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Comprehensive Characterization of *KMT2D* Variants in Korean Patients with Kabuki Syndrome: Expanding the Clinical and Genetic Landscape

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Background: Kabuki syndrome (KS) is a rare disorder characterized by distinctive craniofacial features, developmental delay, short stature, and involvement of multiple organ systems. The genotype–phenotype correlation in KS remains incompletely understood.
Methods: This study aimed to delineate the clinical and genetic spectrum of KS in a cohort of 27 Korean patients. Twenty-seven individuals clinically suspected of KS were evaluated at Pusan National University Children's Hospital between March 2009 and November 2022. Comprehensive assessments were conducted across multiple systems. Statistical comparisons were performed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables (IBM SPSS Statistics v21).
Results: The mean age at diagnosis was 6.90±6.71 years, with an average diagnostic delay of 4.56±5.03 years. All patients exhibited characteristic facial features of KS. Developmental delay was observed in 92.6% of cases, followed by short stature, skeletal and ENT abnormalities (63.0% each), congenital heart disease (59.3%), ophthalmologic issues (51.9%), neurologic and urogenital involvement (48.1% each), immune dysfunction (18.5%), and hematologic malignancy (3.7%). Pathogenic or likely pathogenic *KMT2D* variants were identified in 23 patients (85.2%), while 4 remained genetically undiagnosed. Among the detected variants, 8 were nonsense, 7 frameshift, 6 missense, 1 splicing, and 1 duplication variant; notably, 18 (78.3%) of these were novel. Patients with pathogenic *KMT2D* variants were diagnosed at a significantly younger age compared to variant-negative patients ($P=0.05$). Those harboring truncating variants exhibited a higher burden of multi-organ involvement compared to individuals with non-truncating variants (4.9±1.4 vs. 3.0±2.3; $P=0.016$).
Conclusion: This study broadens the clinical and molecular landscape of Kabuki syndrome in Korean patients.

Key words: Kabuki syndrome, Characterization, Variants, Phenotype

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INTRODUCTION

Kabuki syndrome (KS; OMIM #147920 [KS1], #300867 [KS2]) is a congenital disorder characterized by distinctive craniofacial dysmorphism—such as long palpebral fissures with eversion of the lateral third of the lower eyelid, large or cupped ears—along with multiple congenital anomalies, short stature, and intellectual disability [1-3]. KS has been documented across diverse ethnic groups, including Northern European, Italian, Brazilian, Vietnamese, Indian, Arabic, Chinese, Japanese, Mexican, and African populations [4,5]. The estimated prevalence ranges from 1 in 32,000 to 1 in 86,000 individuals [6,7]. In 2010, *KMT2D* was identified as the primary causative gene, accounting for over 80% of cases [6-9]. Located on chromosome 12q13.12, *KMT2D* comprises 54 exons and plays a critical role in regulating the transcription of genes involved in embryonic development [8].

In 2012, *KDM6A* (lysine demethylase 6A; also known as *UTX*, NM_021140.2) was identified as a second causative gene, responsible for approximately 6% to 10% of cases [10,11]. This gene is located on chromosome Xp11.3 and consists of 29 exons; it modulates gene expression in cooperation with *KMT2D* [6,8]. To date, more than 816 unique *KMT2D* variants associated with KS have been reported, including deletions, insertions, point mutations, and splice-site alterations (Human Gene Mutation Database [HGMD], release 2023.1; http://www.hgmd.org/).

In Korea, a 2014 review identified 12 reported cases of KS [8] with subsequent literature limited to isolated case reports. The present study aims to expand the clinical and molecular understanding of KS by characterizing 27 Korean patients and contributing newly identified *KMT2D* variants to the existing mutational spectrum.

METHODS

Subjects and clinical evaluation

This study included 27 patients diagnosed with KS, all of whom were assessed at Pusan National University Children's Hospital in Yangsan, South Korea, between March 2009 and November 2022. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Comprehensive clinical data were collected for each participant, including age, sex, phenotypic spectrum across multiple systems (cardiologic, endocrinologic, gastrointestinal, hemato-oncologic, neurologic, musculoskeletal, ophthalmologic, otolaryngologic, urogenital, and immune systems), response to growth hormone therapy, and underlying genetic alterations.

