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Reverse Sotos Syndrome Associated With a De Novo 5q35.2-q35.3 Microduplication Encompassing *NSD1* Identified via Pediatric Endocrine Evaluation for Short Stature

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 6-year-old
Final Diagnosis: Reverse Sotos
Symptoms: ASD
Clinical Procedure: —
Specialty: Clinical Biochemistry • Molecular Biology

Objective: Rare disease

Background: High-density single-nucleotide comparative genomic hybridization (HD CGH-SNP) microarrays have improved the detection of copy number variants (CNVs) in dosage-sensitive chromosomal regions. Haploinsufficiency of the *NSD1* gene at the 5q35 locus causes Sotos syndrome, marked by overgrowth, macrocephaly, and neurodevelopmental delay. Conversely, the reciprocal 5q35 microduplication, termed "reverse Sotos syndrome", is an uncommon genomic entity with phenotypic variability that can lead to delayed clinical recognition in general pediatric and endocrine settings.

Case Report: We report the case of a 5-year-old boy evaluated for persistent proportionate short stature (height 96.7 cm, standard deviation score [SDS] -2.28; weight 14.0 kg, SDS -2.15) and microcephaly (head circumference 47.0 cm, SDS -3.33) with delayed bone age (3.5 years at chronological age 5.0). Physical examination revealed trigonocephaly, a long nose, a small mouth with a thin upper lip, and xerosis. Neurodevelopmental assessment demonstrated global developmental delay, language delay, and attention deficit. Cranial computed tomography at age 5 years confirmed trigonocephaly with reduced ventricular dimensions and closed metopic suture. High-density array analysis (CytoScan HD) identified a de novo 1.87 Mb pathogenic gain at 5q35.2-q35.3 encompassing 29 OMIM genes, including *NSD1*. Post-diagnostic multidisciplinary management and genetic counseling (confirming low recurrence risk) were initiated.

Conclusions: This report documents a novel de novo 5q35.2-q35.3 microduplication with defined genomic breakpoints identified through a pediatric short-stature referral. The case reinforces the diagnostic importance of chromosomal microarray testing in children presenting with proportionate growth failure, microcephaly, and developmental delay, illustrating the opposite growth pattern to classic Sotos syndrome.

Keywords: Sotos Syndrome • Intellectual Disability • Genetic Techniques • Haploinsufficiency
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Introduction

Chromosomal microarrays allow high-resolution genome-wide detection of copy number variants (CNVs) in clinical practice. When dosage-sensitive genes are involved, reciprocal deletions and duplications at specific chromosomal loci can produce contrasting physical phenotypes. A classic model is the 5q35.2-q35.3 genomic region. Microdeletions at 5q35, or point mutations involving the nuclear receptor SET domain–containing protein 1 (*NSD1*) gene, represent a major underlying cause of Sotos syndrome, a condition characterized by childhood overgrowth, advanced bone maturation, macrocephaly, characteristic facial dysmorphism, structural brain anomalies, and variable neurodevelopmental impairment [1,2]. *NSD1* encodes a histone methyltransferase that acts as an essential epigenetic modifier [3].

In contrast, reciprocal microduplications at 5q35.2-q35.3 are uncommon and under-recognized in general pediatric care [4,5]. Mechanistically, non-allelic homologous recombination mediated by low-copy repeats flanking the 5q35 region drives these reciprocal deletion and duplication events. At the cellular level, increased dosage of *NSD1* leads to histone H3 lysine 36 (H3K36) hypermethylation and downstream downregulation of the mTOR signaling pathway, resulting in cellular growth restriction that contrasts with the mTOR hyperactivity observed in *NSD1* haploinsufficiency [5].

Clinically, patients with 5q35 microduplication present with an opposing physical phenotype, characterized predominantly by short stature, microcephaly, and delayed bone maturation, while sharing overlapping neurodevelopmental deficits. Because affected children often present to pediatric endocrinology or growth clinics with nonspecific short stature, identifying the underlying genomic alteration requires targeted molecular investigation. The objective of this report is to document a defined de novo 5q35.2-q35.3 microduplication, illustrate how systematic short-stature evaluation leads to the diagnosis of reverse Sotos syndrome, and detail the clinical trajectory and genomic context of this rare entity.

