brown et al 2005a, Tatton-Brown et al 2005b, Visser et al 2005].
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., the 1.9-Mb deletion) may not be detected by these methods.
8. Gene-targeted deletion/duplication analysis may detect an additional 1%-5% of partial-gene deletions.

Epigenetic signature analysis / methylation array. A distinctive epigenetic signature (disorder-specific genome-wide changes in DNA methylation profiles) in peripheral blood leukocytes has been identified in individuals with Sotos syndrome [Aref-Eshghi et al 2019, Aref-Eshghi et al 2020, Levy et al 2021]. Epigenetic signature analysis of a peripheral blood sample or DNA banked from a blood sample can therefore be considered to clarify the diagnosis in individuals with: (1) suggestive clinical findings of Sotos syndrome but in whom no pathogenic or likely pathogenic variant in *NSD1* has been identified via sequence analysis or CMA; or (2) suggestive clinical findings of Sotos syndrome and a *NSD1* variant of uncertain clinical significance identified by molecular genetic testing. For an introduction to epigenetic signature analysis click here.

Clinical Characteristics

Clinical Description

Based on a review of 266 persons with *NSD1* abnormalities, the clinical features of Sotos syndrome were classified as cardinal features (occurring in ≥90% of affected individuals), major features (occurring in 15%-89%), and associated features (occurring in ≥2% and <15% of persons) [Tatton-Brown et al 2005b].

Cardinal features (present in ≥90% of persons with Sotos syndrome)

- Characteristic facial appearance
- Learning disability
- Overgrowth (height and/or head circumference ≥2 SD above mean)

Major features (present in 15%-89% of persons with Sotos syndrome)

- Behavioral findings – most notably autistic spectrum disorder
- Advanced bone age
- Cardiac anomalies
- Cranial MRI/CT abnormalities
- Joint hyperlaxity with or without pes planus
- Maternal preeclampsia
- Neonatal complications
- Renal anomalies
- Scoliosis
- Seizures

Cardinal Features

Characteristic facial appearance. The facial gestalt is the most specific diagnostic criterion for Sotos syndrome, and also the one most open to observer error due to inexperience. The facial gestalt of Sotos syndrome is evident at birth, but becomes most recognizable between ages one and six years. The head is dolichocephalic and the forehead broad and prominent. Often the hair in the frontotemporal region is sparse. The palpebral fissures are usually downslanting. Malar flushing may be present. In childhood the jaw is narrow with a long chin; in adulthood the chin broadens [Allanson & Cole 1996, Tatton-Brown & Rahman 2004]. In older children and adults, the facial features, although still typical, can be more subtle [Allanson & Cole 1996, Tatton-Brown et al 2005b].

Learning disability. Delay of early developmental milestones is very common and motor skills may appear particularly delayed because of a child's large size, hypotonia, and poor coordination. The majority of individuals with Sotos syndrome have some degree of intellectual impairment. The spectrum is broad and ranges from a mild learning disability (affected individuals would be expected to live independently and have their own families) to a severe learning disability (affected individuals would be unlikely to live independently as adults). The level of intellectual impairment generally remains stable throughout life [Tatton-Brown et al 2005b, Foster et al 2019]. The learning disability in children with Sotos syndrome is characterized by relative strength in verbal ability and visuospatial memory but relative weakness in nonverbal reasoning ability and quantitative reasoning [Lane et al 2019].

Overgrowth. Sotos syndrome is associated with overgrowth of prenatal onset. Delivery is typically at term. The average birth length approximates to the 98th centile and the average birth head circumference is between the 91st and 98th centiles. Average birth weight is within the normal range (50th-91st centile).

Before age ten years, affected children often demonstrate rapid linear growth. They are often described as being considerably taller than their peers. Approximately 90% of children have a height and/or head circumference at least 2 SD above the mean [Tatton-Brown et al 2005b]. However, growth is also influenced by parental heights and some individuals do not have growth parameters above the 98th centile [Cole & Hughes 1994, Tatton-Brown et al 2005b].

