



# A Case of Kabuki Make-up Syndrome Type-2 with Autism Spectrum Disorder

*Otizm Spektrum Bozukluğu ile Birlikte Bir Kabuki Make-up Sendromu Tip-2 Olgusu*

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### ABSTRACT

Kabuki make-up syndrome, caused by mutations in the *KDM6A* gene on chromosome Xp11.23, is a rare genetic disorder characterized by distinct facial features such as outward-turned down lateral eyelids, curved and sparse eyebrows, long palpebral fissures, a flattened wide nose, wide ears, mental disability, skeletal anomalies, postnatal growth retardation, and dermatoglyphic anomalies. In this case of KMS type 2, a fourteen-year-old patient was referred to outpatient clinic by a paediatric neurologist. The patient presented with difficulties in forming relationships, mobility issues, and problems with anger management. Given the presence of dysmorphic facial features, an autism spectrum disorder (ASD) diagnosis, and mental retardation, clinician opted for next-generation genome sequencing, which revealed a *de novo* mutation in the *KMDA6A* gene located in the Xp11.3 chromosome region. Although KMS type 2 is a rare genetic syndrome, it is crucial for child psychiatrists to increase their awareness of this condition due to its clinical manifestations, which include ASD and cognitive development delays. This awareness can aid in facilitating early diagnosis and determining the special requirements for managing accompanying comorbid psychiatric conditions and designing tailored educational treatments during follow-up care.

**Keywords:** Kabuki syndrome, autism spectrum disorder, *KDM6A*

### ÖZ

Kabuki make-up sendromu histon modifikasyonu yapan proteinleri kodlayan, dışa dönük aşağı lateral göz kapağı, kavisli seyrek dağınık kaşlar, uzun palpebral fissür, basık geniş burun, geniş öne doğru kulaklarla karakterize yüz; zihinsel yetersizlik, iskelet anomalileri, postnatal büyüme geriliği ve dermatoglik anomalilerle karakterize nadir bir sendromdur. Xp11.23 kromozomunda yer alan *KDM6A* genindeki varyantların mutasyonu taşıyanlar KMS tip 2 olarak adlandırılmıştır. On dört yaşındaki hasta, ilişki kurmakta güçlük, hareketlilik ve öfke kontrol sorunu şikayetleriyle çocuk nörolojisi tarafından polikliniğimize yönlendirilmiştir. Hastanın dismorfik yüz belirtileri ile otizm spektrum bozukluğu (OSB) ve mental retardasyon tanılarının olması nedeniyle yeni nesil genom dizileme uygulanmış, Xp11.3 kromozom bölgesinde bulunan *KMDA6A* geninde *de novo* mutasyon saptanmıştır. KMS tip 2 nadir genetik bir sendrom olmakla birlikte OSB ve bilişsel gelişimde gecikme ile klinik seyir göstermektedir. Bu olgu sunumu, çocuk psikiyatristlerinin KMS tip 2 farkındalığının artması, sendromu tanılamamanın kolaylaşması, hasta takiplerinde eşlik eden komorbid durumlar ve eğitsel tedaviler için gerekli özel gereksinimlerini belirlemeleri açısından önem arz etmektedir.

**Anahtar Kelimeler:** Kabuki sendromu, otizm spektrum bozukluğu, *KDM6A*

## Introduction

Kabuki make-up syndrome (KMS), first described by Matsumoto and Niikawa<sup>1</sup> is characterized by a face with everted downward lateral eyelids, curved sparsely scattered eyebrows, a long palpebral fissure, a flattened broad nose and wide forward ears, mental retardation, skeletal anomalies, and postnatal growth. It is a rare syndrome characterized by retardation and

dermatoglyphic anomalies. KMS received its name due to the unusual facial expressions it causes, which bear a resemblance to the distinctive make-up worn by actors in Kabuki, a traditional form of Japanese theatre. This condition was initially reported in the Japanese population, with a prevalence estimated to be approximately 1 in 32,000 individuals.<sup>2</sup> White et al.<sup>3</sup> calculated the birth prevalence of KMS in Australia and New Zealand as 1/86,000. KMS is a heterogeneous syndrome, and two causative

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genes have been identified so far. The first gene associated with KMS was discovered by Li et al.<sup>4</sup> in 2010. They reported *de novo* heterozygous variants in the *KMT2D* gene, located on chromosome 12q13.<sup>4</sup> Individuals carrying the *KMT2D* gene mutation are categorized as KMS type 1. In 2012, it was identified that variants in the *KDM6A* gene located on chromosome Xp11.23 constitute the second genetic cause of KMS, and those with this mutation are designated as KMS type 2.<sup>5</sup> *KMT2D* and *KDM6A* genes encode histone modification proteins. Little is known about the genes that are transcriptionally controlled by the *KMT2D* complex during development.<sup>6-8</sup> Due to the broad impact of these mutations on transcriptional genes, various organs and systems are affected.<sup>7,9</sup>

