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A Novel *KMT2D* mutation in Kabuki syndrome with elevated liver enzymes and congenital bilateral hip dislocation

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Abstract

Kabuki syndrome (KS) is a rare syndrome that involves defects in a wide range of organs, with each organ showing a different severity of symptoms. Two genes have been associated with patients with KS: lysine (K)-specific demethylase 6A (*KDM6A*) and lysine (K)-specific methyltransferase 2D (*KMT2D*). The study reported the case of an 18-month-old Turkish boy diagnosed with KS. The patient showed a typical appearance: widely separated eyes, sparse eyebrows, long palpebral fissures, blue sclera, large prominent ears, and micrognathia. The patient was operated on because of bilateral hip dislocation and undescended testicles. He was also followed up by pediatric gastroenterology with asymptomatic liver enzyme elevation (AST- 79 U/L, ALT -68 U/L, ALP -52 U/L). The whole exome sequencing analysis revealed a novel pathogenic c.13285 C>T (p.Gln4429Ter) mutation in the KMT2D gene. The genotype-phenotype correlation of KS was not precisely established. As per our knowledge, there is limited literature which gives information about the hepato-biliary manifestations of KS. Here, we propose that the new mutation of the *KMT2D* gene may result in the typical facial features of KS with asymptomatic elevated liver enzymes.

Keywords: Kabuki syndrome, *KDM6A* gene, liver enzymes, nonsense mutation.

INTRODUCTION

Kabuki make-up syndrome/Kabuki syndrome (KMS/KS, OMIM 147920), caused by pathogenic variants in *KMT2D* or *KDM6A* genes, is characterized by distinctive facial features, skeletal anomalies, growth delay, and mental retardation. In the literature, nearly 400 patients with Kabuki syndrome have been described. Most of these patients were from Japan. Kabuki syndrome has five cardinal clinical manifestations. These are defined as characteristic facial appearance, extremity and skeletal anomalies, dermatoglyphic abnormalities, mental retardation, and postnatal growth retardation. [1-3] It has been reported that most KS cases in the literature were diagnosed with a typical facial appearance. KS is often sporadic and most of the patients have a negative family history.[4] Previous reports have determined that pathogenic variants of the lysine-specific methyltransferase 2D (*KMT2D*-autosomal dominant) and lysine-specific demethylase 6A (*KDM6A*-X-linked) genes are the major causes of KS. The mutations in *KMT2D* and *KDM6A* have been found in 56–76% and 5–8% of patients clinically diagnosed with KS, respectively. In approximately 20% of patients, there is no mutation in either *KMT2D* or *KDM6A*.[4,5] Here, we describe a patient who has a new mutation in the KMT2D gene and presents with congenital bilateral hip dislocation, congenital heart defect, elevated liver enzymes, and neuromotor developmental retardation.

CASE REPORT

The patient was an 18-month-old male infant who was referred by the pediatric neurology outpatient clinic for genetic evaluation. He was born at term via normal vaginal delivery with a weight of 3.8 kg and a head circumference of 34 cm. There was no significant family history and his parents were non-consanguineous. His birth was complicated by hypoxia and meconium staining liquor, and he required mechanical ventilation and hypothermia treatment during the neonatal period. The echocardiography examination detected an atrial septal defect (ASD). He had an operation

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for bilateral hip dislocation and undescended testicles. He had swallowing difficulty, and he needed nasogastric tube feeding between 6 and10 months of age. Further analyses showed that he had alkaline gastroesophageal reflux and difficult swallowing liquid food. Laboratory investigations showed abnormal liver function: serum aspartate aminotransferase (AST) 79 IU/L (normal range, 10-40), serum alanine aminotransferase (ALT) 68 IU/L (normal range, 10-40), serum alkaline phosphatase (ALP) 52 IU/L (normal range, 44-147), serum total bilirubin 0.21 mg/dL (normal range, 3-20).

