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Deciphering Growth Patterns in Korean Children With Sotos Syndrome Through the Development of a Disease-Specific Growth Chart

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ABSTRACT

Background: Sotos syndrome (SS) is a rare disorder characterized by overgrowth, distinctive facial features, and intellectual disability that is primarily caused by NSD1 pathogenic variants or 5q35 microdeletions.

Methods: We retrospectively analyzed the clinical characteristics and 339 anthropometric measurements over an average of 4.3 years of follow-up in 57 Korean children with SS. Sex-specific percentile curves for height, weight, and head circumference were developed using a generalized additive model that included factors such as location, scale, and shape.

Results: Males with SS demonstrated higher height before the age of 12.0, greater weight before 10.0, and larger head circumference before 15.5 compared to age- and sex-matched controls. Females with SS displayed higher height before 17.0, greater weight before 10.5, and larger head circumference before 12.0 compared to controls. Bone age was advanced compared to chronological age in 40% of males and 8% of females at their last visit. The predicted and target adult heights were not significantly different between groups. In subgroup analysis, the intragenic variant group ($n = 48$) showed a higher mean standard deviation score of height and weight in males, and head circumference in females compared to the microdeletion group ($n = 9$).

Conclusions: Korean children with genetically confirmed SS exhibited overgrowth in height, weight, and head circumference. Overgrowth phenotypes were more prominent in patients with *NSD1* intragenic variants than in those with microdeletions. This is the first study to provide reference data on the growth of Korean children with SS.

1 | Introduction

Sotos syndrome (SS, OMIM #117550) is a representative overgrowth-intellectual disability syndrome characterized by three cardinal features: distinctive facial features, overgrowth, and intellectual disability, which are observed in at least 90% of affected patients (Tatton-Brown et al. 2005). Distinctive facial features include broad and prominent forehead, sparse fronto-temporal hair, downslanting palpebral fissures, long narrow face, and long chin. These features are the most specific clinical diagnostic criteria of SS and most recognizable between ages 1 and 6 years (Allanson and Cole 1996; Tatton-Brown, Cole, and Rahman 1993–2024). Other major clinical features that occur in 15%–89% of cases include behavioral problems, seizures, brain anomalies, cardiac anomalies, renal anomalies, and various skeletal problems, including advanced bone age (BA), scoliosis, joint hyperlaxity, and neonatal complications such as neonatal jaundice and hypoglycemia (Tatton-Brown et al. 2005).

SS is caused by the loss of nuclear receptor-binding SET domain protein 1 (NSD1) methyltransferase (Kurotaki et al. 2001). Abnormalities include an intragenic sequence variant of *NSD1* or a recurrent 1.9 Mb microdeletion on 5q35 that encompasses *NSD1* (Kurotaki et al. 2001). Patients with an intragenic variant exhibit more prominent overgrowth and less severe learning disability than those with a 5q35 microdeletion (Tatton-Brown et al. 2005; Sohn et al. 2013). However, genotype–phenotype correlations are not apparent for other clinical features (Tatton-Brown et al. 2005).

Children with SS show prenatal overgrowth, especially in height and head circumference, with a mean birth length in approximately the 98th percentile, birth weight in the 50–91th percentile, and head circumference in the 91–98th percentile (Tatton-Brown, Cole, and Rahman 1993–2024). Postnatally, children with SS show significantly higher growth rates during infancy, and rapid linear growth often persists before the age of 10, leading to a height consistently above the 97th percentile during childhood (Tatton-Brown et al. 2005; Tatton-Brown, Cole, and Rahman 1993–2024; Agwu et al. 1999; Karlberg and Wit 1991). The final adult height (FAH) reported in a British cohort study fell within the normal range (Agwu et al. 1999). However, recently published data showed that females with SS had a higher FAH than the normal population (Foster et al. 2019; Fickie et al. 2011). Macrocephaly is also a consistent feature in adulthood for individuals with SS (Foster et al. 2019; Fickie et al. 2011). Currently, there is a lack of standardized growth curves specifically tailored to SS. The main objective of this study was to investigate the clinical characteristics and genotype–phenotype correlation, particularly for the growth patterns of height, weight, and head circumference. Additionally, a secondary aim of the study was to develop growth curves for Korean patients with SS.

2 | Material and Methods

2.1 | Patients

A total of 57 unrelated *de novo* Korean children with SS (35 males and 22 females) who were genetically confirmed between March 2011 and April 2023 were included in this study (Figure S1). The methods used for genetic diagnosis are summarized in Figure S2. Anthropometric measurements, including height, weight, and head circumference, were obtained every 6–12 months during the clinical follow-up. To ensure consistency, measurements obtained during the first 12 months of life were excluded from the analysis of premature infants (i.e., before the 37th week of gestation) (Merker et al. 2018). For patients who underwent craniofacial operations, such as suturectomy ($n = 3$) or ventriculoperitoneal shunt surgery ($n = 2$), only preoperative head circumference data were included in the analysis. Similarly, only pretreatment height and weight data were included for patients treated with gonadotropin-releasing hormone agonists for central precocious puberty ($n = 2$). Medical records including birth history, anthropometric data, and associated clinical features were collected. Body length (cm) in the supine position was recorded until 24 months of age. Height (cm) was measured using a Harpenden stadiometer (Holtain Ltd., Crymych, Wales, UK) in the standing position, weight (kg) was measured using a digital scale (150 A; Cas Co. Ltd., Seoul, Korea) and head circumference (cm) was measured using nondistensible tape. The onset of puberty was defined as the attainment of testicular volume of more than 4 mL in males and the appearance of breast budding in females (Guidi and Sapra 2024). BA was assessed using the Greulich and Pyle atlas (Greulich and Pyle 1959), and advanced BA was defined as when BA showed a difference of more than 2 years ahead of the chronological age (CA). Standard deviation scores (SDS) for height, weight, and head circumference were assigned based on the 2017 Korean National Growth Charts (Kim et al. 2018). Tall stature and macrocephaly were defined as SDS ≥ 2 in height and head circumference, respectively (Tatton-Brown et al. 2005; Foster et al. 2019). The target adult height (TAH) was calculated by adding and subtracting 6.5 cm from the mean parental height for males and females, respectively (Tanner, Goldstein, and Whitehouse 1970). Predicted adult height (PAH) was assessed using the Bayley and Pinneau method based on BA (Bayley and Pinneau 1952).