Diagnosis of KS was based on established criteria [12], which include a history of infantile hypotonia and developmental delay and/or intellectual disability, in addition to at least one of the following major features:

(1) A confirmed pathogenic or likely pathogenic variant in either *KMT2D* or *KDM6A*, and

(2) Characteristic craniofacial dysmorphisms such as elongated palpebral fissures (≥2 SD above the age-specific mean) with eversion of the lateral lower eyelid, accompanied by at least two of the following:

(a) Arched and broad eyebrows with lateral thinning or notching,

(b) Short columella with a depressed nasal tip,

(c) Large, prominent, or cupped ears, and

(d) Persistent fetal fingertip pads.

Involvement of major organ systems was defined by clinical manifestations affecting the cardiovascular, neurological, respiratory, gastrointestinal, or renal systems.

Genetic analysis

Genetic testing was performed following informed consent from all participants or their legal guardians. Genomic DNA was extracted from peripheral blood leukocytes using the Puregene DNA Isolation Kit (Gentra, Minneapolis, MN, USA).

Initial genetic analysis included targeted amplification of the coding regions of *KMT2D* and *KDM6A* using polymerase chain reaction (PCR) with gene-specific primers, followed by direct sequencing on an ABI 3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

For broader molecular profiling, targeted exome sequencing was conducted using the TruSight One Sequencing Panel (Illumina, San Diego, CA, USA) and mapped to the UCSC human genome reference (hg19). In selected cases, whole exome sequencing (WES) was performed using the NovaSeq6000 platform (Illumina, San Diego, CA, USA) with 150 bp paired-end reads. Exonic regions of approximately 22,000 human genes were enriched using one of the following capture kits, depending on the enrollment period: Agilent SureSelect (version C2, December 2018), Twist Bioscience Capture Kit (San Francisco, CA, USA), or xGen Exome Research Panel v2 (Integrated DNA Technologies, Coralville, IA, USA).

Variants were classified and interpreted in accordance with the standards and guidelines established by the American College of Medical Genetics and Genomics (ACMG).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY, USA). Continuous variables were analyzed using the Wilcoxon rank sum test (Mann–Whitney U test), and categorical variables were evaluated using Fisher's exact test. A P-value < 0.05 was considered indicative of statistical significance.

RESULTS

Clinical characteristics of 27 patients with Kabuki syndrome

The clinical profiles of 27 patients with genetically or clinically diagnosed KS are summarized in Table 1. The cohort comprised 14 males and 13 females. The mean gestational age at birth was 38+0 weeks, and the average birth weight was 2.80 ± 0.71 kg (range: 1.50–4.18 kg). Premature birth was observed in 6 patients (22.2%). The mean age at diagnosis was 6.90 ± 6.71 years (range: 0.16–27.18 years). The first clinical symptom appeared at a mean age of 2.34 ± 5.68 years (range: 0.00–26.89 years), with an average diagnostic delay of 4.56 ± 5.03 years (range: 0.12–15.39 years). Developmental delay or intellectual disability (ID) was the most common initial presentation (n = 6), followed by congenital heart disease (n = 5), prenatal ultrasound abnormalities (n = 4), facial dysmorphism (n = 3), seizures (n = 2), and isolated findings such as abnor-

Table 1. Baseline demographic characteristics and comprehensive clinical and genetic profiles of patients with Kabuki syndrome (n=27)

