GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Sotos Syndrome

[*Cerebral Gigantism*]

Trevor RP Cole, MB ChB
Consultant and Honorary Senior Lecturer in Clinical Genetics, Clinical Genetics Unit
Birmingham Womens Hospital
Birmingham
trevor.cole@bham-womens.thenhs.com

Katrina Tatton-Brown, BM BCh
Clinical Research Fellow, Cancer Genetics Section
Institute of Cancer Research
Sutton Surrey
ktbrown.sutpo1.SutDom@icr.ac.uk

Nazneen Rahman, BM BCh, PhD
Professor and Honorary Consultant in Medical Genetics, Cancer Genetics Section
Institute of Cancer Research
Sutton Surrey
Nazneen.Rahman@icr.ac.uk

Initial Posting: December 17, 2004.
Last Update: March 23, 2007.

Summary

Disease characteristics. Sotos syndrome is characterized by the cardinal features of typical facial appearance, overgrowth (height and 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). Sotos syndrome is associated with the major features of behavioral problems, congenital cardiac anomalies, neonatal jaundice, renal anomalies, scoliosis, and seizures. The risk of sacrococcygeal teratoma and neuroblastoma is slightly increased above background risk.

Diagnosis/testing. The diagnosis of Sotos syndrome is established by a combination of clinical findings and molecular genetic testing. *NSD1* is the only gene known to be associated with Sotos syndrome. About 80%-90% of individuals with Sotos syndrome have a demonstrable mutation or deletion of *NSD1*.

Management. *Treatment of manifestations:* referral to appropriate specialists for management of learning disability/speech delays, behavior problems, cardiac abnormalities, renal anomalies, scoliosis, seizures; no intervention if MRI shows ventricular dilatation without raised intracranial pressure. *Surveillance:* annual review for younger children, individuals with many medical complications, and families requiring more support than average; review of older children/teenagers and those individuals without many medical complications less frequently, possibly every two years. *Other:* education of affected individuals and their families regarding natural history, treatment, mode of inheritance, genetic risks to other family members, and consumer-oriented resources; genetic counseling of the young adult regarding risk to offspring.

Genetic counseling. Sotos syndrome is inherited in an autosomal dominant manner. 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%). The risk to offspring of affected

individuals is 50%. Prenatal testing is available for pregnancies at risk when the *NSD1* mutation has been identified in an affected family member.

Diagnosis

Clinical Diagnosis

The clinical diagnosis of Sotos syndrome can be made if an individual has a characteristic facial gestalt, a learning disability, and overgrowth [Rio et al 2003; Turkmen et al 2003; Cecconi et al 2005; Faravelli 2005; Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005; Waggoner et al 2005]. Based upon the analysis of more than 500 individuals with an *NSD1* abnormality, these cardinal features were shown to occur in at least 90% of affected individuals [Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005]. Where an individual does not fulfill all three clinical criteria, the clinical suspicion of Sotos syndrome can be confirmed with genetic testing (see Molecular Genetic Testing).

- **Characteristic facial appearance.** The facial gestalt is the most specific diagnostic criterion for Sotos syndrome and also the feature most open to observer error and inexperience. The gestalt is classic between age one and six years. In older children and adults, the facial features, although still typical, can be more subtle [Allanson & Cole 1996; Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005]. Typical facial features include malar flushing, frontotemporal hair sparsity, high bossed forehead, down-slanting 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.
- **Overgrowth.** Approximately 90% of children have a height and/or head circumference two or more SD above the mean [Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005]. Height may normalize in adulthood, but macrocephaly is usually present at all ages [Agwu et al 1999; Cole, personal communication].
- **Learning disability.** 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 [Ball et al 2005]. The great majority of affected individuals have some degree of intellectual impairment. However, the extent is highly variable, ranging from mild (in which children attend mainstream schools and are likely to be independent in adulthood) to severe (in which lifelong care and support are required) [Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005].

Testing

Cytogenetic testing. Most affected individuals do not have cytogenetic abnormalities. Rarely, a cytogenetic abnormality such as a translocation involving 5q35 results in Sotos syndrome [Kurotaki et al 2002].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *NSD1* is the only gene currently known to be associated with Sotos syndrome. See Allelic Disorders.

