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ORIGINAL ARTICLE

Clinical and Genetic Characteristics of Chinese Patients with Sotos Syndrome: a Cohort Study of 51 Cases

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ABSTRACT

Background: **Sotos syndrome is a rare overgrowth disorder caused by mutations in the nuclear receptor SET domain-containing gene 1 (NSD1) or deletions encompassing NSD1 at 5q35. Comprehensive data on the clinical and genetic characteristics of Chinese patients remain scarce. This study aimed to elucidate the phenotypic and genotypic spectrum of Sotos syndrome in the Chinese population by analyzing the largest cohort of Chinese patients to date.**

Methods: **We conducted a retrospective cohort study. Data were derived from one index case diagnosed at our institution, supplemented by 50 additional cases reported domestically through a systematic literature review (1982 to January 2025). Descriptive statistical analysis was performed on the clinical characteristics and genetic findings of all patients.**

Results: **The cohort comprised 51 patients (36 males, 13 females, 2 of unknown gender). The median age at diagnosis was 12.5 months (range: 1 day - 43 years). The most prominent clinical features were distinctive facial features (96.1%), developmental delay (92.2%), and excessive growth (98.0%). Common systemic involvement included ventricular enlargement (62.7%), congenital heart disease (41.2%), epilepsy or febrile seizures (33.3%), and corpus callosum or brain hypoplasia (31.4%). Malignant tumor incidence was 7.8%. Among 44 patients with genetic results, pathogenic NSD1 gene variants accounted for 68.2%, and 5q35 microdeletions for 29.5%. In cases with defined inheritance patterns, 93.0% involved de novo mutations.**

Conclusions: **This study systematically characterized the clinical and genetic landscape of Sotos syndrome patients in China. The phenotypic spectrum aligns with international reports, but the genetic structure reveals a higher proportion of NSD1 point mutations compared to other East Asian populations. The findings underscore the core value of genetic testing in diagnosis and the necessity of comprehensive multisystem management for patients.**
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Supplementary Data

Table S1. Hormonal and electrolyte dynamics during and during follow-up of indexed cases misdiagnosed as CAH.

Time points	17OHP nmol/L	Cor μg/dL	ACTH pg/mL	K mmol/L	Na mmol/L	Clinical description
At first visit (about 1.5 months of age)	34.4	4.6	50.6	6.2	132	Hydrocortisone and 9α - flucorol softening treatment was initiated on suspicion of congenital adrenal hyperplasia (CAH)
After admission and drug withdrawal (about 5 months of age)	2.03	8.3	30.3	4.78	136	Discontinue all glucocorticoids and mineralocorticoids upon admission
ACTH excitation test (peak)	7.49	30.81	—	—	—	The ACTH stimulation test was performed after drug withdrawal, and the cortisol peak response was normal, suggesting intact adrenal cortical function
1 year follow-up	—	17.7	42.7	4.73	137.4	All hormone and electrolyte levels were within the normal reference range

The table data consolidated the test results before admission and during follow-up in the self-written case reports. The ACTH excitation test values were the peaks measured after injection of adrenocorticotropic hormone. "-" indicates that this item was not tested at that point in time.
K: potassium, Na: sodium, ACTH: adrenocorticotropic hormone, Cor: cortisol, 17OHP: 17-hydroxyprogesterone.
Detection method: AD: High Performance liquid chromatography-tandem mass spectrometry, 17OHP: Chemiluminescence method, DHEA: Enzyme-linked immunosorbent assay (ELISA).

Table S2. Features of fifty chinese patients.

