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# Reverse Sotos Syndrome Associated with a de novo 5q35.2q35.3 Microduplication Encompassing NSD1 in a Paediatric Patient with Short Stature and Microcephaly

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## 1. Abstract

### 1.1. Background

High-density single-nucleotide comparative genomic hybridization (HD CGH-SNP) microarrays have improved the detection of novel copy number variants (CNVs) in dosage-sensitive chromosomal regions. Haploinsufficiency of the NSD1 gene at the 5q35 locus causes Sotos syndrome, a well-characterized disorder marked by overgrowth, macrocephaly, and neurodevelopmental delay. Conversely, the reciprocal 5q35 microduplication-termed “reverse Sotos syndrome”-remains rarely reported, and its varied clinical presentation makes recognition challenging in routine paediatric evaluations.

### 1.2. Case Presentation

We report a 5-year-old male presenting with persistent growth delay, microsomia, microcephaly, and mild intellectual disability. Physical examination revealed distinct dysmorphic features including trigonocephaly, a long nose, a small mouth, and a thin upper lip. High-resolution genetic analysis using a CytoScan™ HD SNP-CNV microarray identified a de novo 1.87 Mb pathogenic gain at 5q35.2q35.3 encompassing 29 OMIM genes, including NSD1.

### 1.3. Conclusions

This case reinforces the diagnostic importance of considering 5q35 microduplication in the differential diagnosis of paediatric patients presenting with unexplained short stature, microcephaly, and neurodevelopmental features. In agreement with previous literature, our clinical observations align with the concept of opposing physical phenotypes resulting from genomic imbalance at the 5q35 locus. High-resolution microarray analysis represents an effective diagnostic approach for resolving complex or nonspecific developmental presentations in rare genomic disorders.

## 2. Introduction

The recent implementation of high-density single-nucleotide comparative genomic hybridization microarrays (HD CGH-SNP microarrays) in clinical practice has revealed with increased precision the existence of novel copy number variants (CNVs) at multiple genomic loci. Copy number variants, i.e., gains or losses of genomic material, can give rise to distinct or opposing physical features when the affected loci contain dosage-sensitive genes. One established example is the 5q35.2-q35.3 region, associated with Sotos syndrome. Classic Sotos syndrome is characterized by childhood overgrowth, advanced bone age, macrocephaly, characteristic facial dysmorphism, variable structural brain anomalies, and intellectual impairment [1]. Microdeletions at 5q35 involving the nuclear receptor SET domain–containing protein 1 (NSD1) gene represent a primary cause of Sotos syndrome and are frequently reported in connection with significant neurodevelopmental involvement [2]. NSD1 encodes a histone methyltransferase initially identified as the causative gene in Sotos syndrome by [3].

In contrast to 5q35 deletions, microduplications at the same locus-often referred to as “reverse Sotos syndrome”-are considerably less common and less well characterized in routine clinical practice [4,5]. Previous reports describe a phenotype that contrasts with classical Sotos syndrome, predominantly featuring short stature, microcephaly, and delayed bone maturation, while sharing overlapping neurodevelopmental and cognitive deficits. Because these patients may first present to endocrine or general paediatric clinics with nonspecific growth failure, identifying the underlying genomic ethology can be difficult.

This report describes a 5-year-old male evaluated primarily for persistent short stature and microcephaly. The objective of this report is to provide confirmatory clinical and molecular documentation of a de novo 5q35.2q35.3 duplication, illustrate how short-stature clinical workups can lead to the identification of reverse Sotos syndrome, and refine the recognizable combination of dysmorphic and neurodevelopmental features that warrant targeted genomic evaluation.

## 3. Clinical Case

A 5-year-old male patient was referred to the paediatric endocrinology clinic for systematic evaluation of persistent short stature and growth delay observed since 3 months of age. There was no relevant family history of growth or neurodevelopmental disorders. The pregnancy was conceived through in vitro fertilization (IVF) without donor sperm, and maternal hypothyroidism was managed during gestation.

Physical examination confirmed marked growth deficit and characteristic dysmorphic features. The child presented in good general physical condition with microsomia, microcephaly, a long nose, a small mouth with a thin upper lip, adenoid facies, and xerosis (dry skin). Anthropometric values at evaluation were: height 96.7 cm (SDS −2.28), head circumference 47 cm (SDS −3.33), and weight 14 kg. Sitting height was 56.1 cm (sitting-height ratio 0.58), with an annualized growth velocity of 4.71 cm/year. Orthopaedic evaluation noted bilateral flat feet with valgus deformity. Non-contrast cranial computed tomography (CT) demonstrated reduced ventricular dimensions consistent with microcephaly, alongside trigonocephaly (Figure 1).

Assessment of neurodevelopment revealed language delay and mild intellectual disability. The patient demonstrated poor academic performance, predominantly attributed to short attention span and inattention in classroom settings. Secondary nocturnal enuresis was also noted and interpreted as secondary to developmental immaturity.

