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Review Article

Kabuki Syndrome: Current Understanding of Symptoms and Treatment Strategies

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Abstract

Kabuki syndrome can be mentioned as one of the most severe and, at the same time, rare genetic abnormalities. The inheritance pattern of this disorder can be an autosomal dominant or X-linked pattern. In this disease, KMT2D AND KDM6A genes are disrupted, which encode histone methyltransferase and histone demethylase, respectively. The severity of the disease and associated signs and symptoms can vary widely but may include distinct facial features, developmental delay, intellectual disability, and limb deformities. Kabuki syndrome treatment may vary based on the specific symptoms that appear in each individual. This review will examine the genes involved in this disease, phenotype, clinical manifestations, ways of diagnosis, and treatment of this disease.

Keywords: Genetic disorder; kabuki; KDM6A; KMT2D; niikawa-kuroki

Introduction

Kabuki syndrome (KS: OMIM 147920) is a rare genetic disorder that has two inheritance patterns: X-linked (associated with the KDM6A gene) and autosomal dominant (associated with the KMT2D gene). Other names for this disease include Kabuki-makeup syndrome (KMS) and Niikawa-Kuroki syndrome. The reason for the name of this disease is the appearance of the face of affected people with the type of make-up of the actors of the traditional Kabuki show in Japan [1-6]. For the first time, this disease was defined and identified in 1981 by two groups of researchers, led by Dr. Norio Nikawa, a Japanese geneticist, and Yoshikazu Kuroki, a Japanese physician. Kabuki syndrome affects women and men in the same proportion and does not increase among certain ethnic groups. Also, its frequency can be considered as one in 32,000 live births. However, since this disease includes a wide range of mild to severe symptoms, some cases of the mild disease may never be detected, and as a result, the number of cases is higher than the estimated amount [7-10].

This heterogeneous disease causes very different symptoms in affected people and varies from person to person. The severity of the disease and associated signs and symptoms can vary widely; still, they may include distinctive facial features, Permanent pads between the fingers, hypermobility of the joints, sensorineural deafness, diaphragmatic hernia, arched eyebrows, and elongated eyelids [11-14]. This disease overlaps with some diseases, such as CHARGE syndrome, Turner syndrome, Van der Woude syndrome, 22q11 deletion syndrome, and other disorders. Therefore, the accurate diagnosis of this disease is both a challenging and vital task because the subsequent treatments and measures to improve the physical condition and the spirit of the patient and his family depend on the correct diagnosis. Since this disease can endanger the affected person's life in severe cases, it is imperative to start treatment early. Also, genetic counseling for family members is one of the most fundamental approaches to prevent more cases. Considering the importance of genetic disorders and their spread in some societies, we reviewed Kabuki syndrome, its disease mechanism, diagnosis, and other related issues.

Role of KMT2D

Set1-like H3K4 HMTs consists of six subsets including KMT2A, KMT2B, KMT2C, KMT2F, KMT2G, and KMT2D. KMT2D (Histone-lysine N-methyltransferase 2D) is a critical histone H3 lysine 4 mono-methyltransferase in mammals [15,16]. The other name of this gene is MLL2, which plays an essential role in the embryo's development and suppressing tumors. A loss of function mutation in the KMT2D gene can cause Kabuki syndrome. Other diseases that can occur due to disruption in this gene include congenital heart disease and some types of cancer, such as pheochromocytoma, non-Hodgkin lymphomas, pancreatic cancer, and prostate cancer [17-26]. An enzyme called methyltransferase, produced by the KMT2D gene changes histones by adding a methyl group. KMT2D, which has been altered, is inoperable. As a result, histone lysine-specific methylation is disturbed [27-33]. This gene is located in the long arm of chromosome 12. KMT2D gene produces a protein with the same name, which has different domains. In the C-Terminal, there is a SET domain that regulates methyltransferase activity, then FYRC and FYRN domains, and then PHD and HMG-I domains. On the N-Terminal side, there are six PHD domains [34-48]. The structure of the KMTD2 protein is shown in Figure 1.

