



Kabuki syndrome: clinical and molecular characteristics

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Kabuki syndrome (KS) is a rare syndrome characterized by multiple congenital anomalies and mental retardation. Other characteristics include a peculiar facial gestalt, short stature, skeletal and visceral abnormalities, cardiac anomalies, and immunological defects. Whole exome sequencing has uncovered the genetic basis of KS. Prior to 2013, there was no molecular genetic information about KS in Korean patients. More recently, direct Sanger sequencing and exome sequencing revealed *KMT2D* variants in 11 Korean patients and a *KDM6A* variant in one Korean patient. The high detection rate of *KMT2D* and *KDM6A* mutations (92.3%) is expected owing to the strict criteria used to establish a clinical diagnosis. Increased awareness and understanding of KS among clinicians is important for diagnosis and management of KS and for primary care of KS patients. Because mutation detection rates rely on the accuracy of the clinical diagnosis and the inclusion or exclusion of atypical cases, recognition of KS will facilitate the identification of novel mutations. A brief review of KS is provided, highlighting the clinical and genetic characteristics of patients with KS.

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Introduction

Kabuki syndrome (KS, OMIM# 147920) is a rare syndrome characterized by distinct dysmorphic facial features, postnatal growth retardation, intellectual disabilities, skeletal abnormalities, and unusual dermatoglyphic patterns. It is usually detected sporadically and has a wide spectrum of clinical manifestations¹. Recently identified as a genetic syndrome via whole exome sequencing², KS has been increasingly recognized in the primary care setting, and in many cases, its underlying etiology has been discovered. KS is diagnosed and managed by pediatricians. To enhance the understanding of patients with KS among pediatricians, this review focuses on the clinical and molecular genetic characteristics of these patients.

What is KS?

In 1969, Japanese geneticist Norio Niikawa encountered a young patient presenting with unusual facial features and mental retardation. Whether this was a never before diagnosed condition with a genetic underpinning was unclear. Over the next several years, Niikawa treated several other children with the same symptoms in his outpatient clinic, furthering support for a new disorder¹. In 1981, two independent groups in Japan separately described this disorder in the *Journal of Pediatrics*³. Because its characteristic facial features

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resembled the make-up of actors in Kabuki, the traditional Japanese theater, the term ‘Kabuki make-up syndrome’ was coined. The most remarkable aspects of KS are the atypical facial features, which usually prompt the clinician to consider this diagnosis⁴. Patients often have long palpebral fissures with eversion of the lateral one-third of the lower eyelid, arched eyebrows with sparseness in the lateral one-third, short columella with a depressed nasal tip, prominent ears, other congenital anomalies, and various health problems⁴.

How common is KS?

KS was initially thought to be specific to Japanese individuals. Its estimated prevalence in Japan is 1/32,000⁵. However, there are now reports of KS in a variety of ethnic groups, including Northern European, Brazilian, Vietnamese, Filipino, East Indian, Arabic, Chinese, Mexican, and African⁴. The global incidence of KS is not known. Although KS is reportedly rare in Korea, its prevalence in this country may be underestimated because of under-recognition of the diagnosis and the paucity of diagnostic tools. Considering the many reports of other populations, the frequency of KS in the Korean population presumably approximates that of the Japanese population. Recently, a multicenter study⁶ confirmed that number of patients newly diagnosed with KS has increased owing to high-quality comprehensive diagnostic services beginning in 2000. A population-based study is required to accurately determine whether the incidence of KS is rising in Korea.

How can we clinically diagnose KS?

