

Genomic Insights into Short Stature in Children Born Small for Gestational Age: A Korean Multicenter Exome Study

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Abstract

Context: Most infants born small for gestational age (SGA) experience catch-up growth within 2 years, while 10% to 15% remain short. The cause of this persistent growth failure remains unknown.

Objective: To investigate the genetic causes of SGA with short stature (SGA-SS) due to failure of catch-up growth.

Methods: A total of 191 children from multicenter SGA-SS cohorts across 7 hospitals in South Korea underwent whole-exome sequencing. Identified copy number variants (CNVs) were confirmed via chromosomal microarray analysis.

Results: Genetic variants were identified in 34 children (17.8% diagnostic rate). CNVs accounted for 50% (17/34), including 6 children with 22q11.2 microdeletion syndrome, predominantly exhibiting mild dysmorphic features without severe intellectual disability (ID), developmental delay (DD) or severe anomalies. Single-nucleotide variants (SNVs) were identified in 17 children (17/34, 50%). One had compound heterozygous mutations in *SLC26A2*, 1 likely pathogenic mutation, and another of uncertain significance. The remaining children had heterozygous variants, including 5 pathogenic variants in *COL2A1*, *ACAN*, *SALL1*, *TAOK1*, *ANKRD11* and 11 likely pathogenic variants in *PIK3R1*, *PLAG1*, *SCUBE3*, *COL9A2* (in 2 patients), *SMAD4*, *PTPN11* (in 2 patients), *CDKN1C*, *ACAN*, *NF1*. A novel familial Silver-Russell syndrome case was linked to a *CDKN1C* mutation. Genetic causes were identified in 14 (58.3%) of 24 patients with ID/DD: 9 with CNVs and 5 with SNVs.

Conclusion: SGA-SS has a heterogeneous genetic basis, with CNVs significantly contributing. The variable presentation of 22q11.2 microdeletion syndrome highlights its relevance. A genetic diagnosis is more likely in familial cases or those with ID/DD, supporting the utility of genetic testing.

Key Words: small for gestational age, short stature, whole exome sequencing

Small for gestational age (SGA) refers to infants who are smaller than the normative range for their gestational age and sex. However, the criteria used to define SGA vary across studies. The World Health Organization defines SGA as infants with birth weight below the 10th percentile for sex and gestational age, whereas consensus statements define SGA as birth weight and/or length of at least 2 SDs below the mean (1–3).

Up to 90% of children with SGA achieve catch-up growth within the first 2 years of life. Those who fail to catch up are

classified as small for gestational age with short stature (SGA-SS) and are eligible for recombinant human GH (rhGH) treatment (1, 2). In Korea, the National Health Insurance covers rhGH therapy for children with SGA who fail to achieve catch-up growth by 4 years of age, using birth weight below the third percentile based on Korean birth weight reference standards as the criterion for SGA (4).

The etiology of SGA is multifactorial and involves genetic, epigenetic, environmental, and maternal factors (5). In particular, imprinting disorders such as Silver-Russell syndrome

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(SRS), Temple syndrome, and IMAGe syndrome (intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital malformations) are known contributors to SGA-SS and should be considered in the differential diagnosis (6-9).

In addition to imprinting disorders, the genetic causes of SGA-SS are diverse. However, most affected children fail to exhibit overt syndromic features, which makes genetic diagnosis challenging. Recent advances in next-generation sequencing technology have enabled the identification of genetic causes associated with SGA-SS (10, 11). Moreover, understanding the genetic basis of SGA-SS can provide insights into the pathophysiology of growth and assist in predicting the prognosis and response to rhGH therapy.

Variable diagnostic yields have been reported for genetic testing in SGA-SS; 15% in nonsyndromic SGA-SS cases (12), 22.1% in a Japanese SGA-SS cohort (11), and 42% in a Czech single-center SGA-SS cohort (10). In Korea, research on the genetic causes of SGA-SS is limited, with only a small single-center study reported to date (13).

In this multicenter study, we aimed to identify the genetic causes underlying the failure to achieve catch-up growth in children with relatively nonsyndromic SGA in Korea. We performed whole-exome sequencing (WES) with integrated screening for copy number variants (CNVs) and analyzed the prevalence and characteristics of both CNVs and single-nucleotide variants (SNVs) in this population.

Materials and Methods

Subjects and Clinical Assessment

A total of 191 children were recruited from 7 university hospitals in South Korea. In this study, SGA was defined as birth weight or length below the third percentile according to the Korean birth weight reference standards (4). Failure to achieve catch-up growth was defined as a height below the third percentile, equivalent to a SD score (SDS) of -1.89 , after 2 years of age based on age- and sex-matched normative data (14).

All participants were assessed using the Netchine-Harison Clinical Scoring System (NH-CSS). Subjects with a score of ≥ 4 were clinically suspected to have SRS (15) and were excluded from the study. Children with mild facial dysmorphism, mild intellectual disability (ID), or minor anomalies, such as cryptorchidism, sensory neural hearing loss, or strabismus, were included. Patients with endocrine disorders, including primary hypothyroidism (encompassing congenital hypothyroidism, subclinical hypothyroidism), drug-induced hypothyroidism, or GH deficiency, were also eligible for inclusion. Cushing syndrome, a condition known to independently cause growth retardation, was excluded, whereas adrenal insufficiency, a cardinal manifestation of IMAGe syndrome, was not specified among the exclusion criteria (Fig. 1).

The clinical data were collected retrospectively. The SDSs for height and body weight were calculated based on the Korean National Growth Charts for children and adolescents (14). All statistical analyses were performed using R software (Version 4.4.3, Windows). *P*-values $< .05$ were deemed statistically significant.

All participants were born to nonconsanguineous Korean parents. Peripheral blood or buccal smear samples were collected after informed consent was obtained from the patients and their parents. Clinical photographs of patients carrying

pathogenic/likely pathogenic variants or variants of uncertain significance (VUS) were obtained with informed consent from their legal guardians. The study was approved by the institutional review boards of all participating hospitals (approval numbers are provided in the ethics section).

Molecular Analysis

WES

High molecular weight genomic DNA was extracted from the patient's whole blood-EDTA or buccal swab samples using the QIAamp DNA Blood Mini Kit (Qiagen) and AccuBuccal DNA Preparation Kit (Accugene), respectively. WES was performed according to the CAP/CLIA-validated standard operating protocol. Exome capture was performed using the xGen Exome Research Panel v2 (Integrated DNA Technologies, Coralville, IA, USA). Sequencing was performed using the NovaSeq platform (Illumina, San Diego, CA, USA) with 150bp paired-end reads. Sequencing data were aligned to either the GRCh37/hg19 or GRCh38/hg38 human reference genome using BWA-MEM and processed for variant calling using GATK (16, 17). CNVs were called using 3bCNV, an internally developed tool that utilizes the depth-of-coverage information for each exon, MANTA, and SavvyCNV (18, 19). High-quality variants were annotated, filtered, and classified using EVIDENCE, which incorporates the Ensembl Variant Effect Predictor for annotation and American College of Medical Genetics and Genomics (ACMG) guidelines for variant classification (20-22). SpliceAI was used for splicing prediction (23). Medical geneticists and physicians manually reviewed the filtered and classified variant lists, and the most likely variants that could explain the patient's phenotype were selected.

Chromosomal microarray

Chromosomal microarray (CMA) was performed using the CytoScan Dx assay platform (Thermo Fisher Scientific, Waltham, MA, USA). Genomic DNA (250 ng) extracted from peripheral blood or buccal swabs was digested with NspI and amplified by ligation-mediated PCR. The PCR product was purified, quantified, fragmented using DNase I, labeled with biotin, and hybridized overnight (16-18 hours) with a CytoScan Dx array. After hybridization, the samples were washed and stained with streptavidin using the GeneChip Fluidics Station 450. The array was scanned using GeneChip Scanner 3000 to generate a CEL file. The CEL file was analyzed using the Chromosome Analysis Suite Dx (Thermo Fisher Scientific) and converted to a CYCHP file to visualize the genomic copy number and absence of heterozygosity. The pathogenicity of the detected CNVs was classified based on CNV scoring metrics in the ACMG/ClinGen Technical Standards (24).