Clinical uses

- Confirmatory diagnosis
- Prenatal diagnosis

Clinical testing

- **Intragenic mutation scanning.** Among non-Japanese individuals with a possible diagnosis of Sotos syndrome, mutation screening (by sequence, heteroduplex or dHPLC analysis) detects intragenic mutations in 27%-93% [Douglas et al 2003; Rio et al 2003; Turkmen et al 2003; Cecconi et al 2005; Faravelli 2005; Melchior et al 2005; Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005; Waggoner et al 2005]. This variability in detection rate reflects different eligibility criteria for screening. In the Melchior study, *NSD1* mutation screening was undertaken in any case referred with a possible diagnosis of Sotos syndrome from many clinicians with differing levels of expertise of the condition [Melchior et al 2005]. In contrast, both the Tatton-Brown and Turkmen studies achieved a *NSD1* detection rate of at least 90% in individuals in whom a clinical diagnosis of Sotos syndrome had been made by clinicians with expertise in the condition [Turkmen et al 2003; Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005].

  Limited mutation screening has been undertaken in Japanese individuals, but intragenic mutations account for a minority (~12%) of Japanese individuals with Sotos syndrome [Kurotaki et al 2003]

- **5q35 microdeletion analysis.** Among those with classic Sotos syndrome, about 50% of individuals of Japanese heritage [Kurotaki et al 2003] and 10% of individuals of non-Japanese heritage have a 5q35 microdeletion that encompasses *NSD1* [Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005]. The majority are generated by nonallelic homologous recombination between flanking low-copy repeats [Kurotaki et al 2003; Tatton-Brown, Douglas, Coleman, Baujat, Chandler et al 2005; Visser et al 2005]. The microdeletions can be detected with equal sensitivity by FISH or multiplex ligation-dependent probe amplification (MLPA) [Douglas et al 2003; Kurotaki et al 2003; Rio et al 2003; Turkmen et al 2003; Cecconi et al 2005; Tatton-Brown, Douglas, Coleman, Baujat, Chandler et al 2005; Visser et al 2005; Waggoner et al 2005].

- **Partial gene deletions.** Partial gene deletions (i.e., deletion of one or more exons) are responsible for an estimated 5% of Sotos syndrome cases [Douglas et al 2005; Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005]. MLPA, which includes probes for all the exons, can be used to detect these abnormalities. However, care in the interpretation of single-exon deletions must be exercised and these should, where possible, be confirmed by a second method such as long-range PCR. FISH cannot detect partial gene deletions. Deletions encompassing exons one and two are most common, likely reflecting the high density of Alu repeats in flanking sequence [Douglas et al 2005].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Sotos Syndrome

Test Method	Mutations Detected	Mutation Detection Frequency [1]		Test Availability
		Japanese	Non-Japanese	
Mutation detection (sequence analysis / heteroduplex / dHPLC)	*NSD1* sequence variants (base substitution and frameshift mutation)	~12% [2]	27%-93% [3]	Clinical Testing
MPLA	5q35 microdeletion encompassing *NSD1* and *NSD1* partial gene deletions	~70% [4]	~15% [4]	
FISH	5q35 microdeletion encompassing *NSD1*	~70% [2]	~10% [3]	

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

2. Kurotaki et al 2003, Miyake et al 2003, Tei et al 2006

3. Douglas et al 2003; Rio et al 2003; Turkmen et al 2003; Cecconi et al 2005; Faravelli 2005; Melchior et al 2005; Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005; Waggoner et al 2005

4. The contribution of partial gene deletions to Sotos syndrome in Japanese individuals is currently unknown [Douglas et al 2005; Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005].

Interpretation of test results. All frameshift and nonsense mutations, splicing variants at consensus residues, partial gene deletions, and microdeletions encompassing *NSD1* are predicted to be pathogenic.

Missense variants require more careful interpretation.

- *De novo*f variants are highly likely to be pathogenic.
- Missense variants outside conserved domains should be assumed to be polymorphisms in the absence of additional data in favor of pathogenicity (such as demonstration that the variant is *de novo*).
- Pathogenic missense mutations typically occur at conserved, functionally relevant residues within protein domains [Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005].

For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

If a diagnosis of Sotos syndrome is suspected, *NSD1* molecular testing should be considered to confirm the clinical diagnosis and to provide information about risk of recurrence. The results of screening 435 individuals have been described [Waggoner et al 2005].

Note: If a molecular diagnosis of Sotos syndrome has been made, x-rays for bone age and MRI scan of the brain are not required to confirm the diagnosis.