2.2 | Statistical Analysis

Anthropometric data were divided into 6-month intervals and graphed to construct smooth centile curves based on the patient's sex using the generalized additive model for location, scale, and shape using the GAMLSS package in R (Rigby and Stasinopoulos 2005). These curves were generated using the Lambda-Mu-Sigma method (Cole and Green 1992) and an extension developed by Rigby and Stasinopolus (Rigby and Stasinopoulos 2005). This method assumes that the growth variable conforms to non-normal distributions, such as the truncated standard normal Box-Cox Cole Green (BCCGo) distribution, truncated standard normal Box-Cox distribution power exponential (BCPEo), and truncated Box-Cox t (BCTo) distribution. All data are presented as mean ± standard deviation (SD) along with the number of subjects (percentage). Comparisons of growth data with normal Korean population data on Tables 1 and 2 were conducted using the *t*-test and Mann–Whitney *U* test. We organized the age groups into 0.5-year intervals for this analysis. For head circumference after 6 years of age, reference values from the general population were derived from measurements obtained at 72 months. The difference in growth patterns between the two genotype groups (e.g., intragenic variant group vs. microdeletion group) was evaluated using SDS, enabling comparisons across different patient groups at various ages. This analysis was conducted using the *t*-test and Mann–Whitney *U* test. Statistical analyses were performed using the SPSS v. 27.0 (SPSS Inc. Chicago, IL, USA) and R software v. 4.3.0 (The Comprehensive R Archive Network, Vienna, Austria). A p value < 0.05 was considered to be significant.

2.3 | Ethical Compliance

This study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB no. 2307-055-1447). The requirement for informed consent was waived due to the retrospective design of this study.

TABLE 1 | Anthropometric data of males with Sotos syndrome compared to the general population.

Age range (years)	N (Ht)	Ht Sotos (cm)	Ht general (cm)	*p*	N (Wt)	Wt Sotos (kg)	Wt general (kg)	*p*	N (HC)	HC Sotos (cm)	HC general (cm)	*p*
0.00–0.49	7	65.80 ± 7.49	59.04 ± 6.29	**0.009**	7	6.86 ± 2.04	5.79 ± 1.82	0.141	7	42.40 ± 2.87	39.27 ± 3.30	**0.017**
0.50–0.99	3	74.80 ± 6.56	71.19 ± 4.13	0.150	3	9.00 ± 1.76	8.83 ± 1.54	0.774	6	48.02 ± 1.03	44.67 ± 2.08	**< 0.001**
1.00–1.49	4	87.25 ± 2.65	78.55 ± 4.25	**< 0.001**	4	13.30 ± 0.63	10.33 ± 1.76	**0.003**	5	50.78 ± 0.31	46.67 ± 2.03	**< 0.001**
1.50–1.99	5	93.16 ± 4.92	84.64 ± 4.62	**< 0.001**	5	15.34 ± 1.49	11.61 ± 2.01	**0.001**	6	52.78 ± 1.30	47.76 ± 2.06	**< 0.001**
2.00–2.49	9	97.47 ± 3.79	89.18 ± 5.07	**< 0.001**	9	16.89 ± 1.56	12.84 ± 2.28	**< 0.001**	9	53.80 ± 1.28	48.55 ± 2.10	**< 0.001**
2.50–2.99	11	100.68 ± 4.07	93.70 ± 5.51	**< 0.001**	11	18.25 ± 2.61	13.98 ± 2.54	**< 0.001**	7	53.87 ± 1.11	49.17 ± 2.15	**< 0.001**
3.00–3.49	14	106.66 ± 3.88	98.21 ± 6.09	**< 0.001**	14	21.44 ± 4.98	15.36 ± 2.35	**< 0.001**	11	54.55 ± 1.07	49.92 ± 2.37	**< 0.001**
3.50–3.99	9	110.10 ± 4.23	101.42 ± 6.25	**< 0.001**	9	22.47 ± 2.43	16.51 ± 2.70	**< 0.001**	7	55.64 ± 1.01	50.32 ± 2.25	**< 0.001**
4.00–4.49	8	113.09 ± 3.22	104.63 ± 6.42	**< 0.001**	8	22.70 ± 2.68	17.68 ± 3.07	**< 0.001**	6	55.05 ± 0.98	50.69 ± 2.18	**< 0.001**
4.50–4.99	7	117.54 ± 4.14	107.84 ± 6.59	**0.001**	7	24.01 ± 3.38	18.86 ± 3.44	**0.002**	6	55.45 ± 0.90	51.02 ± 2.16	**< 0.001**
5.00–5.49	11	119.97 ± 3.70	111.04 ± 6.80	**< 0.001**	11	24.91 ± 3.70	20.06 ± 3.83	**0.002**	10	56.00 ± 1.26	51.30 ± 2.17	**< 0.001**
5.50–5.99	11	124.64 ± 4.19	114.25 ± 7.02	**< 0.001**	11	27.93 ± 4.06	21.39 ± 4.32	**< 0.001**	7	55.89 ± 0.89	51.54 ± 2.18	**< 0.001**
6.00–6.49	7	124.73 ± 4.52	117.40 ± 7.27	**0.028**	7	27.34 ± 4.66	22.87 ± 4.88	**0.054**	6	55.67 ± 1.47	51.68 ± 2.25	**0.001**
6.50–6.99	7	132.40 ± 6.05	120.50 ± 7.48	**0.001**	7	30.84 ± 5.08	24.45 ± 5.49	**0.008**	5	55.96 ± 0.91	51.68 ± 2.25	**0.002**
7.00–7.49	6	133.25 ± 5.57	123.52 ± 7.68	**0.010**	6	30.68 ± 8.20	26.14 ± 6.17	0.133	4	56.85 ± 1.94	51.68 ± 2.25	**0.005**
7.50–7.99	7	139.27 ± 6.74	126.43 ± 7.83	**0.001**	7	35.14 ± 7.46	27.93 ± 6.90	**0.018**	4	56.95 ± 0.71	51.68 ± 2.25	**0.003**
8.00–8.49	7	140.10 ± 7.54	129.24 ± 7.97	**0.009**	7	36.79 ± 11.09	29.81 ± 7.65	0.066	7	56.94 ± 1.67	51.68 ± 2.25	**< 0.001**
8.50–8.99	8	147.18 ± 7.24	132.01 ± 8.13	**< 0.001**	8	42.67 ± 10.70	31.77 ± 8.42	**0.007**	6	57.37 ± 1.33	51.68 ± 2.25	**0.001**
9.00–9.49	6	146.83 ± 8.27	134.76 ± 8.37	**0.009**	6	42.19 ± 12.71	33.81 ± 9.24	0.056	3	57.53 ± 2.24	51.68 ± 2.25	**0.009**
9.50–9.99	16	151.30 ± 6.98	137.52 ± 8.67	**< 0.001**	16	46.43 ± 10.95	35.96 ± 10.11	**0.002**	12	57.52 ± 1.55	51.68 ± 2.25	**< 0.001**
10.00–10.49	8	150.78 ± 6.46	140.33 ± 9.01	**0.004**	8	45.06 ± 10.53	38.20 ± 10.98	0.099	6	57.30 ± 1.89	51.68 ± 2.25	**0.001**
10.50–10.99	5	160.34 ± 11.75	143.24 ± 9.42	**0.006**	5	52.94 ± 16.30	40.53 ± 11.84	0.052	3	59.17 ± 1.61	51.68 ± 2.25	**0.009**
11.00–11.49	7	156.20 ± 3.15	146.29 ± 9.91	**0.014**	7	47.83 ± 7.79	43.00 ± 12.74	0.263	5	57.86 ± 1.96	51.68 ± 2.25	**0.001**
11.50–11.99	5	160.76 ± 7.02	149.52 ± 10.44	**0.042**	5	53.64 ± 15.66	45.60 ± 13.61	0.251	2	59.50 ± 2.83	51.68 ± 2.25	**0.027**
12.00–12.49	5	162.64 ± 5.98	152.88 ± 10.92	0.066	5	50.00 ± 9.06	48.29 ± 14.36	0.811	5	57.86 ± 0.22	51.68 ± 2.25	**0.001**
12.50–12.99	2	170.45 ± 6.01	156.28 ± 11.19	0.074	2	65.18 ± 13.89	51.00 ± 14.95	0.242	0	NA	51.68 ± 2.25	NA
13.00–13.49	2	167.60 ± 1.70	159.57 ± 11.20	0.405	2	55.68 ± 4.91	53.61 ± 15.35	0.841	2	57.75 ± 1.77	51.68 ± 2.25	**0.027**

