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Novel *KDM6A* mutation in a Chinese infant with Kabuki syndrome: A case report

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Abstract

BACKGROUND

Kabuki syndrome (KS) is a rare syndrome characterized by multisystem congenital anomalies and developmental disorder. *KMT2D* and *KDM6A* mutations were identified as the main causative genes in KS patients. There are few case reports and genetic analyses, especially of *KDM6A* gene mutation, in China.

CASE SUMMARY

This study reports a *de novo* *KDM6A* mutation in a Chinese infant with KS. A 2-month-old Chinese baby was diagnosed with KS, which manifested as hypoglycemia, congenital anal atresia at birth, feeding difficulties, hypotonia, and serious postnatal growth retardation. He died of recurrent respiratory infections at age 13 mo. DNA sequencing of his blood DNA revealed a novel *KDM6A* frameshift mutation (c.704_705delAG, p. N236Sfs*26) (GRCh37/hg19).

CONCLUSION

We present a Chinese KS patient with a novel *KDM6A* frameshift mutation (c.704_705delAG, p. N236Sfs*26) (GRCh37/hg19), broadening the mutation spectrum.

Key Words: Kabuki syndrome; *KDM6A*; Gene mutation; Chinese; Case report

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Core Tip: The case report describes a *de novo* *KDM6A* mutation in a Chinese patient with Kabuki syndrome (KS). This novel *KDM6A* frameshift mutation broadens the KS mutation spectrum and knowledge of its clinical manifestations.

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INTRODUCTION

Kabuki syndrome (KS), also termed Kabuki make-up syndrome or Niikawa-Kuroki syndrome, is a congenital anomaly/mental retardation syndrome[1,2] characterized by five main clinical features: a distinctive face, skeletal anomalies, dermatoglyphic abnormalities, mental retardation, and postnatal growth retardation[3]. The incidence of KS is approximately 1 in every 32000 births[4,5], and to date, there have been a number of cases reported in PubMed, showing that KS affects all ethnic populations without preference of gender or race, although it was originally reported in Japan (<https://rarediseases.org/rare-diseases/kabuki-syndrome/>). Nevertheless, due to misdiagnoses and missed diagnoses, the actual number of KS cases is underestimated. In China, there have been only a few cases reported, while the KS type II cases were even rarer (i.e. *KDM6A* mutations)[6-9]. The whole-exome sequencing of KS DNA samples has shown that KS development is mainly caused by mutations of *KMT2D*[10] and *KDM6A*[11]. It includes *KMT2D*-associated, autosomal-dominant KS type I (KS-1) and *KDM6A*-associated, X-linked-dominant KS type II (KS-2) and 56%-70% and 3%-8% of KS patients have mutations in *KMT2D* and *KDM6A*, respectively[12,13], whereas 25%-30% are diagnosed clinically without any known gene mutations[14-16].

In this case report, we identified and diagnosed a 2-month-old Chinese male baby with KS. DNA sequencing of his blood revealed a novel *KDM6A* frameshift mutation (c.704_705delAG, p. N236Sfs*26) (GRCh37/hg19), which clinically led to hypoglycemia, congenital anal atresia at birth, feeding difficulties, hypotonia, and serious postnatal growth retardation, and he died of recurrent respiratory infections at age 13 mo.

CASE PRESENTATION

Chief complaints

A 2-month-old boy was admitted to our hospital due to persistent feeding difficulties, poor weight gain and weak crying for 2 mo.

History of present illness

The patient was the second child of his mother and was born *via* spontaneous vaginal delivery. The gestational age was 34 wk. Apgar score was 10 points. There were no abnormalities in the placenta and umbilical cord except for oligohydramnios (100 mL). At birth, the infant had the following birth parameters: 31.5 cm head circumference, 2.5 kg body weight, and 46 cm length, placing him in the 25-50th percentile in Chinese newborns. Ten minutes later, he was immediately admitted to the neonatal intensive care unit because of transient respiratory difficulty, and was diagnosed with neonatal hypoglycemia and congenital anal atresia. He was thereafter treated with respiratory support, glucose rehydration, and surgical correction of the anal atresia. Three weeks later, he was discharged from the hospital except feeding difficulty and poor weight gain.

