KBG SYNDROME AND 16Q24.3 DELETION

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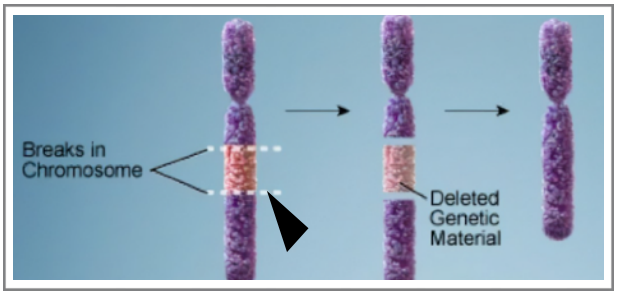

KBG syndrome is a neurodevelopmental disorder with a characteristic facial dysmorphism and frequent involvement of other organs and systems. Clinically, this syndrome has been known since 1975. For many years it was considered as autosomal dominant condition. In 2011, it was found that mutation of the ANKRD11 gene is a causative factor for this syndrome. This gene is located at the long arm of chromosome 16 (16q24.3), and retrospective analysis showed that many of the previously reported patients with deletions of the distal segment of 16q have essentially the same phenotype as patients who have KBG syndrome with ANKRD11 mutations.

Currently, KBG syndrome is considered a condition which may be caused either by mutations of the ANKRD11 gene or deletions of this gene[1]. No less than 60 patients with KBG syndrome caused by deletions in the 16q24.3 region have been reported in literature. At least 20% of patients with KBG syndrome are caused by deletions 16q24.3, and in some publications the ratio between deletions and mutations is even higher[1]. Although the syndrome can be passed on from parent to child, most cases result from de novo mutations.

The gene involved in KBG syndrome, ANKRD11, is known to be a transcriptional coregulator that is crucial for neural development[2]. As a result, individuals often have key clinical manifestations that include neurological developmental delays, characteristic facial dysmorphisms, skeletal anomalies, abnormal behavior, and hearing impairments.

Neurological developmental delays are seen in all patients with KBG. Developmental delays are very prevalent in patients (91%) and manifest in both

delayed speech and walking[1]. Delays themselves may range, however, from mild to moderate. All patients have abnormal behavior disorders along with these developmental delays. Disorders such as obsessive-compulsive disorder (OCD), autism spectrum disorders, attention deficit hyperactivity disorder (ADHD), anxiety, and temper tantrums are all common among patients[1].

Individuals with KBG syndrome have very characteristic facial dysmorphisms. The most uncommon finding is microdontia of the permanent upper incisors – these teeth are unusually large. This feature may be the evocative of this syndrome because other manifestations are relatively common for numerous other genetic disorders. Other dysmorphic features include brachycephaly, synophrys, and hypertelorism. These individuals also may have a specific facial structure in terms of their nose and mouth. The nose tends to be prominent with a high and wide nasal bridge with a bulbous tip and anteverted nares. The area between the nose and the mouth is long, flat, and protuberant. The lips themselves tend to be thin and have a marked cupid's bow[1].

There are several skeletal anomalies that are associated with KBG syndrome. Hand anomalies (70%) such as brachydactyly and fifth finger clinodactyly are common as well as a cleft palate, and a short stature[1]. Many patients also have congenital heart anomalies (30%) including atrioventricular septal defect, ventricular septal defect, atrial septal defect, coarctation of the aorta[3].

Hearing impairment is another common feature of individuals with KBG syndrome. Patients may have a wide range of impairments including bilateral moderate hearing deficit (40%), bilateral mild hearing loss (30%), otitis media (40%), and bilateral glue ear (20%)[3].

Receiving an official diagnosis can be challenging due to a diagnosis being largely based on clinical features[4]. One key feature of the syndrome is the macrodontia of the permanent upper central incisors. However, these teeth are not present yet in small children, so it becomes difficult to not only identify the syndrome, but also diagnose it[3]. Since receiving a diagnosis can be incredibly challenging, it is estimated that the prevalence of the syndrome is more common than actual case numbers show.

In order for a diagnosis to be reached, the individual must have four of the following eight clinical manifestations: characteristic facial anomalies, hand anomalies, macrodontia of upper central permanent incisors, neurological development delays, delayed bone age, costovertebral anomalies, postnatal short stature, and a first degree relative with the same syndrome[5].

These manifestations, however, may not stop an individual from leading a normal life. Most can attend school up through secondary school – some in mainstream schools with support and others receiving special education. Patients also have the capability to develop and maintain close personal relationships as well as have children[1].

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