KS is first identified by a pediatrician after physical examination of the patient and review of his or her medical history. However, clinical diagnosis of KS by pediatricians is often challenging because the phenotype tends to evolve over time, and characteristic facial features, such as long palpebral fissures with everted lower lids, become more evident during childhood¹. Currently, there are no established consensus diagnostic criteria for KS. Traditionally, five cardinal manifestations have been defined⁵: a ‘peculiar face’ (eversion of the lower lateral eyelid, arched eyebrows with the lateral one-third dispersed or sparse, a depressed nasal tip, and prominent ears; present in all patients), skeletal anomalies (deformed spinal column with or without sagittal cleft vertebrae and brachydactyly), dermatoglyphic abnormalities, mild to moderate mental retardation, and postnatal growth deficiency. Less frequent findings include visceral abnormalities, premature breast development in girls, and susceptibility to frequent infections. We recently phenotypically characterized 12 Korean patients with KS (Fig. 1)⁷. All patients showed the characteristic facial dysmorphism, including long palpebral fissures, eversion of the lateral portion of the lower eyelids, and a broad nasal root, and 92% displayed intellectual disabilities. Irrespective of racial differences, the suggested minimal criteria for diagnosis of KS are long palpebral fissures with eversion of the lateral portion of the lower eyelids, broad and arched eyebrows with lateral sparseness, short nasal columella with a depressed nasal tip, prominent or cupped ears, and developmental delay or mental retardation. Most patients with KS have several of these features

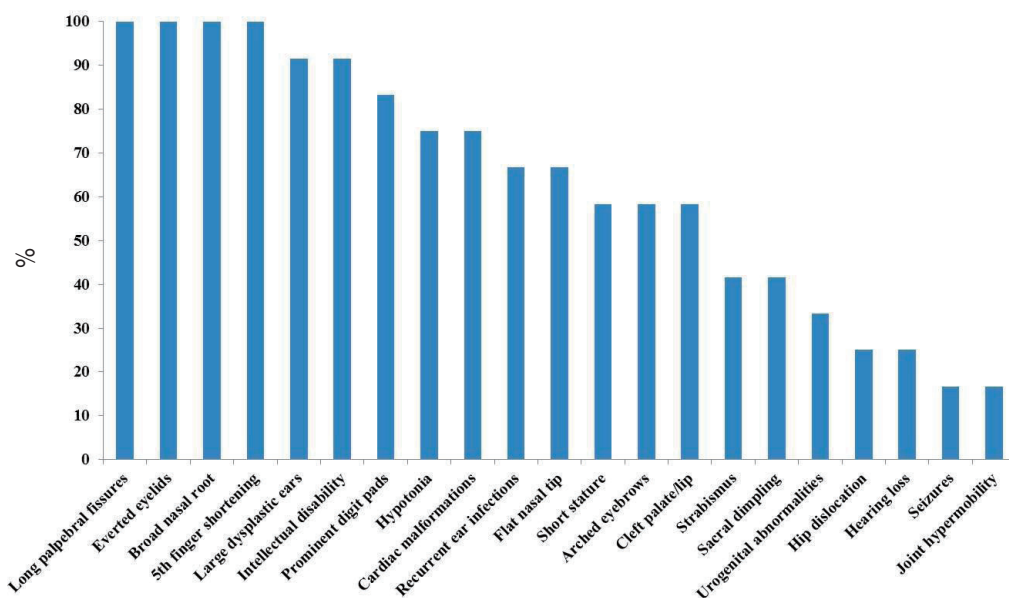


Fig. 1. Phenotypic characterization of Korean patients with Kabuki syndrome. The diverse phenotypes affecting multiple organ systems are noted.

that collectively produce an overall presentation suggestive of KS⁸.

What genes are associated with KS?

The genetic etiology of KS was not elucidated until 2010. At this time, Ng et al.² reported that heterozygous mutations in *KMT2D* (MIM #602113) are the major genetic cause of KS. Subsequent mutation screenings in KS cohorts found a *KMT2D* mutation in 55.8% to 80% of patients^{6,9}. Most mutations were private de novo mutations; familial occurrence with an autosomal dominant pattern has also been reported¹⁰. Most identified mutations are truncating, likely leading to haploinsufficiency of the *KMT2D* protein.