History of past illness

The patient was the second child of Chinese parents who were healthy and non-consanguineous. He was born at 34 weeks' gestation from a healthy 32-year-old woman *via* spontaneous vaginal delivery. Prenatal ultrasound imaging showed that the mother had reduced amniotic fluid level since 32 weeks' gestation and the

amniotic fluid index was 7.0 cm. The ultrasound imaging also suggested mild hydronephrosis with dilatation of the upper ureteral diameter (0.6 cm) on the right kidney. There were no other abnormalities identified. The mother had irregular vaginal bleeding 8 h before delivery. His mother did not suffer from fever or use tobacco, alcohol, or illicit drugs during the entire pregnancy.

Personal and family history

The infant was born at 34 weeks' gestation from a healthy 32-year-old woman *via* spontaneous vaginal delivery and the father was aged 34 years. The parents were healthy and unrelated. The infant had a healthy 4-year-old brother. Family history was unremarkable.

Physical examination

He had severe malnutrition and poor skin elasticity with stable vital signs, but his growth and development level was below the normal range with the 3rd centiles, e.g., his height was 50.0 cm, weight 3.05 kg and head circumference 35.0 cm, and according to the WHO (2006) child growth standards, he was indicated as having postnatal onset of growth retardation. He also had distinctive body features, namely a long palpebral fissure, arched eyebrow, lateral sparse of the eyebrow, long eyelashes, and high-arched palate, but short nasal columella with a broad and depressed nasal tip (Figure 1). His palms had a simian crease. He also showed weak crying, muscle hypotonia, and motor delay and could not lift his head and accomplish a test of audio and visual tracking.

Laboratory examinations

Routine blood analyses revealed mild anemia (hemoglobin, 98 g/L), blood sugar level was low (2.31 mmol/L; normal range, 3.9–6.1 mmol/L) and his blood ammonia level was high (76 μ mol/L; normal range, < 60 μ mol/L). The level of insulin-like growth factor 1 was low (< 25 ng/mL) and growth hormone (GH) level was in the normal range. Liver, kidney and thyroid functions and electrolyte level were normal. Laboratory tests of urine and blood samples did not show any amino acid or aliphatic acid metabolic disorders. Furthermore, his chromosome count was normal (46, XY).

Imaging examinations

Cardiac ultrasound revealed patent foramen ovale and ductus arteriosus, and urological ultrasound indicated mild hydronephrosis and dilatation in the right kidney. Brain magnetic resonance imaging revealed corpus callosum hypoplasia, enlarged ventricles, and white matter dysplasia. Chest X-ray and abdominal ultrasound showed no apparent abnormality. Ophthalmological examination revealed hypoplasia of the optic nerve and retina with hearing loss in both ears (Table 1).

Further diagnostic work-up

As this infant showed peculiar facial features, multisystem anomalies, persistent feeding difficulties, hypoglycemia, and serious postnatal growth deficiency, KS diagnosis was indicated. Thus, the venous blood samples from both patient and parents were collected for whole-exome sequencing to confirm the diagnosis. Data from the infant's sample showed a novel *KDM6A* frameshift mutation (c.704_705delAG, p. N236Sfs*26) (GRCh37/hg19), whereas blood samples from his parents showed no abnormality (Figure 2).

FINAL DIAGNOSIS

The final diagnosis of the presented case was KS due to a novel *KDM6A* frameshift mutation (c.704_705delAG, p. N236Sfs*26) (GRCh37/hg19).

TREATMENT

There are no curable treatment options for KS currently available. At age 6 mo, the patient's physical development parameters were as follows: weight 5.0 kg, head circumference 37.5 cm and body length 61.5 cm, (all < 3rd percentiles). The patient was started on GH replacement therapy. At the same time, rehabilitation training was carried out.