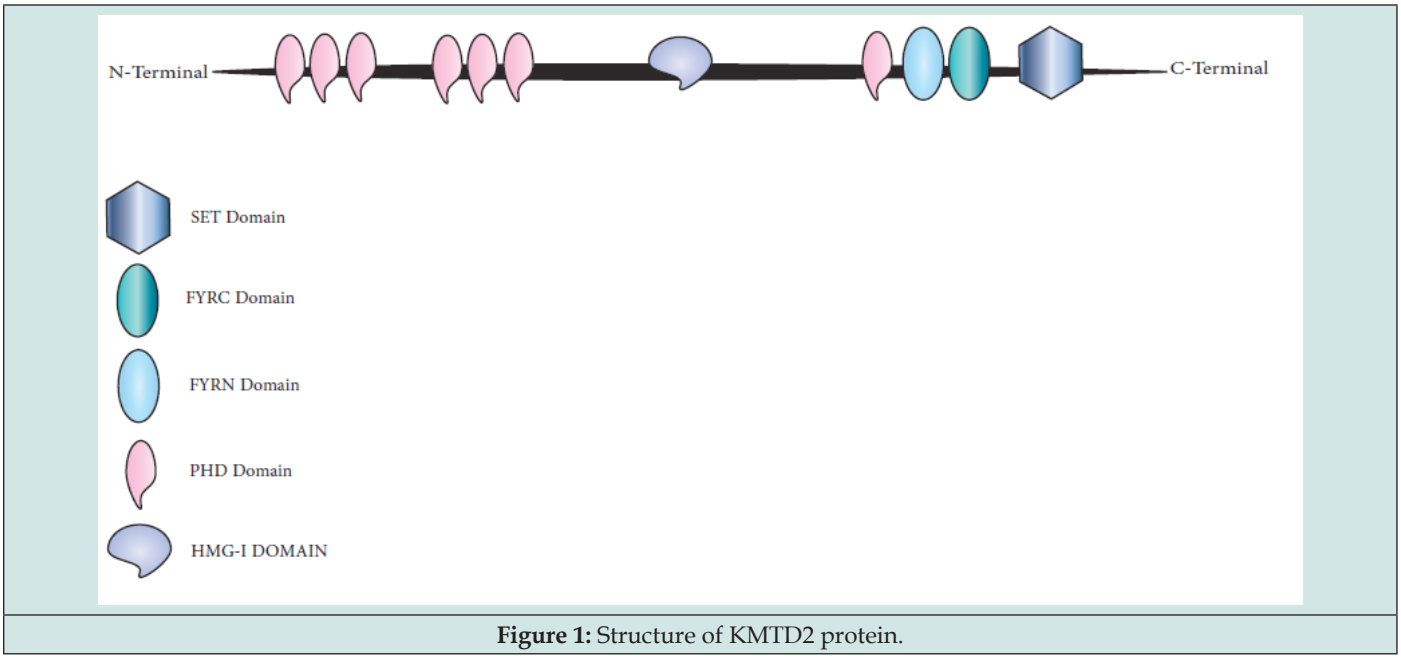

Figure 1: Structure of KMTD2 protein.

