# A Novel NSD1 Mutation in Sotos Syndrome: The Second Genetically Confirmed Case from Oman

Ashwaq Al Balushi[1]* and Aisha Al Balushi[2]

[1]Pediatric Residency Training Program, Oman Medical Specialty Board, Muscat, Oman

[2]Department of Genetics, Royal Hospital, National Genetic Centre, Muscat, Oman

Received: 09 April 2025

Accepted: 1 July 2025

*Corresponding author:ashwaq6albalushi@gmail.com*

**DOI 10.5001/omj.2028.36**

**Abstract**

Sotos syndrome (SoS) is a rare genetic overgrowth disorder caused by mutations in the NSD1 gene. It is characterized by excessive growth in early childhood, distinctive facial features, developmental delay, and variable associated comorbidities. Here, we report the second genetically confirmed case of SoS in Oman, following the first case documented by Alsaffar et al.[1] This case involves a four-year-old girl presenting with speech delay, distinctive dysmorphic features, and overgrowth. Whole exome sequencing confirmed a de novo pathogenic mutation in the NSD1 gene (NM_022455.4:c.3958C>T; p.Arg1320Ter), which has been associated with SoS. By comparing our case with the previously documented Omani case and other cases from the Middle East, we seek to enhance understanding of Sotos syndrome in the region, emphasize early diagnosis, and highlight the need for increased awareness among healthcare professionals.

**Keywords:** Sotos syndrome; *NSD1* Gene; Overgrowth Syndrome; Developmental Delay; Dysmorphic Features; Middle East; Oman; Genetic Disorder.

## Introduction

Sotos syndrome (SoS) is an autosomal dominant overgrowth disorder first described by Juan Sotos in 1964.[2] It is primarily caused by mutations in the NSD1 gene, identified as the disease-causing gene in 2002.[3] Though the exact prevalence is uncertain, SoS is estimated to affect approximately 1 in 14,000 live births.[4] The clinical features include excessive growth during early childhood, macrocephaly, characteristic facial dysmorphism(frontal bossing, sparse hair, and a prominent jaw), and developmental delay.[5]

SoS has been underreported in the Middle East and North Africa (MENA) region, with limited documented cases. A literature review revealed only two genetically confirmed cases in MENA before the first Omani case: one from Egypt in 2016 and another from Saudi Arabia in 2018.[6] The first case reported in Oman, described by Alsaffar et al., involved a 10-year-old boy presenting with tall stature, macrocephaly, and behavioral difficulties.[1] Our case represents the second genetically confirmed SoS case in Oman and one of the few reported in the region.

## Case Report

A four-year-old girl was referred from a local polyclinic to the National Genetic Center due to concerns about speech delay and distinctive facial features. Her parents also noted that she was significantly taller than her peers. She was born full-term via spontaneous vaginal delivery after an uneventful pregnancy. She had a short NICU stay for hypoglycemia, but no significant perinatal complications. The patient comes from a non-consanguineous family and has four healthy siblings, with no reported family history of genetic disorders or similar phenotypic features, pedigree illustrated down [ figure 1].

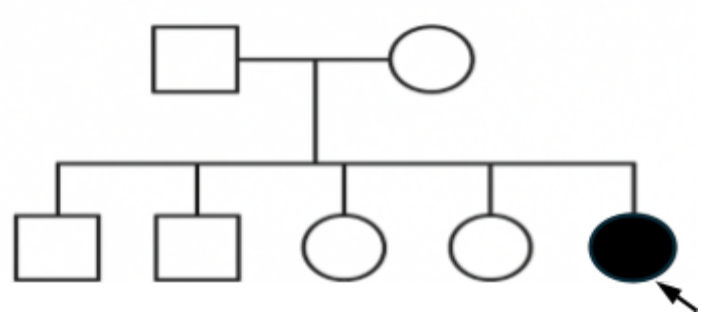

**Figure 1**: Family pedigree diagram.

Developmentally, she exhibited delays in both walking and speech, achieving these milestones at the age of two years. Behaviorall, she demonstrated self-directed aggression and frequent anger outbursts, leading to her enrollment in behavioral therapy at Al Masara hospital.

On clinical examination, her height was 113 cm, weight 23 kg, and head circumference 52 cm, all above the 97th percentile for her age. She exhibited characteristic dysmorphic facial features consistent with Sotos syndrome in terms of frontal bossing, dolichocephaly, long chin and prominent jaw, tall stature, and large hands and feet [figure 2]. No joint hyperlaxity was observed. Bone age assessment was not performed at the time but is planned for future follow-up.

**Figure 2:** Facial dysmorphic features including frontal bossing, long chin, and prominent jaw. Note: A side profile image would better demonstrate dolichocephaly; however, it was not available due to consent limitations.

Cardiovascular examination revealed a soft systolic murmur, though echocardiography findings were normal. Respiratory examination showed clear chest sounds. Her skin exhibited areas of hyperpigmentation, and neurological assessment did not reveal any focal deficits.

Further investigations revealed a chorioretinal coloboma involving the optic disc and macula on ophthalmologic evaluation, while audiology and echocardiography assessments were normal. Renal function tests, including urea and electrolytes, were within normal limits.