	Number	Gender	Diagnostic age	Birth weight kg	Birth length cm	Distinctive facial appearance				Develop-mental delay	Over-growth		NSD1	Other clinical characteristics
						spare fronto-temporal hair	broad and pro-minentfore head	downslanting palpebral fissures	long chin		head circumference	height		
Wang, B. D. 1982 (https://www.cnki.com.cn/Article/CJFDTOTAL-SHYX198206029.htm)	1	male	12 years	4.55	56	-	+	-	-	+	+	+	/	-
Zhao, D. H. 1987 (https://xueshu.baidu.com/ndscholar/browse/detail?paperid=122y0re01v660j60vy4106u0v3737188&site=xueshu_se)	2	male	2 years	4.7	56	-	-	+	+	+	+	+	/	febrile seizure, cerebral atrophy, ventricular enlargement, cryptorchidism
Zheng, F. S. 1992 (https://www.zhangqiaokeyan.com/academic-journal-n_national-medical-journal-china thesis/0201256720065.html)	3	male	8 years 11 months	4.2	/	+	+	+	+	+	+	+	/	epilepsy, ventricular dilatation, congenital heart disease, cryptorchidism
Li, Y. K. 2001 (doi: 10.3760/j.issn:0578-1310.2001.12.021)	4	male	4 years 6 months	4.8	/	-	+	-	+	+	+	+	/	-
Sun, Q. 2009 (https://d.wanfangdata.com.cn/periodical/syeklczz200902030)	5	male	1 year 2 months	3.8	/	+	+	-	-	+	+	+	/	epilepsy, ventricular dilation, thin corpus callosum, atrial septal defect, patent foramen ovale, large hands and feet
Wang, X. 2013 (https://www.cnki.com.cn/Article/CJFDTotal-ZSEK201306024.htm)	6	male	1 year 7 months	3.15	/	+	+	-	+	+	+	+	5q35 micro-deletion	febrile seizures, thin corpus callosum, large hands and feet, strabismus
Huang, W. W. 2013 (https://cpfd.cnki.com.cn/Article/CPFDTOTAL-ZKYX201610001013.htm)	7	-	1 day	-	-	-	-	-	-	+	+	+	5q35.2 - 35.3 (1.8 Mb micro-deletion)	-
Sun, B. J. 2015 (doi: 10.3760/cma.j.issn.1007-9408.2015.02.009)	8	male	6 hours	4.3	50	-	-	-	+	+	+	+	5q35.2 - 35.3 (1.97 Mb micro-deletion)	ventricular dilation, patent ductus arteriosus, patent foramen ovale, hypoglycemia
	9	male	3 days	3.9	49	-	-	-	-	+	-	+	5q35 micro-deletion	patent foramen ovale, hydronephrosis, cleft palate
Kang, L. L. 2016 [10]	10	male	10 months	3.7	50	+	+	-	+	+	+	+	c.5885T>C (P.I1962T)	ventricular dilation
	11	male	11 months	/	/	-	-	-	-	+	-	+	c.5990A>G (P.Y1997C)	dark of scrotum skin
	12	male	6 months	4.8	53	+	+	-	+	+	+	+	c.4118 - 4119insTGACCT (P.L1373Ffs*18)	ventricular dilation

Table S2. Features of fifty chinese patients (continued).