Pt	Age at Dx (yr)	Sex	Short stature	ID/DD	Sz	CHD	Uro-genital problem	CPP	Oph lesions	OTL problem	HO abnor-mality	OBGY problem	Skeletal deformity	Immune dysfuc-tion	Brain MR ab-normality	Gene	NT change	AA change	C	Novelty	Method
K01	1.82	M	N	Y	Y	Y	Y	N	Y	Y	N	N	Y	N	Y	*KMT2D*	c.16501C>T	p.R5501*	P	reported	Sing
K02	7.62	F	N	Y	N	N	N	N	Y	N	N	N	Y	N	NA	*KMT2D*	c.13259G>A	p.R4420Q	VUS	novel	Sing
K03	14.02	F	Y	Y	N	N	Y	N	Y	Y	N	Y	Y	N	NA	*KMT2D*	c.2579delT	p.L860Rfs*70	P	novel	TES
K04	13.04	M	Y	Y	N	Y	N	N	N	Y	N	N	Y	Y	NA	*KMT2D*	c.15670C>T	p.R5224C	LP	novel	Sing
K05	0.40	M	Y	Y	N	Y	N	N	Y	N	N	N	N	N	NA	*KMT2D*	c.5779C>T	p.Q1927*	LP	novel	TES
K06	0.16	M	Y	Y	N	Y	Y	N	N	Y	N	N	N	Y	NA	*KMT2D*	c.12084delC	p.V4029*	LP	novel	TES
K07	6.36	F	Y	Y	N	Y	N	Y	Y	Y	N	Y	Y	Y	N	*KMT2D*	c.8107G>T	p.E2703*	P	novel	Sing
K08	13.79	F	Y	Y	Y	Y	N	N	Y	Y	N	N	Y	N	N	*KMT2D*	c.1506C>T	p.R5021*	P	novel	WES
K09	15.57	M	N	Y	Y	N	N	N	N	N	N	N	N	N	Y	*KMT2D*	c.13732C>A	p.P4578T	VUS	novel	Sing
K10	0.31	F	Y	Y	N	Y	Y	N	Y	Y	N	N	Y	N	NA	*KMT2D*	c.6827dupC	p.P2277Tfs*22	P	novel	TES
K11	4.05	M	N	Y	N	N	N	N	N	Y	N	N	N	N	NA	*KMT2D*	c.16519G>A	p.E5507K	VUS	novel	TES
K12	1.38	M	Y	Y	N	N	N	N	Y	Y	N	N	N	N	NA	*KMT2D*	c.14945G>A	p.W4982*	LP	novel	TES
K13	12.62	F	N	Y	N	N	Y	N	Y	Y	N	N	Y	N	NA	*KMT2D*	c.3906+2T>C	splicing	P	reported	TES
K14	15.43	M	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	N	*KMT2D*	c.10750C>T	p.Q3584T	LP	novel	WGS
K15	0.38	M	N	N	N	Y	Y	N	N	Y	N	N	N	N	NA	*KMT2D*	c.7613dupT	p.Q2540Sfs*115	LP	reported	Pan
K16	2.81	F	Y	Y	N	Y	Y	Y	N	Y	N	N	Y	N	Y	*KMT2D*	c.6595delT	p.Y2199Ifs*65	P	reported	TES
K17	3.07	M	N	Y	N	N	N	N	NA	NA	N	N	N	N	NA	*KMT2D*	c.10151_10171dup	p.T3384_C3390dup	VUS	novel	WES
K18	0.55	F	Y	Y	N	Y	Y	N	N	N	N	N	Y	N	N	*KMT2D*	c.2819C>A	p.S940*	P	novel	WES
K19	3.16	M	N	Y	N	N	Y	N	N	N	N	N	Y	N	NA	*KMT2D*	c.9961C>T	p.R3321*	LP	reported	Pan
K20	4.05	M	Y	Y	N	Y	N	N	Y	N	N	N	Y	Y	NA	*KMT2D*	c.4271G>T	p.C1424F	P	novel	WES
K21	7.13	F	Y	Y	Y	Y	Y	NA	Y	Y	N	N	Y	N	N	*KMT2D*	c.14404delG	p.A4802Qfs*6	P	novel	Sing
K22	2.42	F	Y	Y	Y	Y	Y	N	NA	Y	N	N	Y	N	N	*KMT2D*	c.6553del	p.L2185Wfs*79	P	novel	Sing
K23	0.96	M	N	Y	N	N	N	N	NA	Y	N	N	N	N	NA	*KMT2D*	c.12835dup	p.A4279Gfs*55	LP	novel	Sing
K24	14.27	F	Y	N	N	N	N	N	NA	NA	N	N	Y	N	NA	*ND*	ND	ND	NA	NA	WES
K25	7.62	F	N	Y	Y	N	N	N	N	N	N	N	N	N	NA	*ND*	ND	ND	NA	NA	WES
K26	27.18	F	Y	Y	N	Y	N	N	Y	N	N	N	N	N	N	*ND*	ND	ND	NA	NA	WES
K27	6.23	M	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y	N	NA	*ND*	ND	ND	NA	NA	WGS

Pt, patients; Dx, diagnosis; yr, years old; ID, intellectual disability; DD, developmental delay; Sz, seizure; CHD, congenital heart disease; CPP, central precocious puberty; Oph, ophthalmologic; OTL, otolaryngological; HO, hemato-oncological; OBGY, obstetric & gynecological; NT, nucleotide; AA, aminoacid; C, classification; M, male; F, female; Y, yes; N, no; NA, not applicable; P, pathogenic; LP, likely pathogenic; VUS, variants of uncertain significance; ND, not determined; Sing, single gene analysis; TES, targeted exome sequencing; WES, whole exome sequencing; WGS, whole genome sequencing; Pan, Panel sequencing.