If the clinical diagnosis of Sotos syndrome is uncertain or molecular testing is negative, routine karyotype and fragile X molecular testing should be undertaken.

Genetically Related (Allelic) Disorders

NSD1 abnormalities have high specificity and sensitivity for Sotos syndrome. In more than 500 individuals with overgrowth in childhood, including individuals with Marshall-Smith syndrome, autosomal dominant macrocephaly, and nonspecific overgrowth, *NSD1* mutations were not identified in individuals with clinical diagnoses other than Sotos syndrome [Turkmen et al 2003; Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005; Waggoner et al 2005].

In rare cases, other clinical conditions that show overlap with Sotos syndrome and involve *NSD1* mutations have been reported: a family with macrocephaly, tall stature, and normal intelligence [van Haelst et al 2005]; an individual with Nevo syndrome [Kanemoto et al 2006]; two individuals with Beckwith-Wiedemann syndrome (BWS) [Baujat et al 2004]; and six individuals with Weaver syndrome [Douglas et al 2003, Rio et al 2003].

Weaver and Sotos syndrome show greatest overlap in infancy, and in some of the individuals with Weaver syndrome and *NSD1* mutations, the clinical phenotype evolved over time to be fairly classic of Sotos syndrome [Douglas et al 2003; Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005]. *NSD1* has been excluded in individuals with classic Weaver syndrome, strongly suggesting that the condition is not allelic to Sotos syndrome and is primarily caused by mutation of a different gene.

Baujat et al (2004) reported *NSD1* mutations in two individuals with a clinical diagnosis of BWS. However, neither meets the major diagnostic criteria for BWS (i.e., neither has macroglossia and both have developmental delay) and both showed considerable overlap with Sotos syndrome [Tatton-Brown & Rahman 2004].

Finally, the individual with a 5q35 microdeletion and the Nevo phenotype reported by Kanemoto et al (2006) has many clinical features consistent with a diagnosis of Sotos syndrome. In addition, Nevo syndrome has recently been shown to be caused by biallelic mutations in the *PLOD1* gene (monoallelic disruption of which results in autosomal dominant EDS VIA) [Giunta et al 2005].

Clinical Description

Natural History

Based upon a review of 230 persons with *NSD1* abnormalities, the clinical features of Sotos syndrome were classified as cardinal features (occurring in at least 90% of affected individuals), major features (occurring in 15%-89%), and associated features (occurring in two or more, but fewer than 15% of persons) [Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005].

It is very likely that additional associated features will be recognized as new cases are identified. It is also possible that some associated features, such as constipation, occur at greater frequency than appreciated now and thus could be reclassified as major features in the future.

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

- Characteristic facial appearance
- Learning disability
- Overgrowth

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

- Behavioral problems
- Advanced bone age
- Cardiac anomalies
- Cranial MRI/CT abnormalities
- Joint hyperlaxity/pes planus
- Maternal preeclampsia

- Neonatal complications
- Renal anomalies
- Scoliosis
- Seizures

Cardinal features

- **Characteristic facial appearance.** 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 down-slanting. Malar flushing may be present. At birth, the mandible appears small, but by childhood it is pointed, and in adulthood, often prominent and square [Allanson & Cole 1996, Tatton-Brown & Rahman 2004].
- **Learning disability.** The majority of individuals with Sotos syndrome have some degree of intellectual impairment. The spectrum is broad and ranges from mild learning disability (affected individuals would be expected to live independently and have their own families) to severe learning disability (affected individuals would be unlikely to live independently as adults). It has been suggested that children with Sotos syndrome have particular difficulties with speech and language, particularly expressive language and articulation [Ball et al 2005]. The majority have mild-moderate learning disability and the level of intellectual impairment generally remains stable throughout life [Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005; authors, unpublished data].
- **Growth.** 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. However, average birth weight is within the normal range (between the 50th and 91st centiles).

  Before age ten years, affected children demonstrate rapid linear growth. They are often described as being considerably taller than their peers. Height and/or head circumference are generally 2 SD or more above the mean. 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, Douglas, Coleman, Baujat, Cole et al 2005].

  Data on final adult height are scarce; however, in both men and women, the range of final adult heights is broad [Agwu et al 1999; Tatton-Brown & Rahman, unpublished data].