Case Report

A 5-year-old male patient was referred to the pediatric endocrinology clinic at Hospital Universitario Virgen del Rocío (Seville, Spain) for systematic evaluation of persistent short stature and growth delay noticed since 3 months of age. The child was born at 39 weeks of gestation following an uncomplicated pregnancy conceived via in vitro fertilization using parental gametes; maternal hypothyroidism was well-controlled with levothyroxine during pregnancy. The in vitro fertilization conception history is noted as clinical background; no causal link between assisted reproductive technology and the de novo CNV is inferred. Birth weight was 3150 g (standard deviation score [SDS] -0.42), birth length was 49.0 cm (SDS -0.35), and birth head circumference was 34.0 cm (SDS -0.50), reflecting normal intra-uterine growth. There was no family history of short stature, dysmorphic syndromes, or neurodevelopmental disorders. Target height (mid-parental height) was calculated at 174.5 cm (SDS -0.15) based on maternal height (161 cm, SDS -0.25) and paternal height (175 cm, SDS -0.20).

Physical examination at 5.0 years confirmed proportionate growth failure and facial dysmorphism. Anthropometric parameters evaluated using Spanish pediatric reference charts [6] showed height 96.7 cm (SDS -2.28), weight 14.0 kg (SDS -2.15, body mass index 15.0 kg/m², SDS -1.10), and head circumference 47.0 cm (SDS -3.33). Sitting height was 56.1 cm (sitting-height-to-height ratio 0.58, within normal range for age, confirming proportionate short stature). Annualized growth velocity between ages 4 and 5 was 4.71 cm/year (SDS -1.85). Radiographic assessment of the left hand and wrist demonstrated delayed bone maturation (bone age 3.5 years at chronological age 5.0 years, Greulich and Pyle method). Dysmorphic features included trigonocephaly, a long nose with prominent nasal bridge, a small mouth with a thin upper lip, adenoid facies, and dry skin (xerosis). Orthopedic examination showed bilateral flat feet with valgus posture.

Endocrine evaluation was performed to investigate short stature. Growth hormone stimulation testing (clonidine test) yielded a peak growth hormone of 11.2 ng/mL (ruling out classic growth hormone deficiency). IGF-1 was 88 ng/mL (SDS -0.60) and IGFBP-3 was 2.9 µg/mL (SDS -0.40). Thyroid function was normal (TSH 2.1 mIU/L, free T4 1.2 ng/dL). Celiac screening (anti-tTG IgA) and serum biochemistry/electrolytes were unremarkable.

Neurodevelopmental evaluation revealed global developmental delay. Formal cognitive psychometric testing was not available; therefore, global developmental delay rather than intellectual disability was designated. The child exhibited expressive language delay, short attention span, and behavioral inattention in school settings. Regarding continence, the patient had delayed acquisition of nighttime urinary sphincter control (nocturnal enuresis) without a previous period of sustained dry nights; daytime urinary and bowel continence were fully achieved at age 3.5 years. Renal and urinary tract ultrasonography was performed, showing normal kidney structure without congenital anomalies or post-void residual volume, indicating that enuresis was functional/developmental rather than structural.

Non–contrast-enhanced cranial computed tomography performed at age 5.0 years to evaluate cranial morphology

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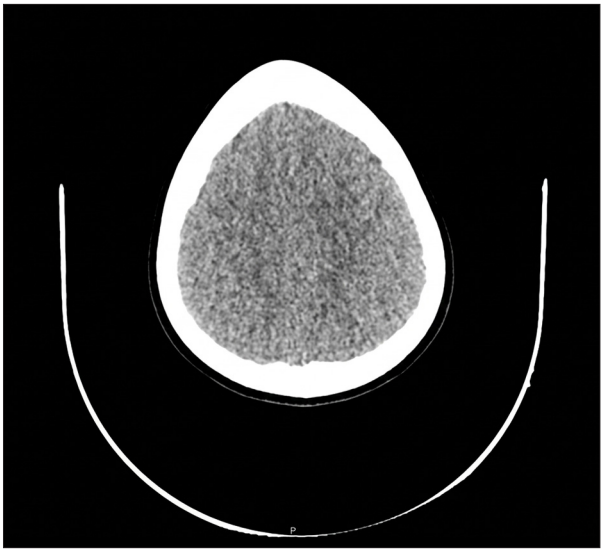


Figure 1. Non-contrast axial brain computed tomography (CT) scan of the index patient at age 5.0 years (axial plane, mid-cranial level). The image demonstrates premature fusion of the metopic suture (metopic synostosis, indicated by pointed anterior cranial vault architecture) producing classic trigonocephaly, along with symmetrically reduced lateral ventricular dimensions consistent with primary microcephaly. No structural brain parenchymal malformations are identified.

demonstrated premature fusion of the metopic suture (metopic synostosis) resulting in trigonocephaly, along with reduced lateral ventricular dimensions consistent with microcephaly (**Figure 1**).