mal hearing test, feeding intolerance, and short stature (each n=1). All patients exhibited typical craniofacial features characteristic of KS, such as long palpebral fissures with eversion of the lateral third of the lower eyelid and/or prominent ears. A majority of patients (92.6%, 25/27) demonstrated global developmental delay or ID. Short stature (height below −2 SD) was identified in 17 patients (63.0%), and 17 patients (63.0%) also exhibited musculoskeletal anomalies including scoliosis or kyphosis (n=13), hip dislocation (n=2), recurrent patellar dislocation (n=1), and cleidocranial dysostosis (n=1). Otolaryngologic manifestations were seen in 17 patients (63.0%), primarily otitis media (n=14) and sensorineural hearing loss (n=8), with less frequent findings of subglottic stenosis (n=1) and obstructive sleep apnea (n=1). Congenital heart disease was present in 16 patients (59.3%), including atrial septal defect (56.3%), ventricular septal defect (43.8%), patent ductus arteriosus (37.5%), and other less common anomalies such as coarctation of the aorta, aortic valve stenosis, and complex congenital heart defects (e.g., hypoplastic left heart syndrome, double outlet right ventricle). Ophthalmologic abnormalities were observed in 14 patients (51.9%), with strabismus being the most prevalent (n=8), followed by ectropion, entropion, and other structural anomalies. Neurological manifestations were present in 13 patients (48.1%), with seizures being the most frequent (n=8). Among those with seizures, electroencephalogram (EEG) findings varied: normal (n=3), focal epilepsy (n=3), and diffuse cerebral dysfunction (n=1). Urogenital anomalies were identified in 13 patients (48.1%), including structural anomalies such as horseshoe kidney (n=5), unilateral renal hypoplasia (n=3), and renal duplication or agenesis. Genital abnormalities included cryptorchidism (n=2), micropenis (n=1), and uterine malformations (n=2). Cleft palate was present in 10 patients (37.0%), and failure to thrive was documented in 9 patients (33.3%). Dental anomalies (n=7, 25.9%) and thyroid disorders (n=6, 22.2%; including both congenital hypothyroidism and Hashimoto's thyroiditis) were also noted. Immunologic abnormalities were reported in 5 patients (18.5%), consisting of T-cell subset deficiencies and hypogammaglobulinemia. One patient developed both stage IV Burkitt's lymphoma and a mature teratoma of the testis.

Efficacy of recombinant human growth hormone (rhGH) therapy

Among 17 patients with short stature, four prepubertal individuals underwent rhGH therapy. Two patients had confirmed growth hormone deficiency via provocation testing. One of these showed a height velocity of 6.0 cm/year after treatment, whereas the other could not be followed long enough for response evaluation. Two additional patients without confirmed GH deficiency also demonstrated favorable responses to rhGH, with annual height velocities of 8.5 cm (height SDS from -2.63 to -2.11) and 8.2 cm (height SDS from -3.55 to -2.69), respectively. The mean height SDS at last follow-up across all treated patients was −1.77 ± 1.51.

Genetic findings in 27 patients with KS

Genetic analysis revealed pathogenic or likely pathogenic variants in *KMT2D* in 23 of 27 patients (85.2%). No causative variants in either *KMT2D* or *KDM6A* were identified in the remaining four patients, two of whom underwent whole genome sequencing (WGS) without revealing additional findings (Fig. 1). Among the *KMT2D* variants, there were 8 nonsense, 7 frameshift, 6 missense, 1 duplication, and 1 splicing variant. Notably, 18 out of 23 variants (78.3%) were novel and absent

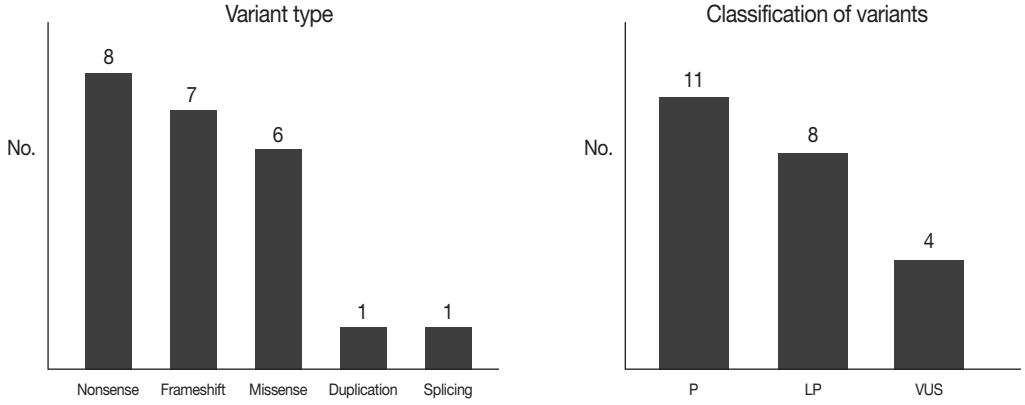


Fig. 1. Genetic profiles of Kabuki syndrome based on variant classification. P, Pathogenic; LP, Likely Pathogenic; VUS, Variant of Uncertain Significance.