(Continues)

TABLE 1 | (Continued)

Age range (years)	N (Ht)	Ht Sotos (cm)	Ht general (cm)	*p*	N (Wt)	Wt Sotos (kg)	Wt general (kg)	*p*	N (HC)	HC Sotos (cm)	HC general (cm)	*p*
13.50–13.99	4	172.93 ± 1.67	162.57 ± 10.93	0.083	4	71.30 ± 12.32	56.08 ± 15.49	0.053	2	59.75 ± 1.77	51.68 ± 2.25	**0.027**
14.00–14.49	3	175.83 ± 11.12	165.22 ± 10.41	0.177	3	74.17 ± 30.29	58.34 ± 15.40	0.329	2	58.25 ± 0.35	51.68 ± 2.25	**0.027**
14.50–14.99	0	NA	167.43 ± 9.82	NA	0	NA	60.35 ± 15.12	NA	0	NA	51.68 ± 2.25	NA
15.00–15.49	2	173.15 ± 9.26	169.17 ± 9.28	0.460	2	77.75 ± 29.06	62.07 ± 14.76	0.267	2	58.25 ± 1.77	51.68 ± 2.25	**0.027**
15.50–15.99	0	NA	170.50 ± 8.86	NA	0	NA	63.54 ± 14.39	NA	0	NA	51.68 ± 2.25	NA
16.00–16.49	2	174.45 ± 8.70	171.52 ± 8.57	0.548	2	75.70 ± 9.90	64.84 ± 14.11	0.332	1	60.50 ± NA	51.68 ± 2.25	0.107
16.50–16.99	1	180.00 ± NA	172.28 ± 8.45	0.357	1	83.10 ± NA	65.90 ± 13.96	0.236	0	NA	51.68 ± 2.25	NA
17.00–17.49	0	NA	172.87 ± 8.43	NA	0	NA	66.80 ± 13.86	NA	0	NA	51.68 ± 2.25	NA
17.50–17.99	2	175.00 ± 11.31	173.42 ± 8.44	0.712	2	70.50 ± 17.68	67.65 ± 13.78	0.611	1	57.80 ± NA	51.68 ± 2.25	0.107
18.00–18.49	1	167.00 ± NA	173.97 ± 8.47	0.497	1	60.00 ± NA	68.49 ± 13.72	0.693	0	NA	51.68 ± 2.25	NA

Note: Data are presented as the mean ± SD or N. Bolded values indicate statistical significance ($p < 0.05$).
Abbreviations: HC, head circumference; Ht, height; NA, not available; N, number; Wt, weight.

3 | Results

3.1 | Patient Characteristics

In 57 children with SS, the mean follow-up duration was 4.3 ± 3.4 years. All patients showed typical facial features, such as a prominent forehead and a pointed chin. At their last visit (8.1 ± 5.6 years), tall stature and macrocephaly were observed in 23 (40%), and 51 (89%) patients, respectively. During follow-up, intellectual disabilities or developmental delays were noted in 49 (86%) patients. Two (4%) patients were diagnosed with autism spectrum disorder, and eight (14%) were diagnosed with attention deficit hyperactivity disorder. Twenty-one (37%) patients had a history of seizures, and nine (43%) had taken antiepileptic drugs. Cardiac anomalies were noted in 28 (49%) patients, including atrial septal defect or patent foramen ovale in 10 (36%), patent ductus arteriosus in 6 (21%), and ventricular septal defect in 2 (7%) patients. Cranial anomalies were observed in 36 (63%), corpus callosum anomalies in 12 (33%), and ventriculomegaly in 10 (28%) patients. Neonatal complications such as neonatal hypotonia, jaundice, and poor feeding were documented in 36 (63%) patients. Renal anomalies such as horseshoe kidney, cystic lesion, renomegaly, small kidney size, or ureteropelvic junction obstruction were observed in six (11%) patients. Pes planus infection and scoliosis were observed in 33 (58%) and 22 (39%) patients, respectively (Table S1).

3.2 | Growth Chart Development

Growth data collected during the follow-up period included 339 measurements from 229 males and 110 females were analyzed. The total number of analyzed data points was 312 for length and height (from 212 males and 100 females), 313 for weight (from 212 males and 101 females), and 251 for head circumference (from 165 males and 86 females) (Table S2). Figures 1–3 display individual data points plotted directly onto the Korean growth curve for the general population. The mean height was consistently higher than that of the general population until 12.0 years of age in males (Table 1) and across all age groups in females (Table 2). Among six patients (four males and two females) who achieved FAH, the FAH SDS was −1.3 ± 0.1 (TAH SDS of −0.8 ± 0.1) for two males, and + 2.3 ± 0.7 (TAH SDS of + 0.5 ± 0.1) for two females. For the weight growth curve, the mean weight was consistently higher than that of the general population until 10.0 years of age in males (Table 1), and 10.5 years of age in females (Table 2). For the head circumference growth curve, the mean head circumference was consistently larger than that of the general population until 15.5 years of age in males (Table 1), and 12.0 years of age in females (Table 2). Standardized growth charts of males and females with SS are presented in Figures S3–S5.