Given proportionate short stature, microcephaly, delayed bone age, cranial synostosis, and global developmental delay, high-density chromosomal microarray analysis was conducted (see Methods). Genomic analysis identified a pathogenic 1.87 Mb copy number gain at 5q35.2-q35.3: arr[GRCh38] 5q35.2q35.3(176,143,676_178,010,864)x3 (**Figure 2**). The duplicated region encompassed 29 OMIM genes, including *NSD1* (**Table 1**). Parental array testing confirmed that both biological parents were wild-type for the locus, establishing that the duplication arose de novo.

Following molecular diagnosis at age 5, the patient had been monitored for 18 months (latest evaluation at age 6.5 years). Current growth parameters demonstrate persistent proportionate short stature: height 104.2 cm (SDS -2.31), weight 16.5 kg (SDS -2.10), and head circumference 48.0 cm (SDS -3.20). Genetic counseling was provided to the family, explaining the de novo nature of the duplication and confirming a very low recurrence risk (< 1%) for future pregnancies. A multidisciplinary clinical management plan was established, including

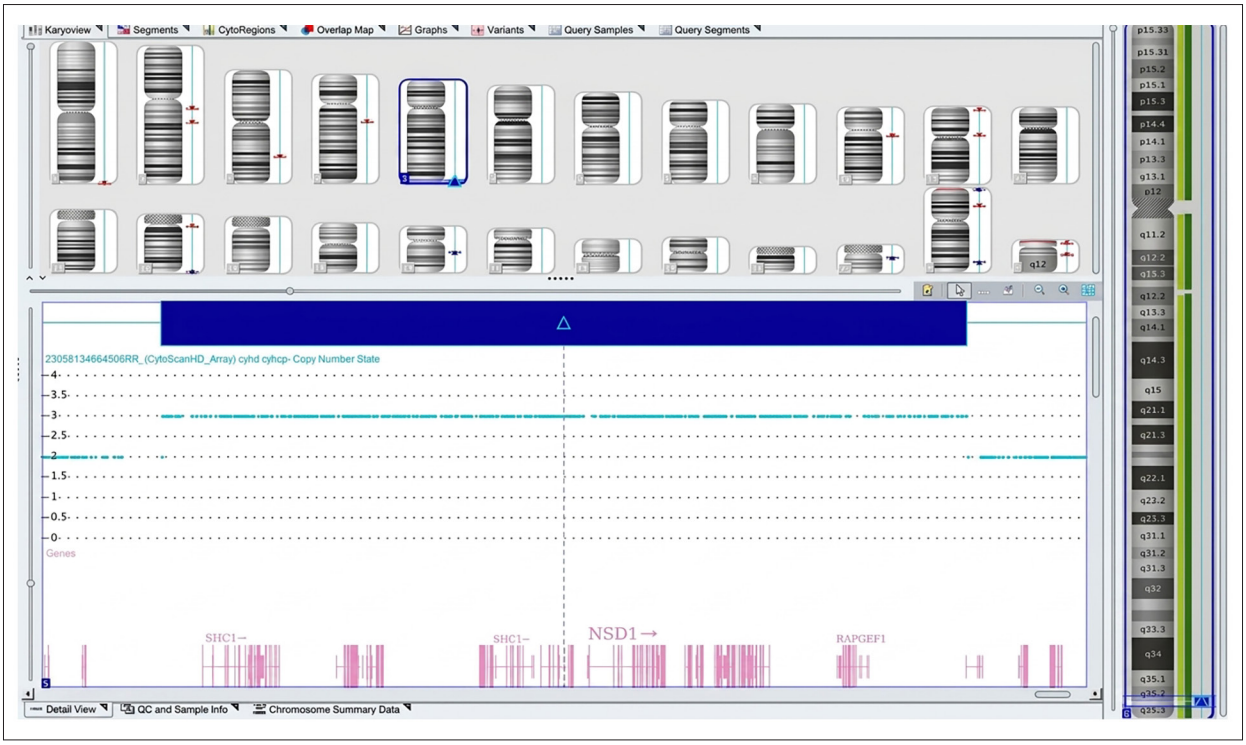


Figure 2. Chromosome Analysis Suite (ChAS v4.5) output display detailing the 1.87 Mb de novo microduplication at 5q35.2-q35.3 (dark blue horizontal bar). Genomic coordinates: arr[GRCh38] 5q35.2q35.3(176,143,676_178,010,864)x3. The log2 ratio track (light blue markers) shows copy number state = 3 (gain) across all probes in the interval. The lower gene track explicitly marks the location of NSD1 and adjacent OMIM genes within the duplicated segment.