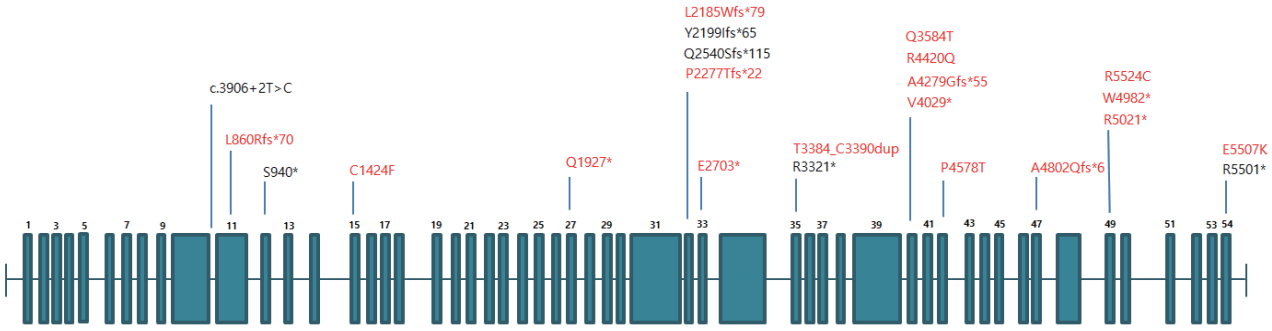


Fig. 2. Detailed mapping of *KMT2D* variants in Kabuki syndrome: Variant type distribution across all 54 exons, with novel variants denoted in red.

Table 2. Comparative analysis of clinical phenotypes between genetically confirmed and genetically unresolved cases of Kabuki syndrome

	Variant-positive KS n=23 (85.2%)		Variant-negative KS n=4 (14.8%)		*P*-value *
Sex (no., %)	M	F	M	F	
	13 (56.5%)	10 (43.5%)	1 (25.0%)	3 (75.0%)	
Age of first symptom onset (yr)					0.122
Median (IQR)	0.03 (1.11)		7.87 (22.23)		
Age at diagnosis (yr)					0.050
Mean±SD	5.70±5.52		13.82±9.56		
Median (range)	3.16 (0.16-15.57)		10.94 (6.23-27.18)		
Current age (yr)					0.147
Mean±SD	9.84±6.05		17.51±9.23		
Median (range)	8.31 (1.28-20.18)		14.34 (10.82-30.54)		
Facial dysmorphism (no., %)	23 (100)		4 (100)		>0.99
Global developmental delay or intellectual disability (no., %)	22 (95.7)		3 (75.0)		0.279
Otolaryngological disorder (no., %)	16 (69.6)		1 (25.0)		0.128
Orthopedic disorder (no., %)	15 (65.2)		2 (50.0)		0.613
Congenital heart disease (no., %)	14 (60.9)		2 (50.0)		0.767
Urogenital disorder (no., %)	12 (52.2)		1 (25.0)		0.325
Short stature (no., %)	14 (60.9)		3 (75.0)		0.576
Ophthalmologic problem (no., %)	12 (52.2)		2 (50.0)		0.937
Cleft palate (no., %)	9 (39.1)		1 (25.0)		>0.99
Feeding intolerance (no., %)	8 (34.8)		0		0.285
Failure to thrive (no., %)	8 (34.8)		1 (25.0)		>0.99
Neurologic problems (no., %)	10 (43.5)		3 (75.0)		0.253
Dental problem (no., %)	7 (30.4)		0		0.545
Seizure (no., %)	6 (26.1)		2 (50.0)		0.489
Immunologic abnormality (no., %)	5 (21.7)		0		0.561
Congenital hyperinsulinemic hypoglycemia (no., %)	3 (13.0)		0		>0.99
Carnitine deficiency (no., %)	1 (4.3)		0		>0.99
Attention deficit hyperactive disorder (no., %)	2 (8.7)		0		>0.99
Malignancy (no., %)	1 (4.3)		0		>0.99
Thyroid disease (no., %)	5 (21.7)		1 (25.0)		>0.99
Central precocious puberty (no., %)	2 (8.7)		0		>0.99
Diabetes mellitus (no., %)	1 (4.3)		0		>0.99
Growth hormone deficiency (no., %)	1 (4.3)		1 (25.0)		0.153

no., numbers; yr, years old; IQR, interquartile range; SD, standard deviation. *Mann-Whitney U test.