Heterozygous deletions in a second gene, *KDM6A* (MIM

#30012⁸), are another cause of KS¹⁰. In 2012, Lederer et al.¹¹ reported the association of heterozygous whole or large partial deletion of *KDM6A* (observed in three patients) with a broad phenotypic spectrum, ranging from typical KS to a milder clinical presentation. A detection rate of 12.5% highlighted the usefulness of array-comparative genomic hybridization as a method for differential diagnosis in *KMT2D*-negative patients¹⁰. In 2013, point mutations in the *KDM6A* coding region in *KMT2D* mutation-negative KS individuals were also identified as KS-related¹². In 2014, splice-site mutations in *KDM6A* were reported in Japanese and Korean patients^{7,13}. Despite the rarity of *KDM6A* mutations in KS patients, *KDM6A* sequencing should be considered in all *KMT2D* mutation-negative KS patients. To date, the genetic basis of KS remains unknown in 20% to 45% of patients⁹, and further investigation is therefore needed. The role of histone modifications in KS also requires clarification, because the pro-

Table 1. Summary of the reported mutations in 12 Korean patients with Kabuki syndrome

Patients	Gene	Mutation type	Exon	Nucleotide change	Amino acid change
1	<i>KTM2D</i>	Missense	15	c.4271G>T	p.C1424F
2	<i>KTM2D</i>	Nonsense	32	c.8107G>T	p.E2703*
3	<i>KTM2D</i>	Small deletion	46	c.14404delG	p.A4802Qfs*6
4	<i>KTM2D</i>	Missense	39	c.13259G>A	p.R4420Q
5	<i>KTM2D</i>	Small deletion	34	c.9164delC	p.P3055Lfs*16
6	<i>KTM2D</i>	Nonsense	39	c.12592C>T	p.R4198*
7	<i>KTM2D</i>	Small insertion	26	c.5775_6insT	p.L1926Sfs*31
8	<i>KTM2D</i>	Small deletion	14	c.4135_6delAT	p.M1379Vfs*52
9	<i>KTM2D</i>	Nonsense	39	c.11515C>T	p.Q3839*
10	<i>KTM2D</i>	Nonsense	39	c.11833C>T	p.Q3945*
11	<i>KTM2D</i>	Small deletion	22	c.5256_5257delGA	p.K1753Afs*34
12	<i>KDM6A</i>	Splicing error	26	c.3876_3878delTAA+1delG	–

Data derived from Cheon CK, et al. J Hum Genet 2014;59:321-5⁷) and Kim SJ, et al. J Pediatr 2013;56:355-8³⁸).

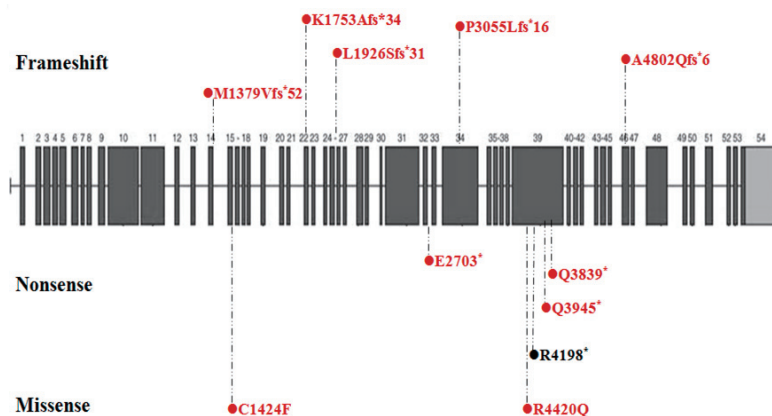


Fig. 2. Distribution of *KMT2D* mutations in Korean patients with Kabuki syndrome. Schematic view of the *KMT2D* protein domains and all coding exons and the location of the *KMT2D* mutations. Dotted lines indicate the exonic location of the mutations identified in patients. Novel mutations are indicated by a red circle.

teins encoded by both *KMT2D* and *KDM6A* are histone modifiers.