	Number	Gender	Diagnostic age	Birth weight kg	Birth length cm	Distinctive facial appearance				Developmental delay	Overgrowth		NSD1	Other clinical characteristics
						spare fronto-temporal hair	broad and pro-minentfore head	downslanting palpebral fissures	long chin		head circumference	height		
Chen, L. L. 2017 (doi: CNKI:SUN: ZYYA.0.2017-05-054)	13	male	9 days	2.95 (34w + 3)	51	-	-	-	-	+	+	+	details unknown	atrial septal defect, patent foramen ovale, hypomyelination of the brain?
Hou, H. L. 2017 (doi: 10.3969/j.issn.1673-5501.2017.06.015)	14	male	5 months	4.1	/	-	+	-	-	+	+	/	c.6622 - 6623insG (p.C2208Wfs*13)	cholestasis
Liu, X. Y. 2018 (https://xueshu.baidu.com/ndscholar/browse/detail?paperid=1q040870n46e0250y0130gb01w672148&site=xueshu_se)	15	male	1 year 9 months	4.1	/	+	+	+	-	+	+	+	Exon5 frameshift mutation, details unknown	epilepsy, atrial septal defect, large hands and feet
Zhao. M. 2018 (doi: 10.7499/j.issn.1008-8830.2018.06.010)	16	male	7 months	4.2	51	-	+	+	+	+	+	+	5q35.2 - 35.3 (1.75 Mb micro-deletion)	ventricular dilation, cerebral dysplasia
	17	male	10 months	3.6	50	-	+	+	-	+	-	-	c.1157T>G (p.F386L)	ventricular dilation
	18	male	1 year 1 months	3.5	53	+	-	+	+	+	+	+	c.1177G>T	ventricular dilation
Zhang, H. Z. 2018 (https://med.wanfangdata.com.cn/Paper/Detail?dbid=WF_QK&id=PeriodicalPaper_zgbjyy-kp201826497)	19	female	8 months	4.45	/	+	+	-	-	+	-	+	c.1806delT (p.C602fs)	ventricular dilation, femoral head dysplasia
Lu, Y. G. 2018 (doi: 10.3969/j.issn.1673-8640.2018.04.018)	20	male	8 months	4.1	/	+	+	+	-	+	+	+	5q35.2 - 35.3 (1907 kb micro-deletion)	ventricular dilation, dysgenesis of corpus callosum, patent ductus arteriosus, large hands and feet, finger deformity
	21	male	3 years	/	/	+	+	+	+	+	+	+	c.1262G>A (p.W421*)	epilepsy, ventricular dilation, patent ductus arteriosus, autism spectrum disorder?
Yang, X. 2018 (doi: 10.3969/j.issn.1004-8189.2018.09.014)	22	male	5 years	/	/	/	/	/	/	+	/	/	5q35.1 -35.3 (9069 kb micro-deletion)	epilepsy
Sun, Y. K. 2019 (doi: CNKI:SUN: QEYY.0.2019-04-024)	23	male	8 months	4.35	/	+	+	+	+	+	+	+	5q35.2 -35.3 (1.54 Mb micro-deletion)	epilepsy, ventricular dilation, ventricular septal defect, patent foramen ovale, renal cyst, large hands and feet, dark skin
Luo, Y. Q. 2020 (doi: 10.3760/cma.j.issn.1003-9406.2020.02.006)	24	male	6 years	3.24	/	-	+	-	+	+	+	+	5q35.2 -35.3 (5077 Mb micro-deletion)	ventricular dilation, patent ductus arteriosus, atrial septal defect, scoliosis

Table S2. Features of fifty chinese patients (continued).