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Table 1. OMIM genes located within the 1.87 Mb 5q35.2-q35.3 duplicated interval arr[GRCh38] 5q35.2q35.3(176,143,676_178,010,864)x3.

Gene symbol	OMIM #	Proposed functional relevance/clinical associations
NSD1	606681	Histone methyltransferase (H3K36); primary driver of 5q35 dosage phenotype (short stature, microcephaly)
PROP1	601538	Pituitary transcription factor; mutations cause combined pituitary hormone deficiency
FGFR4	134935	Fibroblast growth factor receptor; involved in skeletal growth, bone development, and cell signaling
DBN1	126660	Drebrin 1; actin-binding protein key for dendritic spine morphogenesis and synaptic plasticity
RGS14	602513	Regulator of G-protein signaling 14; expressed in brain, modulates synaptic plasticity and learning
SLC34A1	182309	Sodium-phosphate cotransporter; renal phosphate transport, associated with nephrolithiasis/hypophosphatemia
DDX41	608170	DEAD-box helicase 41; RNA processing, germline mutations predispose to hematologic malignancies
B4GALT7	604327	Galactosyltransferase; mutations cause Ehlers-Danlos syndrome (progeroid/spondylodysplastic type)
UIMC1	609433	BRCA1-interacting protein; double-strand DNA break repair and genomic stability
F12	610619	Coagulation factor XII; involved in blood coagulation and hereditary angioedema type III
20 additional genes*	-	*SNCB*, *PDLIM7*, *NOP16*, *FAM193B*, *GPRIN1*, *ZNF346*, *CLTB*, *PRR7*, *PFN3*, *PRELID1*, *HK3*, *RAB24*, *GRK6*, *UNC5A*, *DOK3*, *MXD3*, *LMAN2*, *FAF2*, *SIMC1*, *CLTB*

pediatric endocrinology monitoring (annual growth and bone age assessment), developmental/speech therapy support, educational accommodation for attention deficit, and pediatric neurology oversight. No growth hormone therapy had been initiated to date, as endogenous growth hormone secretion was preserved.

Material and Methods

Genomic DNA was extracted from peripheral whole blood of the index patient and biological parents using standard automated procedures. Copy number analysis was performed using the CytoScan HD SNP/CNV array (Thermo Fisher Scientific / Applied Biosystems, Santa Clara, CA, USA), which contains 2.67 million probes across the genome (750 000 SNPs and 1.9 million non-polymorphic CNV probes). Hybridization, washing, scanning, and data extraction were executed per manufacturer protocol. Data were processed using Chromosome Analysis Suite (ChAS) v4.2/v4.5 (Thermo Fisher Scientific) referenced to GRCh38/hg38 genome assembly. Clinical interpretation was facilitated by Franklin (Genoox, Israel). CNVs > 10 kb were classified according to ACMG/ClinGen guidelines.

Discussion

The clinical phenotype of 5q35 microduplications represents an emerging genomic syndrome with features opposite to those of 5q35 microdeletions causing Sotos syndrome. Sotos syndrome is characterized by childhood overgrowth, macrocephaly, advanced bone age, and a characteristic facial appearance, with genotype–phenotype correlations well documented in affected individuals [1-3]. In contrast, reciprocal 5q35.2-q35.3 microduplications have been associated with proportionate short stature, microcephaly, delayed bone age, and variable dysmorphic features [4,5]. Overlapping features between deletion and duplication carriers include developmental and speech delays, behavioral difficulties, and other neurodevelopmental manifestations [4-10,11].

The 1.87 Mb duplicated region in our patient contained 29 OMIM genes (**Table 1**). Although increased *NSD1* dosage is considered the principal contributor to the characteristic growth phenotype, other genes within the duplicated interval may modify the clinical presentation. For example, *FGFR4* is involved in growth factor signaling [12], *PROP1* is essential for pituitary development and anterior pituitary hormone production [13], and *DBN1* and *RGS14* have functions relevant to

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Table 2. Comparative summary of reported 5q35 microduplication cases and present case.