Given the combination of proportionate short stature, microcephaly, subtle facial dysmorphology, and neurodevelopmental delay, a high-resolution CGH-SNP microarray was requested to investigate the underlying genetic ethology of his phenotype. Genomic analysis identified a pathogenic copy number gain classified according to ACMG guidelines: arr [GRCh38] 5q35 .2q35.3(176143676_178010864) x3 (Figure 2). The duplicated segment spanned 1.87 Mb and encompassed 29 OMIM genes, including NSD1 (OMIM 606681), as well as RGS14 (602513), PDLIM7 (605903), SNCB (602569), DBN1 (126660), NOP16 (612861), FGFR4 (134935), FAM193B (615813), GPRIN1 (611239), ZNF346 (605308), CLTB (118970), PRR7 (618306), PFN3 (612812), PRELID1 (605733), HK3 (142570), RAB24 (612415), GRK6 (600869), UNC5A (607869), DOK3 (611435), MXD3 (609450), UIMC1 (609433), LMAN2 (609551), F12 (610619), FAF2 (616935), SIMC1 (618102), SLC34A1 (182309), DDX41 (608170), B4GALT7 (604327), and PROP1 (601538).

Parental segregation testing was subsequently performed using the same microarray platform. The 5q35.2q35.3 duplication was absent in both biological parents, confirming that the genomic alteration arose de novo.

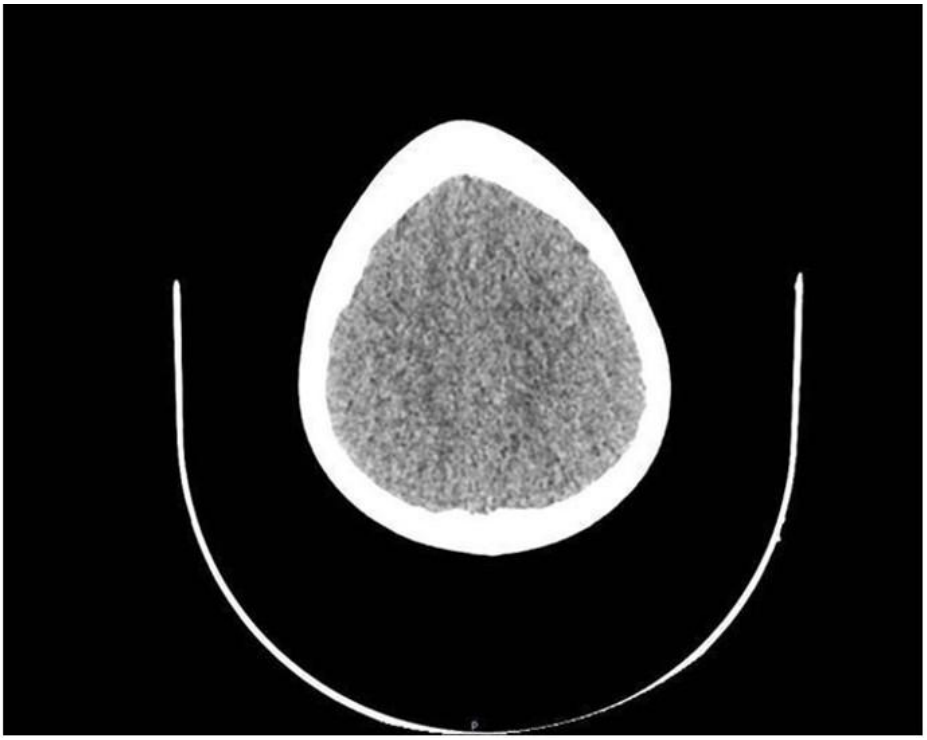

**Figure 1**: Non-contrast brain CT scan of the patient demonstrating trigonocephaly and structural features associated with microcephaly.

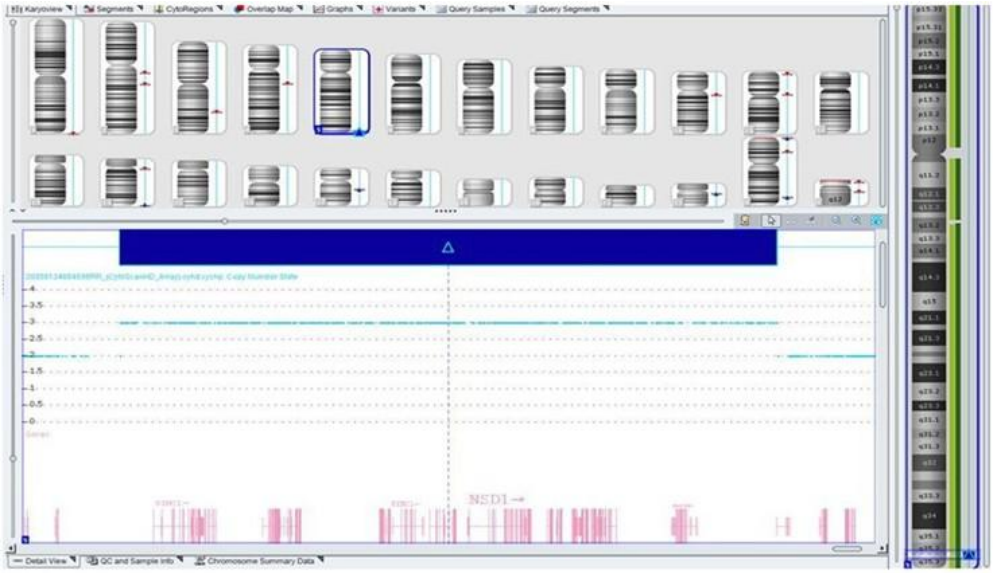


**Figure 2**: Chromosome Analysis Suite (ChAS) output image detailing the 1.87 Mb de novo microduplication at 5q35.2q35.3 (dark blue bar) encompassing the NSD1 gene. Light blue markers indicate the copy number state (x3) across probes in the region.

