PROFILING A BRAZILIAN COHORT IN SOTOS SYNDROME: A REVIEW OF 9 INDIVIDUALS

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INTRODUCTION

Sotos syndrome (SS, OMIM #117550) is an autosomal dominant overgrowth syndrome characterized by macrocephaly, distinctive facial features, and variable intellectual disability, caused by haploinsufficiency of the Nuclear Receptor SET Domain–containing protein 1 (*NSD1)* gene located at 5q35.

OBJECTIVES

In this study, we aimed to characterize the clinical and molecular spectrum of a Brazilian cohort of 9 individuals with SS.

METHODS

A multicentric retrospective study of clinical and molecular findings in individuals presenting with clinical features of SS investigated through whole genome sequencing or cytogenomic techniques.

RESULTS AND DISCUSSION

The sex ratio was 6:3 (M:F), ages at first consultation ranged between 5 months and 14 years, and the mean age at molecular diagnosis was 17,1 years (2-33y). All exhibited variable degrees of intellectual disability (6 with mild, 2 with moderate ID, and 1 with severe) and long face, 8 presented with prominent forehead (88%), 6 patients with sparse frontotemporal hair (66%), and 5 with dolichocephaly (54%), findings that collectively define the *Gestalt* of SS (Figure 1).

Figure 2: Serial photos of patients 2 and 3 from childhood to adulthood.

Eight patients exhibited central nervous system anomalies (88%), four patients with congenital heart defects (44%), the most frequent defect being mitral and tricuspid regurgitation (3/9). Additionally, renal abnormalities were observed in 4 patients, all of them presenting with hydronephrosis.

Our molecular data were consistent with the profile of SS, with a clear predominance of *NSD1* nonsense variants amongst single-nucleotide variants (50%) (Figure 2) and only one patient harboring a 5q35 microdeletion, aligning with the molecular profile of non-Japanese SS patients.

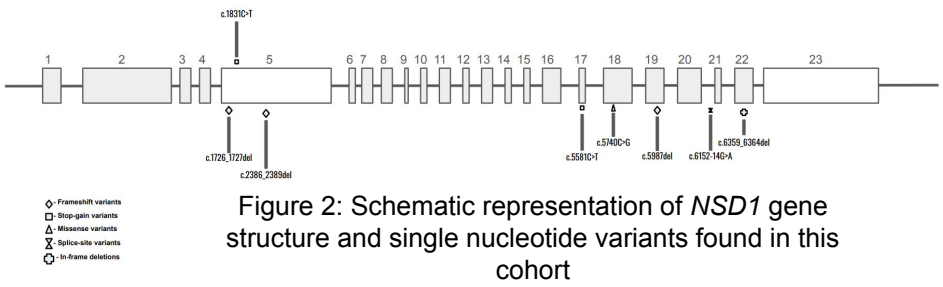

Figure 2: Schematic representation of *NSD1* gene structure and single nucleotide variants found in this cohort

Table 1 summarizes the clinical and molecular findings.

Table 1: Molecular data and clinical features of the patients

Patient number (n)	1	2	3	4	5
Sex	M	M	M	F	M
Age at first consultation	7m	8m	2y1m	10m	1y3m
Stature	76 cm (>*p*99)	76cm (>*p*97)	103,5 cm (>*p*99)	85 cm (>*p*97)	83cm (*p*93)
Weight	9,5kg (*p*91)	*8600g* (>*p*97)	17kg (>*p*99)	11,3kg (>*p*97)	12kg (*p*94)
OFC	50,5 cm (>*p*99)	*46,5cm* (>*p*97)	52,5 cm (>*p*99)	nd	51,5cm (>*p*99)
Birth length	59cm	nd	53 cm	56 cm	49cm
Birth weigth	4560g	3130g	3530g	4150g	3090g
OFC at birth	38cm	nd	nd	nd	35cm
Dolichocephaly	+	+	+	+	+
Prominent forehead	+	+	+	+	+
Frontoparietal sparse hair	+	+	+	+	+
Long face	+	+	+	+	+
Downslanted palpebral fissures	+	+	+	+	+
Strabismus	-	+	-	+	-
Prognatism	-	-	-	-	+
Pointed chin	+	+	+	+	+
Dental abnormalities	+	-	+	-	-
Large hands and feet	+	+	+	+	nd
Joint hyperlaxity	-	+	+	nd	-
Scoliosis	+	+	-	-	+
DD/ID	mild	mild	mild	mild	severe
Behavioral abnormality	+	+	+	+	+
Seizures	-	-	+	+	+
Tumor	-	-	-	-	-
Advanced bone age	+	+	+	+	nd
Cardiac abnormality	-	-	-	+	-
Renal abnormality	-	-	-	+	+
Abnormal neuroimaging	+	+	+	+	+
NSD1 variant	c.6152-14G>A	c.5581C>T	c.2386 2389del	c.5987del	NSD1 deletion
Protein change	p.?	p.Arg1861*	p.(Glu796Ilefs*10)	p.(Phe1996Serfs*6)	
Classification	Likely Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic

Patient number (n)	6	7	8	9
Sex	F	M	M	F
Age at first consultation	1y5m	10y3m	14y7m	8y9m
Stature	91 cm (>p99)	151 cm (>p97)	175 cm (p85)	143cm (>p97)
Weight	14 kg (p95)	37 kg (p75-90)	89 kg (>p97)	39 kg (p95)
OFC	53,5 cm (>p99)	57,5 (>p98)	57cm (p97)	53,5 cm (p50-98)
Birth length	51 cm	49 cm	55 cm	49cm
Birth weigth	3448g	3135g	3800g	3355g
OFC at birth	36,5 cm	35 cm	nd	34,5 cm
Dolichocephaly	-	-	-	-
Prominent forehead	+	+	+	-
Frontoparietal sparse hair	+	-	-	-
Long face	+	+	+	+
Downslanted palpebral fissures	+	-	+	-
Strabismus	-	+	-	-
Prognatism	-	-	-	-
Pointed chin	-	+	+	+
Dental abnormalities	-	+	-	-
Large hands and feet	+	-	+	+
Joint hyperlaxity	+	-	-	-
Scoliosis	-	+	-	-
DD/ID	mild	mild	moderate	Moderate
Behavioral abnormality	+	+	+	+
Seizures	-	+	-	-
Tumor	-	-	-	-
Advanced bone age	nd	-	+	nd
Cardiac abnormality	-	+	+	+
Renal abnormality	-	+	+	-
Abnormal neuroimaging	+	+	+	-
NSD1 variant	c.1831C>T	c.5740C>G	c.1726_1727del	c.6359_6364del
Protein change	p.(Arg611*)	p.(Arg1914Gly)	p.(Asn576Hisfs*7)	p.(Glu2120_Phe2122delinsVal)
Classification	Pathogenic	Likely Pathogenic	Likely Pathogenic	VUS

Key: + = present; - = absent; DD/ID = developmental delay / intellectual disability; F = female; M = male; nd = no data; OFC = occipitofrontal circumference; VUS = variant of uncertain significance.

CONCLUSION

This case series expands the clinical and molecular data on SS, presenting a novel variant and shedding light on uncommon manifestations, as well as a previously unreported feature in this condition associated with syndromic overgrowth that could be attributed to a multiple diagnoses scenario.

REFERENCES

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