To date, 12 Korean patients with suspected KS in whom direct Sanger sequencing or exome sequencing was performed have been shown to express *KMT2D* (n=11) and *KDM6A* (n=1) variants (Table 1). All mutations were *de novo*, and each patient had a unique mutation. The 11 *KMT2D* mutations included five small insertions or deletions causing frameshifts, four nonsense mutations, and two missense mutations (Fig. 2). Ten (90.9%) were novel, and nine (81.8%) resulted in a truncated or shortened protein product. The mutations identified were relatively evenly distributed across exons 14 to 46 of the *KMT2D* gene, without a definite hot spot. However, four mutations were located in exon 39, which contains several regions that suggest the presence of a mutational hot spot (i.e., that encode long polyglutamine tracts)⁷.

The high detection rate of *KMT2D* and *KDM6A* mutations (92.3%) is expected owing to the strict criteria used to establish a clinical diagnosis⁹. Therefore, exhaustive mutation analysis of *KMT2D* and *KDM6A* may be a useful first step toward early diagnosis and counseling of Korean patients with KS. About 140 different mutations in the *KMT2D* gene have been reported in patients with KS (<http://www.hgmd.org>). Of these, 54 are nonsense mutations, 39 are small deletion mutations, 20 are missense mutations, 13 are small insertion mutations, nine are splicing mutations, three are small indel mutations, one is a gross deletion mutation, and one is a complex rearrangement. Including the 10 novel mutations reported in Korea, there are 57 nonsense, 42 small deletions, 22 missense, and 15 small insertions mutations (Fig. 3).

Molecular mechanism of pathogenicity

KMT2D was identified and characterized in 1997. It encodes a histone H3 lysine 4 (H3K4)-specific methyltransferase needed for

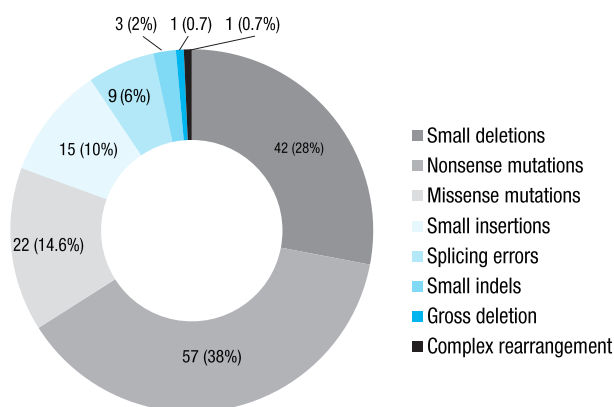


Fig. 3. Frequencies of *KMT2D* mutations. The diagram shows the numbers and percentages of the *KMT2D* mutations listed in the Human Gene Mutation Database and 11 novel mutations identified in Korea.

H3K4 di- and trimethylation, a hallmark of an active transcription state¹⁴. H3K4 methyltransferases act in stable multiprotein complexes that contain shared components as well as distinct components that denote the specific function of the complex¹⁰. *KMT2D* proteins contain a catalytic domain termed the SET domain, as do other histone methyltransferases, which are evolutionarily homologous to the *Drosophila* trithorax protein. The Su(var)3-9 and enhancer of zeste (SET) domains are also highly conserved in evolution¹⁵. The *KMT2D* complex ensures the transcription of constitutively expressed genes via H3K4 trimethylation. As part of the ASC-2 complex (ASCOM), *KMT2D* facilitates its binding to target genes¹⁶. Actions of ASCOM include the removal of repressive epigenetic marks, polycomb displacement, and positioning of activating methylation marks¹⁷.

KDM6A encodes a histone H3 lysine-27 (H3K27) demethylase¹⁴. It is important for general chromatin remodeling and interacts with *KMT2D* in a conserved SET-1-like complex that trimethylates H3K4. *KDM6A* and *KMT2D* interact with each other and are both trithorax-like proteins¹⁸. *KMT2D* methylates H3K4, and *KDM6A* demethylates H3K27, which activates transcription; conversely loss of *KMT2D* or *KDM6A* function represses transcription¹⁹. Little is known of the genes transcriptionally regulated by *KMT2D* complexes during development. Determination of the underlying pathogenesis of KS, including the functions of the proteins in these complexes during cell differentiation and growth is required¹⁰.