Study	Size	Growth/bone age	Head size	Neurodevelopmental characteristics	Other clinical features
Novara et al (2014) [4]	0.4-3.8 Mb (various)	Short stature, delayed bone age	Microcephaly	Speech delay, mild ID/GDD	Small mouth, thin lip, joint laxity
Sachwitz et al (2017) [11]	0.3-2.1 Mb	Postnatal growth delay (SRS-like)	Microcephaly / normal	Developmental delay	Triangular face, feeding difficulties
Reis et al (2017) [12]	1.5 Mb de novo	Short stature (-2.5 SDS)	Microcephaly (-3.0 SDS)	Global developmental delay	Dysmorphic facial traits, flat feet
Park et al (2018) [13]	1.8 Mb	Short stature	Microcephaly	Developmental delay	Unexplained pancytopenia reported
van der Lugt et al (2023) [14]	0.2-2.5 Mb (distal region)	Short stature (variable)	Microcephaly / borderline	Speech delay, learning disability	Intrafamilial variability described
Present case (2026)	1.87 Mb de novo GRCh38	Proportionate short stature (-2.28 SDS), delayed bone age	Microcephaly (-3.33 SDS), trigonocephaly	Global developmental delay, speech delay	Small mouth, thin lip, xerosis, valgus flat feet, enuresis

neuronal signaling and cellular processes [14]. However, the contribution of these genes to our patient's phenotype remains speculative and was not directly investigated. The distal breakpoint of the duplication was located near genomic coordinate 178.01 Mb, consistent with the critical region discussed by van der Lugt et al (2023), who refined the distal boundary of the 5q35 duplication syndrome region and documented intrafamilial variability [6].

Quintero-Rivera et al demonstrated that *NSD1* duplication is associated with *NSD1* overexpression, increased H3K36 trimethylation, and downregulation of the mTOR (mechanistic target of rapamycin) signaling pathway [5]. Given the central role of mTOR signaling in cellular growth, protein synthesis, and proliferation, this proposed mechanism provides a plausible explanation for the growth restriction, microcephaly, and delayed bone maturation observed in individuals with 5q35 duplication syndrome. This contrasts with the established role of *NSD1* haploinsufficiency in Sotos syndrome, in which reduced *NSD1* dosage is associated with somatic overgrowth [2,3,5]. These opposing phenotypes support a dosage-sensitive role for *NSD1* in growth regulation.

Neuroimaging in our patient revealed trigonocephaly associated with metopic craniosynostosis and small ventricular dimensions. Although macrocephaly is a recognized feature of Sotos syndrome [2,3,10], craniosynostosis and the specific ventricular findings in our patient should be interpreted as individual clinical observations rather than established features of 5q35 duplication syndrome [4,6-8]. Our patient's neurodevelopmental findings are consistent with the developmental and behavioral manifestations reported in previous cases of 5q35 microduplication [4-7] (**Table 2**). Additionally, 5q35 microduplication should be considered in the differential diagnosis of Silver-Russell syndrome (SRS). Sachwitz et al described *NSD1* duplications in individuals with SRS-like features, including growth restriction and other characteristic clinical findings [9]. In our patient, the absence of body asymmetry and the reported normal intrauterine growth favored a diagnosis of 5q35 microduplication over classic SRS, although these findings alone do not definitively exclude SRS.

This report has several limitations inherent to single-case clinical reports. Formal psychometric cognitive testing (eg, WPPSI or WISC) could not be performed because of the patient's age and attention limitations; neurodevelopment was therefore assessed using clinical developmental milestones. Functional studies, including *NSD1* mRNA quantification and assessment of mTOR pathway activity through phosphoprotein analysis, were not conducted. Finally, adult height and complete pubertal progression remain to be documented during long-term follow-up.

Conclusions

This case documents a de novo 1.87 Mb 5q35.2-q35.3 microduplication in a pediatric patient identified through evaluation for proportionate short stature and microcephaly. Our clinical observations align with published evidence that 5q35 duplications produce physical traits opposite to Sotos syndrome, driven by *NSD1* overexpression and mTOR pathway downregulation. In pediatric practice, 5q35 microduplication should be

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included in the differential diagnosis of children presenting with unexplained short stature, microcephaly, cranial synostosis, and global developmental delay. High-density chromosomal microarray analysis provides a reliable diagnostic tool, enabling early etiology identification, precise recurrence risk counseling (< 1% for de novo cases), and structured multidisciplinary follow-up.

Consent for Publication

Written consent was obtained by patient's parents and is scanned into documentation.

Informed Consent Statement

All study participants provided informed written consent prior to study enrollment.

Institution Where Work Was Done

Hospital Universitario Virgen del Rocío, Seville, Spain.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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