3.3 | Association Between PAH and TAH

The SDS of PAH at the last visit was + 0.0 ± 1.2 in males (10.0 ± 3.0 years old), and + 0.4 ± 1.0 in females (8.6 ± 3.3 years old). For 28 males and 19 females with available TAH data, the mean SDS of TAH was −0.1 ± 0.9 for males and + 0.3 ± 0.6

TABLE 2 | Anthropometric data of females with Sotos syndrome compared to the general population.

Age range (years)	N (Ht)	Ht Sotos (cm)	Ht general (cm)	*p*	N (Wt)	Wt Sotos (kg)	Wt general (kg)	*p*	N (HC)	HC Sotos (cm)	HC general (cm)	*P*
0.00–0.49	4	63.18 ± 9.34	57.64 ± 5.98	0.082	5	6.54 ± 2.00	5.37 ± 1.68	0.141	6	41.68 ± 5.64	38.37 ± 3.18	**0.024**
0.50–0.99	5	77.74 ± 4.25	69.35 ± 4.37	**< 0.001**	5	10.30 ± 2.00	8.20 ± 1.60	**0.028**	6	46.90 ± 1.95	43.50 ± 2.18	**< 0.001**
1.00–1.49	4	83.60 ± 2.33	76.90 ± 4.56	**0.005**	4	12.38 ± 1.18	9.69 ± 1.85	**0.011**	5	50.00 ± 2.52	45.51 ± 2.12	**0.001**
1.50–1.99	5	88.88 ± 1.11	83.15 ± 4.91	**0.018**	5	14.40 ± 2.27	10.99 ± 2.10	**0.014**	8	52.68 ± 2.50	46.65 ± 2.13	**< 0.001**
2.00–2.49	9	96.02 ± 3.68	87.84 ± 5.30	**< 0.001**	9	16.22 ± 2.02	12.28 ± 2.36	**< 0.001**	8	52.99 ± 2.70	47.51 ± 2.14	**< 0.001**
2.50–2.99	3	98.70 ± 2.69	92.54 ± 5.69	0.072	3	16.53 ± 4.06	13.51 ± 2.64	0.115	3	56.17 ± 1.26	48.18 ± 2.14	**0.003**
3.00–3.49	5	104.52 ± 3.03	96.86 ± 6.11	**0.010**	5	19.97 ± 2.12	14.76 ± 2.31	**0.001**	5	56.10 ± 1.14	49.05 ± 2.32	**< 0.001**
3.50–3.99	5	108.34 ± 2.06	100.15 ± 6.23	**0.004**	5	21.35 ± 2.15	15.92 ± 2.66	**0.001**	4	53.78 ± 2.44	49.44 ± 2.26	**0.009**
4.00–4.49	2	114.85 ± 7.28	103.43 ± 6.33	0.060	2	23.60 ± 3.68	17.09 ± 3.02	**0.035**	2	56.40 ± 0.14	49.78 ± 2.21	**0.016**
4.50–4.99	5	117.02 ± 0.83	106.69 ± 6.44	**< 0.001**	5	25.17 ± 1.96	18.28 ± 3.40	**0.001**	4	55.95 ± 2.87	50.10 ± 2.16	**0.002**
5.00–5.49	6	121.47 ± 2.08	109.92 ± 6.56	**< 0.001**	6	25.17 ± 2.34	19.48 ± 3.79	**0.002**	4	57.20 ± 1.90	50.43 ± 2.13	**0.001**
5.50–5.99	2	126.80 ± 1.98	113.07 ± 6.71	**0.016**	2	26.58 ± 2.51	20.77 ± 4.27	0.079	1	55.80 ± NA	50.78 ± 2.13	0.087
6.00–6.49	3	130.47 ± 7.62	116.17 ± 6.92	**0.008**	3	31.88 ± 8.10	22.16 ± 4.83	**0.030**	3	57.00 ± 2.02	50.98 ± 2.20	**0.009**
6.50–6.99	3	127.47 ± 0.92	119.25 ± 7.17	**0.045**	3	26.82 ± 1.41	23.66 ± 5.45	0.299	2	54.55 ± 0.78	50.98 ± 2.20	**0.042**
7.00–7.49	6	132.93 ± 5.03	122.30 ± 7.46	**0.003**	6	32.54 ± 6.47	25.28 ± 6.11	**0.025**	3	56.60 ± 2.13	50.98 ± 2.20	**0.013**
7.50–7.99	2	132.55 ± 5.02	125.31 ± 7.77	0.224	2	28.83 ± 4.00	26.99 ± 6.80	0.569	2	55.00 ± 0.00	50.98 ± 2.20	**0.027**
8.00–8.49	1	138.60 ± NA	128.31 ± 8.09	0.188	1	32.80 ± NA	28.82 ± 7.53	0.599	1	56.70 ± NA	50.98 ± 2.20	0.107
8.50–8.99	2	140.60 ± 2.26	131.36 ± 8.44	0.131	2	37.80 ± 0.00	30.76 ± 8.27	0.218	2	56.05 ± 0.64	50.98 ± 2.20	**0.027**
9.00–9.49	3	149.67 ± 7.35	134.45 ± 8.79	**0.016**	3	45.33 ± 10.89	32.82 ± 9.04	0.072	2	58.60 ± 0.99	50.98 ± 2.20	**0.027**
9.50–9.99	3	148.73 ± 4.07	137.62 ± 9.14	**0.043**	3	41.23 ± 2.25	34.98 ± 9.83	0.260	2	57.50 ± 1.41	50.98 ± 2.20	**0.027**
10.00–10.49	2	160.10 ± 7.50	140.80 ± 9.45	**0.023**	2	58.45 ± 9.55	37.24 ± 10.61	**0.031**	2	59.25 ± 0.35	50.98 ± 2.20	**0.027**
10.50–10.99	3	154.53 ± 4.52	143.93 ± 9.64	0.072	3	44.58 ± 2.88	39.56 ± 11.30	0.461	3	57.43 ± 1.01	50.98 ± 2.20	**0.009**
11.00–11.49	1	161.80 ± NA	146.94 ± 9.65	0.105	1	56.15 ± NA	41.90 ± 11.86	0.236	1	59.50 ± NA	50.98 ± 2.20	0.107
11.50–11.99	4	161.30 ± 4.93	149.75 ± 9.50	**0.020**	4	50.96 ± 4.27	44.16 ± 12.27	0.282	3	57.33 ± 1.26	50.98 ± 2.20	**0.009**
12.00–12.49	1	166.70 ± NA	152.28 ± 9.22	0.087	1	55.50 ± NA	46.32 ± 12.50	0.483	1	59.00 ± NA	50.98 ± 2.20	0.107