Clinical evaluation and management of patients with KS

Suggested evaluation and management procedures for patients with KS according to organ system are summarized in review articles^{5,9}.

1. Body weight and growth

KS patients are typically born with normal growth parameters, but fail to thrive during infancy and show postnatal growth retardation because of feeding problems caused by poorly coordinated sucking and swallowing, as well as gastroesophageal reflux in some patients⁵. Feeding problems requiring a nasogastric tube or even gastrostomy have been documented in 65% to 74% of KS cases⁶. More than half the patients fail to thrive in infancy, and 57% have a body mass index in the overweight or obese range in middle childhood or adolescence²⁰. Clinicians should inform the families of KS patients of the increased risk of obesity to promote awareness and early dietary intervention⁴.

2. Otolaryngological findings

The most common otolaryngological findings of KS include

dysmorphic pinnae, otitis media, and hearing loss²¹). Middle ear infections occur in approximately 70% of patients and can lead to conductive hearing loss and hinder speech acquisition². Conductive hearing loss appears to be the most frequent hearing impairment, followed by a sensorineural type of hearing loss. About 95% of KS patients have normal vestibular function¹⁰.

3. Ophthalmological findings

Ocular abnormalities have been described in 38% to 61% of KS patients¹⁰. The most common findings include ptosis, strabismus, and blue sclera¹. Less common findings include coloboma of the iris and retina, refractive anomalies, Peter's anomaly, and congenital corneal staphyloma²². Severe visual impairment is rare in KS.

4. Cardiac malformations

Congenital heart defects are often observed in KS patients with frequencies of approximately 40% and 50% according to different literature reviews¹. The most frequent malformations are atrial septal defects, ventricular septal defects, and aortic coarctation¹. Coarctation of the aorta seems to be much more common in male patients than female patients⁸. Heart defects are equally frequent in patients with and without *KMT2D* mutations¹⁰. We recently reported hearing defects in 75.0% of KS patients; defects included Scimitar syndrome, coarctation of the aorta, ventricular septal defects, atrial septal defects, interrupted aortic arches, patent ductus arteriosus, and hypoplastic left heart syndrome⁷.

5. Gastrointestinal abnormalities

Gastrointestinal complications are very rare. Intestinal malrotation, abnormalities of the anus or rectum in the form of anal atresia, anovestibular fistula, and anteriorly placed anus have been reported^{1,5,23}. Previously described liver anomalies include biliary atresia, hepatic fibrosis, and sclerosing cholangitis²³. Recently, a child with KS displayed inflammatory bowel disease²⁴.

6. Urogenital abnormalities

Urinary tract anomalies are present in 30% to 40% of KS patients¹⁰ and include hydronephrosis, abnormal kidney position, renal hypoplasia or dysplasia, and fusion defects in the kidneys^{1,8}. Renal malformations are significantly more common in patients with a *KMT2D* mutation¹⁰. Genital anomalies include cryptorchidism (25%), small penis (10%), and hypospadias^{1,5,25}. In our previous study, 36.3% of patients with a mutation in the *KMT2D* gene had renal duplication, multicystic dysplastic kidneys, ectopic kidneys, or a duplicated ureter⁷.

7. Endocrinological findings

Premature thelarche has been described in 41% of KS patients with a *KMT2D* mutation compared with 4% in mutation-negative patients⁹. It was not necessarily associated with other signs of

precocious puberty¹⁰. Its underlying cause in KS patients is uncertain, but could be secondary to low hypothalamic sensitivity to the suppressive effects of sex hormones on gonadotropin secretion²⁶. Rare findings in KS include hypothyroidism, hyperinsulinism hypoglycemia, diabetes insipidus, primary ovary dysfunction, and abnormal pituitary findings on magnetic resonance images^{3,20}. Postnatal growth hormone deficiency was observed in 83% of KS patients⁵. Our recent study showed short stature in 50.0% of KS patients with *KMT2D* mutations⁷. Considering the possibility of associated medical problems, such as skeletal and hematologic abnormalities, the benefits and side effects of growth hormone therapy for KS patients of short stature require further investigation in large patient cohorts¹⁰.