Table 1 Summary of the main clinical features of the patient

Organ	Manifestations
Eye	(1) Long palpebral fissure, arched eyebrow, long eyelashes; and (2) sparse lateral eyebrows, optic nerve, and retina hypoplasia
Ear	Hearing loss
Nose	Short columella with depressed nasal tip, wide nasal bridge
Oral cavity	High-arched palate
Dermatoglyphic	Simian crease
Limbs and joints	Joint laxity
Head	High forehead and hairline
Heart	Patent ductus arteriosus, patent foramen ovale
Gastrointestinal	Anal atresia, persistent feeding difficulties
Genitourinary	Mild hydronephrosis and dilatation on the right kidney
Metabolic	Persistent hypoglycemia, mild high blood lactic acid levels
Immunologic	Immune dysfunction, frequent pulmonary infections
Neurologic	Hypotonia, weak crying
Neuroimaging	Corpus callosum hypoplasia, enlarge ventricles, and white matter dysplasia
Growth delay	Normal growth parameters at birth, postnatal growth retardation, motor delay
Intellectual disability	Mental retardation
Endocrine system	Low insulin-like growth factor 1 deficiency

OUTCOME AND FOLLOW-UP

The therapeutic effects were unsatisfactory. There was no improvement in growth and development. At age 7 mo, the patient had recurrent respiratory tract infection. He died of pulmonary infection at age 13 mo after failure of treatment and rescuing.

DISCUSSION

KS, a rare congenital disorder, was first reported in 1981 by two groups of Japanese physicians[4,5]. The estimated prevalence in Japan is approximately 1/32000 *versus* 1/86000 in Australia and New Zealand or in Europe and America[14,15]. KS cases have also been reported in China and our PubMed search showed that only six KS-2 cases have been so far reported in Mainland Chin [6-9], indicating that our current case is the seventh. The typical KS features include facial abnormality (long palpebral fissures with eversion of the lateral third of the lower eyelid; arched and broad eyebrows; sparse lateral eyebrows; short columella with depressed nasal tip; large, prominent, or cupped ears); postnatal growth retardation; mild to moderate intellectual impairment; scoliosis deformity; short and small fifth finger; susceptibility to infection; visceral deformity; dermatoglyphic abnormalities; blue sclera; hearing impairment; hypotonia; lack of GH; and other abnormalities[16]. *KMT2D* and *KDM6A* are two pathogenic genes that have been identified in KS. *KMT2D* gene mutation leads to KS type I, which is autosomal dominant; *KMT2D* gene encodes the lysine specific methyltransferase 2D, a methyltransferase that specifically modifies the lysine residue at the fourth acid lysine (H3K4) on histone H3 and catalyzes H3K4 from unmethylation to mono-, di- and/or tri-methylation[17]. The set domain of *KMT2D* protein is responsible for the activity of this part of methyltransferase, type I is common. In contrast, *KDM6A* gene mutations leads to KS II, an X-linked dominant inherited disease[13]. *KDM6A* gene encodes the lysine demethyltransferase 6A. The differences between KS type I and II are that: (1) KS I has obvious facial features, and is more likely to have kidney disease, joint dislocation, and palatal abnormalities; and (2) KS II is more likely to have hypoglycemia due to hyperinsulinism, hypertrichosis, long halluces, and large central incisors[13]. Furthermore, KS II is characterized by clinical manifestations of feeding difficulties, hypotonia, retarded growth, and short stature



Figure 1 Facial features of the patient. At age 3 mo, he had a long palpebral fissure (A), arched and broad eyebrows with the lateral third displaying sparseness (B), long eyelashes (A), but short columella with depressed nasal tip (C), wide nasal bridge, and high-arched palate as well as a high forehead and hairline (D).

[12,18]. In terms of developmental delay and cognitive impairment, male patients are more affected than females[13]. Both KDM6A and KMT2D are components of the activation signal cofactor complex whose function is to remove inhibitory epigenetic markers and deposit activated methylation markers on the chromatin, and then recruit RNA polymerase II complex to activate chromatin[19]. A previous study demonstrated that the KDM6A KS variants might impair functions of the histone demethylase through various mechanisms, including alteration of the protein integrity, local environment, molecular interactions and protein dynamics[20]. KDM6A protein plays a critical role in cell differentiation, development, and cancer, and is also important in differentiation of embryonic stem cells and development of various tissues, and alteration of KDM6A protein functions and expression results in developmental defects, growth retardation, multiple congenital organ malformations, and hematological and immunological anomalies[21].