Sanger sequencing

Sanger sequencing was performed to validate each variant identified by WES. Variant-specific primers were designed using Primer3 software. PCR amplification was conducted under the following conditions: initial denaturation at 95 °C for 2 minutes; 35 cycles of denaturation at 95 °C for 15 seconds, annealing at 56 °C for 15 seconds, and extension at 72 °C for 30 seconds; followed by a final extension at 72 °C for 7 minutes. The amplified PCR products were subjected

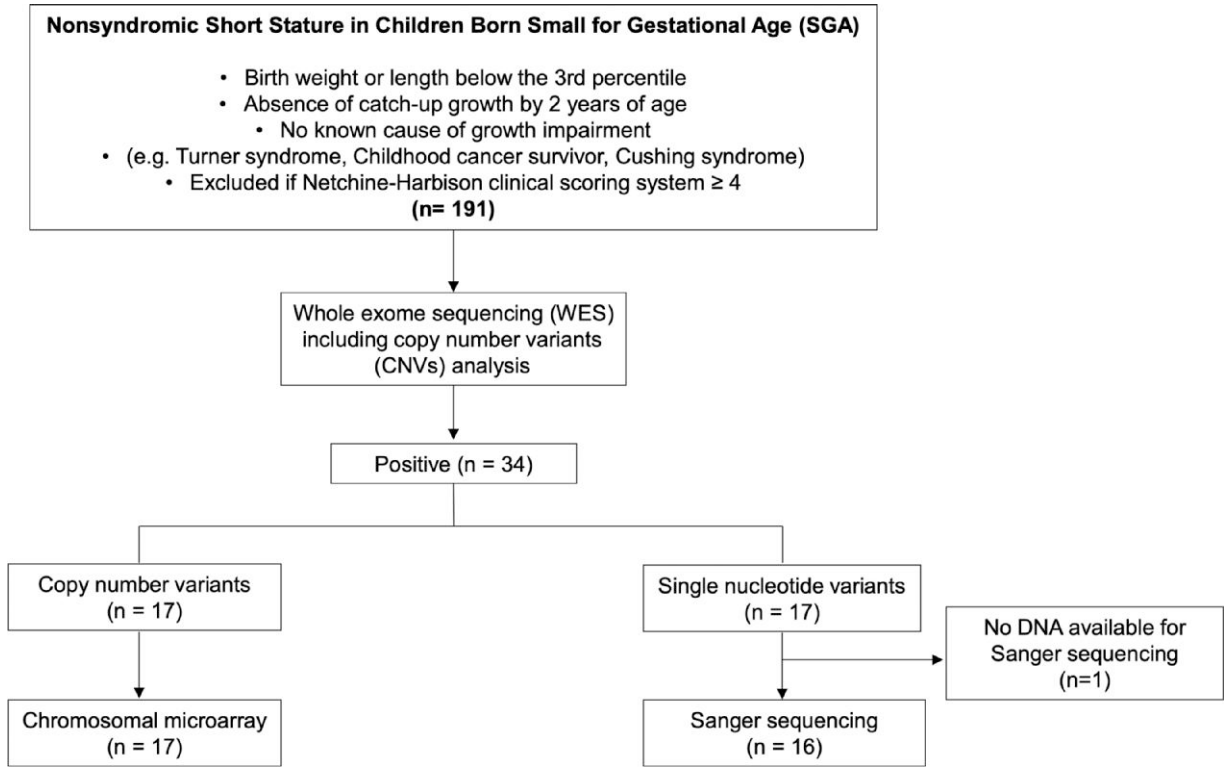


Figure 1. Flowchart illustrating patient enrollment and genetic analyses performed in the study.

to Sanger sequencing using an ABI 3730XL Genetic Analyzer (Applied Biosystems®). Sequence data were analyzed using Chromas software.

Results

Clinical Characteristics of the Study Cohort

The clinical characteristics of the 191 patients with SGS-SS are summarized in Table 1. Of the 191 patients, 54 (28.3%) were preterm births. The study primarily included children with nonsyndromic SGA-SS, as evidenced by the low prevalence of ID (12.6%), congenital minor anomalies (6.8%), and congenital heart disease (3.1%). Approximately 68.6% of the patients exhibited no additional clinical features beyond short stature. Based on the NH-CSS, 90% of patients had a clinical score of 1 or 2 (Table 1).

Genetic Findings in SGA-SS

Genetic abnormalities of CNVs and SNVs are summarized in Tables 2 and 3, respectively.

CNVs

Genetic abnormalities related to pre- and postnatal growth retardation were identified in 34 of the 191 patients (17.8%). Half of these abnormalities were CNVs (17/34, 50%) (Table 2), all present in the heterozygous state.

The 22q11.21 region was the most frequently affected, identified as a microdeletion in 6 patients and as a duplication in a 7-year-old male patient. Deletions in the 15q26.3 region, which includes the *IGF1R* gene, were identified in 2 patients (patient 8 and patient 17, respectively). Upon the identification of a 1.5 Mb microdeletion at 7q11.23, patient 14, who presented with developmental delay (DD), distinctive facial

features, and annular pancreas, was diagnosed with Williams syndrome. Patient 16, born prematurely and presenting with mild ID, epilepsy, and hypothyroidism, harbored a 5p15.33 deletion encompassing the cri-du-chat syndrome (CdCS) region. Her hypothyroidism is likely attributable to the long-term use of oxcarbazepine, given her normal TSH level of 2.89 μ IU/mL and slightly reduced free T4 level of 0.86 ng/dL (reference range: 0.92-1.68) (25).

2q11.1q12.1 duplication, 19q13.12 deletion, and 1q24.2q25.1 deletion were classified as pathogenic CNVs. Conversely, the 20q11.23 deletion and 17p13.1p12 duplication were classified as VUS. Interestingly, patient 15 carried 2 CNVs: a 3q27.1 deletion (classified as likely pathogenic) and a 5q22.2 duplication (classified as VUS).

In this cohort, patients with 22q11.2 microdeletion syndrome (22q11.2 DS) exhibited a relatively mild clinical phenotype, including subtle dysmorphic features and mild DD, without notable congenital anomalies or hypocalcemia (Table 4). Although patients 4 and 5 were siblings who inherited the 22q11.2 microdeletion from their mother, they exhibited distinct clinical phenotypes. Patient 4 presented with a cleft lip, a typical feature of 22q11.2 DS, whereas patient 5 had no cleft anomaly but showed neurodevelopmental problems, ID, and attention deficit hyperactivity disorder, highlighting the broad phenotypic spectrum of this syndrome, even within the same family (Fig. 2).

SNVs

Of the 191 patients with SGA-SS, 17 had SNVs in growth-related genes (Table 3). Among these, 16 patients carried heterozygous variants, whereas patient 21 harbored compound heterozygous variants in the *SLC26A2* gene. According to the ACMG guidelines, 5 variants were classified

Table 1. Clinical characteristics of the study cohort

Characteristics	Patients with SGA-SS (n = 191)
General information	
Male: Female	107:84
Age at first evaluation (years)	6.12 ± 2.66 (2-14)
Birth information	
Gestational age (weeks)	37.96 ± 2.00 (30-41)
Birth weight (kg)	2.27 ± 0.42 (0.82-2.8)
Growth-related parameter	
Height SDS at first visit	−2.38 ± 0.54 (−4.69–−1.89)
Mid-parental height SDS	−0.81 ± 0.77 (−3.52-1.57)
Familial short stature ^a	56 (29.3%)
GH treatment	175 (91.6%)
Height SDS at last visit	−1.15 ± 0.93 (−4.52-1.12)
Other clinical findings (%)	
Preterm birth	54 (28.3)
Precocious puberty/early puberty	49 (25.7)
Intellectual disability/developmental delay ^b	24 (12.6)
Skeletal abnormalities	15 (7.9)
Minor anomalies	13 (6.8)
Congenital heart disease	6 (3.1)
Complete GH deficiency ^c	6 (3.1)
Primary congenital hypothyroidism	3 (1.6)
Subclinical hypothyroidism	1 (0.5)
Drug-induced hypothyroidism	1 (0.5)
Netchine-Harbison Clinical Scoring System (%)	
3	19 (9.95)
2	125 (65.4)
1	47 (24.6)

Data are presented as the mean ± SD (ranges) for continuous variables and absolute numbers (%) for categorical variables.
Abbreviations: SDS, SD score; SGA-SS, small for gestational age with short stature.
^aFamilial short stature was defined when at least 1 parent had a height below the third percentile (−1.89 SDS).
^bPatients enrolled in this study presented with borderline to mild intellectual disability; none of them exhibited severe intellectual disability.
^cComplete GH deficiency was defined as having a peak GH level below 5 ng/mL.

as pathogenic and were identified in *COL2A1*, *ACAN*, *SALL1*, *TAOK1*, and *ANKRD11* genes. Twelve variants were classified as likely pathogenic and were identified in *PIK3R1*, *PLAG1*, *SCUBE3*, *COL9A2* (in 2 patients), *SMAD4*, *PTPN11* (in 2 patients), *CDKN1C*, *ACAN*, *NF1*, and *SLC26A2*. One variant in *SLC26A2* was classified as a VUS.

Categorization according to the molecular mechanisms underlying short stature (26) revealed that the most frequently observed mechanism was defects in intracellular pathways (10/17, 58.8%), followed by abnormalities in the cartilage extracellular matrix (6/17, 35.3%) (Table 5). No variants related to the GH-IGF-1 axis were identified. A heterozygous variant in *SCUBE3*, a gene involved in bone morphogenetic protein signaling, was identified in patient 24.