8. Skeletal findings

Skeletal abnormalities occur in about 80% of KS cases; they include rib anomalies, vertebrae malformations, scoliosis, cleft hand, and brachydactyly and/or clinodactyly of the fifth digit^{1,10}. Cranial abnormalities include coronal and metopic synostosis, incomplete development of the frontal and/or maxillary sinuses, digital impression of the skull, and underdevelopment of the mastoid processes²⁷.

9. Skin and connective tissue

Persistent fetal finger pads are a common and distinctive symptom of KS. Another common finding is an abnormal dermatoglyphic pattern, such as the absence of the digital triradius 'c' and 'd' and the presence of interdigital triradii, as well as hypothenar and interdigital ulnar loop patterns, which occur in almost all patients (96%) with KS⁷. Involvement of the connective tissue in KS has been proposed because of the combination of facial laxity, joint hyperlaxity, and joint dislocations¹⁰. Joint hypermobility is present in one-half to three-quarters of patients, and joint dislocations, particularly of the hips, patellae, and shoulders, are not uncommon¹. Habitual joint dislocations in 32% of patients with *KMT2D* mutations compared with 9% in patients without *KMT2D* mutations have been reported²⁸.

10. KS and cancer

To date, there are eight individuals with both KS and cancer worldwide, including two with neuroblastoma and one each with hepatoblastoma, low-grade fibromyxoid sarcoma, acute lymphocytic leukemia, Epstein-Barr virus (EBV)-positive Burkitt's lymphoma, EBV-negative Burkitt's lymphoma, and synovial sarcoma^{7,8,29}. Whether KS predisposes individuals to cancer remains uncertain¹⁰.

11. Immunologic/hematologic abnormalities

Patients with KS are vulnerable to infection in regions including the middle ear and upper airway tract. Decreased IgA and IgG

levels were observed in 79% and 42% of patients, respectively³⁰, and severe immunodeficiency with hypogammaglobulinemia requiring intravenous administration of intravenous immunoglobulin has been reported in several patients³¹. Scherer et al.³² described a 2-year-old girl with typical KS who developed acute lymphocytic leukemia. Autoimmune diseases, including idiopathic thrombocytopenic purpura and/or hemolytic anemia, and vitiligo are rarely seen in patients with KS³³. Careful hematological investigation and surveillance is essential for early detection of immunologic or hematologic disease in patients with KS.

12. Neurological symptoms and development/behavior problems

Hypotonia and seizures may accompany the psychomotor development of KS patients¹⁰. Muscular hypotonia seems to be most striking in newborns and has been observed in 51% to 98% of patients^{3,10}. Seizures mainly of the focal type originate predominantly in the temporo-occipital or frontocentral area and are well-controlled by antiepileptic drugs, resulting in a favorable prognosis³⁴. We observed seizures in 16.7% of individuals with *KMT2D* mutations; all showed good responses to antiepileptic medications⁷. Patients with KS often exhibit nonspecific cerebral atrophy, ventriculomegaly, and microcephaly⁸. Several patients with autism or autistic-like behavior characterized by difficulties in both communication and peer interactions have been described^{1,35}, suggesting that KS is a differential diagnosis in patients with facial dysmorphism presenting with autism spectrum disorder. Consistent with previous reports⁵⁻⁷, we observed varying degrees of intellectual disability in 91.7% of KS patients with *KMT2D* mutations³⁶.