from public databases such as ESP6500, 1000 Genomes, dbSNP137, and KPGP. According to ACMG guidelines, variants were classified as pathogenic (n = 11), likely pathogenic (n = 8), or of uncertain significance (n = 4). Each patient harbored a unique, non-recurrent mutation. The variants were widely distributed throughout exons 1 to 54 of *KMT2D*, although clustering was observed in exons 32, 40, and 49 (Fig. 2).

Clinical comparison between variant-positive and variant-negative Patients

Comparison between variant-positive (n = 23) and variant-negative (n = 4) patients revealed a statistically significant younger age at diagnosis in the variant-positive group ($P = 0.05$) (Table 2).

Clinical comparison between truncating and non-truncating variant groups

When comparing patients with truncating variants (nonsense and frameshift) and those with non-truncating variants (missense, splicing, duplication), the truncating variant group exhibited a significantly higher burden of major organ involvement (mean 4.9 ± 1.4 vs. 3.0 ± 2.3, $P = 0.016$) (Table 3).

Clinical comparison between mutational hotspot and non-hotspot groups

Patients with mutations located in identified *KMT2D* hotspot exons (32, 40, 49) were compared with those harboring mutations outside these regions. No statistically significant differences in clinical manifestations were observed between the two groups (Supplementary Table 1).

DISCUSSION

In this study, we comprehensively analyzed the clinical and genetic features of 27 patients with KS in Korea. As a syndrome characterized by distinct craniofacial dysmorphisms, early recognition based on clinical suspicion remains crucial for timely diagnosis. This is underscored by our high diagnostic yield (85.2%) for pathogenic variants in *KMT2D*, which reflects both the recognizability of the syndrome and the importance of clinician awareness [13].

Global developmental delay or intellectual disability was observed in 92.6% of our cohort, consistent with previous reports [6]. Developmental delay in KS is multifactorial and may result from cognitive dysfunction, hypotonia, skeletal anomalies, cardiac defects, gastrointestinal complications, and hearing impairment [6]. In addition, short stature, musculoskeletal abnormalities, otolaryngologic disorders, congenital heart disease (CHD), and ophthalmologic anomalies were all present in more than half of the patients (63.0%, 63.0%, 63.0%, 59.3%, and 51.9%, respectively), highlighting the multisystemic nature of KS (Fig. 3).

CHD are among the most commonly reported systemic findings in KS, with prevalence varying across studies but generally estimated at around 70% [6,7]. In our cohort, CHD was identified in 59.3% of patients. This is consistent with the known role of *KMT2D* in murine cardiogenesis [14,15]. Consistent with previous literature, left-sided lesions such as atrial septal defect, ventricular septal defect, and coarctation of the aorta were predominant [5–7,13,14]. Interestingly, one patient (K20) harboring a novel *KMT2D* variant (c.4271G>T) exhibited scimitar syndrome, a rare vascular anomaly seldom reported in KS [5,8,16]. This patient also had T-cell dysfunction, characteristic facial features, and was later diagnosed with partial growth hormone (GH) deficiency, illustrating the complex interplay between genotype and multisystem involvement.

Short stature, reported in up to 70% of KS patients [6,14], was observed in 63.0% of our cohort. Emerging evidence sug-

Table 3. Clinical characterization of Kabuki syndrome according to truncating versus non-truncating *KMT2D* mutations

	Truncating variant group (N = 15)	Non-truncating variant group (N = 8)	*P*-value
Major organ involvements (mean ± SD)	4.9 ± 1.4	3.0 ± 2.3	0.016*
Congenital heart defects (no., %)	11 (73.3)	3 (37.5)	0.179†
Global developmental delay or intellectual disability (no., %)	14 (93.3)	8 (100)	>0.99†
Seizure (no., %)	4 (26.7)	2 (25.0)	>0.99†
Immune dysfunction (no., %)	2 (13.3)	3 (37.5)	0.297†
Short stature (no., %)	11 (73.3)	3 (37.5)	0.179†
Ophthalmologic lesion (no., %)	8 (53.3)	4 (50.0)	>0.99†
Urogenital anomaly (no., %)	10 (66.7)	2 (25.0)	0.089†

no., numbers; SD, standard deviation. *Mann-Whitney U test; †Fisher's exact test.