The following were the findings: serum alpha 1 antitrypsin 150 mg/dL (normal range, 100-300), serum ceruloplasmin 4.3 mg/dL (normal range, 7.44±9.45) and serum bile acids (fasting) 3.1 μmol/L (normal range, 3.85-9.43). The patient was followed up by pediatric gastroenterology due to elevated liver enzymes. His abdomino-pelvic ultrasound was normal. He had generalized hypotonia. The patient had not attained developmental milestones like peers. His psychomotor development was delayed, including speech. He could sit without support at 14 months of age, crawl at 18 months of age, and walk at 21 months of age. Psychomotor development was delayed with speech disturbance. He could speak only single words but not complete sentences. Upon physical examination; he had a weight of 13.3 kg (25th -50th percentile), a height of 93.4 cm (75th percentile), and head circumference of 47 cm (10th -25th percentile). A dysmorphology assessment revealed long palpebral fissures (separation between the upper and lower eyelids), eversion of the lower lateral eyelids, arched eyebrows with sparse hair on the outer lateral halves, epicanthus (a vertical skin fold covering the inner angle of the eye), a depressed nasal tip, a broad nasal root, large cupped ears, abnormal upper incisors, and a broad protruding philtrum (infranasal depression) (Figure 1). The G-banding karyotype analysis showed a normal 46, XY male karyotype. Molecular genetic testing of the *FMR1* (fragile X syndrome) gene was normal. Copy number and single-nucleotide polymorphism analyses suggested that the patient did not have a variation in copy number. Based on these characteristic clinical features, which were typical of KS (Table 1), we performed whole exome sequencing (WES) as we could not study the KMT2D and KDM6A mutations alone due to limitations in our genetic laboratory contract. The patient had a pathogenic variant in exon 40 of the *KMT2D* gene (c.13285C>T; p.Gln4429Ter). This is a novel nonsense mutation of the *KMT2D* gene, resulting in the premature termination of protein synthesis. This variant was predicted as a pathogenic mutation by Mutation Taster. The mutation was not found in the dbSNP, 1000G, HGMD, or ExAC databases. Segregation analysis revealed that clinically unaffected healthy mother and father carried a wild type allele. The mutation was not inherited; it was *de novo*.

DISCUSSION

KS was first described in 1981 by Niikawa and Kuroki in Japan but is now reported in many other ethnic groups as well. The KS affects both genders equally.[6,7] The etiology of KS is unclear but, an autosomal dominant pattern of inheritance with variable expression has been suggested. KS patients are usually diagnosed based on characteristic clinical features.[8] There is no specific laboratory or histologic tool that has been found to assist diagnosis.[9] A new consensus for clinical diagnostic criteria for KS have been published in 2019. A person of any age can be diagnosed with KS if they have a history of infantile hypotonia, developmental delay, and/or intellectual disability, as well as one or both

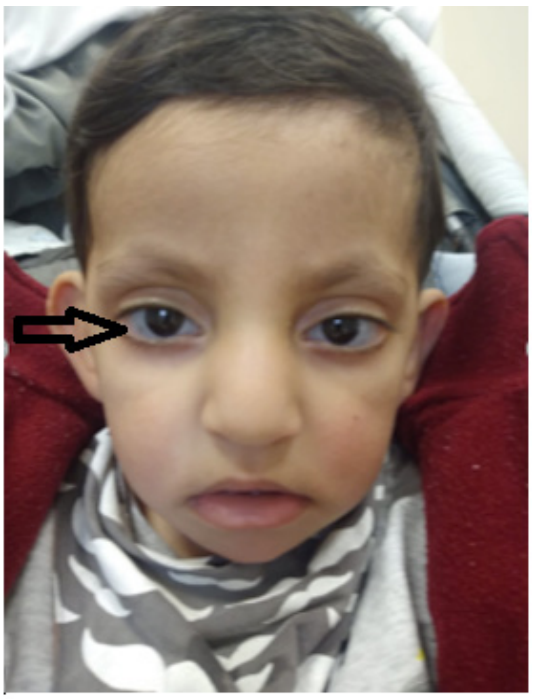

Figure 1. Typical patient abnormalities; sparse eyebrows, long palpebral fissures with eversion of the lateral part of the lower eyelid, epicanthic folds, blue sclera, large prominent ears, micrognathia.

Table 1: Major and Minor Features of KS patients.[10]

Major features	Patients with KS (cumulative percent)	Present Case
Characteristic face	100	+
Long palpebral fissures	99	+
Abnormal dermatoglyphics	96	+
Short nasal septum	92	+
Persistent fingertip pad	89	-
Malformed ear	87	+
Intelligence quotient <80	84	+
Developmental delay	84	+
Prominent ears	84	+
Joint laxity	74	+
High-arched palate	72	+
Hypotonia	68	+
Minor features		
Cardiovascular anomaly	42	+
Blue sclerae	31	+
Hearing loss	27	-
Cryptorchidism	24	+
Congenital hip dislocations	18	+ (bilateral)
Seizures	17	-
Asymptomatic elevated liver enzymes	Not known	+
Laryngomalacia	Not known	+

of the following major criteria: (1) a pathogenic or likely pathogenic variant in the KMT2D or KDM6A gene; (2) typical dysmorphic features (long palpebral fissures with eversion of the lateral third of the lower eyelid) and two or more of the following features (3) arched and broad eyebrows with the lateral third displaying notching or sparseness; short columella with depressed nasal tip; large, prominent or cupped ears and persistent fingertip pads.[10] No phenotypic differences were found between *KMT2D* and *KDM6A*-associated Kabuki syndrome in the literature.