Height may normalize in adulthood, but macrocephaly is usually present at all ages [Agwu et al 1999, Foster et al 2019]. Data on final adult height are scarce; however, in both men and women, the range of final adult height is broad [Agwu et al 1999, Foster et al 2019].

The de Boer et al [2005] study of auxologic data supports that of Agwu et al [1999] and shows that individuals with an *NSD1* pathogenic variant have an increased arm span / height ratio, decreased sitting/standing height ratio, and increased hand length. These data suggest that the increased height in Sotos syndrome is predominantly the result of an increase in limb length [Agwu et al 1999, de Boer et al 2005].

Major Features

Behavioral findings. A wide range of behavioral findings are common at all ages: autistic spectrum disorder, phobias, and aggression have been described [Sheth et al 2015; Lane et al 2017; Lane et al 2019; Foster et al 2019; Tatton-Brown, personal communication]. Often difficulty with peer group relationships is precipitated by large size, naiveté, and lack of awareness of social cues [Finegan et al 1994]. These observations were confirmed in a study of individuals with a clinical diagnosis of Sotos syndrome (some with and some without an *NSD1* pathogenic variant); it was additionally noted that attention-deficit/hyperactivity disorder is not common among individuals with Sotos syndrome [de Boer et al 2006].

Advanced bone age. Bone age often reflects the accelerated growth velocity and is advanced in 75%-80% of prepubertal children. However, bone age interpretation is influenced by the "threshold" taken as significant, the method of assessment, subjective interpretative error, and the age at which the assessment is made.

Cardiac anomalies. About 20% of individuals have cardiac anomalies that range in severity from single, often self-limiting anomalies (including patent ductus arteriosus, atrial septal defect, and ventricular septal defect) to more severe, complex cardiac abnormalities. Two unrelated individuals with Sotos syndrome have been shown to have left ventricular non-compaction [Martinez et al 2011]. Three adults with Sotos syndrome and aortic dilatation have been reported [Hood et al 2016].

Cranial MRI/CT abnormalities are identified in the majority of individuals with Sotos syndrome and an *NSD1* pathogenic variant. Ventricular dilatation (particularly in the trigone region) is most frequently identified; other abnormalities include midline changes (hypoplasia or agenesis of the corpus callosum, mega cisterna magna, cavum septum pellucidum), cerebral atrophy, and small cerebellar vermis [Waggoner et al 2005].

Joint hyperlaxity / pes planus. Joint laxity is reported in at least 20% of individuals with Sotos syndrome.

Maternal preeclampsia occurs in about 15% of pregnancies of children with Sotos syndrome.

Neonatal complications. Neonates may have jaundice (~65%), hypotonia (~75%), and poor feeding (~70%). These complications tend to resolve spontaneously, but in a small minority intervention is required.

Renal anomalies. About 15% of individuals with an *NSD1* pathogenic variant have a renal anomaly; vesicoureteral reflux is the most common. Some individuals may have quiescent vesicoureteral reflux and may present in adulthood with renal impairment.

Scoliosis. Present in about 30% of affected individuals, scoliosis is rarely severe enough to require bracing or surgery.

Seizures. Approximately 25% of individuals with Sotos syndrome develop non-febrile seizures at some point in their lives and some require ongoing therapy. Absence, tonic-clonic, myoclonic, and partial complex seizures have all been reported.

Associated Features

Tumors occur in approximately 3% of persons with Sotos syndrome. The broad range includes sacrococcygeal teratoma, neuroblastoma, presacral ganglioma, acute lymphoblastic leukemia, small-cell lung cancer, and astrocytoma [Hersh et al 1992, Tatton-Brown & Rahman 2004, Theodoulou et al 2015]. De Boer and colleagues have characterized and reviewed these findings and compared persons with Sotos syndrome who have *NSD1* pathogenic variants to those who do not [de Boer et al 2006].