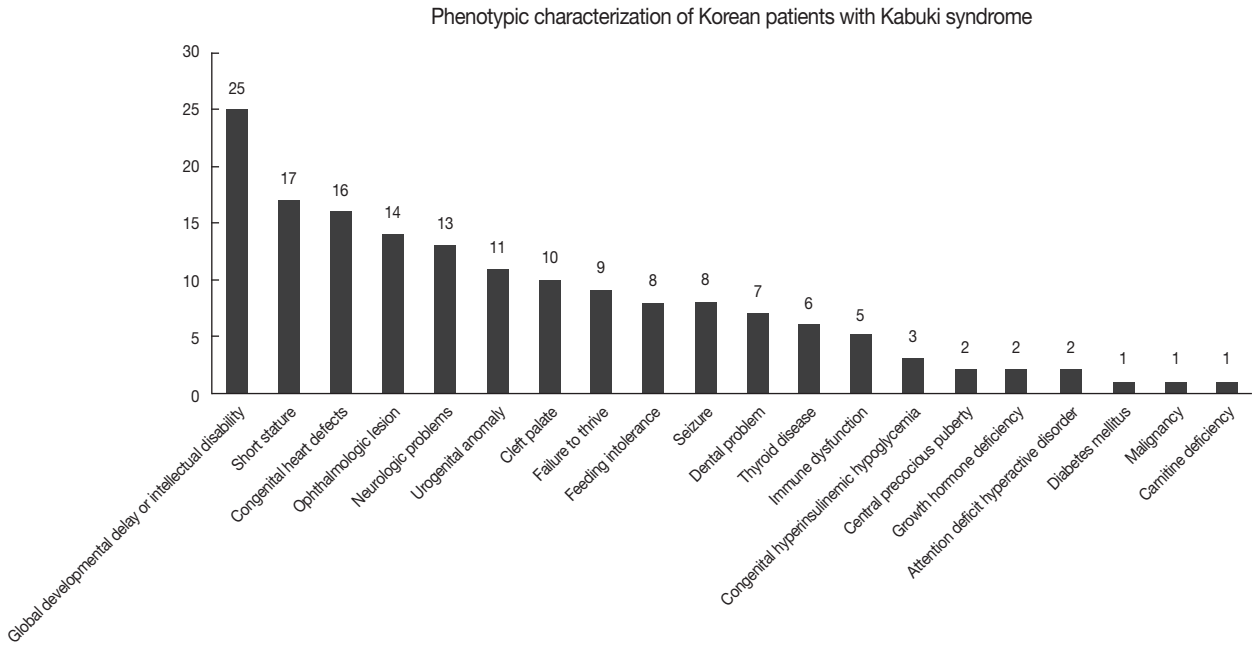


Fig. 3. Comprehensive phenotypic characterization of Korean patients with Kabuki syndrome, highlighting the multisystemic involvement and the extensive spectrum of clinical manifestations.

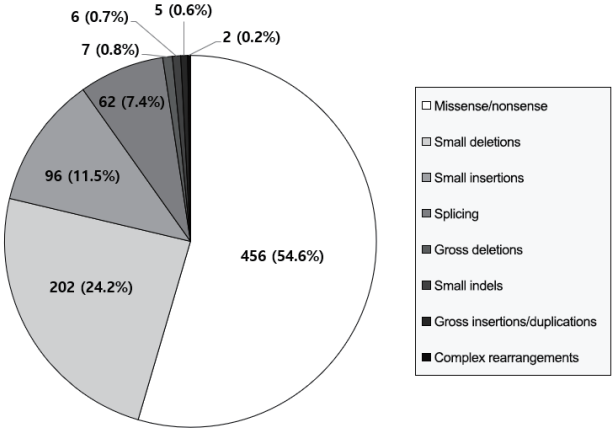


Fig. 4. Distribution of *KMT2D* variant frequencies, encompassing previously reported mutations cataloged in the HGMD alongside 18 novel variants identified in the present study.

gests that *KMT2D* variants may impair growth via disruption of the GH/IGF-1 axis or modulation of SOX9 expression, as demonstrated in animal models [14]. rhGH therapy has shown efficacy in improving linear growth in some KS patients [6,17], although no consensus guidelines currently exist. In our study, among the four patients who received rhGH therapy, two showed favorable growth responses despite the absence of confirmed GH deficiency, suggesting potential benefit in select patients. However, one patient with confirmed GH deficiency had a suboptimal response, emphasizing the need for individualized treatment strategies and further clinical trials to establish therapeutic guidelines in KS.