	Number	Gender	Diagnostic age	Birth weight kg	Birth length cm	Distinctive facial appearance				Developmental delay	Overgrowth		NSD1	Other clinical characteristics
						spare fronto-temporal hair	broad and pro-minentfore head	downslanting palpebral fissures	long chin		head circumference	height		
Shi, K. L. 2020 (doi: 10.3877/cma.j.issn.1674-0785.2020.12.018)	25	female	1 year 6 months	4.6	/	+	+	+	+	+	+	+	c.4378 + 1_c.4378 + 4delGTGA	ventricular dilation, flat feet, valgus foot
Zheng, H. X. 2021 (doi: 10.3969/j.issn.1673-8640.2021.02.003)	26	male	6 years 11 months	3.4	/	-	+	-	+	+	+	+	c.5854C>T (P.R1952W) inherited from father	hydrocephalus, febrile convulsions, enlargement of the left heart
Ke, Z. L. 2021 (doi: 10.3969/j.issn.1672-4194.2021.03.018)	27	female	1 year 8 months	3.4	48	+	+	+	-	+	+	-	5q35.2 - 35.3 (1.96 Mb micro-deletion)	ventricular dilation, atrial septal defect, hypoglycemia, valgus foot
Hou, Y. H. 2021 (doi: 10.1002/jdn.70032)	28	male	5 months	3.99	/	+	+	-	+	+	+	+	c.5791T>C (P.C1931R)	broadening of cerebral gyri, abnormal signals of lateral ventricles, large hands and feet
Wang, X. 2021 (doi: 10.16751/j.cnki.2095-4646.2021.03.0258)	29	male	9 days	4.2	53	+	+	+	+	-	+	+	5q35.2 - 35.3 (2.02 Mb micro-deletion)	epilepsy, ventricular dilation, hypoglycemia
Zhao, Y. H. 2021 (doi: 10.3969/j.issn.1002-266X.2021.18.015)	30	male	2 years 4 months	/	/	+	+	+	+	+	+	+	5q35.2 - 35.3 (1.797 Mb micro-deletion)	epilepsy, hypoplasia of the corpus callosum, talipes plnus
Jin, H. Y. 2022 (https://doi.org/10.3390/medicina58070968)	31	male	3 days	3.15 (35w + 6)	50	-	+	-	+	-	+	+	c.5000C>A (p.A1667E)	patent ductus arteriosus, atrial septal defect, polycystic kidney disease, abnormal hearing, hypoglycemia
Mu, J. L. 2022 (doi: 10.3877/cma.j.issn.1673-5250.2022.06.011)	32	male	3 years 10 months	4.3	52	+	+	+	+	+	+	+	c.6007_6009 + 1delAAAG	ventricular dilation, dysplasia of the corpus callosum, cryptorchidism
LI, H. H. 2022 (doi: 10.13819/j.issn.2096-708X.2022.06.015)	33	female	3 years 11 months	4.7	55	-	+	+	-	+	+	+	c.6454c>T (PR2152*)	patent foramen ovale, lateral ventricular dilation
Zhang, B. B. 2022 (Sotos syndrome with a de novo mutation of NSD1 gene: a case report. Chinese Medical Case Repository 2022;4:e07275)	34	male	3 years 6 months	3.3	53	+	+	+	+	+	+	+	c.5622 + 1G>A	lateral ventricular dilation, hypoglycemia
Li, P. 2023 (doi: 10.13481/j.1671-587X.20230123)	35	male	1 year 9 months	4.59	/	+	+	-	+	+	+	+	c. 5965C>T (P.E1989*)	epilepsy, patent foramen ovale, necrotizing enterocolitis, enlargement of the cisterna magna

Table S2. Features of fifty chinese patients (continued).