A mutation in *PIK3R1* associated with SHORT syndrome was identified in patient 19, who presented with scoliosis, glaucoma, and mild insulin resistance, with a Homeostatic Model Assessment for Insulin Resistance value of 3.3 at 19

years of age. He inherited a likely pathogenic variant from his mother, who was 147 cm (−3.05 SDS) in height.

Pathogenic variants associated with established syndromes were identified in 3 patients. Patient 23 carried a pathogenic *SALL1* variant (c.3160C>T, p.Arg1054Ter); however, his clinical presentation did not align with the typical features of Townes-Brocks syndrome, such as an imperforate anus and dysplastic ears. Patient 27 had a heterozygous *SMAD4* variant (c.1498A>G, p.Ile500Val) and exhibited facial features characteristic of Myhre syndrome, although other features such as progressive connective tissue disorder or cardiovascular disease were absent. Patient 31, who had an *NF1* variant, presented with multiple café-au-lait spots on the trunk but did not meet the full clinical criteria for neurofibromatosis type 1.

Two patients with *PTPN11* variants were diagnosed with Noonan syndrome. Patient 28 exhibited DD, severe growth retardation, congenital heart disease (atrial septal defect), and cryptorchidism; however, his facial features were inconsistent with the typical Noonan syndrome phenotype (Fig. 2). In contrast, patient 34 had facial features characteristic of Noonan syndrome without other congenital anomalies. She inherited a likely pathogenic *PTPN11* variant from her mother, who was 150 cm (−2.36 SDS) in height.

Gene variants associated with neurodevelopmental disorders were identified in patient 26 (*TAOK1*) and patient 32 (*ANKRD11*), both presenting with ID/DD and short stature.

Six patients harbored pathogenic variants in genes related to the cartilage extracellular matrix, *COL2A1*, *COL9A2*, *ACAN*, and *SLC26A2*, although none exhibited distinctive skeletal abnormalities.

Six patients inherited heterozygous variants from their parents, including 1 with SHORT syndrome (patient 19), 2 with *ACAN* variants (patients 20 and 33), 1 with *CDKN1C*-related SRS (patient 29), 1 with a *COL9A2* variant (patient 30), and 1 with Noonan syndrome (patient 34). Notably, the fathers of patients 20 and 33, both carrying heterozygous *ACAN* variant, exhibited significantly reduced adult height, with height SDS values of −3.15 (158 cm, father of patient 20) and −5.54 (146.8 cm, father of patient 33).

Familial SRS with a *CDKN1C* Mutation

To the best of our knowledge, we report the first familial case of SRS with a *CDKN1C* mutation in Korea in our study cohort (Fig. 3). The patient was born at 33 weeks and 4 days of gestation with a birth weight of 1.13 kg, which was below −2 SDS. She presented with camptodactyly of the right fifth finger at birth, which was surgically repaired at 6 years of age. She first visited the pediatric endocrinology clinic at 4 years of age with a height SDS of −2.25 and initiated rhGH therapy. Following 3 years of rhGH therapy, her height SDS increased to −0.91. WES revealed an SNV in the *CDKN1C* gene (c.835C>T, p.Arg279Cys), which was inherited from the patient’s mother, who had a height SDS of −5.24 (138 cm). The same variant was also identified in the proband’s grandmother, who had a height SDS of −4.99 (139 cm). The patient’s mother had a history of gestational diabetes and, currently, was diagnosed with prediabetes; the grandmother was also diagnosed with diabetes.

Discussion

In this multicenter study conducted across 7 hospitals in South Korea, we identified genetic abnormalities in 34 of 191

Table 2. Genetic results and clinical characteristics of SGA-SS patients with copy number variants

No.	Sex	Age	Results	Suspected abnormal region in CMA (length)	Classification	GA (weeks)	BW at birth (kg)	Age at first visit (years)	Initial HT-SDS	MPH-SDS	GH Tx	HT-SDS at last visit	Clinical features and dysmorphism
1	M	8	22q11.21 deletion	18 916 842-21 465 659 (2.5Mb)	Pathogenic	40	2.7	5	-1.91	-0.35	Y	0.46	Small ears
2	F	10	22q11.21 deletion	18 916 842-21 465 659 (2.5Mb)	Pathogenic	39	2.6	4	-2.72	-0.21	Y	-0.84	Precocious puberty, mild developmental delay, ventricular septal defect, hypertelorism, short palpebral fissure, bulbous nose, low-set ear, downturned mouth
3	F	6	22q11.21 deletion	18 916 842-21 465 659 (2.5Mb)	Pathogenic	37	2.2	4	-2.72	-0.52	Y	-1.20	Bulbous nose, downturned mouth
4	F	13	22q11.21 deletion	18 916 827-21 465 662 (2.5Mb)	Pathogenic	39	2.4	11	-3.45	-1.37	Y	-3.39	Cleft lip, bulbous nose
5	M	11	22q11.21 deletion	18 916 842-21 465 659 (2.5Mb)	Pathogenic	38	2.56	10	-4.69	-1.28	Y	-4.52	Mild intellectual disability, ADHD, bulbous nose, downturned mouth
6	M	9	22q11.21 deletion	18 916 842-21 465 659 (2.5Mb)	Pathogenic	33	1.2	6	-2.51	-0.72	Y	-1.19	Tetralogy of fallot
7	M	7	22q11.21 duplication	18 916 842-21 465 659 (2.5Mb)	Pathogenic	37	2.2	7	-2.78	-0.72	ND	NA	Coarctation of aorta
8	F	13	15q26.2q26.3 deletion	98 493 875-102 429 112 (3.6Mb)	Pathogenic	39	2.09	6	-4.2	-1.37	Y	-2.39	Developmental delay, broad nasal bridge and tip, hypertelorism, precocious puberty
9	M	13	2q11.1q12.1 duplication	95 327 499-103 361 483 (8.0Mb)	Pathogenic	38	2.3	9	-1.93	-0.63	Y	-0.79	
10	M	8	20q11.23 deletion	36 112 979-37 159 680 (1.0Mb)	Uncertain significance	38	2.34	6	-1.94	-1.28	Y	-0.62	Mild developmental delay, triangular face, micrognathia
11	M	7	19q13.12 deletion	36 197 195-35 295 989 (98Kb)	Pathogenic	40	2.62	7	-2.65	0.54	ND	NA	Intellectual disability, mild ptosis, small chin
12	F	12	17p13.1p12 duplication	9 910 114-10 751 276 (814Kb)	Uncertain significance	40	2.5	12	-2.55	-2.02	Y	-1.43	GH deficiency, ovarian cyst

(continued)

Table 2. Continued

No.	Sex	Age	Results	Suspected abnormal region in CMA (length)	Classification	GA (weeks)	BW at birth (kg)	Age at first visit (years)	Initial HT-SDS	MPH-SDS	GH Tx	HT-SDS at last visit	Clinical features and dysmorphism
13	F	9	1q24.2;q25.1 deletion	170 535 957–173 637 042 (3.1Mb)	Pathogenic	38	2.38	6	–3.08	–1.26	Y	–1.54	Down-slanting palpebral fissure, scoliosis, Rathke’s cleft cyst
14	M	5	7q11.23 deletion	72 612 042–74 143 060 (1.5Mb)	Pathogenic	38	2.3	4	–2.13	–0.08	Y	–1.28	Congenital hypothyroidism, developmental delay (walk alone at 30 months), annular pancreas, low-set and large ears
15	F	4	3q27.1 deletion	183 975 938–184 206 679 (231Kb)	Likely pathogenic	40	2.48	2	–2.67	–1.91	Y	–2.45	Congenital hypothyroidism, language developmental delay, hypertelorism, epicanthal fold
			5q22.2 duplication	112 301 041–113 054 166 (753Kb)	Uncertain significance								
16	F	12	5p15.33 deletion	113 576–4 340 429 (4.2Mb)	Pathogenic	34	1.47	4	–3.14	–0.42	Y	–1.66	Preterm birth, mild intellectual disability, bronchopulmonary dysplasia, epilepsy, drug-induced hypothyroidism, hypertrichosis, hypertelorism, thick eyebrows
17	F	11	15q26.3 deletion	99 160 823–110 311 125 (1.2Mb)	Pathogenic	38	2.26	3	–2.02	–0.84	Y	–0.58	Family history of SGA-SS (mother), microcephaly on fetal sonography, broad nasal bridge and tip, normal intelligence

Abbreviations: ADHD, attention deficit hyperactivity disorder; BW, body weight; CMA, chromosomal microarray; F, female; GA, gestational age; GH Tx, recombinant human GH treatment; HT-SDS, height SD score; M, male; MPH-SDS, mid-parental height SD score; NA, not available; ND, no data; SDS, SD score; SGA-SS, small for gestational age with short stature; Y, yes.