Various other clinical features have been associated with Sotos syndrome. Some associated features, such as constipation and hearing issues caused by chronic otitis media, are common. The following features are seen in ≥2% and <15% of individuals with Sotos syndrome [Tatton-Brown et al 2005b]:

- Astigmatism
- Cataract
- Cholesteatoma
- Conductive hearing loss
- Constipation
- Contractures
- Craniosynostosis
- Cryptorchidism
- Gastroesophageal reflux
- Hemangioma
- Hemihypertrophy
- Hirschsprung's disease
- Hydrocele
- Hypercalcemia
- Hypermetropia
- Hypodontia
- Hypoplastic nails
- Hypospadias
- Hypothyroidism
- Inguinal hernia
- Myopia
- Neonatal hypoglycemia
- Nystagmus
- Pectus excavatum
- Phimosis
- Skin hyperpigmentation
- Skin hypopigmentation
- Strabismus
- Subpleural blebs
- Talipes equinovarus
- Umbilical hernia
- Vertebral anomalies
- 2/3 toe syndactyly

Genotype-Phenotype Correlations

Through the evaluation of 234 individuals with Sotos syndrome with an *NSD1* abnormality, it has been shown that, in general, individuals with a 5q35 microdeletion have less overgrowth and more severe learning disability than individuals with an intragenic pathogenic variant [Tatton-Brown et al 2005b].

Genotype-phenotype correlations between intragenic pathogenic variants and 5q35 microdeletions are not evident for other clinical features associated with Sotos syndrome (i.e., cardiac abnormalities, renal anomalies, seizures, scoliosis) – nor were correlations observed between type of intragenic pathogenic variant (missense vs truncating) and phenotype or between position of pathogenic variant (5' vs 3') and phenotype [Tatton-Brown et al 2005b].

Penetrance

NSD1 molecular testing is now routinely undertaken in diagnostic genetic laboratories. To date, no unaffected parent or sib with an *NSD1* pathogenic variant has been reported [Douglas et al 2003, Rio et al 2003, Türkmen et al 2003, Tatton-Brown et al 2005b]. Thus, Sotos syndrome appears to be a fully penetrant condition.

Of note, expressivity is highly variable. Individuals with the same pathogenic variant, even within the same family, can be affected differently [Tatton-Brown et al 2005b, Donnelly et al 2011].

Nomenclature

Sotos syndrome has previously been referred to as cerebral gigantism. This term is now outdated and should no longer be used.

Prevalence

Sotos syndrome is estimated to occur in 1:14,000 live births [Authors, unpublished data].

Genetically Related (Allelic) Disorders

NSD1 abnormalities have a high specificity and sensitivity for Sotos syndrome. Molecular genetic testing failed to identify pathogenic variants in *NSD1* in more than 500 individuals with clinical diagnoses other than Sotos syndrome, including Marshall-Smith syndrome, nonspecific overgrowth, and individuals with macrocephaly in association with autism spectrum disorders [Türkmen et al 2003, Tatton-Brown et al 2005b, Waggoner et al 2005, Buxbaum et al 2007].

Differential Diagnosis

Overgrowth conditions that may be confused with Sotos syndrome are summarized in Table 2.

Table 2. Overgrowth Conditions to Consider in the Differential Diagnosis of Sotos Syndrome

Differential Disorder	Gene(s)	MOI	Clinical Features of Differential Disorder	
			Overlapping w/Sotos syndrome	Distinguishing from Sotos syndrome
EZH2-related Weaver syndrome (Weaver-Smith syndrome) [1]	*EZH2* [2]	AD	• Typical but subtle facial appearance, esp in early childhood [3] • ↑ height; macrocephaly; scoliosis; ligamentous laxity • Frequently hypotonic at birth (may present w/ mixed central hypotonia / peripheral hypertonia)	• Round face shape w/ocular hypertelorism • Prognathism is not a feature of Weaver syndrome, but chin appears "stuck on," frequently w/a horizontal crease between chin & lower lip. • Assoc joint problems (e.g., camptodactyly & contractures) • Infants often have hoarse, low-pitched cry.