Our patient had a typical KS. Craniofacial dysmorphism affects 90–100% of KS patients. The most common facial features of patients include long eyelids, hypertelorism, ptosis, strabismus, blue sclerae, bowed eyebrows with scarce hair, long and curved eyelashes, short columella with flattened nasal tip; large and prominent ears; micrognathia, retrognathia, cleft lip/palate, high-arched palate, and dental anomalies.[11]

Musculoskeletal abnormalities present in 88% of KS cases vary; they include brachydactyly, clinodactyly of the 5th finger, scoliosis, joint hyperextensibility, and hip dislocation. Mental retardation is expressed in a mild to moderate range. Psychomotor development is delayed due to very frequent sensory deficits, particularly hearing and hypotonia.[4,12] Heart defects are seen in 42% of KS patients. The most common types of heart defects are septal defects and coarctation of the aorta (25%). Central nervous system anomalies have been described in KS patients as microcephaly, arachnoid cysts, hydrocephalus with stenosis of the aqueduct, cerebellar atrophy, and polymicrogyria.[13] The presence of seizures is often reported and concerns 10 to 40% of patients. Endocrine disorders are common (deficiency in growth hormone, recurrent hypoglycemia, precocious puberty, hypo- or hyperthyroidism, diabetes insipidus). The incidence of hip dislocation in KS is thought to be rare (18%). There can be increased susceptibility to recurrent respiratory tract infections in patients with KS.[14] In our case, most of these manifestations were

noted and the diagnosis was established based on those clinical features.

In the present case, a novel nonsense mutation in exon 40 of the *KMT2D* (c.13285C>T; p.Gln4429Ter) was identified. This mutation is a loss-of-function mutation in which codon 2545 is replaced with a termination codon, resulting in truncation of the encoded *KMT2D* protein product. The identification of *KMT2D* gene mutation in 2010 has played a very important role in the diagnosis of KS patients in recent years. Ng *et al*. performed WES on 110 cases clinically diagnosed with KS. *KMT2D* gene mutations have been identified in approximately 74% (81/110) of individuals with KS.[15] In another study consisting of 100 patients with KS, 76 cases with *KMT2D* variants and four cases with *KDM6A* variants have been reported.[16] Numerous de novo *KMT2D* mutations have been identified in KS cases. Rarely, *KMT2D* mutations have been shown to be transmitted from parent-to-child due to autosomal dominant inheritance.[17] Both parents of our patient did not have *KMT2D* mutations, which indicates that the patient has a de novo genetic mutation. Till date, hepato-biliary manifestations of patients with KS have been reported. Ewart-Toland *et al*. reported the first case of Kabuki syndrome with hepatic anomalies.[18] Non-alcoholic fatty liver disease, idiopathic hepatic fibrosis, biliary atresia, and sclerosing cholangitis have been reported in KS patients.[19-22] Although, the cause of high liver enzymes secondary to the *KMT2D* gene is unknown, it has been suggested that this may be due to affecting notch signaling pathways. Previous findings demonstrate that *KMT2D* regulates vasculogenesis and angiogenesis, provide evidence for interactions between *KMT2D* and notch signaling.[23]

Ming *et al*. determined that KS is associated with an increased incidence of autoimmune disorders. Autoimmune disorders may be manifestations of abnormal immune regulation. In several patients with KS, autoimmune abnormalities such as idiopathic thrombocytopenic purpura, hemolytic anemia, thyroiditis, and vitiligo have been reported to be associated with KS.[24]

Our patient is being followed in pediatric gastroenterology due to elevated liver enzymes (ALT and AST). Hepato-biliary disorders should be considered in the evaluation of patients with KS. Patients with KS must also be monitored for gastrointestinal abnormalities..

In conclusion, in patients with known dysmorphic facial findings with growth retardation, mental retardation, congenital bilateral hip dislocation, congenital heart defect, swallowing difficulty, and asymptomatic elevated liver enzymes, KS should be considered, and other system examinations should be performed in detail.

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DISCLOSURE

Conflict of interest: None

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