(Continues)

TABLE 2 | (Continued)

Age range (years)	N (Ht)	Ht Sotos (cm)	Ht general (cm)	*p*	N (Wt)	Wt Sotos (kg)	Wt general (kg)	*p*	N (HC)	HC Sotos (cm)	HC general (cm)	*P*
12.50–12.99	3	172.00 ± 1.82	154.44 ± 8.86	**0.003**	3	63.10 ± 11.46	48.28 ± 12.54	0.099	1	61.50 ± NA	50.98 ± 2.20	0.107
13.00–13.49	0	NA	156.21 ± 8.52	NA	0	NA	49.98 ± 12.43	NA	0	NA	50.98 ± 2.20	NA
13.50–13.99	2	173.50 ± 0.71	157.50 ± 8.29	**0.016**	2	58.00 ± 1.41	51.41 ± 12.25	0.488	1	59.00 ± NA	50.98 ± 2.20	0.107
14.00–14.49	0	NA	158.41 ± 8.14	NA	0	NA	52.59 ± 12.04	NA	0	NA	50.98 ± 2.20	NA
14.50–14.99	1	175.20 ± NA	159.04 ± 8.06	0.087	1	62.70 ± NA	53.55 ± 11.79	0.469	0	NA	50.98 ± 2.20	NA
15.00–15.49	0	NA	159.51 ± 7.99	NA	0	NA	54.29 ± 11.57	NA	0	NA	50.98 ± 2.20	NA
15.50–15.99	0	NA	159.88 ± 7.93	NA	0	NA	54.83 ± 11.39	NA	0	NA	50.98 ± 2.20	NA
16.00–16.49	1	176.00 ± NA	160.14 ± 7.85	0.087	1	61.30 ± NA	55.22 ± 11.23	0.693	0	NA	50.98 ± 2.20	NA
16.50–16.99	2	172.55 ± 3.18	160.34 ± 7.76	**0.026**	2	62.95 ± 1.91	55.44 ± 11.11	0.388	0	NA	50.98 ± 2.20	NA
17.00–17.49	1	176.90 ± NA	160.56 ± 7.69	0.087	1	60.45 ± NA	55.55 ± 11.01	0.693	1	60.10 ± NA	50.98 ± 2.20	0.107
17.50–17.99	1	175.50 ± NA	160.77 ± 7.64	0.087	1	61.20 ± NA	55.63 ± 10.93	0.693	0	NA	50.98 ± 2.20	NA

Note: Data are presented as the mean ± SD or N. Bolded values indicate statistical significance ($p < 0.05$).
Abbreviations: HC, head circumference; Ht, height; NA, not available; No, number; Wt, weight.

for females. Among 24 patients (16 males and eight females) with both PAH and TAH data, PAH and TAH were not significantly different among males (176.3 ± 7.0 cm vs. 174.7 ± 5.3 cm, at 10.4 years old) or females (166.0 ± 6.7 cm vs. 162.9 ± 2.9 cm, at 8.2 years old). Among 33 children (20 males and 13 females) for whom BA was evaluated at their last visit, BA was advanced than CA in eight (40%) males (13.0 ± 2.6 years vs. 10.5 ± 2.5 years, $p = 0.011$) and one (8%) female (9.0 years vs. 5.6 years). Of the 19 patients for whom pubertal onset data were available, 10 were in the prepubertal state. Among nine pubertal patients, six males began puberty at a mean age of 10.4 ± 1.6 years, and three females began puberty at a mean age of 10.2 ± 0.5 years, with an average age of menarche of 11.7 ± 1.2 years.

3.4 | Comparison of Growth Patterns and Clinical Characteristics by Genotypes

Genetic testing revealed that 48 (84%) patients had an *NSD1* intragenic variant, while the remaining nine (16%) patients had a 5q35 microdeletion. The growth parameters according to molecular subtype are presented in Figure 4. The intragenic variant group ($n = 48$) showed a higher mean SDS for height (+2.1 ± 1.0 vs. +0.5 ± 1.0, $p < 0.001$) and weight (+1.7 ± 1.3 vs. +0.7 ± 1.2, $p = 0.010$) in males, and head circumference in females (+3.9 ± 1.6 vs. +2.6 ± 0.5, $p < 0.001$) when compared with the microdeletion group ($n = 9$). Genotype–phenotype correlations were not significant for clinical characteristics other than growth patterns between the two genotype groups, and there was no difference between variant types (i.e., missense vs. truncating variants) in each clinical phenotype.

4 | Discussion

Korean children with genetically confirmed SS exhibited higher height, weight, and head circumference than the general population from birth throughout childhood, particularly for height and head circumference. At the last visit, BA had advanced in 40% of male and 8% of female patients, while PAH and FAH did not differ from TAH in patients with available data. Compared to those in the microdeletion group, the intragenic variant group showed greater height and weight in males, and a larger head circumference in females.

This study highlighted that children with SS had greater height and larger head circumferences than the general population, which are associated with excessive prenatal growth (Tatton-Brown, Cole, and Rahman 1993–2024). According to the growth data in 40 British patients with SS aged 2–31 years, the mean height SDS at the ages of 2 and 6 years was +3.6 and +3.0 for males, and +3.6 and +3.8 for females, respectively, which was consistent with our findings (mean height SDS at the age of 2 and 6 years was +2.7 and 2.0 for males, and +2.5 and +2.6 for females) (Agwu et al. 1999). Another study that included 175 European patients aged 1–10 years with confirmed *NSD1* abnormalities reported that 90% of the affected patients displayed tall stature and/or macrocephaly, with 60% showing both height and head circumferences above the 99.6th percentile (Tatton-Brown et al. 2005). In the growth data of 21 molecularly confirmed adults with SS, 86% had macrocephaly, and the