Table 3. Genetic results and clinical characteristics of SGA-SS patients with single-nucleotide variants

No.	Sex	Age	Gene	NM_number	Nucleotide change	Protein change	ACMG classification (evidence)	Inherited from	GA (wks)	BW at birth (kg)	Age at first visit (yrs)	Initial HT-SDS	MPH-SDS	GH Tx	HT-SDS at last visit	Clinical features and dysmorphism
18	F	15	<i>COL2A1</i>	NM_001844.5	c.2167G > A	p.Gly723Ser	Pathogenic (PS2, PM1, PM2, PM5, PP3, PP5)	De novo	36	1.77	4	-3.93	-0.21	Y	-2.45	
19	M	19	<i>PIK3R1</i>	NM_181523.3	c.1892G > A	p.Arg631Gln	Likely pathogenic (PM1, PM2, PP3, PP5)	Mother	38	2.0	12	-3.68	-2.44	Y	-4.04	Scoliosis, glaucoma, myopia, insulin resistance, lipoatrophy, small chin, deep-set eyes, normal intelligence
20	F	12	<i>ACAN</i>	NM_001369268.1	c.1216del	p.Glu406Arg fsTer19	Pathogenic (PVSI1, PM2, PP1)	Father	40	2.04	11	-3.44	-2.7	Y	-3.47	Precocious puberty, advanced bone age
21	F	12	<i>SLC26A2</i>	NM_000112.4	c.2018A > T	p.Asp673Val	Likely pathogenic (PS3, PM1, PM2, PP3)	Mother	39	2.5	5	-2.58	-1.15	Y	-0.35	
			<i>SLC26A2</i>	NM_000112.4	c.1512G > A	p.Met504Ile	VUS (PM1, PM2, PP3)	Father								
22	F	11	<i>PLAG1</i>	NM_002655.3	c.199C > T	p.Gln67Ter	Likely pathogenic (PVSI1, PM2, PP3)	Unknown	39	2.58	11	-2.56	-1.05	Y	-2.3	Precocious puberty
23	M	3	<i>SALL1</i>	NM_002968.3	c.3160C > T	p.Arg1054Ter	Pathogenic (PVSI1, PM2, PP5)	Unknown	40	2.34	3	-2.39	-1.47	ND	NA	Subclinical hypo-thyroidism,
24	M	11	<i>SCUBE3</i>	NM_152753.4	c.222C > A	p.Cys74Ter	Likely pathogenic (PVSI1, PM2)	Unknown	39	2.6	3	-3.32	-1.00	Y	-1.52	long nose, thick lips
25	F	6	<i>COL9A2</i>	NM_001852.4	c.340-2A > G	—	Likely pathogenic (PVSI1, PM2)	Unknown	38	2.36	3	-2.12	-0.21	Y	-0.62	Developmental delay
26	F	12	<i>TIAOK1</i>	NM_020791.4	c.2422G > T	p.Glu808Ter	Pathogenic (PVSI1, PS2, PM2, PP3)	De novo	40	2.62	6	-2.10	-0.84	Y	-0.35	Developmental delay (especially language)
27	F	9	<i>SMAD4</i>	NM_005359.6	c.1498A > G	p.Ile500Val	Likely pathogenic (PS2, PM1, PP3, PP5)	De novo	38	2.3	3	-2.63	-0.32	Y	-2.2	Developmental delay (especially language)

(continued)

Table 3. Continued

No.	Sex	Age	Gene	NM_number	Nucleotide change	Protein change	ACMG classification (evidence)	Inherited from	GA (wks)	BW at birth (kg)	Age at first visit (yrs)	Initial HT-SDS	MPH-SDS	GH Tx	HT-SDS at last visit	Clinical features and dysmorphism
28	M	6	<i>PTPN11</i>	NM_002834.5	c.1508G > A	p.Gly503Glu	Likely pathogenic (PVS1, PM1, PP3, PP5)	De novo	37	1.94	5	-3.62	-0.26	Y	-3.01	Mild developmental delay, ASD, cryptorchidism, short neck, low hairline
29	F	7	<i>CDKN1C</i>	NM_000076.2	c.835C > T	p.Arg279Cys	Likely pathogenic (PM1, PM5, PP1, PP3)	Mother	33	1.1	4	-2.25	-3.4	Y	-0.91	Camptodactyly, family history of SGA-SS
30	M	11	<i>COL9A2</i>	NM_001852.4	c.150 + 1G > A	—	Likely pathogenic (PVS1, PM2)	Mother	35	1.37	4	-2.31	0.36	Y	-1.19	Congenital cataract, high arched palate, scoliosis,
31	F	11	<i>NFI</i>	NM_001042492.3	c.2970_2972del	p.Met992del	Likely pathogenic (PS3, PM1, PM4)	De novo	39	2.48	2	-2.47	-0.73	Y	-1.94	Multiple café-au-lait spots, precocious puberty
32	M	6	<i>ANKRD11</i>	NM_013275.6	c.2398_2401del	p.Glu800AsnfsTer62	Pathogenic (PVS1, PP4, PP5)	De novo	39	2.6	2	-3.03	-1.57	Y	-3.28	Developmental delay, hypertelorism, down-slanting palpebral fissure
33	M	14	<i>ACAN</i>	NM_001369268.1	c.7255G > A	p.Asp2419Asn	Likely pathogenic (PM1, PM2, PP1, PP5)	Father	38	2.58	12	-1.9	-3.19	Y	-1.98	
34	F	16	<i>PTPN11</i>	NM_002834.5	c.794G > A	p.Arg265Gln	Likely pathogenic (PM1, PM5, PP1, PP3, PP5)	Mother	39	2.45	7	-2.87	-2.14	Y	-1.67	Hypertelorism, long palpebral fissure, bulbous nose, obesity

Abbreviations: ACMG, American College of Medical Genetics and Genomics; ASD, atrial septal defect; BW, body weight; F, female; GA, gestational age; GH Tx, recombinant human GH treatment; HT-SDS, height SD score; M, male; MPH-SDS, mid-parental height SD score; NA, not available; ND, no data; NM_, NCBI Reference Sequence (RefSeq) mRNA accession number; PM, pathogenic moderate; PP, pathogenic supporting; PS, pathogenic strong; PVS, pathogenic very strong; SDS, SD score; SGA-SS, small for gestational age with short stature; wks, weeks; Y, yes; yrs, years.

patients with SGA-SS, with a diagnostic rate of 17.8%. Previous studies on SGA-SS cohorts have reported variable diagnostic yields ranging from 12.8% to 42%, depending

Table 4. Summary of clinical features of 6 patients with 22q11.2 microdeletion syndrome

Patient number	1	2	3	4	5	6	Number/ total
Small for gestational age	Y	Y	Y	Y	Y	Y	6/6
Postnatal growth retardation	Y	Y	Y	Y	Y	Y	6/6
Microcephaly	N	Y	N	N	N	N	1/6
Pointed chin	Y	Y	Y	N	N	N	3/6
Short palpebral fissures	Y	Y	Y	N	N	N	3/6
Broad nasal tip	Y	Y	Y	Y	N	N	4/6
Hypoplastic alae nasi	Y	Y	Y	Y	Y	N	5/6
Cleft lip/cleft palate	N	N	N	Y	N	N	1/6
Thin upper lip	N	N	N	Y	N	N	1/6
Congenital heart disease	N	Y ^a	N	N	N	Y ^b	2/6
Developmental delay/ intellectual disability	Y	Y	N	N	Y	N	3/6
Immune deficiency	N	N	N	N	N	N	0/6
Hypoparathyroidism including hypocalcemia	N	N	N	N	N	N	0/6
Ocular anomalies including myopia	N	N	Y	N	N	N	1/6
Hearing defect	N	N	N	N	N	N	0/6

Abbreviations: N, no; Y, yes.
^aVentricular septal defect.
^bTetralogy of Fallot.

on the presence of syndromic features and inclusion criteria (10, 11, 51, 52). Our cohort primarily comprised relatively nonsyndromic patients, as indicated by their clinical characteristics (Table 1). Notably, similar detection rates have been reported in nonsyndromic SGA-SS cohorts, including 16.7% in a Chinese study (51) and 22.1% in a Japanese study (11), corroborating our findings. The large sample size and ethnic homogeneity of our Korean cohort underscore the strength and relevance of our analysis.

In our cohort, CNVs and SNVs were detected at equal frequencies (17/191; 8.9% each). This relatively high CNV detection rate could be attributed to the systematic screening of CNVs using WES data for all participants. CNVs were detected using multiple algorithms, including 3bCNV, an internally developed tool, and other previously established software, such as MANTA and SavvyCNV (18, 19), which analyze the depth of coverage across exons, with the findings validated using CMA. No discrepancies were observed between the WES-based and CMA results, underscoring the reliability of next-generation sequencing data for CNV detection in clinical settings. Previous studies have also identified CNVs in approximately 9% to 10% of patients with SGA-SS using various platforms, including array comparative genomic hybridization, single-nucleotide polymorphism arrays (11, 52), and open-source software such as CNVkit (51).