While KMS is characterized by postnatal growth retardation, distinctive facial features, dermatoglyphic anomalies, skeletal dysplasia, intellectual disability, central nervous system malformation, and immunological defects, it is important to note that individuals with KMS may also present with other associated conditions. These additional features may include congenital heart defects, genitourinary anomalies, anal atresia, ptosis, strabismus, and gastrointestinal anomalies. KMS is a complex syndrome with a wide range of possible clinical manifestations.<sup>10-14</sup> Oral anomalies are common in KMS, including abnormalities of the dentition such as micrognathia, hypodontia, diastema, high palate, cleft lip/palate, bifid tongue and uvula, and screwdriver-shaped incisors.<sup>15-17</sup> It has also been reported that KMS has an increased susceptibility to infections and autoimmune diseases, seizures, endocrinological abnormalities, premature larking in women, nutritional problems, and hearing loss.<sup>14</sup>

Studies conducted on individuals diagnosed with KMS have indicated that many of them exhibited hyperactivity and autistic features.<sup>10,12</sup> In addition, although KMS is characterized by intellectual disability, many patients have been found to have autism or autistic-like behaviours and have difficulties in both communication and peer interactions.<sup>10</sup> In this case report, we aim to contribute to the literature by presenting a case diagnosed with KMS type 2, who was also evaluated at an autism spectrum disorder (ASD) clinic in our outpatient facility. We will provide an overview of the current findings related to this case.

## Case Report

This study was conducted in full compliance with applicable ethical principles, including the 1964 Declaration of Helsinki of the World Medical Association and its later version, and written and verbal consent was obtained from the patient's parents for this publication.

A fourteen-year-old boy was referred to our outpatient clinic by the paediatric neurologist due to complaints of difficulty in forming relationships, mobility issues, and challenges with anger management. Upon examination, the patient exhibited dysmorphic features including a long face, protruding ears, crooked teeth, a high palate, flattened nasal root, everted downward lateral eyelids, and a shortened fifth finger. The

examination of the heart and lungs revealed normal sounds with no additional sounds or murmurs. The examination also noted that the abdomen was slightly distended, but there were no signs of organomegaly. Male external genitalia were observed. Both the lower and upper extremities displayed four-fifths strength. Deep tendon reflexes were found to be normal. A range of laboratory tests, including hemogram, biochemistry parameters, thyroid parameters, iron profile, zinc, copper, and lead levels, all returned within normal ranges. Additionally, the urine tests for very long-chain fatty acids, organic acids, and mucopolysaccharidoses all produced negative results. Additional investigations, including screenings for tandem MS, biotinide activity, and sphingolipidoses, all yielded negative results. Moreover, brain magnetic resonance imaging, electroencephalography, and electromyography did not reveal any abnormalities, remaining within normal limits. In the hearing test, a loss of 20 dB was identified in both ears.

Following the examination and assessments conducted by the child neurologist, a consultation was sought from the child psychiatry outpatient clinic. During the history-taking from the mother, it was revealed that the patient began walking at the age of three, his speech development occurred after receiving special education around the age of five, he had not yet learned to read and write, and he consistently lagged his peers in self-expression. It was noted that he faced difficulties in making friends, usually preferred spending time alone, and exhibited a strong preoccupation with car brands. In the patient's medical history, it was discovered that he was the second surviving child born during his mother's second pregnancy. He was delivered via a challenging caesarean section at the appropriate time and weighed 2800 grams at birth. After birth, he did not require incubator care or oxygen support and did not experience jaundice. He received breast milk for approximately six months but encountered difficulty with breastfeeding and could not continue afterwards.

Developmentally, he began sitting with support at 18 months of age and achieved independent sitting at 24 months. At the age of three, he experienced febrile convulsions, but no medication was administered for this. In terms of the patient's family history, it was revealed that there were no distinctive features in the ancestry, and there was no consanguinity between the parents.

In the psychiatric examination, which took place with a male adolescent wearing age-appropriate and culturally suitable clothing, several observations were made. The adolescent appeared to be conscious and cooperatively oriented; however, he did not make eye contact, did not respond to the conversation during the interaction, provided brief responses related to his obsession, attempted to carry on the conversation unilaterally, displayed minimal facial expressions, and exhibited stereotypical movements such as clapping his hands. These observations are indicative of certain behavioural and communication traits often associated with neurodevelopmental disorders. In the psychiatric evaluation, the patient exhibited shallow affect, a euthymic mood, and cognitive functions such as attention,

memory, and perception that were lagging those of his peers. His psychomotor activity was elevated. During the administration of the Wechsler Intelligence Scale for Children-Revised (WISC-R) intelligence test, it was noted that he did not make eye contact with the examiner, did not follow instructions, and displayed stereotypical hand movements. The results of the WISC-R intelligence test indicated a verbal score of 42, a performance score of 40, and a total score of 40, which are consistent with moderate mental retardation. Teacher evaluation form and Turgay ADHD Scale were evaluated. The Childhood Autism Rating Scale (CARS) score, as assessed by the examiner, was determined to be forty-one. As a result of the applied K-SADS-PL and Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition ASD diagnostic criteria; the case was diagnosed with autism spectrum disorder, motor and mental retardation and attention deficit hyperactivity disorder.