From a genetic perspective, our study identified a diverse spectrum of *KMT2D* variants, including 18 novel variants. According to the HGMD, over 800 *KMT2D* mutations have been reported to date, encompassing various mutation types such as missense/nonsense variants, small insertions/deletions, and splicing changes. In our cohort, we identified 14 missense/nonsense variants, 4 small deletions, 3 insertions, 1 duplication, and 1 splicing variant—most of which were previously unreported. These novel findings significantly contribute to expanding the mutational landscape of *KMT2D* in KS (Fig. 4).

Interestingly, our analysis revealed a clustering of variants within exons 32, 40, and 49, which accounted for a substantial proportion of both truncating and non-truncating variants. However, unlike previous studies reporting frequent mutations in exons 10, 11, 31, 34, 39, and 48 [18,19], our data suggest a different pattern of mutational hotspots. This discrepancy raises the possibility of ethnic or population-specific variations in *KMT2D* mutation distribution, which warrants validation in larger, multi-ethnic cohorts.

Furthermore, our findings support previous observations suggesting genotype-phenotype correlations. Patients with truncating variants (nonsense and frameshift) exhibited significantly greater involvement of major organ systems compared

to those with non-truncating variants, consistent with prior studies indicating a more severe phenotype associated with loss-of-function mutations [20]. These results emphasize the clinical utility of variant classification in anticipating disease severity and guiding comprehensive, system-based evaluations in affected individuals.

Despite these insights, our study has several limitations. First, 4 of the 27 clinically diagnosed patients (14.8%) lacked identifiable pathogenic variants in *KMT2D* or *KDM6A*. This is in line with prior reports indicating that 20%–45% of KS cases remain genetically unresolved [19]. Additional techniques such as multiplex ligation-dependent probe amplification (MLPA) may uncover larger deletions or duplications not detectable by sequencing. Mosaic variants may also account for some of the unexplained cases, as demonstrated by Montano et al. [21], who identified mosaic *KMT2D* variants in 12 patients (1 novel and 11 previously reported cases). Epigenetic profiling and pyrosequencing analyses may further enhance diagnostic yield in genetically elusive cases [7,13,22].

Second, as this study was conducted at a single institution, the findings may not be generalizable. Future multi-center, prospective studies with larger cohorts are essential to validate genotype-phenotype correlations and better understand the ethnic variability in KS presentation.

This study offers a comprehensive overview of the clinical and genetic characteristics of Korean patients with KS. We identified 18 novel *KMT2D* variants and demonstrated potential genotype-phenotype associations, particularly the more severe clinical features observed in patients with truncating variants. Our findings broaden the mutational spectrum of *KMT2D* and underscore the importance of early recognition, systemic evaluation, and personalized management strategies in KS. Further studies are warranted to refine diagnostic tools and therapeutic approaches, as well as to explore the underlying mechanisms of phenotypic variability in this complex syndrome.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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AUTHOR CONTRIBUTIONS

Conceptualization: Cheon CK. Methodology: Lee J, Cheon CK. Formal analysis: Lee J, Cheon CK. Writing original draft preparation: Lee J, Cheon CK. Writing review: Cheon CK. Supervision: Cheon CK. All authors have read and agreed to the published version of the manuscript.

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Supplementary Table 1. Comparison of clinical features between the mutational hotspots group and the mutational non-hotspots group

	Mutational hotspots group (N=11)	Mutational non-hotspots group (N=12)	*P*-value
Major organ involvements			0.651*
Median (IQR)	5.00 (3)	4.50 (4)	
Congenital heart defects (no., %)	8 (72.7)	6 (50.0)	0.400†
Global developmental delay or intellectual disability (no., %)	10 (90.9)	12 (100)	0.478†
Seizure (no., %)	3 (27.3)	3 (25.0)	>0.99†
Immune dysfunction (no., %)	3 (27.3)	2 (16.7)	0.640†
Short stature (no., %)	8 (72.7)	6 (50.0)	0.400†
Ophthalmologic lesion (no., %)	5 (45.5)	7 (58.3)	0.684†
Urogenital anomaly (no., %)	7 (63.6)	5 (41.7)	0.414†

no., numbers; IQR, interquartile range. *Mann-Whitney U test; †Fisher's exact test.