## 4. Materials and Methods

A clinical case review was conducted through prospective consultation at Hospital Universitario Virgen del Rocío, Seville, Spain. Genomic DNA extracted from whole blood was analysed using the CytoScan™ HD SNP/CNV genomic array (Applied Biosystems™, USA), which comprises 2.67 million markers for copy number analysis, including 750,000 SNPs and 1.9 million non-polymorphic probes. Genomic coordinates were referenced to the GRCh38 (Hg38) genome build. Hybridization, data extraction, and analysis were performed according to the manufacturer's instructions. Data were analyzed using the Affymetrix Chromosome Analysis Suite v4.5 (Applied Biosystems™, USA), with assisted interpretation and reporting via Franklin (Genoox, Israel). Copy number variants (CNVs) larger than 10 kb and regions of loss of heterozygosity (LOH) greater than 2.0 Mb were assessed. CNV classification followed the recommendations of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen)

## 5. Discussion

Patients with 5q35 microdeletions (Sotos syndrome) characteristically present with variable cognitive impairment, speech delays, and behavioural differences, including features associated with autism spectrum conditions [6]. In our patient, neurodevelopmental assessment demonstrated language acquisition delay, attention deficit, and mild intellectual disability. These observations are fully consistent with clinical descriptions reported in prior cases of 5q35 microduplication [4,5]. Neuroimaging findings in 5q35 anomalies can include altered ventricular morphology; while trigone ventricular dilation is classic in Sotos syndrome, the altered cranial architecture and trigonocephaly observed in our case further emphasize the structural craniofacial consequences of this genomic region.

From a mechanistic standpoint, published functional literature demonstrates that NSD1 encodes a histone methyltransferase targeting H3K36, acting as an epigenetic regulator of transcriptional programs during development [7]. Epigenetic models suggest that precise dosage of chromatin-modifying enzymes is essential for normal neural maturation [8,9]. This biological framework offers a plausible explanation for why both deletions and duplications involving NSD1 manifest with neurodevelopmental and cognitive impairments, even though their physical somatic effects differ markedly.

The physical presentation in this 5-year-old patient highlights the clinical contrast with classical Sotos syndrome. While Sotos syndrome is defined by overgrowth, macrocephaly, and advanced bone maturation, our patient presented with persistent growth failure, microsomia, microcephaly, trigonocephaly, and dysmorphic facial features (long nose, small mouth, and thin upper lip). Skeletal features such as flat feet with valgus posture were also noted. As noted in literature reviews, skeletal anomalies including scoliosis, flat feet, and joint hypermobility have been described in rare copy number gains at 5q35 [10]. Additional clinical features such as dry skin (xerosis) were present in our case, expanding the descriptive presentation of this rare entity.

This case underlines the utility of genomic copy number profiling when evaluating patients with complex or underdiagnosed growth and neurodevelopmental phenotypes. Distinguishing 5q35 duplications from microdeletions is critical for aligning genetic findings with clinical expectations. While both CNV types present with neurodevelopmental delays, the physical traits observed here support prior literature describing reciprocal phenotypes resulting from dosage imbalances at 5q35.

Several reports have progressively added to the knowledge of 5q35 duplications, including studies by [11-14], and [15]. By documenting this case, we contribute further clinical and molecular evidence illustrating that presentation through a paediatric short-stature clinic can serve as a key entry point for diagnosing reverse Sotos syndrome.

## 6. Conclusions

This case of a de novo 1.87 Mb 5q35.2q35.3 microduplication illustrates the clinical presentation of “reverse Sotos syndrome” in a paediatric patient initially evaluated for persistent short stature. Our findings are consistent with published evidence indicating that while 5q35 microdeletions cause overgrowth and macrocephaly, microduplications at the same locus tend to manifest with reduced growth parameters, microcephaly, and characteristic dysmorphic features.

In clinical practice, 5q35 microduplication should be considered within the differential diagnosis for children presenting with unexplained short stature, microcephaly, dysmorphic facial traits, and neurodevelopmental delay. High-resolution CGH-SNP microarray testing serves as an effective diagnostic tool in this setting, facilitating accurate genetic ethology identification, informing family counselling, and supporting appropriate multidisciplinary paediatric follow-up.

## 7. Consent for Publication

Written informed consent was obtained from the patient’s parents for publication of this case report and accompanying images. A copy of the written consent is available for review.

### 8. Declaration Of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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