Role of KDM6A

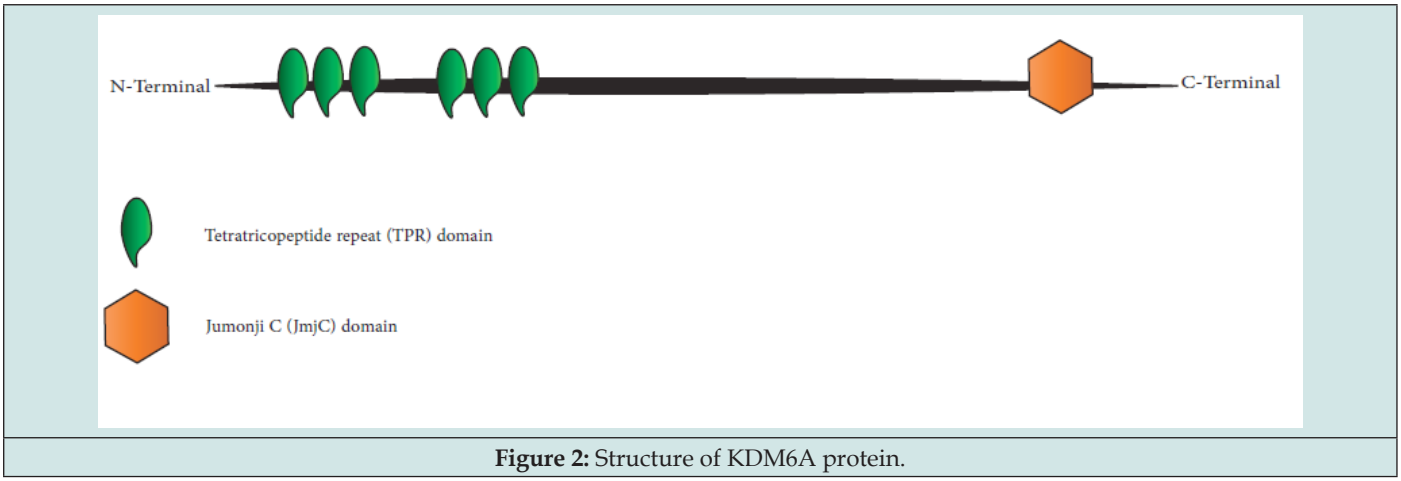

Figure 2: Structure of KDM6A protein.

KDM6A (Lysine-specific demethylase 6A) belongs to the 2-oxoglutarate (2OG)-dependent dioxygenase family, which is a protein-coding gene whose protein product plays a role in normal development and tumor suppression. Another name for this gene is UTX, located in Xp11.3 and causes random inactivation of one of the X chromosomes [49,50]. Its mutation can cause various diseases such as Kabuki syndrome and cancers such as multiple myeloma, breast, and colon. A methyl group from lysine is removed by the

KDM6A gene product, an enzyme that demethylates histones. KDM6A with a mutation cannot function, and developmental abnormalities result from the disruption of histone lysine-specific demethylation. The protein product of the KDM6A gene has six domains on the N-Terminal side called tetratricopeptide repeat (TPR) and one on the C-Terminal side called Jumonji C (JmjC) that play a role in regulating demethylation [51-54]. The structure of the KDM6A protein is shown in Figure 2.

Clinical Features

The symptoms of Kabuki syndrome overlap with various diseases such as CHARGE syndrome, Turner syndrome, Van der Woude syndrome, 22q11 deletion syndrome, and other disorders [55-65]. However, the clinical symptoms of this disease can be generally categorized as follows:

Facial Features

About one-third of patients have also been reported to have mid-face hypoplasia, hypodontia, cleft palate, and a trapezoidal philtrum. Over 40% of people with KS have dental anomalies. Other signs and symptoms that can be seen in almost all affected individuals include persistently drooping eyelids, arched eyebrows, a sunken tip to the nose, a long eyelid furrow, long eyelashes, a small chin, and a wide nose [66-71]. Figure 3 shows a picture of a person with Kabuki syndrome.

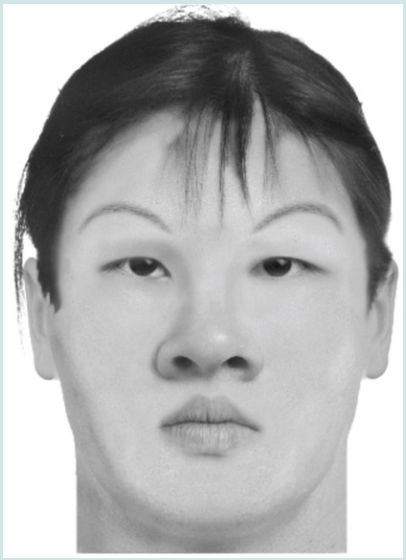

Figure 3: Image related to Kabuki syndrome facial features. Note the wide nose with a flat tip, downward cleft eyelids, and arched eyebrows. (Note: out of respect for patients' rights, this image is not related to a natural person and is designed by the software).

Features of hearing

15 to 25 percent of patients have hearing and ear issues. Some of the most typical otolaryngologic findings in KS include dysmorphic pinnae, large, cup-shaped ears, otitis media, and hearing loss. It seems that otitis media is expected [72,73].

Characteristics of the Reproductive and Urinary System

Over 30% of KS patients have some form of renal abnormalities, such as hydronephrosis, renal hypoplasia or dysplasia, or kidney fusion defects, such as the horseshoe kidney, like CHARGE syndrome. Patients with kidneys that were noticeably dysplastic required transplantation. About 31% of cases have been reported to have hypospadias, small penis, and cryptorchidism [74-78].