Table 2. continued from previous page.

Differential Disorder	Gene(s)	MOI	Clinical Features of Differential Disorder	
			Overlapping w/Sotos syndrome	Distinguishing from Sotos syndrome
EED-related overgrowth (Cohen-Gibson syndrome) [1]	*EED*	AD	• Typical but subtle facial appearance, esp in early childhood • ↑ height; macrocephaly; scoliosis; ligamentous laxity • Frequently hypotonic at birth (may present w/ mixed central hypotonia / peripheral hypertonia)	• The face is subtly different, w/ hypertelorism, round face, & "stuck-on" chin. • Other features that do not overlap w/Sotos syndrome are most similar to Weaver syndrome.
SUZ12-overgrowth syndrome [1, 4]	*SUZ12*	AD	• Typical but subtle facial appearance, esp in early childhood • ↑ height; macrocephaly; scoliosis; ligamentous laxity • Frequently hypotonic at birth (may present w/ mixed central hypotonia / peripheral hypertonia)	Features that do not overlap w/Sotos syndrome are most similar to Weaver syndrome.
Beckwith-Wiedemann syndrome (BWS)	See footnote 5.	AD	Frequently weight &/or height are ≥2 SD at birth.	• BWS should be clinically distinguishable from Sotos syndrome (molecular testing is indicated in persons w/ clinical overlap). [6] • Macroglossia • Anterior earlobe creases / helical pits • Omphalocele • Visceromegaly • ↑ risk of embryonal tumors, esp Wilms tumor
Simpson-Golabi-Behmel syndrome type 1	*GPC3* *GPC4*	XL	• Pre- & postnatal overgrowth • Variable ID	• Predominantly affects males • Polydactyly • Supernumerary nipples • Diastasis recti • Pectus excavatum • Facial gestalt differs. [7]
Bannayan-Riley-Ruvalcaba syndrome (See *PTEN* Hamartoma Tumor Syndrome.)	*PTEN*	AD	• Macrocephaly • Somewhat similar facial gestalt • May be assoc w/autistic spectrum disorder	• Vascular malformations • Hamartomatous polyps of distal ileum & colon • Pigmented macules on shaft of penis • Lipomas • ↑ risk of thyroid & breast cancer [7]

Table 2. continued from previous page.

Differential Disorder	Gene(s)	MOI	Clinical Features of Differential Disorder	
			Overlapping w/Sotos syndrome	Distinguishing from Sotos syndrome
Fragile X syndrome (See *FMR1*-Related Disorders.)	*FMR1*	XL	• Macrocephaly • ID • Typical but subtle facial appearance may overlap w/ Sotos syndrome: dolicocephalic head shape, prominent jaw & forehead.	• Predominantly affects males • Affected males often have large ears; not common in Sotos syndrome. • Macro-orchidism after puberty [8]
Nevoid basal cell carcinoma syndrome (Gorlin syndrome)	*PTCH* *SUFU*	AD	• Recognizable appearance w/macrocephaly, bossing of forehead, & coarse facial features (in ~60% of affected persons) • Head circumference ↑ to >98th centile until age 10-18 mos	• Development of multiple jaw keratocysts, frequently beginning in 2nd decade • Basal cell carcinomas usually from 3rd decade onward • Skeletal anomalies (e.g., bifid ribs or wedge-shaped vertebrae) • Absence, usually, of DD [8]
NFIX-related Malan syndrome [9]	*NFIX*	AD	• Characteristic facial appearance w/ dolicocephaly, prominent forehead, & downslanting palpebral fissures • Scoliosis; ↑ height (>2 SD) in childhood • Assoc w/variable ID	• Ophthalmic abnormalities are common in Malan syndrome; less common in Sotos syndrome. • ↑ height is less common in older children & adults. [8]

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. Given the overlap in findings between Sotos syndrome, Weaver syndrome, Cohen-Gibson syndrome, and *SUZ12*-related overgrowth, in probands with features suggestive of Weaver syndrome, the recommended testing order is *NSD1*, followed by *EZH2*, followed by *EED*, followed by *SUZ12*.