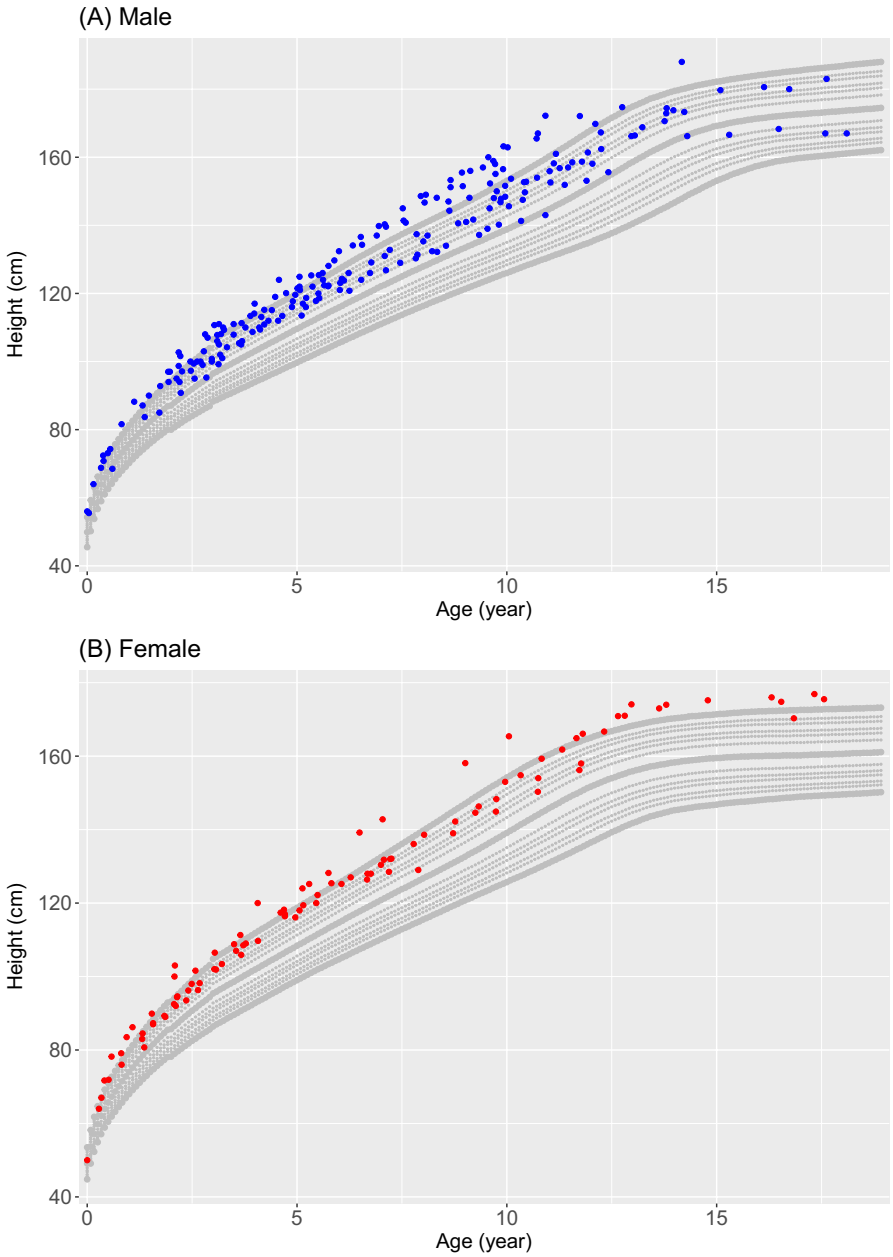

FIGURE 1 | Scatter plots of height for (A) males and (B) females with SS. The *x*-axis represents age (years) and the *y*-axis represents height (cm). The gray dots represent the 2017 Korean National Growth Charts. The 1st, 3rd, 5th, 10th, 15th, 25th, 50th, 75th, 85th, 90th, 95th, 97th, and 99th percentiles are shown from bottom to top; the 1st, 50th, and 99th percentiles are indicated with bold dots.

mean head circumference was reported to be + 2.4 SD in males and + 2.7 SD in females in 44 adult patients (Foster et al. 2019; Fickie et al. 2011).

To date, reports on BA and pubertal development in children diagnosed with SS are limited. In this study, advanced BA was observed in 40% of males and 8% of females who were evaluated for BA at their last visit. BA was advanced in 84% of 37 patients with clinically diagnosed SS and 76% of 239 patients with molecularly confirmed SS (Tatton-Brown et al. 2005; Cole and Hughes 1994). Among 13 patients with clinical SS in a UK cohort of 40 patients, all displayed advanced BA (Agwu et al. 1999). While the timing of puberty onset (10.2 years) in females were compatible to that (11.0 years) of the general Korean population, earlier tendency of puberty onset (10.2 years) was observed in males than the general population (12.7 years) (Hong 2011). Of the 40 patients in the UK SS cohort, 13 clinically diagnosed with SS displayed early onset of puberty (Agwu et al. 1999). Although the number of subjects that were followed to menarche was limited, the average age at menarche in the three females in our study (11.7 years) tended to be earlier than that in the general Korean population (12.6 years) (Seo et al. 2020). In 12 British females with a clinical diagnosis of SS, the age of menarche showed a wide range (8.9–15.4 years), with the mean age of 12.2 years that was earlier than that in the general British population (13.0 years), although there was no significant difference between these groups (Agwu et al. 1999). However, in a recent British study of 27 females with molecularly confirmed SS, the median age of menarche was approximately 13 years, similar to that of the general British population (Foster et al. 2019). In addition, the onset of puberty in