While the present study utilized WES and CMA for genetic diagnosis, it is noteworthy that whole genome sequencing (WGS) offers additional advantages, particularly in detecting variants in regulatory regions and deep intronic sequences that are beyond the reach of WES. To the best of our knowledge, studies applying WGS to investigate the genetic etiology of short stature remain very limited. In a recent meta-analysis (53), the overall diagnostic yield of WGS was higher

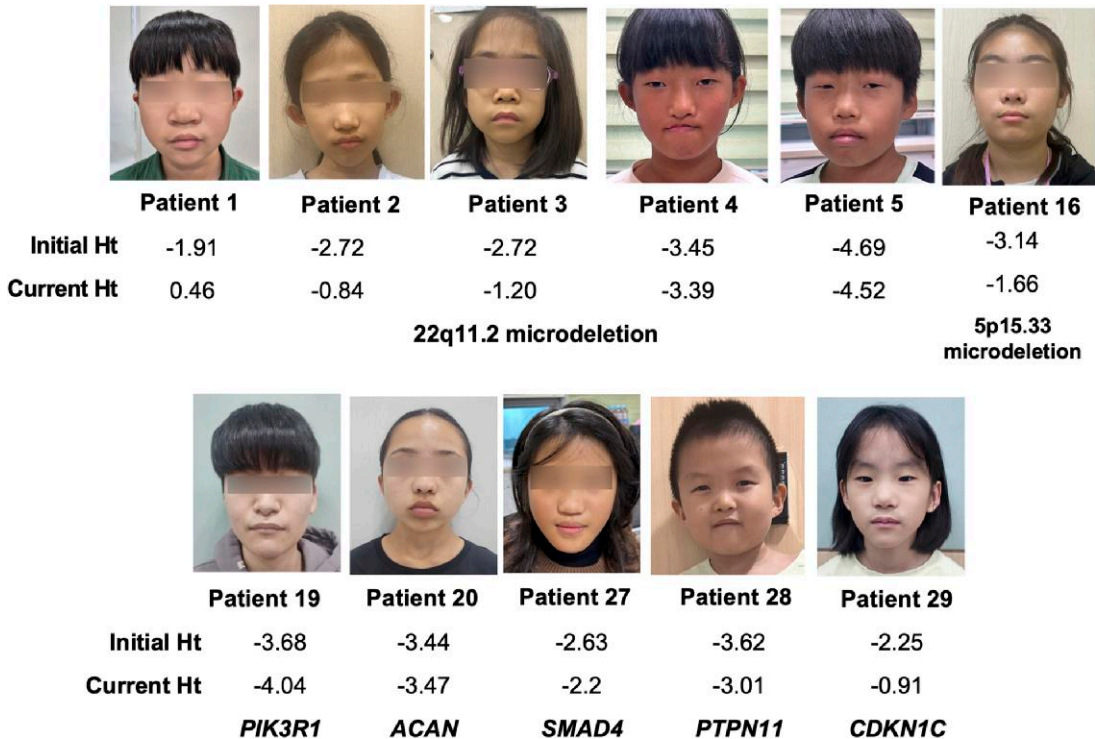


Figure 2. Clinical photographs of patients with identified genetic abnormalities, along with their height SD score at the initial visit ("Initial Ht") and at the time of photography ("Current Ht").

Table 5. Summary of identified genes and their molecular mechanism affecting growth

Genes	Function	OMIM disorder	Previous reports related to SGA	References
Defects in intracellular pathways				
<i>PIK3R1</i>	Involved in PI3K signaling cascade, regulates the downstream targets of the PI3K-AKT-mTOR pathway	SHORT syndrome	+	(27, 28)
<i>PLAG1</i>	Transcription factor expressed during fetal development, regulates several growth factors, including IGF-2	Silver-Russell syndrome	+	(29, 30)
<i>SALL1</i>	Transcriptional repressor involved in organogenesis	Townes-Brocks syndrome	+	(31, 32)
<i>TAOK1</i>	Serine/threonine-protein kinase involved in various processes, such as p38/MAPK14 stress-activated MAPK cascade, DNA damage response, and regulation of cytoskeleton stability	Developmental delay with or without intellectual impairment or behavioral abnormalities	+	(33, 34)
<i>SMAD4</i>	Coactivator and mediator of signal transduction by TGF- β	Myhre syndrome	+	(35, 36)
<i>PTPN11</i>	Positively regulates the MAPK signal transduction pathway	Noonan syndrome	+	(37, 38)
<i>CDKN1C</i>	Negative regulator of cell proliferation	IMAGE syndrome Atypical Silver-Russell syndrome	+	(9, 39)
<i>NF1</i>	Regulator of Ras activity in the RAS-MAPK pathway	Neurofibromatosis, type 1	+	(40, 41)
<i>ANKRD11</i>	Chromatin regulator that modulates histone acetylation and gene expression in neural precursor cells; may also regulate bone homeostasis	KBG syndrome	+	(42, 43)
Defects in cartilage extracellular matrix				
<i>COL2A1</i>	Major component of cartilage (type II collagen)	Spondyloepiphyseal dysplasia	+	(10, 44)
<i>COL9A2</i>	Encodes the α -2 subunit of collagen type IX	Epiphyseal dysplasia	+	(10, 45)
<i>ACAN</i>	Major component of the extracellular matrix of cartilaginous tissues	Short stature and advanced bone age, with or without early-onset osteoarthritis and/or osteochondritis dissecans	+	(46, 47)
<i>SLC26A2</i>	Sulfate transporter mediating sulfate uptake into chondrocytes to maintain adequate sulfation of proteoglycans, which is needed for cartilage development	Epiphyseal dysplasia	—	(48, 49)
Paracrine signaling defect				
<i>SCUBE3</i>	Multifunctional cell surface-anchored glycoproteins functioning as coreceptors of bone morphogenetic protein signaling	Short stature, facial dysmorphism, and skeletal anomalies with or without cardiac anomalies	+	(50)

“+” denotes the presence of previous reports related to SGA; “—” denotes no prior reports.

Abbreviations: KBG, Kallmann-Biegel; MAPK, mitogen-activated protein kinase; OMIM, Online Mendelian Inheritance in Man; PI3K, phosphatidylinositol 3 kinase; SGA, small for gestational age.

(38.6%, 95% confidence interval: 32.6–45.0) than that of WES (37.8%, 95% confidence interval: 32.9–42.9), with greater benefits observed for Mendelian diseases. Moreover, WGS eliminates the need for confirming CNVs by additional methods such as CMA or multiplex ligation-dependent probe amplification. However, its high cost and the complexity of data interpretation should be considered when selecting the most appropriate diagnostic approach.

Among the detected CNVs, 22q11.2 DS was the most frequently observed, identified in 6 patients. Intrauterine growth retardation and short stature are known endocrine features of 22q11.2 DS, occurring in approximately 4% and 15% of cases, respectively (54). Its highly variable phenotypic expression often leads to delayed diagnosis (55). This was evident in our cohort, in which affected individuals exhibited only mild DD/ID and subtle dysmorphic features. Patients 4 and 5 exhibited intrafamilial variability despite sharing the same deletion and inheritance patterns. All patients carried a deletion spanning the LCR22A-D region, a typical breakpoint pattern

of proximal 22q11.2 DS (56, 57). One patient carried a duplication in this region, consistent with 22q11.2 duplication syndrome, demonstrating a broad phenotypic spectrum overlapping with 22q11.2 DS.

Two patients (patients 8 and 17) had a microdeletion at 15q26.3, involving the IGF-1 receptor (*IGF1R*) gene, which plays a critical role in both pre- and postnatal growth. Although rare, the 15q26.3 microdeletion has been established as a genetic cause of SGA-SS (58). The clinical severity in these cases reportedly varies depending on the deletion size. Patient 8, with a larger 3.6 Mb deletion, exhibited DD and severe growth failure despite rhGH therapy (height SDS of -2.39 after rhGH therapy). Conversely, patient 17, with a smaller 1.2 Mb deletion, had a milder phenotype without DD and responded well to rhGH therapy (height SDS of -0.58 after rhGH therapy). Considering patient 17, the deletion was maternally inherited, with her mother also having a history of SGA at birth and exhibiting adult short stature (height SDS of -2.59 , 149 cm), suggesting familial transmission.