2. Weaver syndrome, caused by pathogenic variants in another histone methyl transferase gene, *EZH2*, is a clinical entity distinct from Sotos syndrome [Tatton-Brown et al 2011, Gibson et al 2012].

3. In some individuals thought to have Weaver syndrome but in whom *NSD1* pathogenic variants were identified, the clinical phenotype evolved to be consistent with Sotos syndrome [Douglas et al 2003, Rio et al 2003, Tatton-Brown et al 2005b].

4. Imagawa et al [2017]

5. Molecular genetic testing can identify epigenetic and genomic alterations of chromosome 11p15 in individuals with BWS: (1) loss of methylation on the maternal chromosome at imprinting center 2 (IC2) in 50% of affected individuals; (2) paternal uniparental disomy for chromosome 11p15 in 20%; and (3) gain of methylation on the maternal chromosome at imprinting center 1 (IC1) in 5%. Sequence analysis of *CDKN1C* identifies pathogenic variants in approximately 40% of familial cases and 5%-10% of cases with no family history of BWS. Approximately 85% of individuals with BWS have no family history of BWS while approximately 15% have a family history consistent with autosomal dominant transmission of BWS.

6. NSD1 pathogenic variants were reported in two individuals with BWS; however, the individuals do not fulfill diagnostic criteria for BWS and do fulfill diagnostic criteria for Sotos syndrome [Baujat et al 2004, Tatton-Brown & Rahman 2004].

7. Detailed clinical examination & molecular genetic testing should differentiate the disorder from Sotos syndrome.

8. Usually distinguishable from Sotos syndrome on clinical grounds; molecular testing confirms the diagnosis.

9. Priolo et al [2018]

Other conditions to consider in the differential diagnosis of Sotos syndrome include the following:

- **Chromosome abnormalities.** A Sotos syndrome-like phenotype has been associated with 4p duplications, mosaic 20p trisomy [Faivre et al 2000], and 22q13.3 deletion syndrome.
- **Nonspecific overgrowth.** Many individuals with overgrowth do not fulfill the diagnostic criteria for any of the above conditions but nevertheless have other features (e.g., learning difficulties, distinctive facial

features) that suggest an underlying genetic cause. Nonspecific overgrowth is likely to be a heterogeneous group of conditions with multiple causes.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Sotos syndrome, the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended [Tatton-Brown & Rahman 2007]:

- A thorough history to identify known features of Sotos syndrome: learning difficulties, cardiac and renal anomalies, seizures, and scoliosis
- Physical examination including cardiac auscultation, blood pressure measurement, and back examination for scoliosis
- Investigations to detect abnormalities before they result in significant morbidity or mortality:
  - In children in whom the diagnosis has just been established, echocardiogram and renal ultrasound examination
  - In adults in whom the diagnosis has just been established, renal ultrasound examination to evaluate for kidney damage from quiescent chronic vesicoureteral reflux
  - Referral for audiologic assessment. Conductive hearing loss may occur at an increased frequency in Sotos syndrome; thus, the threshold for referral should be low.
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

When clinical manifestations (e.g., cardiac anomalies, renal anomalies, scoliosis, or seizures) are identified, referral to the appropriate specialist is recommended.