	Number	Gender	Diagnostic age	Birth weight kg	Birth length cm	Distinctive facial appearance				Developmental delay	Overgrowth		NSD1	Other clinical characteristics
						spare fronto-temporal hair	broad and pro-minentfore head	downslanting palpebral fissures	long chin		head circumference	height		
Qi, Q. Y. 2023 (https://d.wanfangdata.com.cn/periodical/gsyy202305028)	36	female	3 years 8 months	4.25	/	+	+	-	-	+	+	+	c.6455G>A (p.R2152Q)	epilepsy
Xu, H. L. 2023 (doi: 10.3969/j.issn.1673-5323.2023.01.011)	37	male	4 months	3.75	51	+	+	+	+	+	+	+	5q35.2 - 35.3 (1.942Mb micro-deletion)	dysplasia of the corpus callosum, patent foramen ovale, large hands and feet, polydactyly, neuroblastoma
Lu, D. F. 2023 (doi: 10.3390/children10071111)	38	male	1 day	1.82 31w + 4 (P64)	42 (P59)	+	+	+	+	+	-	+	c.4765 + 1G>A	ventricular widening and corpus callosum hypoplasia, patent ductus arteriosus, atrial septal defect, bronchopulmonary dysplasia
Liu, X. T. 2023 (doi: 10.1002/brb3.3290)	39	female	3 years 11 months	3.3	/	+	+	+	+	+	+	+	c.6095G> A (p.W203)	seizure, hand deformities, ventricle was slightly larger
Chen, S. 2023 (doi: 10.1097/MD.0000000000036169)	40	male	1 year	3.85	54	+	+	-	+	+	+	+	c.3536delA inherited from mother	ventriculmegaly,thin corpus callosum, hypoglycemia
Li, Y. F. 2024 (doi: 10.1007/s10620-023-08229-0)	41	female	43 years	/	/	/	/	/	/	/	/	/	/	Li-Fraumeni (signet-ring cell carcinoma)
Yang, Y. J. 2024 (doi: 10.12998/wjcc.v12.i22.5131)	42	female	7 years	2.9	50	-	-	-	-	-	+	+	c.4605C>T inherited from father	attention-deficit/hyperactivity disorder (ADHD)
Zhang, K. L. 2024 (doi: 10.3760/cma.j.issn.1673-4408.2024.11.016)	43	male	8 months	4.47	52	+	+	-	+	+	+	+	c.6477_6482del (p. C2159_Pro2160del)	bilateral widening of the extracerebral spaces in the temporal lobes
Ren, Z. 2024 (doi: 10.1186/s12920-024-01889-5)	44	/	1 year 11 months	/	/	+	+	+	-	+	+	+	c.2686C>T (p.Q896X)	bilateral ventricular enlargement, dysplasia of the corpus callosum, atrial septal defect
	45	male	4 months	/	/	+	-	+	-	+	+	+	c.2858_2859 delCT (p.S953X)	loose and thickened left ventricular apex myocardial tissue structure, enlargement of bifrontal extracerebral space and bilateral ventricles, thinning of the corpus callosum

Table S2. Features of fifty chinese patients (continued).

	Number	Gender	Diagnostic age	Birth weight kg	Birth length cm	Distinctive facial appearance				Developmental delay	Overgrowth		NSD1	Other clinical characteristics
						spare fronto-temporal hair	broad and pro-minentfore head	downslanting palpebral fissures	long chin		head circumference	height		
Ren, Z. 2024 (doi: 10.1186/s12920-024-01889-5)	46	female	5 months	/	/	+	+	+	+	+	+	+	5q35.2 - 35.3 (176, 516, 604 -176, 639, 249) × 1	widening of extracerebral space in the bilateral frontotemporal region, irregular enlargement of the bilateral ventricles, thinner corpus callosum, atrial septal defect
	47	female	5 months	/	/	+	-	+	+	+	+	+	c.6397T>G (p.C2133G)	widening of bilateral frontotemporal extracerebral space, irregular widening of the bilateral ventricles, slightly thinner callosum, atrial septal defect
Qu, X. Y. 2024 (doi: 10.3969/j.issn.1004-8189.2024.08.024)	48	female	4 years	4.2	54	+	+	-	+	+	+	+	c.4765 + 1G>C	convulsions, bilateral widening of the lateral ventricles
Yue, X. Z. 2024 (doi: 10.1186/s12887-024-04636-y)	49	male	1 year	/	/	+	+	-	+	+	+	+	c.5510 - 1G>A	autism, pinealoblastoma
Our case	50	male	4 months	3.6	/	+	+	-	+	+	+	+	c.3550G>T (p.E1184*)	Ventricular dilation, atrial septal defect, arrhythmia, ventricular premature beats, bilateral renal cysts

+: There are related manifestations, -: There are no related manifestations, /: Relevant information is not mentioned in the article.
m: month, y: year.

Table S3. 51 Clinical characteristics of low frequency in chinese patients with Sotos syndrome (incidence ≤ 20%).

Characteristics	Number/total number of cases	Percentage (%)
Huge hands and feet	9/51	17.6
Hypoglycemia	7/51	13.7
Various kidney abnormalities (such as cysts and hydronephrosis)	6/51	11.8
Malignant tumor	4/51	7.8

The incidence of the features listed in this table is relatively low. The denominator of the percentage is the number of cases with corresponding valid records (n = 51).