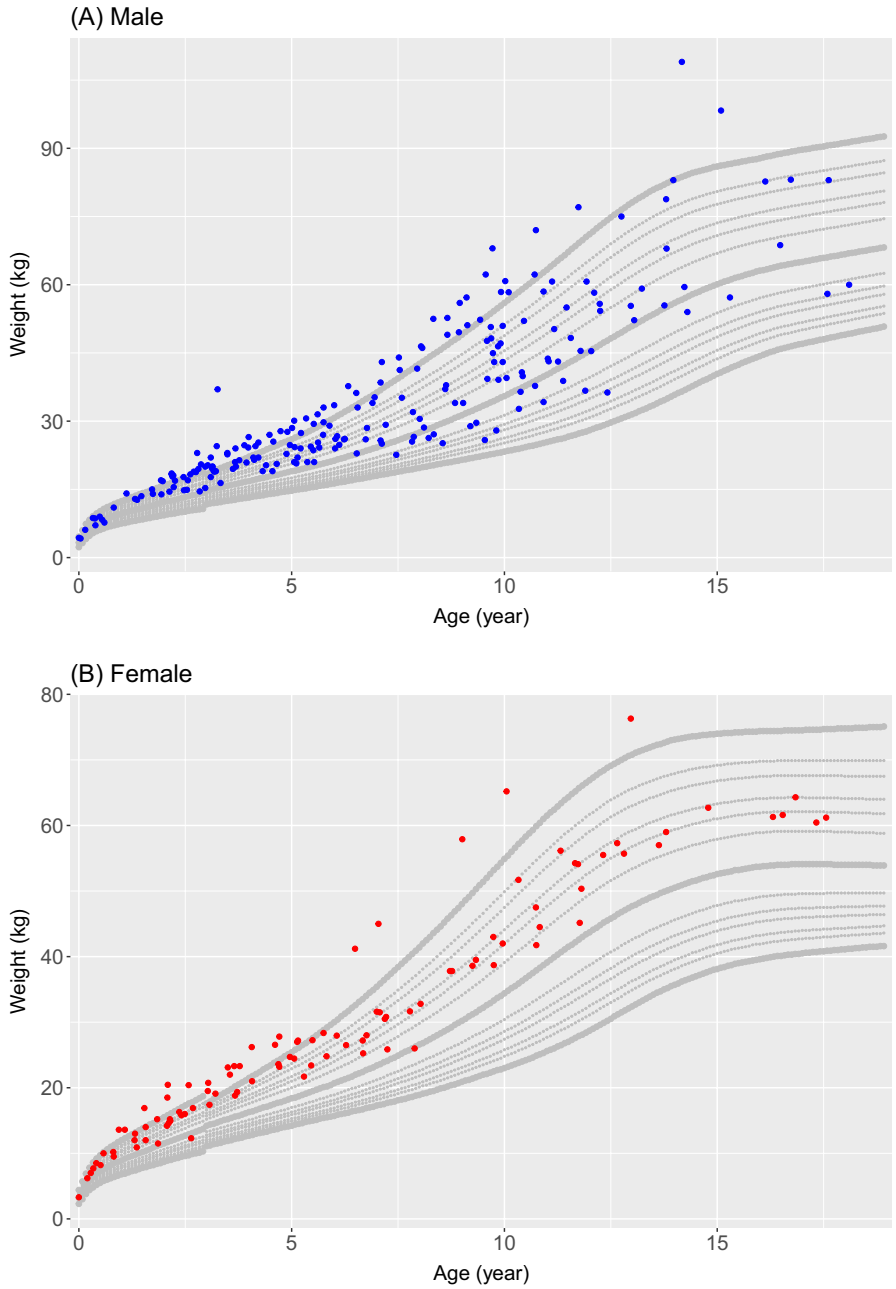

FIGURE 2 | Scatter plots of the weight for (A) males and (B) females with SS. The *x*-axis represents age (years) and the *y*-axis represents weight (kg). The gray dots represent the 2017 Korean National Growth Charts, with the 1st, 3rd, 5th, 10th, 15th, 25th, 50th, 75th, 85th, 90th, 95th, 97th, and 99th percentiles shown from bottom to top; and the 1st, 50th, and 99th percentiles indicated with bold dots.

males was similar to that of the general population in the UK (Foster et al. 2019).

Information of FAH in patients with SS is limited. We found that FAH was within the normal range in both sexes. In previous study of adults with SS, the mean FAH was 182 cm (75th percentile) and 174 cm (97th percentile) in males and females, respectively (Fickie et al. 2011). In addition, a sex difference in the FAH was reported, with a median adult height of + 1.9 SD in females and + 0.5 SD in males (Foster et al. 2019). FAH was significantly higher than the TAH in a previous British cohort (Agwu et al. 1999). In our cohort, among the few patients who attained their final height, females tended to be higher than general population, which could be attributed to their appropriate BA for CA, although there was no significant difference between FAH and TAH. These findings collectively illustrate excessive growth in height during childhood in patients with SS; however, further details on BA, puberty timing, and FAH in patients with SS remain to be elucidated.

Our results of genotype–phenotype correlations between intragenic variants and microdeletion groups were consistent with previous results that showed more prominent overgrowth in patients with an *NSD1* intragenic variant than in those with a microdeletion (Tatton-Brown et al. 2005; Sohn et al. 2013). Other clinical features associated with SS, including cardiac, renal, skeletal anomalies, and neurological findings, were not significantly different between the two genotype groups. Moreover,