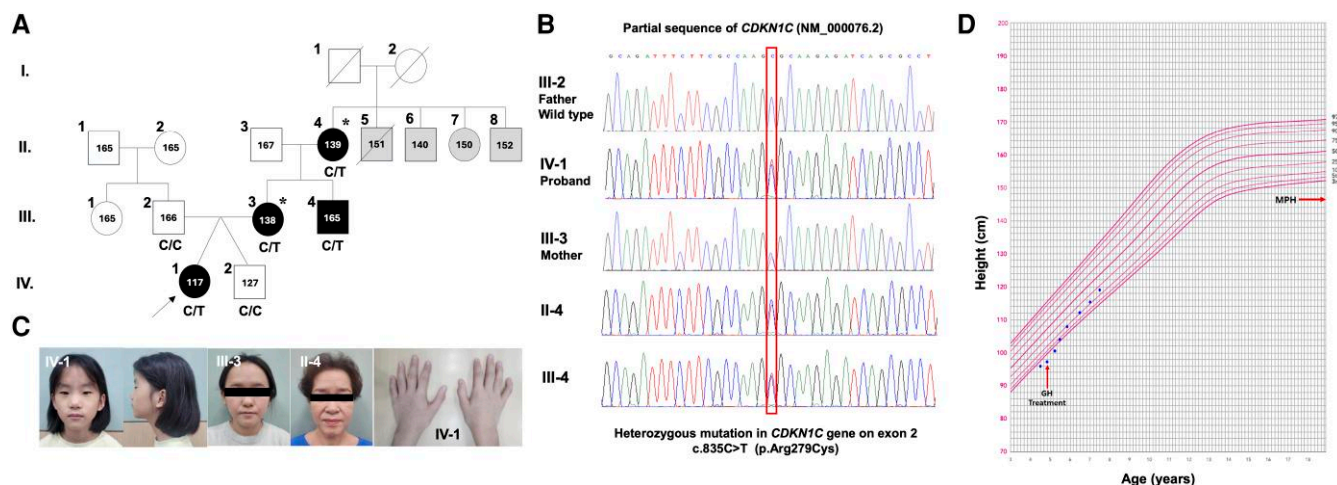


Figure 3. (A) Pedigree chart of patient 29. Numbers within the circles or squares indicate the height of each individual (in cm). Genetic testing was not performed on family members II-5 to II-8 (shaded in gray); however, their short stature suggests they may carry the *CDKN1C* variant. Black asterisks to the right of circles indicate a history of diabetes mellitus. (B) Sanger sequencing results of the *CDKN1C* (NM_000076.2) showing the c.835C > T [C/T] variant in the proband (IV-1), mother (III-3), grandmother (II-4), and uncle (III-4). II-2 (the father) carries the wild-type allele [C/C]. (C) Clinical images of the proband, mother, and grandmother. Patient 29 presents with camptodactyly of the right fifth finger. (D) Growth chart of patient 29. The vertical arrow marks the initiation of recombinant human GH therapy.

Abbreviation: MPH, mid-parental height.

Additional chromosomal microdeletion syndromes identified in this cohort included Williams syndrome (patient 14) and CdCS (patient 16). Both SGA and short stature are characteristic features of Williams syndrome and are detected in approximately 50% of cases (59). CdCS is associated with terminal deletions of chromosome 5p, with typical features mapped to the critical region spanning 5p15.2 to 5p15.3 (60). Patient 16 had a deletion in the 5p15.33 region, which partially overlaps the critical region for CdCS, possibly explaining the relatively mild phenotype.

Although some CNVs in our cohort were classified as VUS, they may still be clinically relevant. 17p13.1 microduplication observed in patient 12 has been previously reported in individuals with short stature (61, 62), including 1 patient with SGA. Likewise, a 20q11.2 microdeletion detected in patient 10 partially overlapped with previously reported deletions associated with skeletal abnormalities, feeding difficulties, dysmorphic features, and DD (63); however, patient 10 exhibited only mild DD and subtle dysmorphic features. These cases highlight the importance of reevaluating VUS with the accumulation of additional evidence.

In several cases, patients with recognizable syndromes, such as Myhre syndrome (patient 27) and neurofibromatosis type 1 (patient 31), did not exhibit a full phenotypic spectrum. Given that the clinical features of some syndromes evolve gradually, regular monitoring and follow-up are recommended to ensure the early detection of emerging morbidities.

Two genes (*TAOK1*, *ANKRD11*) associated with neurodevelopmental disorders were identified in patient 26 and patient 32, respectively. Short stature is observed in 40% to 77% of patients with Kallmann-Biegel syndrome (*ANKRD11* gene mutation) (64), whereas it is less frequently reported in *TAOK1*-related disorders, occurring in only 9% to 20% of cases (65).

Although 6 patients had pathogenic variants in cartilage extracellular matrix-related genes (*COL2A1*, *COL9A2*, *ACAN*, and *SLC26A2*), none exhibited overt skeletal dysplasia, which is consistent with the findings of previous studies (11, 12). Moreover, this finding further corroborates that genetic variants

affecting skeletal development can be present even in the absence of typical radiographic findings. Therefore, these genes should be considered in the differential diagnosis of nonsyndromic short stature.

Although we attempted to exclude SRS clinically using the NH-CSS criteria, we identified 2 genetic variants associated with SRS: *PLAG1* and *CDKN1C*. *CDKN1C* is a cyclin-dependent kinase inhibitor and a negative regulator of cell proliferation. *CDKN1C* is an imprinted gene only expressed when maternally inherited (66). Loss-of-function mutations in *CDKN1C* are associated with Beckwith-Wiedemann syndrome (67). In contrast, gain-of-function mutations within the proliferating cell nuclear antigen-binding domain of *CDKN1C* have been identified as a cause of IMAGe syndrome (8). More recently, familial cases of SRS associated with *CDKN1C* mutations in the proliferating cell nuclear antigen-binding domain have been reported (Fig. 4) (9, 38, 68–71). Notably, a change in amino acid position 279 has been extensively reported (38, 68, 70, 71), indicating that this region is a mutational hotspot associated with an atypical SRS phenotype. In our patient, we identified a missense variant affecting the same position but resulting in a different amino acid substitution (p.Arg279Cys). Family members of patient 29 carrying the *CDKN1C* c.835C > T variant did not present with IMAGe syndrome features such as adrenal insufficiency or metaphyseal dysplasia; however, they did exhibit pre- and postnatal growth retardation and diabetes, as observed in the proband's mother and grandmother (Fig. 3). The *CDKN1C* c.835C > T (p.Arg279Cys) variant, inherited maternally, is considered the causative mutation for SRS in this family.

Patient 22 carried a heterozygous *PLAG1* c.199C > T (p.Gln67Ter) variant and presented with SGA-SS and precocious puberty without other clinical features of SRS. Previous studies have also reported SRS diagnoses in children who did not meet the NH-CSS criteria (10). These findings highlight the need to consider SRS in the differential diagnosis of SGA-SS, even in the absence of typical phenotypes.

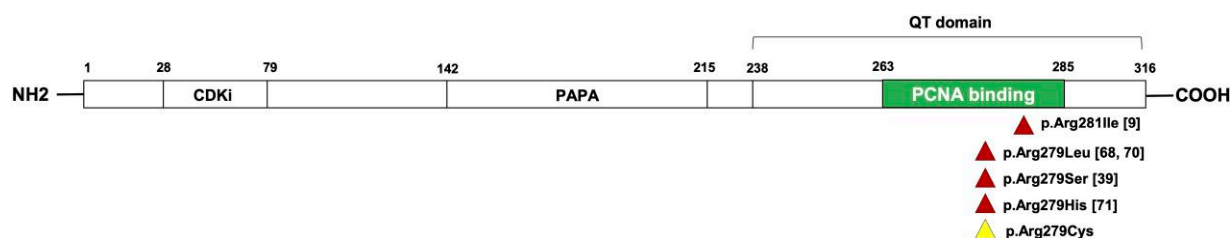


Figure 4. Schematic diagram illustrating the CDKN1C protein (NP_000067.1) [9]. Amino acid residue numbering and known protein domains are indicated. Missense variants associated with atypical SRS are located within the PCNA-binding domain. Numbers in parentheses indicate references for the variants. Previously reported SRS-related variants are indicated by red arrowheads [9, 39, 68, 70, 71], while the yellow arrowhead represents the missense variant identified in this study.

Abbreviations: CDKI, cyclin-dependent kinase inhibitor; PAPA, Pro-Ala-Pro-Ala repeat; QT, carboxyterminal domain; PCNA, proliferating cell nuclear antigen; SRS, Silver-Russell syndrome.

Patient 24 harbored a heterozygous *SCUBE3* c.222C>A (p.Cys74Ter) variant in the epidermal growth factor-like domain. While biallelic inactivating variants in *SCUBE3* have been linked to a recently described developmental disorder involving defective bone morphogenetic protein signaling (49), our patient exhibited isolated short stature (initial height of -3.32 SDS) with subtle facial features (eg, long/triangular face, high nasal bridge, and long nose). Given the high probability of loss-of-function intolerance (pLI) (1.0) and low loss-of-function observed/expected upper bound fraction (0.402) scores of the gene in gnomAD, *SCUBE3* is highly intolerant to haploinsufficiency. These findings highlight the possibility of a dominant-negative effect on height, although further evidence is required to confirm this hypothesis.