If brain MRI has been performed and ventricular dilatation demonstrated, shunting should not usually be necessary as the "arrested hydrocephalus" associated with Sotos syndrome is typically not obstructive and not associated with raised intracranial pressure. If raised intracranial pressure is suspected, investigation and management in consultation with neurologists and neurosurgeons would be appropriate.

Developmental Delay / Intellectual Disability Management Issues

For difficulties with learning/behavior/speech that can be found in individuals with Sotos syndrome, the following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.

- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction. Assuming that the individual is safe to eat by mouth, feeding therapy – typically from an occupational or speech therapist – is recommended for affected individuals who have difficulty feeding due to poor oral motor control.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavioral management strategies or providing prescription medications when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Prevention of Secondary Complications

Antibiotic prophylaxis is indicated in individuals with vesicoureteral reflux.

Surveillance

Regular evaluation by a general pediatrician is recommended for younger children, individuals with many medical complications needing coordination of medical specialists, and families requiring more support than average [Tatton-Brown & Rahman 2007].

The clinician may wish to evaluate older children, teenagers, and those individuals without many medical complications less frequently.

Table 3. Recommended Surveillance for Individuals with Sotos Syndrome

System/Concern	Evaluation	Frequency
Cardiac	Eval by cardiologist	At clinical review
	Echocardiogram	• Baseline echocardiogram at diagnosis • Need for & timing of follow-up studies determined by cardiologist
	Blood pressure check	At clinical review
Skeletal	Examine spine for curvature.	
Urinary tract	Urinalysis, urine culture for quiescent urine infection	
Eyes	Ophthalmologic exam	Where there are concerns
Ears	Hearing test	

Note: Cancer screening is not recommended [Villani et al 2017]:

- The absolute risk of sacrococcygeal teratoma and neuroblastoma is low (~1%) [Tatton-Brown et al 2005b, Tatton-Brown & Rahman 2007, Foster et al 2019]. This level of risk does not warrant routine screening, particularly as screening for neuroblastoma has not been shown to decrease mortality and can lead to false positive results [Schilling et al 2002].
- Wilms tumor risk is not significantly increased and routine renal ultrasound examination is not indicated [Scott et al 2006].

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Sotos syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- About 5% of individuals diagnosed with Sotos syndrome have an affected parent.
- The remaining approximately 95% of individuals have a *de novo* pathogenic variant.
- If a parent of an individual with an identified *NSD1* pathogenic variant does not have any clinical features of Sotos syndrome, that parent is very unlikely to be heterozygous for a pathogenic variant in *NSD1*. This can be confirmed with molecular genetic testing of the parent for the *NSD1* pathogenic variant identified in the proband.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant is most likely *de novo* in the proband. Another possible explanation is germline mosaicism in a parent; germline mosaicism is rare with only one recent report of somatic and germline mosaicism in the unaffected father of an affected individual [Kamien et al 2016].

Sibs of a proband. The risk to the sibs of a proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or has an *NSD1* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. Intrafamilial clinical variability has been reported [Tatton-Brown et al 2005b].
- If the parents have not been tested for the *NSD1* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for Sotos syndrome because of the possibility of parental germline mosaicism [Kamien et al 2016].

Offspring of a proband

- Each child of an individual with Sotos syndrome has a 50% chance of inheriting the *NSD1* pathogenic variant.
- Phenotypic expression can vary from one generation to the next and thus it is not possible to accurately predict how offspring may be affected.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *NSD1* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with Sotos syndrome has the *NSD1* pathogenic variant or clinical evidence of the disorder, it is extremely likely that the proband has a *de novo* pathogenic variant. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *NSD1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Note that phenotypic expression can vary from one

generation to the next; thus, it is not possible to accurately predict phenotype on the basis of prenatal molecular genetic test results.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Ultrasound examination. Prenatal diagnosis cannot be accurately accomplished by ultrasound examination: the features of Sotos syndrome likely to be detected by ultrasound examination, such as macrocephaly and increased length, are nonspecific.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Sotos Syndrome Support Association (SSSA)**
  Phone: 888-246-7772
  Email: info@sotosyndrome.org
  sotossyndrome.org
- **Child Growth Foundation**
  United Kingdom
  Phone: 0208 995 0257
  Email: info@childgrowthfoundation.org
  childgrowthfoundation.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Sotos Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
NSD1	5q35.3	Histone-lysine N-methyltransferase, H3 lysine-36 specific	Nuclear receptor binding SET Domain protein 1 (NSD1) @ LOVD	NSD1	NSD1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Sotos Syndrome (View All in OMIM)