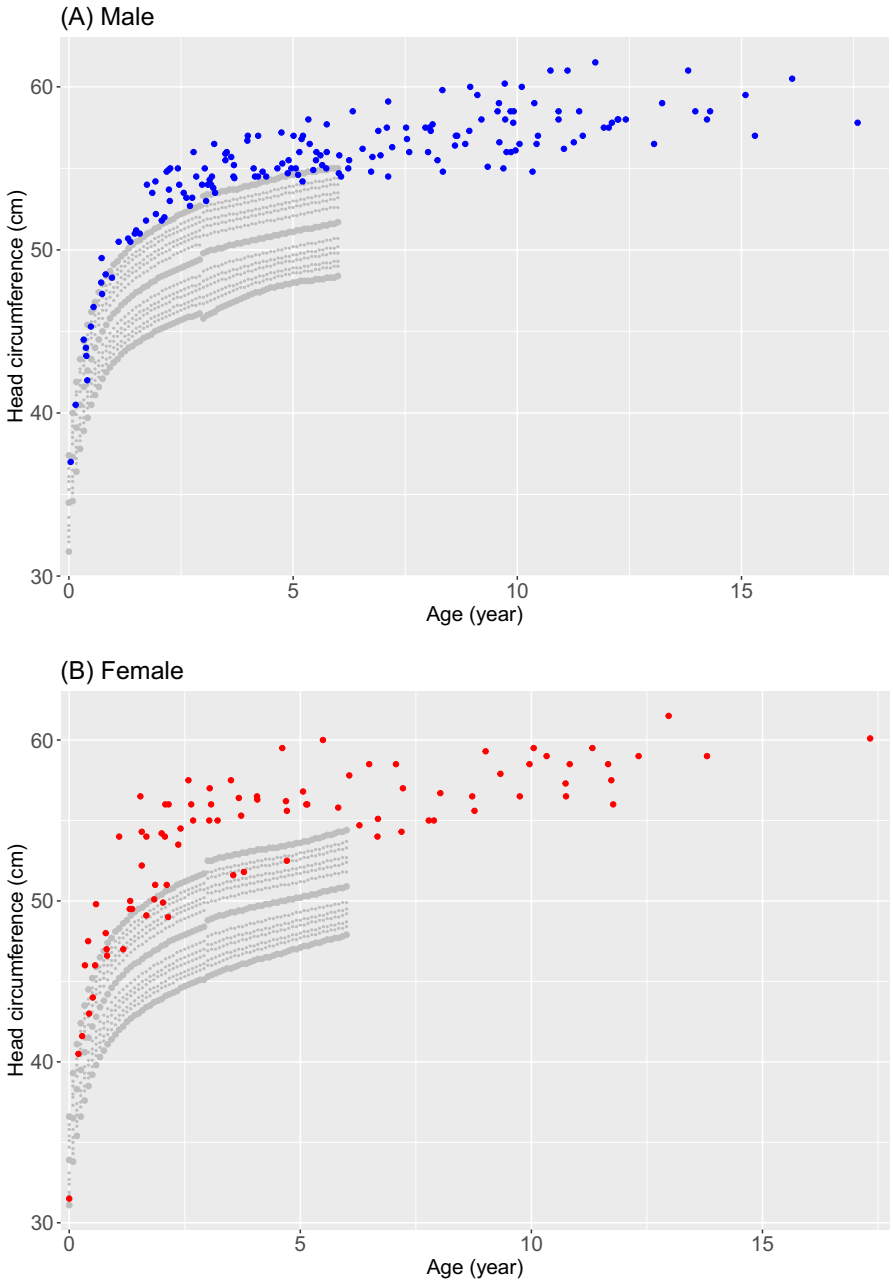

FIGURE 3 | Scatter plots of head circumferences for (A) males and (B) females with SS. The *x*-axis represents age (years) and the *y*-axis represents head circumference (cm). The gray dots represent the 2017 Korean National Growth Charts, with the 1st, 3rd, 5th, 10th, 15th, 25th, 50th, 75th, 85th, 90th, 95th, 97th, and 99th percentiles shown from bottom to top; and the 1st, 50th, and 99th percentiles indicated with bold dots.

there was no difference in phenotype according to the type of intragenic pathogenic variant (missense vs. truncating) or position of variants (5′ vs. 3′) in our study, consistent with a previous study (Tatton-Brown et al. 2005).

This study had several limitations. First, owing to the relatively young age of the patients, we could not evaluate complete growth patterns throughout adolescence and adulthood in all enrolled patients. Additionally, the retrospective nature of the study resulted in missing data such as growth data, information on BA, puberty, and FAH, leading us to present the growth patterns of SS patients in Korea rather than proposing a new and standard growth curve for SS. Second, the study was conducted at a single tertiary center and therefore, there might be a referral bias that potentially influenced the results. Third, a limited number of patients were included, limiting the ability to sufficiently revealing genotype–phenotype correlations of various clinical characteristics and establishing standardized centile growth curves, particularly for head circumference in females. Despite these limitations, this study can be meaningful in that each patient has been measuring continuously and repeatedly over a long period of time and it is the largest retrospective analysis for SS conducted in South Korea.

In conclusion, Korean children with genetically confirmed SS exhibited overgrowth in height, weight, and head circumference. Overgrowth phenotypes were more prominent in

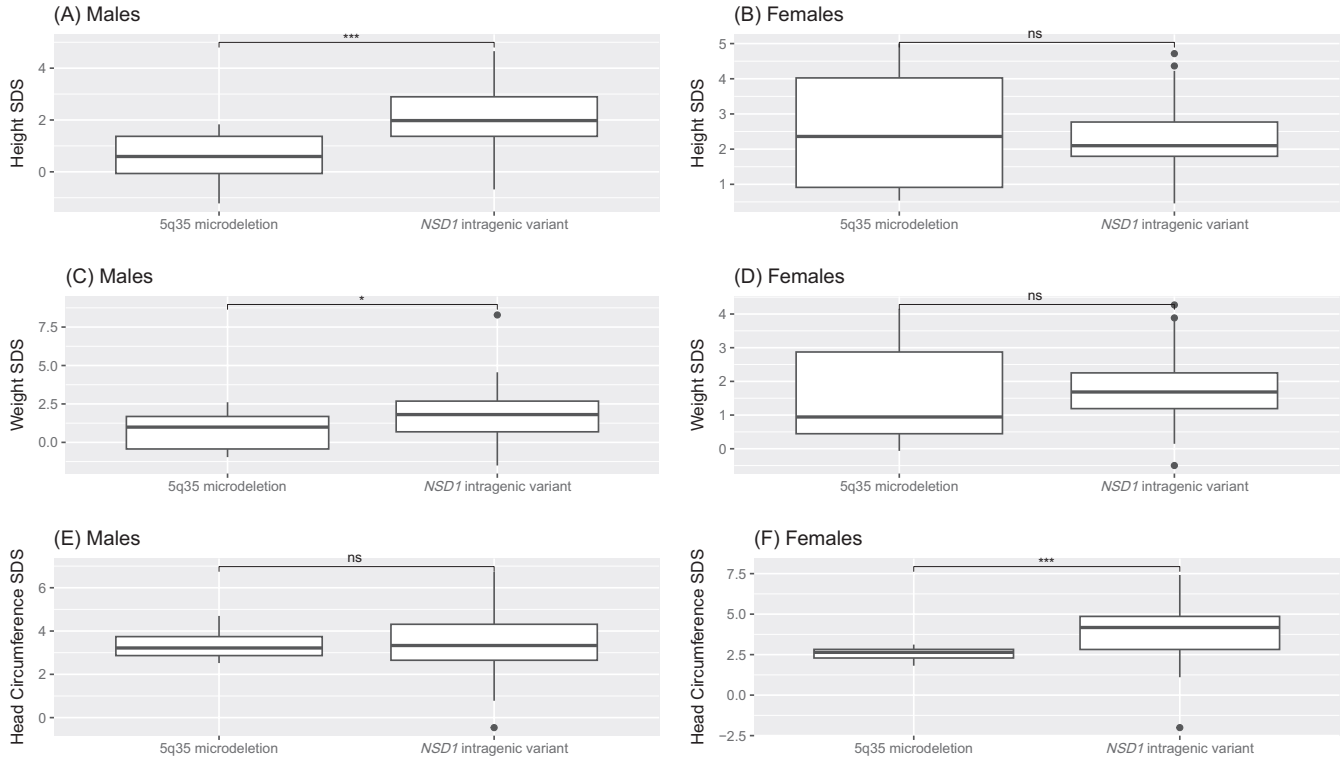

FIGURE 4 | Comparison of anthropometric indices of children with SS by genotype. The height SDS for (A) males and (B) females. The weight SDS for (C) males and (D) females. The head circumference SDS for (E) males and (F) females. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ns, $p > 0.05$.

patients with *NSD1* intragenic variants than in those with microdeletions. This is the first study to provide reference data on the growth of Korean children with SS. A nationwide cohort study is warranted to track the overall growth patterns in adulthood and to fully understand the genotype–phenotype correlations in SS.

Author Contributions

Naye Choi and Jung Min Ko designed and conceived of the study. Naye Choi, Hwa Young Kim, and Jung Min Ko were involved in data collection and interpretation. Naye Choi, Hwa Young Kim, and Jung Min Ko conducted the literature search and drafted the manuscript. All the authors have read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All the data used for the analysis are shown in the figure and tables in this article. Data sharing is applicable to this article if requested by other investigators to replicate the results.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.