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The Role of Development in Kabuki Syndrome: A Review

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Abstract
Kabuki Syndrome (KS) is a rare genetic disorder characterized by multiple developmental abnormalities, and varying degrees of cognitive impairment. Hallmark features of this disorder typically include distinctive facial features, skeletal and dermatoglyphic abnormalities, intellectual disability, and postnatal short stature. These features form the basis for diagnosis, though individuals suffering from KS will present a host of other ailments spanning from cardiovascular and digestive abnormalities, to immunological deficiencies. The majority of cases arise due to de novo mutations, but KS can be inherited through autosomal dominance. Genes identified as suspect in the disease's manifestation include KMT2D and KMD6A, which are both involved in histone modification. Mutations in these genes account for 75% of those clinically diagnosed with KS. Treatment is centered around the mitigation of symptomology unique to each patient, and early diagnosis is crucial to improving prognosis. Recent findings have shown that neurological and immunological pathology has potential for improvement in animal models, as well as the role of hypoinsulinism in the manifestation of hypotonia and growth retardation. This presentation seeks to review recent data on KS, and to provide information on the role of development in this disease.

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I. Abstract

Kabuki Syndrome (KS) is a rare genetic disorder characterized by multiple developmental abnormalities, and varying degrees of cognitive impairment. Hallmark features of this disorder typically include distinctive facial features, skeletal and dermatoglyphic abnormalities, intellectual disability, and postnatal short stature. These features form the basis for diagnosis, though individuals suffering from KS will present a host of other ailments spanning from cardiovascular and digestive abnormalities, to immunological deficiencies. The majority of cases arise due to de novo mutations, but KS can be inherited through autosomal dominance. Genes identified as suspect in the disease’s manifestation include KMT2D and KMD6A, which are both involved in histone modification. Mutations in these genes account for 75% of those clinically diagnosed with KS. Treatment is centered around the mitigation of symptomology unique to each patient, and early diagnosis is crucial to improving prognosis. Recent findings have shown that neurological and immunological pathology has potential for informing animal models, as well as the role of hyposinulism in the manifestation of hypotonia and growth retardation. This presentation seeks to review recent data on KS, and to provide information on the role of development in this disease.

II. Diagnosis

Diagnosis of KS can be confirmed via genetic testing for mutations in KMT2D or KMD6A gene mutations, though 30% of patients with KMS do not have a mutation in either of these genes. Blood tests have been made available to those who may suspect this mutation runs in their family, including fetal blood tests.

Patients with an unknown mutation are diagnosed based on symptomology, patient history, and thorough clinical evaluation. Symptom based diagnosis of KS involves an individual exhibiting at least 4 of these 5 common symptoms: distinctive facial features (fig. 4), skeletal abnormalities (fig. 1), intellectual disability, dermatoglyphic abnormalities such as persistent fetal finger pads, and postnatal short stature (fig. 2).

Figure 1. Elongated halluces of the feet in two patients with KS. A common example of skeletal abnormalities [11].

Figure 2. Persistent fetal finger pads as found in a patient with KS [15].

Table 1. Signaling pathways dysregulated in KMT2D mutations: Implications ASCOM’s role in development [6].

<table>
<thead>
<tr>
<th>Signaling Pathway</th>
<th>Bmp2/3</th>
<th>Kdm4c</th>
<th>Ptc1</th>
<th>Pdgf</th>
<th>Salc</th>
<th>Gbph</th>
<th>Mef2a</th>
<th>Pten</th>
<th>Gsk3b</th>
<th>Pten</th>
</tr>
</thead>
<tbody>
<tr>
<td>KMT2D</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
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Symptoms such as hypotonia can often be the result of hypoglycemia, which may be undiagnosed in patients presenting with a mutation in KMD6A [5].

III. Mutations

KMT2D and KMD6A both code for methyltransferases involved in histone modification and chromatin modeling (fig. 3), and are part of the large protein complex ASCOM [9,10]. This complex seems to play an important role in expressing cell signaling intermediaries important to development (tab. 1). Unfortunately, the mechanisms behind these interactions are poorly understood, though the ASCOM complex appears to be essential in the differential expression of many genes.

Figure 3. Chromosomal locations of KMT2D (above) and KMD6A (below). KMT2D codes for Histone methyltransferase H3K4me2/me3 and KMD6A codes for Lysine Demethylase 6A [9].

IV. Effects on Development in Select Organ Systems

Mouse model studies have found that the S100A gene cluster is profoundly suppressed in KS mutations, explaining this complex’s important role in cardiovascular development. Other pathways implicated in pathology include: wnt/beta-catenin, cardiac stem cell differentiation, cAMP signaling, b-cell development, and cardiac beta-adrenergic signaling [6].

Zebrafish studies simulating KS mutations show that both proteins play a role in development, especially within craniofacial, brain, and cardiac morphogenesis [14]. Haplosufficiency in either of these genes results in hypoplasia of pharyngeal arches, explaining KS craniofacial abnormalities (fig 6).

Cardiac development was impaired specifically within cardiac looping involution, resulting in septal defects, and abnormal development of the ventricles and atria. Embryological development of the midbrain also appeared to be altered. Examination of midbrain cells indicated neuronal precursor cells had an impaired ability to differentiate [14].

Neurological Impairment

Patients often present mild intellectual impairment, as well as experience partial seizures. Neurological structures do not seem grossly affected, though hipotonia and atrophy of the ventricles have been found [2]. It is hypothesized that seizures are the result of cerebellum hyperexcitability rather than neurological malformations. Mouse models of heterozygous KMT2D mutation exhibited a decreased dente gyrus mass and lowered hippocampal functioning, supporting prior findings of neurological impairment in KS. Interestingly, researchers of this study found that inhibition of histone deacetylation could mitigate neurological impairment during development in these models [3].

Immunological Deficiency

KS seems to generate symptoms in patients that are similar to common variable immunodeficiency as a result of either autoimmunity, or decreased serum antibodies. Patients often suffer from chronic upper respiratory infections, and otitis media, which may contribute to hearing loss [13]. A study of 14 female patients with KMT2D mutations showed that lymphocyte proliferation did not seem to be markedly affected, though differentiation of memory cells was impaired. Cytokine production was also reduced (IL-2, IL-12, IFN gamma), as well as serum Ab-IgG, IgG2, and IgA. CD4 molecules also appeared to be reduced [12]. Patients treated with supplemental antibodies seemed to have reduced occurrence of bacterial infection [12].

Cardiac Abnormalities

Congenital heart defects are found in roughly 40-50% of patients with KS, and are not limited to either of the two mutations. Frequently found malformations are atrial septal defects, ventricular septal defects and aortic coarctation [4]. Surgical intervention is sometimes required to mitigate these defects. KMT2D haplosuffcient mouse models show a general narrowing of the ascending aorta. Those with a complete KMT2D knockout exhibit decreased cardiomycyte proliferation and inviability, implicating this gene’s role in cardiac formation during development [1].

Figure 4. Typical facial gestalt seen in KS. Craniofacial abnormalities include pronounced ears, depressed nasal tip, arched eyebrows, and elongated palpebral fissures [7].

Figure 5. Comparison of embryological pharyngeal clefts in WT and knockout zebrafish [14].

V. References

[15] Zebrafish study simulating KMT2D mutations show that both proteins play a role in development, especially within craniofacial, brain, and cardiac morphogenesis. Developmental Biology. 405(2):211-219.