117550	SOTOS SYNDROME; SOTOS
606681	NUCLEAR RECEPTOR-BINDING SET DOMAIN PROTEIN 1; NSD1

Gene structure. *NSD1* comprises 22 coding exons (NM_022455.4). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 100 pathogenic variants have been reported. No mutational hot spots have been identified [Douglas et al 2003, Kurotaki et al 2003, Rio et al 2003, Türkmen et al 2003, Faravelli 2005, Tatton-Brown et al 2005b]. See Table A.

A recurrent 1.9-Mb 5q35 microdeletion encompassing *NSD1* has been reported in most Japanese and some non-Japanese individuals with Sotos syndrome [Kurotaki et al 2003, Tatton-Brown et al 2005a, Tatton-Brown et al 2005b, Visser et al 2005]. Further data about population distribution of this microdeletion are not yet available. The majority of microdeletions are generated by nonallelic homologous recombination between flanking low-copy repeats [Kurotaki et al 2003, Tatton-Brown et al 2005a, Visser et al 2005]. Many of these recurrent deletions have the same breakpoints, and a specific chromatin structure may increase recurrent crossover events and predispose to recombination hot spots at 5q35 [Visser et al 2005].

Normal gene product. Only limited data exist regarding the functions of the 2,696-amino acid protein encoded by *NSD1*: histone-lysine N-methyltransferase, H3 lysine-36, and H4 lysine-20 specific. It is expressed in the brain, kidney, skeletal muscle, spleen, thymus, and lung.

NSD1 contains at least 12 functional domains:

- Two nuclear receptor interaction domains (NID^{-L} and NID^{+L})
- Two proline-tryptophan-tryptophan-proline (PWWP) domains
- Five plant homeo domains (PHD)
- A SET (su(var)3-9, enhancer of zeste, trithorax) domain

The most distinctive of these domains are the SET and associated SAC (SET-associated Cys-rich) domains, which are found in histone methyltransferases that regulate chromatin states. The SET domain of NSD1 has unique histone specificity, methylating lysine residue 36 on histone H3, and lysine residue 20 on histone H4 (K36H3 and K20H4) [Rayasam et al 2003]. PHDs are also typically found in proteins that act at the chromatin level, and PWWP domains are implicated in protein-protein interactions and are often found in methyltransferases.

The nuclear receptors of NSD1, NID^{-L}, and NID^{+L} are typical of those found in corepressors and coactivators [Huang et al 1998]. The presence of these distinctive domains suggests that NSD1 is a histone methyltransferase that acts as a transcriptional intermediary factor capable of both negatively and positively influencing transcription, depending on the cellular context [Kurotaki et al 2001].

Abnormal gene product. Sotos syndrome results from loss of NSD1 function. How functional abrogation of NSD1 results in Sotos syndrome is not currently known.

Chapter Notes

Revision History

- 1 December 2022 (sw) Revision: epigenetic signature analysis (Establishing the Diagnosis)
- 1 August 2019 (ha) Comprehensive update posted live
- 19 November 2015 (me) Comprehensive update posted live
- 8 March 2012 (me) Comprehensive update posted live
- 10 December 2009 (me) Comprehensive update posted live
- 23 March 2007 (me) Comprehensive update posted live
- 17 December 2004 (me) Review posted live
- 26 May 2004 (tc) Original submission

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