Among the 24 patients with ID/DD, 14 (58.3%) had a confirmed genetic diagnosis, including 9 with CNVs and 5 with SNVs. Fisher's exact test showed that, among patients with SGA-SS, those with ID/DD were approximately 10 times more likely to have genetic abnormalities than those without ID/DD (odds ratio = 10.09, $P < .05$; data not shown). These findings emphasize the value of comprehensive genetic analysis in patients with SGA-SS, especially in the presence of ID/DD.

This study is notable for its large cohort size; systematic CNV screening of all WES samples; and focus on a genetically homogeneous, relatively nonsyndromic SGA-SS population. However, this study has some limitations. Notably, SRS was only clinically assessed using NH-CSS without DNA methylation testing, limiting the accuracy of SRS exclusion. Genetic variants located in regulatory regions or deep introns may be missed by WES; therefore, WGS may be required in future studies to improve the identification of genetic diagnoses.

In conclusion, the genetic causes of SGA-SS are highly heterogeneous. Our findings revealed that CNVs markedly contribute to the etiology of SGA-SS, even in nonsyndromic cases. The phenotypic spectrum of 22q11.2 DS is broad and should be considered in the differential diagnosis of SGA-SS. Furthermore, the presence of ID/DD or a family history of SGA-SS may increase the likelihood of identifying an underlying genetic cause, underscoring the clinical utility of genetic testing in these populations.

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Disclosures

The authors have no conflicts of interest to disclose.

Data Availability

Some or all of the datasets generated and/or analyzed during the present study are not publicly available in order to protect patient confidentiality but may be obtained from the corresponding author upon reasonable request.

Ethics Declarations

This study was approved by the institutional review boards (IRB) of all participating hospitals: Hallym University Sacred Heart Hospital: IRB No. 2020-08-006; Soonchunhyang University Hospital: IRB No. 2024-03-038; Chosun University Hospital: IRB No. 2023-11-026; Kangdong Sacred Heart Hospital: IRB No. 2020-08-003; Hallym University Dongtan Sacred Heart Hospital: IRB No. 2023-05-104-001; Hallym University Kangnam Sacred Heart Hospital: IRB No. 2022-10-020-001; Hallym University Chuncheon Sacred Heart Hospital: IRB No. 2023-08-015-006.

References

1. Clayton PE, Cianfarani S, Czernichow P, Johannsson G, Rapaport R, Rogol A. Management of the child born small for gestational age through to adulthood: a consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. *J Clin Endocrinol Metab*. 2007;92(3):804-810.
2. Lee PA, Chernauek SD, Hokken-Koelega ACS, Czernichow P. International Small for Gestational Age Advisory Board consensus development conference statement: management of short children born small for gestational age, April 24-October 1, 2001. *Pediatrics*. 2003;111(6):1253-1261.
3. de Onis M, Habicht JP. Anthropometric reference data for international use: recommendations from a World Health Organization Expert Committee. *Am J Clin Nutr*. 1996;64(4):650-658.
4. Lim JS, Lim SW, Ahn JH, Song BS, Shim KS, Hwang IT. New Korean reference for birth weight by gestational age and sex: data from the Korean Statistical Information Service (2008-2012). *Ann Pediatr Endocrinol Metab*. 2014;19(3):146-153.

5. Finken MJJ, van der Steen M, Smeets CCJ, *et al.* Children born small for gestational age: differential diagnosis, molecular genetic evaluation, and implications. *Endocr Rev.* 2018;39(6):851-894.
6. Wakeling EL, Brioude F, Lokulo-Sodipe O, *et al.* Diagnosis and management of Silver-Russell syndrome: first international consensus statement. *Nat Rev Endocrinol.* 2017;13(2):105-124.
7. Ioannides Y, Lokulo-Sodipe K, Mackay DJG, Davies JH, Temple IK. Temple syndrome: improving the recognition of an underdiagnosed chromosome 14 imprinting disorder: an analysis of 51 published cases. *J Med Genet.* 2014;51(8):495-501.
8. Arboleda VA, Lee H, Parnaik R, *et al.* Mutations in the PCNA-binding domain of CDKN1C cause IMaGE syndrome. *Nat Genet.* 2012;44(7):788-792.
9. Kerns SL, Guevara-Aguirre J, Andrew S, *et al.* A novel variant in CDKN1C is associated with intrauterine growth restriction, short stature, and early-adulthood-onset diabetes. *J Clin Endocrinol Metab.* 2014;99(10):E2117-E2122.
10. Toni L, Plachy L, Dusatkova P, *et al.* The genetic landscape of children born small for gestational age with persistent short stature. *Horm Res Paediatr.* 2024;97(1):40-52.
11. Hara-Isono K, Nakamura A, Fuke T, *et al.* Pathogenic copy number and sequence variants in children born SGA with short stature without imprinting disorders. *J Clin Endocrinol Metab.* 2022;107(8):e3121-e3133.
12. Freire BL, Homma TK, Funari MFA, *et al.* Multigene sequencing analysis of children born small for gestational age with isolated short stature. *J Clin Endocrinol Metab.* 2019;104(6):2023-2030.
13. Park SJ, Lee N, Jeong SH, Jeong MH, Byun SY, Park KH. Genetic aspects of small for gestational age infants using targeted-exome sequencing and whole-exome sequencing: a single center study. *J Clin Med.* 2022;11(13):3710.
14. Kim JH, Yun S, Hwang S-S, *et al.* The 2017 Korean national growth charts for children and adolescents: development, improvement, and prospects. *Korean J Pediatr.* 2018;61(5):135.
15. Azzi S, Salem J, Thibaud N, *et al.* A prospective study validating a clinical scoring system and demonstrating phenotypical-genotypical correlations in Silver-Russell syndrome. *J Med Genet.* 2015;52(7):446-453.
16. Van der Auwera GA, Carneiro MO, Hartl C, *et al.* From FastQ data to high confidence variant calls: the genome analysis toolkit best practices pipeline. *Curr Protoc Bioinformatics.* 2013;43(1):11.10.1-11.10.33.
17. Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. *Bioinformatics.* 2009;25(14):1754-1760.
18. Chen X, Schulz-Trieglaff O, Shaw R, *et al.* Manta: rapid detection of structural variants and indels for germline and cancer sequencing applications. *Bioinformatics.* 2016;32(8):1220-1222.
19. Laver TW, De Franco E, Johnson MB, *et al.* SavvyCNV: genome-wide CNV calling from off-target reads. *PLoS Comput Biol.* 2022;18(3):e1009940.
20. Seo GH, Kim T, Choi IH, *et al.* Diagnostic yield and clinical utility of whole exome sequencing using an automated variant prioritization system, EVIDENCE. *Clin Genet.* 2020;98(6):562-570.
21. Richards S, Aziz N, Bale S, *et al.* Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17(5):405-424.
22. McLaren W, Gil L, Hunt SE, *et al.* The ensembl variant effect predictor. *Genome Biol.* 2016;17(1):122.
23. Jaganathan K, Kyriazopoulou Panagiotopoulou S, McRae JF, *et al.* Predicting splicing from primary sequence with deep learning. *Cell.* 2019;176(3):535-548.e24.
24. Riggs ER, Andersen EF, Cherry AM, *et al.* Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). *Genet Med.* 2020;22(2):245-257.
25. Han Y, Yang J, Zhong R, Guo X, Cai M, Lin W. Side effects of long-term oral anti-seizure drugs on thyroid hormones in patients with epilepsy: a systematic review and network meta-analysis. *Neurol Sci.* 2022;43(9):5217-5227.
26. Jee YH, Andrade AC, Baron J, Nilsson O. Genetics of short stature. *Endocrinol Metab Clin North Am.* 2017;46(2):259-281.
27. Hoyle J, Yulug IG, Egan SE, Fisher EMC. The gene that encodes the phosphatidylinositol-3 kinase regulatory subunit (p85 alpha) maps to chromosome 13 in the mouse. *Genomics.* 1994;24(2):400-402.
28. Dymment DA, Smith AC, Alcantara D, *et al.* Mutations in PIK3R1 cause SHORT syndrome. *Am J Hum Genet.* 2013;93(1):158-166.
29. Abi Habib W, Brioude F, Edouard T, *et al.* Genetic disruption of the oncogenic HMGA2-PLAG1-IGF2 pathway causes fetal growth restriction. *Genet Med.* 2018;20(2):250-258.
30. Karim L, Takeda H, Lin L, *et al.* Variants modulating the expression of a chromosome domain encompassing PLAG1 influence bovine stature. *Nat Genet.* 2011;43(5):405-413.
31. Kiefer SM, Ohlemiller KK, Yang J, McDill BW, Kohlhasse J, Rauchman M. Expression of a truncated Sall1 transcriptional repressor is responsible for Townes-Brocks syndrome birth defects. *Hum Mol Genet.* 2003;12(17):2221-2227.
32. Seo YJ, Lee KE, Ko JM, Kim G-H, Yoo H-W. Variable expression observed in a Korean family with Townes-Brocks syndrome caused by a SALL1 mutation. *J Genet Med.* 2015;12(1):44-48.
33. Dulovic-Mahlow M, Trinh J, Kandaswamy KK, *et al.* De Novo variants in TAOK1 cause neurodevelopmental disorders. *Am J Hum Genet.* 2019;105(1):213-220.
34. Woerden GM, Bos M, Konink C, *et al.* TAOK1 is associated with neurodevelopmental disorder and essential for neuronal maturation and cortical development. *Hum Mutat.* 2021;42(4):445-459.
35. Piccolo P, Mithbaokar P, Sabatino V, *et al.* SMAD4 mutations causing Myhre syndrome result in disorganization of extracellular matrix improved by losartan. *Eur J Hum Genet.* 2014;22(8):988-994.
36. Lim D, Kim JH, Lee J. Myhre syndrome: the first case in Korea. *Ann Pediatr Endocrinol Metab.* 2021;26(3):210-214.
37. Tartaglia M, Kalidas K, Shaw A, *et al.* PTPN11 mutations in Noonan syndrome: molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. *Am J Hum Genet.* 2002;70(6):1555-1563.
38. Ferreira LV, Souza SAL, Arnhold IJP, Mendonca BB, Jorge AAL. PTPN11 (protein tyrosine phosphatase, nonreceptor type 11) mutations and response to growth hormone therapy in children with Noonan syndrome. *J Clin Endocrinol Metab.* 2005;90(9):5156-5160.
39. Binder G, Ziegler J, Schweizer R, *et al.* Novel mutation points to a hot spot in CDKN1C causing Silver-Russell syndrome. *Clin Epigenetics.* 2020;12(1):152.
40. Tettamanti G, Mogensen H, Kampitsi C-E, Nordgren A, Feychting M. Birth characteristics among children diagnosed with neurofibromatosis type 1 and tuberous sclerosis. *J Pediatr.* 2021;239:200-205.e2.
41. Vassilopoulou-Sellin R, Woods D, Quintos MT, Needle M, Klein MJ. Short stature in children and adults with neurofibromatosis. *Pediatr Nurs.* 1995;21(2):149-153.
42. Kierzkowska O, Sarino K, Carter D, *et al.* Documentation and prevalence of prenatal and neonatal outcomes in a cohort of individuals with KBG syndrome. *Am J Med Genet A.* 2023;191(9):2364-2375.
43. Reynaert N, Ockeloen CW, Säwendahl L, *et al.* Short stature in KBG syndrome: first responses to growth hormone treatment. *Horm Res Paediatr.* 2015;83(5):361-364.
44. Kim Y-M, Lim H-H, Kim E, *et al.* Exploring the genetic causes for postnatal growth failure in children born non-small for gestational age. *J Clin Med.* 2023;12(20):6508.
45. Chen M, Miao H, Liang H, *et al.* Clinical characteristics of short-stature patients with collagen gene mutation and the therapeutic response to rhGH. *Front Endocrinol (Lausanne).* 2022;13:820001.

