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Sotos Syndrome Type 1 and Type 2: Case Series of 4 Pediatric Patients with Variants in *NSD1* and *NFIX* Genes

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Sotos syndrome is a rare genetic disorder with autosomal dominant inheritance, marked by overgrowth with macrocephaly, a distinctive facial appearance, and intellectual impairment. It occurs due to pathogenic variants encompassing the NSD1 gene. In addition, Sotos-like syndromes are also recognized, including Malan syndrome, known as Sotos syndrome type 2, which is caused by variants encompassing the NFIX gene.
Herein we present a series of 3 pediatric patients diagnosed with Sotos syndrome type 1 and 1 patient with Sotos syndrome type 2 and discuss their genotypes and phenotypes.

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1. INTRODUCTION

Sotos syndrome (SOTOS1, OMIM #117550) is a rare autosomal dominant disorder, initially described in 1964 by Sotos et al. [1]. It occurs due to variants encompassing the Nuclear receptor binding SET domain-containing protein 1 (NSD1) gene, located on chromosomal locus 5q35, responsible for coding the NSD1 protein that was isolated and characterized by Kurotaki et al. in 2001 [2]. Some Sotos-like syndromes beyond SOTOS1 are known; one of them is Malan syndrome (OMIM #614753), widely identified as Sotos syndrome type 2 (SOTOS2). It is caused by variants encompassing the Nuclear Factor 1 X (NFIX) gene located on chromosomal locus 19p13 that codes the NFIX protein [3-6]. Both NSD1 and NFIX proteins are described to play a role in controlling cell growth and differentiation [7,8].

The estimated prevalence at birth of SOTOS1 is approximately 1 in 10,000 to 14,000 newborns [9], while of SOTOS2 less than 1 in 1,000,000 [3].

In this case series, our aim is to present 3 children with variants in NSD1 (SOTOS1), and 1 child with a variant in the NFIX gene (SOTOS2) and discuss their genotypes and phenotypes.

2. CASE PRESENTATIONS

This study enrolled 4 pediatric patients. Variant coordinates are after the Human Genome Variation Society (HGVS) nomenclature as provided by the laboratory reports. The classes of the variants are defined according to the standards and guidelines for the interpretation of sequence variants of the American College of Medical Genetics and Genomics (AMCG) and the Association for Molecular Pathology (AMP). The clinical information (phenotype) indicated below follows the Human Phenotype Ontology (HPO) nomenclature. The head circumference was measured and the standard deviation (SD) was evaluated and inscribed in the cases with macrocephaly. Table 1 presents the summary of our patients' genetic data.

Patient 1:

Patient 1 is a 10-year-old boy that presented abnormal facial shape, abnormal hair morphology, abnormal dental color, atrial septal defect, delayed speech and language development, encephalopathy, hypodontia, hypothyroidism, intellectual disability, macrocephaly (head circumference 2 SD above the mean), motor delay, muscular hypotonia, nystagmus, scoliosis, seizures, sensorineural hearing impairment, and strabismus. The age at onset was 13 months. Nothing significant was reported in the family history. A likely pathogenic (class 2) heterozygous deletion encompassing exons 1 and 2 of the NFIX gene was identified by CNV analysis and reaffirmed by MLPA. The status of the variant (inherited/de novo) is not known.

Patient 2:

Patient 2 is a 9-year-old boy that presented abnormal facial shape, abnormality of cardiovascular system morphology, aortic aneurysm, brain atrophy, conductive hearing impairment, delayed speech and language development, encephalopathy, generalized hypotonia, global developmental delay, growth abnormality, hyperreflexia, hypertelorism, hypodontia, intellectual disability, large hands, long foot, macrocephaly (head circumference 2.5 SD above the mean), mandibular prognathia, mitral regurgitation, motor delay, neurodevelopmental abnormality, prominent forehead, scoliosis, seizures, and tall stature. The age at onset was 6 months old. Nothing significant was reported in the family history. A pathogenic (class 1) heterozygous de novo deletion encompassing exons 10 to 21 of the NSD1 gene was identified by CNV analysis and reaffirmed by MLPA.

Patient 3:

Patient 3 is a 6-year-old girl that presented abnormal hair morphology, ataxia, atrial septal defect, brain atrophy, cerebral palsy, encephalopathy, hyperreflexia, mandibular prognathia, seizures, and spasticity. The age at onset was 9 months. Nothing significant was reported in the family history. A likely pathogenic (class 2) heterozygous de novo variant with coordinates c.1212_1213del of the NSD1 gene was identified through NGS data analysis.