  The de Boer et al (2005) study of auxologic data supports that of Agwu et al (1999) and shows that *NSD1*-positive individuals 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 problems.** Behavioral problems are common at all ages. Often difficulty with peer group relationships is precipitated by large size, naiveté, and lack of awareness of social cues [Rutter & Cole 1991, Finegan et al 1994]. These findings have recently been confirmed in *NSD1*-positive children/adults; it was additionally

noted that ADHD is not usually associated with Sotos syndrome [de Boer et al 2006].

- **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 abnormalities.** About 20% of individuals have cardiac anomalies that range in severity from single, often self-limiting anomalies, such as PDA, ASD, and VSD, to more severe, complex cardiac abnormalities. Only a minority require surgical intervention.
- **Cranial MRI/CT abnormalities** are identified in the majority of individuals with Sotos syndrome and a *NSD1* mutation. Ventricular dilatation (particularly in the trigone region) is most frequently identified, but other abnormalities include midline changes (hypoplasia or agenesis of the corpus callosum, mega cisterna magna, wide/cavum septum pellucidum), cerebral atrophy, and small cerebellar vermis [Schaefer et al 1997; Waggoner et al 2005; Rahman, unpublished data].
- **Joint hyperlaxity/pes planus.** Joint laxity is reported in approximately 20% of individuals with Sotos syndrome.
- **Pregnancy.** Complications in pregnancy may occur. In particular, preeclampsia occurs in about 15% of pregnancies.
- **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 abnormalities.** About 15% of individuals with an *NSD1* abnormality have a renal abnormality of which vesico-ureteric reflux is the most common. Some individuals may have quiescent vesico-ureteric reflux and may present in adulthood with renal impairment.
- **Scoliosis.** Present in about 30% of affected individuals, scoliosis is only rarely severe enough to require bracing or surgery.
- **Seizures.** About 25% of individuals with Sotos syndrome develop seizures at some point in their lives and some require ongoing therapy. Absence, tonic-clonic, myoclonic, and partial complex seizures have all been reported.

Other

- **Tumors.** Tumors occur in approximately 3% of persons with Sotos syndrome and include sacrococcygeal teratoma, neuroblastoma, presacral ganglioma, acute lymphoblastic leukemia (ALL) and small cell lung cancer [Tatton-Brown & Rahman 2004]. De Boer and colleagues have characterized and reviewed these problems and compared persons with Sotos syndrome who have *NSD1* mutations 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 problems caused by chronic otitis media, are common. If future studies show that some associated features occur in more than 15% of individuals with Sotos syndrome and therefore at higher frequencies than in the general population, these features may be secondary to disruption of *NSD1* rather than incidental findings.

Associated features of Sotos syndrome

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

Genotype-Phenotype Correlations

Through 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 mutation [Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005].

Genotype-phenotype correlations are not evident between intragenic mutations and 5q35 microdeletions for other clinical features associated with Sotos syndrome (i.e., cardiac abnormalities, renal anomalies, seizures, scoliosis). In addition, no correlations were observed between type of intragenic mutation (missense vs truncating) and phenotype or between position of mutation (5' vs 3') and phenotype [Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005].

Penetrance

More than 100 parental samples have been screened [Douglas et al 2003; Rio et al 2003; Turkmen et al 2003; Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005]. To date, an *NSD1* mutation or deletion has not been identified in any unaffected parents or unaffected siblings of children with *NSD1*-positive Sotos syndrome. Thus, Sotos syndrome appears to be a fully penetrant condition.

Of note, expressivity is highly variable. Individuals with the same mutation, even within the same family, can be affected differently [Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005].

Anticipation

Anticipation has not been reported in Sotos syndrome.

Nomenclature

Sotos syndrome is eponymously named after Juan Sotos, who reported five children with overgrowth, learning disability and a characteristic facial appearance in 1964.

Prevalence

Sotos syndrome is estimated to occur in one in 14,000 live births [Rahman, unpublished data].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Overgrowth conditions that may be confused with Sotos syndrome:

- **Weaver syndrome (also known as Weaver-Smith syndrome).** No molecular testing is currently available; thus, the diagnosis is made on clinical grounds. Affected individuals are overgrown, have a typical facial appearance, are frequently hypertonic at birth, and often have associated joint problems such as clinodactyly and contractures. The classic facial appearance overlaps with that of Sotos syndrome, particularly in infancy. However, the face in Weaver syndrome is round in shape with ocular hypertelorism. Prognathism is not a feature, but the chin appears "stuck on" and, frequently, a horizontal crease is present between the chin and lower lip. Because of the clinical overlap between Weaver syndrome and Sotos syndrome, *NSD1* testing should be undertaken if a diagnosis of Weaver syndrome is suspected.
- **Beckwith-Wiedemann syndrome (BWS).** Individuals with BWS typically have height and weight at least 2 SD above the mean; macrosomia is a major diagnostic criterion. However, many of the other findings in BWS, including macroglossia, anterior ear lobe creases/helical pits, omphalocele, and visceromegaly, are not evident in Sotos syndrome. Molecular testing confirms the clinical diagnosis in 70%-80% of individuals with BWS (loss of methylation at KvDMR1, uniparental disomy for 11p15, mutations of *CDKN1C*, and chromosomal abnormalities of 11p15). Of note, although Baujat et al (2004) reported *NSD1* mutations in two individuals with BWS, the individuals do not fulfill the diagnostic criteria for BWS and do fulfill the diagnostic criteria for Sotos syndrome (see Genetically Related Disorders). BWS should be distinguishable from Sotos syndrome clinically. Individuals with clinical overlap should have molecular testing for both conditions.
- **Simpson-Golabi-Behmel syndrome (SGBS).** This X-linked condition is also associated with pre- and postnatal overgrowth in males. However, other features of SGBS not typically found in Sotos syndrome include polydactyly, supernumary nipples, diastasis recti, and pectus excavatum. Also, the facial gestalt differs between the two disorders. Microdeletions and mutations of *GPC3* encoding the protein glypican 3 are causative.
- **Bannayan-Riley-Ruvalcaba syndrome**. This autosomal dominant condition is characterized by macrocephaly, vascular malformations, hamartomatous polyps of the distal ileum and colon, pigmented macules on the shaft of the penis, lipomas, and increased risk of thyroid and breast cancer. Mutations of *PTEN* have been found in about 60% of cases [Marsh et al 1997]. (See *PTEN* Tumor Hamartoma Syndrome.) A somewhat similar facial gestalt in combination with overgrowth may lead to confusion with Sotos syndrome, but a detailed clinical examination and molecular genetic testing should differentiate the two conditions.
- **Benign familial macrocephaly.** This autosomal dominant condition is characterized by dolico- or macrocephaly in an individual who is otherwise neurologically normal. It is likely a heterogeneous condition and is usually a diagnosis of exclusion.
- **Fragile X syndrome**. Similarities may exist between fragile X syndrome and Sotos syndrome. However, the two conditions are usually distinguishable on clinical grounds. Molecular testing reliably distinguishes the two conditions.
- **Nevoid basal cell carcinoma syndrome (NBCCS, or Gorlin syndrome)** is characterized by the development of multiple jaw keratocysts, frequently beginning

in the second decade of life, and/or basal cell carcinomas usually from the third decade onwards. Most individuals have skeletal anomalies such as bifid ribs or wedge-shaped vertebrae. About 60% of individuals have a recognizable appearance with macrocephaly, bossing of the forehead, and coarse facial features. Head circumference increases above the 98th centile until age ten to 18 months, but is not usually associated with global developmental delay. NBCCS is caused by germline mutations of the gene *PTCH*. Inheritance is autosomal dominant.

- **Chromosomal abnormalities.** A Sotos syndrome-like phenotype has been associated with 4p duplications [Partington et al 1997], mosaic 20p trisomy [Faivre et al 2000], and 22q13.3 deletion syndrome. Karyotyping should identify these chromosome abnormalities.
- **Nonspecific overgrowth.** Many individuals with overgrowth do not fulfill the diagnostic criteria for any of the above conditions but nevertheless have other features (such as learning difficulties and 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 in an individual diagnosed with Sotos syndrome, a thorough history should be taken to identify known features/associations of the disorder: learning difficulties, cardiac and renal anomalies, seizures, and scoliosis.

Physical examination should include cardiac auscultation, blood pressure measurement and back examination for scoliosis.

Investigations to detect abnormalities before they result in significant morbidity/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 renal damage from quiescent chronic vesico-ureteric 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.

Treatment of Manifestations

When clinical problems (e.g., cardiac abnormalities, seizures, renal problems, scoliosis) or difficulties with learning/behavior/speech are identified, referral to the appropriate specialist is recommended.

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

Some children in North America have been prescribed ritalin with varying success; in Europe, behavioral management strategies are more commonly used, again with varying success.