Genetic testing via whole exome sequencing identified a de novo heterozygous pathogenic variant in the NSD1 gene (c.3958C>T; p.Arg1320Ter). This mutation introduces a premature stop codon, resulting in a shortened, nonfunctional protein, which confirms the diagnosis of Sotos syndrome. A karyotype analysis was not performed due to high clinical suspicion of a single-gene disorder, confirmed via sequencing.

## Discussion

Sotos syndrome is characterized by early overgrowth, facial dysmorphism, and developmental delay. The NSD1 gene, located on chromosome 5q35, encodes a nuclear receptor histone methyltransferase essential for chromatin modification and gene expression. Mutations in this gene lead to haploinsufficiency, disturbing chromatin regulation and resulting in the typical SoS phenotype.[7]

The first Omani case (Alsaffar et al.) involved a 10-year-old boy with macrocephaly, tall stature, and behavioral issues emerging at age six.[1] In contrast, our case involves a four-year-old girl, diagnosed at a younger age due to early recognition of developmental delays.

The Saudi Arabian case (2018) described a seven-year-old male with a different NSD1 mutation, p.Tyr1988*fsX14, exhibiting significant intellectual disability and severe speech delay.[6]

The Egyptian case (2016) presented an eight-year-old girl with mild cognitive impairment and macrocephaly but no significant behavioral problems.[6]

This comparison highlights the phenotypic variability of SoS, emphasizing the need for early genetic testing to confirm diagnoses and guide management strategies. Compared to the previous Omani case, this patient was diagnosed earlier, is female, and presented with notable behavioral features from a younger age. A comparative summary of the current case with other reported cases is presented in Table 1.

**Table 1.** Comparison of Sotos Syndrome cases from the Middle East region.

| Feature | Current Case (Oman) | Previous Omani Case[1] | Saudi Case[6] | Egyptian Case[6] |
|---|---|---|---|---|
| **Age at Diagnosis** | 4 years | 10 years | 7 years | 8 years |
| **Gender** | Female | Male | Male | Female |
| **NSD1 Mutation** | p.Arg1320Ter | Not specified | p.Tyr1988*fsX14 | Not specified |
| **Growth** | Tall stature | Tall stature | Tall stature | Microcephalic |
| **Developmental delay** | Speech delay, delayed walking | Developmental delay | Severe speech delay | Mild cognitive impairment |
| **Bahavioural issues** | Aggression, anger outbursts | Behavioral issues | Intellectual disability | Non reported |

### Differential Diagnosis

Sotos syndrome shares overlapping features with other overgrowth syndromes, making differential diagnosis essential:

Weaver syndrome typically presents with advanced bone age and camptodactyly[8].

Bannayan-Riley-Ruvalcaba syndrome is characterized by lipomas and pigmented macules on the glans penis.[8]

**Clinical Implications & Recommendations**

*Early Recognition & Diagnosis:*

Delayed diagnosis may affect management and intervention strategies.

Genetic Counseling: Families benefit from genetic education regarding recurrence risks.

Multidisciplinary Approach: Coordinated care involving pediatrics, genetics, neurology, and behavioral therapy is essential for optimizing patient outcomes.

Follow-up is ongoing to monitor for scoliosis, early puberty, neurodevelopmental progress, and other features associated with Sotos syndrome.

## Conclusion

This report describes the second genetically confirmed case of Sotos syndrome in Oman, reinforcing the importance of genetic testing for children presenting with overgrowth, developmental delay, and characteristic dysmorphic features. Given the rarity of SoS in the MENA region, this report aims to enhance awareness among clinicians and encourage further documentation of cases. Early diagnosis and a multidisciplinary approach are crucial for improved patient care.

## Disclosures

The authors declare no conflicts of interest. Verbal parental consent was obtained for the publication of the patient's photograph for research purposes.

## References


1. Alsaffar H, Al Shidhani A, Zadjali A, Hameed ZS, Ullah I, Al Maawali A. De novo NSD1 mutation leading to Sotos syndrome – First case report from Oman. J Diabetes Endocr Pract.2021;4:202-5.

2. Sotos JF, Dodge PR, Muirhead D, Crawford JD, Talbot NB. Cerebral gigantism in childhood: A syndrome of excessively rapid growth with acromegalic features and a nonprogressive neurologic disorder. N Engl J Med. 1964;271:109-16.

3. Kurotaki N, Harada N, Shimokawa O, et al. Fifty microdeletions among 112 cases of Sotos syndrome: low copy repeats possibly mediate the common deletion. Hum Mutat.2003;22(3):378-87.

4. Tatton-Brown K, Rahman N. Sotos syndrome. Eur J Hum Genet. 2007;15(3):264-71.

5. Cole TR, Hughes HE. Sotos syndrome: A study of 19 cases. J Med Genet. 1994;31(1):20-7.

6. Al-Shehri A, Al-Rikabi A, Al-Qahtani A, et al. Sotos syndrome: A case report of the first genetically proven case from Saudi Arabia with a novel mutation in the NSD1 gene. Saudi Med J. 2018;39(5):517-21.

7. Wakeling EL, Neumann TE, Kratz CP, et al. Molecular and clinical characterization of overgrowth syndromes: A systematic review. Am J Med Genet C Semin Med Genet.2017;175(2):343-69.

8. Tatton-Brown K, Weksberg R. Genetic overgrowth syndromes – Clinical and molecular aspects. J Med Genet. 2013;50(1):1-10.