Given the combination of dysmorphic features, motor and mental retardation, and symptoms of ASD in the patient, a genetic examination was requested for further assessment. Additionally, the patient was referred to a dentist for evaluation of dental pathologies.

During the oral examination, a clinical assessment revealed the presence of plaque and calculus accumulations as well as a Class III occlusion. The examination also identified that the patient had a deep palate, and both skeletal and dental findings were noted to be similar to those of the patient's father. It was further observed that the patient's oral hygiene was inadequate. The patient's dentition appeared crowded, and a posterior crossbite was evident. In the oral radiological examination, panoramic films taken from the patient revealed the presence of multiple cavities and previous restorative treatments in the anterior region of the mouth. Furthermore, it was noted that the patient was missing both upper wisdom teeth bilaterally. Pulp stones were also observed within the pulp chambers of the molar teeth. These findings suggest a need for comprehensive dental care and treatment.

In the genetic examination, initial molecular studies were conducted, which included a karyotype analysis, array comparative genomic hybridization, cytosine-guanine-guanine (CGG) repeat analysis for Fragile X syndrome, and a whole exome sequencing test. All these initial tests returned unremarkable results. However, due to continued clinical suspicion, a next-generation genome sequencing was performed, revealing a de novo hemizygous mutation (c.3797C>T, p.Ser1266Leu) in the *KDM6A* gene (NM\_021140.3) located on the Xp11.3 chromosome region. This mutation confirmed the diagnosis of KMS type 2.

All remaining imaging studies, including skeletal examination and renal ultrasound, did not show any significant abnormalities. To address the attention deficit and hyperactivity disorder, the patient was initiated on the long-acting form of methylphenidate (36 mg/kg). As part of the management of autism spectrum disorder, aripiprazole 2.5mg/kg was added to the treatment plan to address the aggression displayed by the patient.

Special education support was continued, with the inclusion of a mental module tailored to the young person's specific educational needs, as well as a new module to address ASD symptoms. Regular follow-up appointments were scheduled, and these revealed improvements in the patient's eye contact, reciprocity, and the quality of conversation in sixth appointment. At the second follow-up, there was also a decrease in mobility and aggression. Prior to the study, informed consent was obtained from the patient's family.

## Discussion

ASD is a neurodevelopmental condition characterized by communication and interaction limitations, along with stereotypic movements. The aetiology of ASD is known to involve multiple genetic factors, many of which are associated with genes responsible for transcriptional regulation and chromatin restructuring. These genetic factors are believed to influence neurodevelopment, including the development of ASD, by impacting neurons through epigenetic mechanisms that involve modifications to DNA and histones, particularly in certain genetic syndromes.<sup>18</sup>

In the literature, there have been a limited number of reported cases of KMS type 2 co-occurring with ASD. This case serves to highlight the importance of recognizing syndromes that may accompany ASD and underscores the need for comprehensive evaluations of syndromes that present alongside ASD, given their multifaceted nature and potential genetic underpinnings. Understanding the complex interplay of genetic factors and their impact on neurodevelopment is crucial for both diagnosis and the development of targeted interventions and support for individuals with these co-occurring conditions.

KMS (Niikawa-Kuroki syndrome) was first described in the literature by Kuroki et al.<sup>13</sup> in 1981 in ten unrelated Japanese children with a characteristic series of multiple congenital anomalies and mental retardation. KMS is a rare syndrome characterized by facial, mental disability, skeletal anomalies, postnatal growth retardation, and dermatoglyphic anomalies.<sup>1</sup> Point mutations in *KDMT2A*, large intragenic deletions and duplications, and exon deletions in the *KDM6A* gene have been identified as the underlying causes.<sup>4,5</sup> *KMT2D* and *KDM6A* genes encode histone modification proteins, and it is known that mutations in these genes have a wide effect on transcriptional genes, affecting many organs and systems, especially the nervous system.<sup>7,9</sup> It has been reported that neurodevelopmental disorders such as ASD and attention deficit and hyperactivity disorder are observed in KMS by affecting histone modification transcriptional genes.<sup>19,20</sup>