Surveillance

Annual review is recommended for younger children (possibly those age <5 years), individuals with many medical complications needing coordination of medical specialists, and families requiring more support than average.

The clinician may wish to review older children/teenagers and those individuals without many medical complications less frequently, possibly every two years.

The following are approriate at the clinical review:

- Thorough history to identify known clinical sequelae of Sotos syndrome
- Examination for curvature of the spine
- Cardiac auscultation
- Blood pressure measurement
- Referral for audiologic assessment if hearing is a concern or if the child has had many upper respiratory tract infections
- Urine dipstick to investigate quiescent urine infection
- Referral to the appropriate clinical specialist if problems are identified

Note: Cancer screening is not recommended. (1) The absolute risk of sacrococcygeal teratoma and neuroblastoma is low (~1%) [Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005; Tatton-Brown & Rahman 2007]. 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]. (2) Wilms tumor risk is not significantly increased and routine renal ultrasound examination is not indicated.

Testing 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 for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may

face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

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 *de novo* mutations.
- If a parent of an individual with an identified *NSD1* aberration does not have any clinical features of Sotos syndrome, that parent is very unlikely to have an *NSD1* aberration. This can be confirmed with molecular genetic testing if the *NSD1* mutation has been identified in the proband.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband has a pathogenic mutation, the risk to the sibs of inheriting Sotos syndrome is 50%.
- The risk to the sibs of a proband with clinically unaffected parents is less than 1%. This residual risk is based upon the theoretical risk for germline mosaicism and the background risk of a second *de novo* mutation occurring in the same family. To date, no recurrences caused by germline mosaicism have been reported.

Offspring of a proband

- Each child of an individual with an identified *NSD1* aberration or a clinical diagnosis of Sotos syndrome has a 50% chance of inheriting the mutation.
- 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 of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members may be at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the pathogenic mutation or clinical evidence of the disorder, it is extremely likely that the proband has a *de novo* mutation. However, possible nonmedical explanations including alternate paternity or maternity (i.e., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant

in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The pathogenic allele of an affected family member must be identified in the family before prenatal testing can be performed.

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.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Sotos Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
NSD1	5q35	Histone-lysine N-methyltransferase, H3 lysine-36 and H4 lysine-20 specific

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot

Table B. OMIM Entries for Sotos Syndrome

117550	SOTOS SYNDROME
606681	NUCLEAR RECEPTOR-BINDING Su-var, ENHANCER OF ZESTE, AND TRITHORAX DOMAIN PROTEIN 1; NSD1

Table C. Genomic Databases for Sotos Syndrome

Gene Symbol	Entrez Gene	HGMD
NSD1	64324 (MIM No. 606681)	NSD1

For a description of the genomic databases listed, click here

Normal allelic variants: *NSD1* consists of 22 coding exons. Many polymorphisms have been identified [Douglas et al 2003; Kurotaki et al 2003; Rio et al 2003; Turkmen et al 2003; Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005].

Pathologic allelic variants: More than 100 pathogenic mutations have been published. No mutational hot spots have been identified [Douglas et al 2003; Kurotaki et al 2003; Rio et al

2003; Turkmen et al 2003; Faravelli 2005; Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005]. See Genomic Databases Table above.

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, Douglas, Coleman, Baujat, Chandler et al 2005; Tatton-Brown, Douglas, Coleman, Baujat, Cole et al 2005; 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 histone-lysine N-methyltransferase, H3 lysine-36 and H4 lysine-20 specific (NSD1), a protein of 2696 amino acids. It is expressed in the brain, kidney, skeletal muscle, spleen, thymus, and lung. NSD1 contains at least 12 functional domains including two nuclear receptor interaction domains (NID^{-L} and NID^{+L}), two proline-tryptophan-tryptophan-proline (PWWP) domains, five plant homeo domains (PHD), and 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 K36 on H3 and K20 on H4 [Rayasam et al 2003]. PHD domains 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: It is currently unknown how functional abrogation of NSD1 results in Sotos syndrome.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Sotos Syndrome Support Association
P.O. Box 4626
Wheaton IL 60187
Phone: 888-246-7772
Email: sssa@well.com
www.well.com/sssa/

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

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Chapter Notes

Revision History

- 23 March 2007 (me) Comprehensive update posted to live Web site
- 17 December 2004 (me) Review posted to live Web site
- 26 May 2004 (tc) Original submission