In our current case, the patient was diagnosed with early-stage disease, possibly because of his serious symptoms that caused his early death. This patient had most of the KS clinical manifestations and the diagnosis was established based on these clinical findings (*i.e.*, preterm at age 34 wk), transient respiratory difficulty at birth, persistent hypoglycemia, and congenital anal atresia in the neonatal period. Moreover, the patient had persistent feeding difficulty, weak crying, hypotonia, and postnatal growth retardation, as well as distinctive facial features, multiple congenital internal malformations and increased infection susceptibility, which are consistent with KS diagnostic criteria [13]. Our current case report confirmed that KS is associated with novel KDM6A frameshift mutation (c.704_705delAG, p. N236Sfs*26) (GRCh37/hg19). Taken together, the data show that KS is genetically heterogeneous. Further studies with a larger number of KS cases will provide a better understanding of KS pathogenesis, and provide novel strategies to prevent and control KS.

Previous Chinese studies[8,9] have reported that KS patients have typical facial features, including the long palpebral fissures, sparse lateral or notched eyebrows, depressed nasal tip and large ears. However, the microcephaly, cleft lip/palate, and cardiac defects occurred less frequently in Chinese KS patients. Moreover, these studies[8,9] also showed the brain abnormalities, such as thinning of the pituitary and



Figure 2 Sanger sequencing of the patient and his parent's DNA samples. A: The reference corresponding DNA sequences of *KDM6A* gene from the NCBI GenBank; B: DNA sequence of the DNA sample from the patient. The DNA sequencing data demonstrated AG deletion (chr23:44911001_44911002delAG, c.702_703delAG, p. N236Sfs*26); C, D: DNA sequence of the samples from his parents. The data showed no *KDM6A* gene mutation.

myelination of the cerebral white matter in Chinese KS patients, suggesting a strong association between various brain abnormalities and KS.

It is worth noting that KS is a congenital multiple organ dysplasia and to date, there is no unique and specific perinatal diagnostic methodology. Long *et al* reported two infants who presented with prenatal hydrops/ascites, who were subsequently diagnosed with KS[22]. Guo showed the final diagnosis KS II of a 3-month-old patient with congenital hydrocephalus and suggested that congenital hydrocephalus was closely associated with KS II[7], while Rosenberg *et al*[23] collected retrospective data from 49 individuals with KS and over one third had complications of polyhydramnios, and reduced placental weight also complicated KS pregnancies, suggesting that the differential diagnosis for polyhydramnios in the absence of intrauterine growth retardation should include KS. A Chinese study[24] reported that a 24-week-old fetus was diagnosed with KS II using the chromosomal microarray analysis plus growth retardation and cardiovascular and musculoskeletal abnormalities using routine color Doppler ultrasonography. Another previous study[25] retrospectively reviewed 11 patients and showed that prenatal ultrasound was an important tool, while a molecular technique was also important in KS diagnosis. The most frequent ultrasound features observed were cardiac anomalies (49.4%), followed by polyhydramnios or oligohydramnios (28.9%), genitourinary anomalies (26.5%), single umbilical artery (15.7%), intrauterine growth restriction (14.5%) and hydrops fetalis/pleural effusion/ascites (12.0%); 50.6% of which had more than one abnormal antenatal ultrasound finding. These enlighten us that there are no distinct signs in fetuses to suggest the KS diagnosis prenatally. More and more investigators have suggested that prenatal phenotypic heterogeneity is associated with KS. If fetal ultrasound abnormalities show one or more deformities, KS should be considered. We need to complete a relevant gene analysis as soon as possible to realize early diagnosis and early intervention.

CONCLUSION

This case report identified a *de novo* frameshift *KDM6A* mutation localized on chromosome Xp11 (c.704_705delAG, p. N236Sfs*26) (GRCh37/hg19) in a Chinese male

infant with KS. After literature review, we believe that his severe clinical manifestations were part of the KS II phenotype spectrum. Our data support the investigation of a genotype-phenotype correlation, which explains the phenotypic variability of KS II. This case provides more information about the mutational spectrum of KS II.

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