In the differential diagnosis, CHARGE syndrome, which is characterized by heart defects, growth-developmental retardation, genitourinary system anomalies, ear anomalies and hearing loss, and coloboma, comes to mind. Although our case's growth and development retardation, hearing loss, and ear anomaly are similar to CHARGE syndrome, the absence of cardiac defect, absence of eye coloboma, absence of heart

defect, and absence of mutation in the *CHD7* gene enables the distinction of KMS from CHARGE syndrome.<sup>21-24</sup> 22q11 deletion syndrome is another syndrome that comes to mind in the differential diagnosis. 22q11 deletion syndrome; It shows symptoms such as heart defects, droopy ears, cleft palate-lip, genitourinary system anomalies, mental retardation, convulsion, droopy eyelids, polydactyly, gastrointestinal problems, growth and development retardation, immunodeficiency, and dental problems, and it must be differentiated from KMS.<sup>25</sup> In our case, although the presence of convulsions in the history, ear anomaly, mental retardation, growth and development retardation, and dental anomalies suggest 22q11 deletion syndrome, no heart defect was observed, no immunodeficiency was detected, no cleft palate or lip, and as a result of genetic evaluation, a *de novo* hemizygous mutation was found in the *KDM6A* gene. It excludes the diagnosis of 22q11 deletion syndrome. The case exhibited a long face, large ears, a high palate, mental retardation, and symptoms of autism spectrum disorder, which raised suspicion of Fragile X syndrome in the differential diagnosis. However, the desired genetic testing resulted in a normal outcome with 30 CGG repeats.<sup>26</sup>

In KMS cases in the literature, hypodontia, diastema, and high palate are commonly observed, and in this case, crowded teeth and a high palate were observed in the patient, where bilateral upper wisdom teeth were not visible at all. Apart from this, no deficiency was observed in other permanent teeth.<sup>15-17,27-29</sup> Long face, prominent ears, crooked teeth, high palate, flattened nasal root, outward-turning down lateral eyelid, short fifth finger, hypotonia, previous history of febrile convulsions, mental retardation, and autism spectrum disorder, and as a result of new generation genome sequencing, our case was diagnosed with KMS type 2 due to the *KDM6A* hemizygous mutation.

KMS is a multi-system disorder, and its treatment is not yet known. In KMS, which has no specific treatment, treatment is conducted symptomatically on a patient-specific basis. Depending on the affected system, see paediatrics for growth and development delay, dentist for dental anomalies, cleft lip and high palate, orthopaedics for skeletal system anomalies, paediatric cardiology for congenital heart defects, paediatric urology for genitourinary anomalies, paediatric gastroenterology for anal atresia and gastrointestinal anomalies. Ophthalmology consultations for ptosis and strabismus, otolaryngology consultations for hearing loss, and paediatric neurology consultations for epileptic seizures and appropriate treatment are required in a multifaceted manner. Applied behaviour analysis, early Denver method, and developmental, individual difference, and relationship-based/floortime may be recommended for intervention in the ASD social-communicative symptom cluster. Speech and language therapies for speech-language disorders and hearing loss, physiotherapy for retardation in fine and gross motor skills, sensory integration for sensory problems, occupational therapy, and special education for delay intervention in cognitive development, inclusive education, or special subclass education appropriate to the child's mental capacity. Support forms the

basis of individual symptomatic treatment of KMS. Although these recommended treatments are symptomatic individual treatments for symptoms, the effectiveness of these treatments is not yet fully known. It is necessary to investigate the long-term effectiveness of the applied treatments and specific treatment options for KMS.

## Conclusion

In conclusion, it is crucial to consider KMS, even though it is a rare condition, in children presenting with atypical facial features, dysmorphic characteristics ASD, and cognitive developmental delays. Following detection, it is advisable to consult specialists in paediatrics, child neurology, paediatric urology, and paediatric cardiology for genetic guidance and evaluation of potential medical comorbidities associated with the disease. Additionally, referrals to specialists in gastroenterology, orthopaedics, ophthalmology, and dentistry are necessary to address the multifaceted needs of these individuals. Child psychiatrists play an essential role in increasing awareness of KMS, aiding in the diagnosis of children with dysmorphic features, and identifying any accompanying psychiatric conditions. Furthermore, child psychiatrists are instrumental in providing specialized educational treatments during follow-up care for individuals with KMS. This comprehensive approach is essential in improving the quality of life and overall well-being of individuals with KMS.

## Ethics

**Informed Consent:** Informed consent was obtained from the patient's family.

## Footnotes

## Authorship Contributions

Surgical and Medical Practices: Y.S.N., Concept: Y.S.N., M.E.N., Design: Y.S.N., M.E.N., Data Collection or Processing: Y.S.N., M.E.N., Analysis or Interpretation: Y.S.N., M.E.N., Literature Search: Y.S.N., M.E.N., Writing: Y.S.N., M.E.N.

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