46. Kim SJ, Yoon JS, Hwang IT. A novel heterozygous ACAN variant in a short patient born small for gestational age with recurrent patellar dislocation: a case report. *J Clin Res Pediatr Endocrinol.* 2022;14(4):481-484.
47. Hauer NN, Sticht H, Boppudi S, *et al.* Genetic screening confirms heterozygous mutations in ACAN as a major cause of idiopathic short stature. *Sci Rep.* 2017;7(1):12225.
48. Karniski LP. Mutations in the diastrophic dysplasia sulfate transporter (DTDST) gene: correlation between sulfate transport activity and chondrodysplasia phenotype. *Hum Mol Genet.* 2001;10(14):1485-1490.
49. Li S, Sheng Y, Wang X, *et al.* Biallelic variants in SLC26A2 cause multiple epiphyseal dysplasia-4 by disturbing chondrocyte homeostasis. *Orphanet J Rare Dis.* 2024;19(1):245.
50. Lin Y-C, Niceta M, Muto V, *et al.* SCUBE3 loss-of-function causes a recognizable recessive developmental disorder due to defective bone morphogenetic protein signaling. *Am J Hum Genet.* 2021;108(1):115-133.
51. Li X, Yao R, Chang G, *et al.* Clinical profiles and genetic spectra of 814 Chinese children with short stature. *J Clin Endocrinol Metab.* 2022;107(4):972-985.
52. Peeters S, Declerck K, Thomas M, *et al.* DNA methylation profiling and genomic analysis in 20 children with short stature who were born small for gestational age. *J Clin Endocrinol Metab.* 2020;105(12):e4730-e4741.
53. Nurchis MC, Altamura G, Riccardi MT, *et al.* Whole genome sequencing diagnostic yield for paediatric patients with suspected genetic disorders: systematic review, meta-analysis, and GRADE assessment. *Arch Public Health.* 2023;81(1):93.
54. Choi J-H, Shin Y-L, Kim G-H, *et al.* Endocrine manifestations of chromosome 22q11.2 microdeletion syndrome. *Horm Res.* 2005;63(6):294-299.
55. McDonald-McGinn DM, Sullivan KE, Marino B, *et al.* 22q11.2 deletion syndrome. *Nat Rev Dis Primers.* 2015;1(1):15071.
56. Mikhail FM, Burnside RD, Rush B, *et al.* The recurrent distal 22q11.2 microdeletions are often de novo and do not represent a single clinical entity: a proposed categorization system. *Genet Med.* 2014;16(1):92-100.
57. Morrow BE, McDonald-McGinn DM, Emanuel BS, Vermeesch JR, Scambler PJ. Molecular genetics of 22q11.2 deletion syndrome. *Am J Med Genet A.* 2018;176(10):2070-2081.
58. Rudaks LI, Nicholl JK, Bratkovic D, Barnett CP. Short stature due to 15q26 microdeletion involving IGF1R: report of an additional case and review of the literature. *Am J Med Genet A.* 2011;155a(12):3139-3143.
59. Li F-F, Chen W-J, Yao D, *et al.* Clinical phenotypes study of 231 children with Williams syndrome in China: a single-center retrospective study. *Mol Genet Genomic Med.* 2022;10(12):e2069.
60. Laczmanska I, Stembalska A, Gil J, Czernomazowicz H, Sasiadek M. Cri du chat syndrome determined by the 5p15.3-->pter deletion--diagnostic problems. *Eur J Med Genet.* 2006;49(1):87-92.
61. Coutton C, Devillard F, Vieville G, *et al.* 17p13.1 microduplication in a boy with Silver-Russell syndrome features and intellectual disability. *Am J Med Genet A.* 2012;158a(10):2564-2570.
62. Leka-Emiri S, Petrou V, Manolagos E, *et al.* 17p13.1 microduplication syndrome in a child, familial short stature, and growth hormone deficiency: a case report and review of the literature. *Mol Syndromol.* 2019;9(6):300-305.
63. Jedraszak G, Demeer B, Mathieu-Dramard M, *et al.* Clinical and molecular characterization of the 20q11.2 microdeletion syndrome: six new patients. *Am J Med Genet A.* 2015;167a(3):504-511.
64. Goldenberg A, Riccardi F, Tessier A, *et al.* Clinical and molecular findings in 39 patients with KBG syndrome caused by deletion or mutation of ANKRD11. *Am J Med Genet A.* 2016;170(11):2847-2859.
65. Elkhateeb N, Crookes R, Spiller M, *et al.* Expanding the phenotype and genotype spectrum of TAOK1 neurodevelopmental disorder and delineating TAOK2 neurodevelopmental disorder. *Genet Med.* 2024;27(3):101348.
66. Matsuoka S, Edwards MC, Bai C, *et al.* p57KIP2, a structurally distinct member of the p21CIP1 Cdk inhibitor family, is a candidate tumor suppressor gene. *Genes Dev.* 1995;9(6):650-662.
67. Brioude F, Kalish JM, Mussa A, *et al.* Expert consensus document: clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement. *Nat Rev Endocrinol.* 2018;14(4):229-249.
68. Brioude F, Oliver-Petit I, Blaise A, *et al.* CDKN1C mutation affecting the PCNA-binding domain as a cause of familial Russell Silver syndrome. *J Med Genet.* 2013;50(12):823-830.
69. Inoue T, Nakamura A, Iwahashi-Odano M, *et al.* Contribution of gene mutations to Silver-Russell syndrome phenotype: multigene sequencing analysis in 92 etiology-unknown patients. *Clin Epigenetics.* 2020;12(1):86.
70. Sabir AH, Ryan G, Mohammed Z, *et al.* Familial Russell-Silver syndrome like phenotype in the PCNA domain of the CDKN1C gene, a further case. *Case Rep Genet.* 2019;2019:1398250.
71. Li J, Chen L-N, He H-L. CDKN1C gene mutation causing familial Silver-Russell syndrome: a case report and review of literature. *World J Clin Cases.* 2023;11(19):4655-4663.