Developmental Delay

Patients with KS appear to experience specific delays in language and speech maturation, and these delays or absences may be present in KS patients. During the first year of life, most patients experience failure to thrive and postnatal growth retardation. Although they eat a healthy diet, these individuals may not grow to their full height and have excessive obesity [79-85].

Eye Features

About 35 to 60 percent of patients with KS have ophthalmologic abnormalities. Strabismus and blue sclerae are among the most typical findings. Refractive errors, cataracts, delayed visual maturation, optic nerve hypoplasia, ptosis, nystagmus, palsy of the third cranial nerve, and Marcus Gunn's phenomenon are less frequent findings [86-88].

Heart Problems

The prevalence of congenital heart defects in this population has been estimated to be between 40 and 50 percent, and many different congenital heart defects have been described in patients with KS. Juxta ductal coarctation of the aorta, a relatively uncommon heart defect, appears to be the most frequent finding, followed by VSD and ASD. Males seem to experience coarctation of the aorta in KS much more frequently than females [89-91].

Digestive Problems

While malrotation of the intestines has been documented in a few patients with KS, gastrointestinal abnormalities are uncommon, occurring in only about 7% of cases. Instead, most patients with KS have abnormalities of the anus or rectum, such as anal atresia, anovestibular fistulas, or anteriorly placed anuses. Additionally, biliary atresia and neonatal sclerosing cholangitis that required a liver transplant have been documented [92-95].

Abnormalities related to the Brain

Autism or behaviors resembling autism have been identified in several patients. 90% of affected patients exhibit mild to severe mental retardation, and in most cases, their IQ level is below 85. Only 10% of affected patients have average intelligence. Seizures occur in 15 to 40% of KS patients. A large arachnoid cyst, polymicrogyria, non-specific cerebral atrophy or enlarged ventricles, and significant brain structural abnormalities have all been seen in MRI studies of KS patients [96-100].

Skeletal Abnormalities

In KS, skeletal abnormalities are frequent. Other abnormalities include the sagittal cleft, short fifth digits with short fifth metacarpals, cone-shaped proximal second through fifth phalange epiphyses, coronal synostosis, dislocation of the hip joints, and various vertebral anomalies [101-107].

Ways to diagnose Kabuki

For prenatal diagnosis of patients with KS, the ultrasound method can detect some abnormalities, such as the lack of proper development of fingers or toes, twisting of the intestine, facial abnormalities, and other features. Individuals with specific morphological features associated with KS may be candidates for genetic testing for KMT2D and KDM6A genes at birth [108]. In addition, sometimes, the symptoms of the disease are minimal, and NGS can be done to be sure. Currently, there are no consensus diagnostic criteria for KS; however, five principal components can be used for the early diagnosis of KS, including skeletal abnormalities, specific facial features, mental retardation, developmental delay, and interdigital pads.

Therapeutic Approaches

Kabuki disease can present various phenotypes and complications depending on the mutated gene and the general conditions. The proposed treatment depends on the phenotype and the affected organ because not all individuals with this disease exhibit the same symptoms. In addition, there is no universally effective cure for this illness [109,110]. All available treatments have aimed to improve patients' quality of life because there is currently no proven standard treatment for this illness. Genetic counseling is one of the most crucial recommendations to Kabuki patients and their family because it can aid in more effective and better disease management. Since this patient exhibits symptoms almost from birth, medical monitoring is required to prevent severe complications of the disease because, occasionally, some of the complexities of this condition can endanger a person's life. For kids with Kabuki, pediatricians are frequently the first point of contact for medical attention. The psychology of illness should be one of the key topics covered during treatment. People close to the affected person or in charge of their care may experience emotional stress. For these people to live peaceful daily lives with their ill loved ones, psychological counseling is helpful. Cognitive difficulties can be one of the signs of Kabuki. Although not all affected patients have this disease, it is better to educate those who do so that they can safeguard their health from the disease's emergency.

Conclusion

KMT2D and KDM6A genes contribute to the complex genetic condition known as Kabuki. It appears that more tests should be considered to find additional causes of this disease and that genome sequencing can be helpful. However, some genes effective in causing the disease to remain unknown. Furthermore, there is no known cure for this illness, and all current therapies mainly serve as supportive care. CRISPR/Cas9 and gene therapy research may someday result in the ability to treat this genetic condition.

Conflict of Interest

The author declares that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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