Genotype-phenotype correlation

Genetic changes causing KS have been recently discovered via exome sequencing, resulting in improved clinical diagnosis and more accurate genotype-phenotype correlations. However, correlations between mutation type and the phenotype of KS patients have yet to be definitively established. In a screen of 81 KS patients with or without *KMT2D* or *KTM6A* mutations, Miyake et al.²⁸ observed the following. First, cleft lip/palate was more frequent in the mutation-positive group. Second, developmental delay and intellectual disabilities were detected in all patients with mutations but only in some patients without mutations. Third, blue sclera, lower lip pits, spine/rib abnormalities, hip joint dislocation, umbilical hernia, kidney abnormalities, cryptorchidism, liver/spleen abnormalities, premature thelarche, neonatal hyperbilirubinemia, and anemia were observed only in the mutation-positive group. Fourth, high arched eyebrows, short fifth fingers, and hypotonia in infancy were more common in individuals with

KMT2D mutations compared with *KDM6A* mutations, whereas the opposite was true for short stature. Fifth, patients with truncating mutations more frequently had prominent ears and hypotonia and a more atypical facial appearance than patients without truncating-type mutations.

Patients with *KDM6A* mutations display a variety of phenotypes, ranging from typical KS to a milder clinical presentation^{11,12}. Banka et al.¹³ noted that patients with *KDM6A* mutations have hypotonia and feeding difficulties during infancy and poor postnatal growth and short stature. They suggested that hypertrichosis, long halluces, and large central incisors may be useful indicators of an underlying *KDM6A* mutation, even if facial dysmorphism is variable. Developmental delay and learning disabilities are generally moderate to severe in boys but mild to moderate in girls with *KDM6A* mutations¹³. We recently described a female patient with a *KDM6A* mutation who presented with typical facial dysmorphism, including long palpebral fissures, lateral eversion of the lower eyelid, short nasal septum, severe mental retardation, profound short stature, cardiac abnormality, recurrent infection, and Chiari malformation⁷.

Expert consultation and family genetic counseling

As KS is a multisystem disorder, people with KS may require various diagnostic and screening tests, assessments, referrals, and multidisciplinary interventions at different stages of their lives. Early diagnosis of the disease is crucial in regard to patient management of his or her associated medical problems and for prompt family and genetic counseling, and serves as a starting point for therapeutic interventions. Most reported *KMT2D* and *KDM6A* mutations are *de novo* mutations found in sporadic cases. In a few cases, an affected person is believed to have inherited the mutation from an affected parent. KS caused by mutations in the *KMT2D* gene is inherited in an autosomal dominant manner, whereas KS caused by mutations in the *KDM6A* gene is inherited in an X-linked inheritance manner. The *KDM6A* gene is located on the X chromosome, which is one of the two sex chromosomes. In women, a mutation in one of the two copies of the gene in each cell is sufficient to cause KS. In men, a mutation in the only copy of the gene causes the disorder. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Current research

Recently, a genetically engineered mouse model of KS with a heterozygous deletion in the gene encoding the lysine-specific methyltransferase 2D (*Kmt2d*) was developed. These mice (termed

Kmt2d+/bGeo) have impaired methyltransferase function³⁷. *In vitro* reporter alleles demonstrated reduced acetylation of histone H4 and histone H3 lysine K4 trimethylation (H3K4me3) in fibroblasts derived from Kmt2d+/bGeo embryos. Oral administration of the histone deacetylase inhibitor AR-42 to either young (1–2 months old) or adult (5–6 months old) Kmt2d+/bGeo mice eliminated the structural and functional deficits in the dentate gyrus in association with restoration of H3K4 trimethylation³⁷. H3K4me3 deficiency in the dentate gyrus granule cell layer of Kmt2d+/bGeo mice correlated with reduced neurogenesis and hippocampal memory defects in an *in vivo* analysis, suggesting that KS could be treated by modulating the epigenetic machinery.

Conclusions

Considering the increasing number of patients newly diagnosed with KS owing to advanced comprehensive diagnostic services, clinicians need to be aware of KS and to look for a combination of abnormal medical conditions in patients with KS to prevent further complications. A greater understanding of patients with KS will allow physicians to better provide primary care to the patients and their families. It will also facilitate the detection of KS mutations, which depends on the accuracy of clinical diagnosis and the inclusion or exclusion of atypical cases. A population-based study is needed to accurately estimate the incidence of pediatric KS in Korea.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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