Patient 4:

Patient 4 is a 5-year-old boy that presented abnormal hair morphology, almond-shaped

palpebral fissure, broad forehead, cerebral palsy, downturned corners of the mouth, encephalopathy, growth hormone excess, highly arched eyebrow, macrocephaly (head circumference 2 SD above mean) and spasticity. The age at onset was 12 months. Nothing significant was reported in the family history. A pathogenic (class 1) heterozygous de novo variant with coordinates c.5581C>T of the NSD1 gene was identified through NGS-CNV analysis.

3. DISCUSSION

3.1 Genotype

According to Tatton-Brown et al, the detection of a heterozygous pathogenic or likely pathogenic variant encompassing the NSD1 gene on molecular genetic testing confirms the diagnosis of SOTOS1 in a proband [10]. Patient #2 has a large deletion of the NSD1 gene. The disease-associated mechanism is loss of coding sequence but the predicted amino acid change is unknown. Patient #3 variant creates a shift in the reading frame starting at codon 405, the new reading frame ends in a stop codon 4 positions downstream; thus its disease-associated mechanism is frameshift. The predicted amino acid change is p.(Lys405Argfs*5). Patient #4 variant creates a premature stop codon; thus its disease-associated mechanism is nonsense. The predicted amino acid change is p.(Arg1861*).

Interestingly, over 95% of individuals with SOTOS1 present a de novo event [10]; indeed, all the NSD1 variants of our patients were not inherited.

Regarding SOTOS2, the discovery of variants in the NFIX gene on genetic testing is insufficient to validate the diagnosis since mutations in the NFIX gene can induce Marshall-Smith syndrome too, an allelic disorder with a dissimilar phenotype to SOTOS2. Patient #1 has a large deletion of the NSD1 gene. The disease-associated mechanism is loss of coding sequence but the predicted amino acid change is unknown.

3.2 Phenotype

Sotos syndrome is known as an overgrowth disorder. Overgrowth is defined by Tatton-Brown and Weksberg as “global or regional excess growth compared either to an equivalent body part or the age-related peer group” [11]. It has a variety of clinical manifestations, but it is characterized by a distinctive facial appearance, overgrowth with macrocephaly, and intellectual impairment, discovered in at least 90% of afflicted individuals. The clinical diagnosis of Sotos syndrome should be suspected in individuals with the features presented in Table 2, as described by Tatton-Brown et al. [10].

Patients #1 and #2 have 3 cardinal features and 4 major features, patient #3 has 1 cardinal feature, and 3 major features, while patient #4 has 2 cardinal features and 1 major feature.

In closing, considering both genetic and clinical information, patient #1 was diagnosed with Sotos syndrome type 2, while the rest of the patients with Sotos syndrome type 1.

Table 1. Summary of genetic data

No./ Sex	Gene/ Diagnosis	Variant coordinates	Amino acid change	Variant type	Variant status	Disease-associated mechanism	Class. ACMG
1/ M	NFIX/ SOTOS2	deletion exons 1-2	-	deletion	-	loss	class 2
2/ M	NSD1/ SOTOS1	deletion exons 10-21	-	deletion	de novo	loss	class 1
3/ F	NSD1/ SOTOS1	c.1212_1213del	p.(Lys405Argfs*5)	deletion	de novo	frameshift	class 2
4/ F	NSD1/ SOTOS1	c.5581C>T	p.(Arg1861*)	substitution	de novo	nonsense	class 1

Class. ACMG, classification according to the American College of Medical Genetics and Genomics; F, female; M, male; No., number; NFIX, Nuclear factor 1 X gene; NSD1, Nuclear receptor binding SET domain-containing protein 1 gene; -, unknown

Table 2. Clinical features found on patients with Sotos syndrome

CARDINAL FEATURES (present in ≥90% of patients)
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 ▪ long narrow face (particularly bitemporal narrowing) ▪ long chin ▪ malar flushing
Learning disability
▪ early developmental delay ▪ mild-to-severe intellectual impairment
Overgrowth
▪ height and/or head circumference ≥2 SD above the mean ▪ macrocephaly usually present at all ages
Note: Facial shape is retained into adulthood; with time the chin becomes broader. Height may normalize in adulthood.
MAJOR FEATURES (present in 15%-89% of patients)
▪ 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
ASSOCIATED FEATURES
▪ tumors ▪ various other clinical features

4. CONCLUSION

Sotos syndrome is an overgrowth genetic disorder with clinical diversity that is challenging to diagnose merely on genetic testing or clinical information; conversely, genetic test results must be evaluated in the context of clinical findings, family history, or other data.

CONSENT

All authors declare that written informed consent was obtained from the patients' parents for publication of this case series.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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