**Abstract**

We report 2 cases of Kabuki syndrome (KS) with MLL2 gene mutation. The first patient showed c.10440+2, T>G alteration of the MLL2 gene, which is a novel mutation that is not documented in the literature. The second patient exhibited 2 heterozygous mutations: c.13606C>T mutation (in exon 40) and c.13839+89dupTGACGT (IVS41+89dupGACGT). The c.13606C>T mutation caused an amino acid change of p.Arg4536X, which has been associated with KS. However, c.13839+89dupTGACGT (IVS41+89dupGACGT) is an unknown variant or novel mutation. Both patients had typical facial features with long palpebral fissures, sparse and arched eyebrows, and large protruding ears. They also exhibited cardiac and renal problems and limb abnormality of clinodactyly with high finger pads. They both showed mental and developmental delays, which may have been due to hypotonia and the central origin. On the basis of the aforementioned symptoms, we summarised the cardinal symptoms of KS and determined the diagnostic indications for these patients.

**Key words**

Clinodactyly; Finger pads; Kabuki syndrome (KS); Long palpebral fissures

**Introduction**

Kabuki syndrome (KS) is a congenital mental retardation syndrome with abnormal features including postnatal dwarfism, a peculiar face characterised by long palpebral fissures with eversion of the lateral third of the lower eyelids (reminiscent of the make-up of actors of Kabuki, a traditional form of Japanese theater), a broad and depressed nasal tip, large prominent earlobes, a cleft or high arched palate, scoliosis, a short fifth finger, the persistence of finger pads, radiographic abnormalities of the vertebrae, hands, and hip joints, and recurrent otitis media in infancy.\(^1\) KS-1 (KABUK1) is caused by a heterozygous mutation in the MLL2 gene (OMIM 602113) on chromosome 12q12-q14. However, KS-2 (KABUK2) (OMIM 300867) is caused by a mutation in the KDM6A gene (OMIM 300128) on chromosome Xp11.3. The majority of reported cases have been sporadic, but parent-to-child transmission in more than half a dozen instances suggests that KS is an autosomal dominant disorder.\(^2\) In Taiwan, in 1994, Wang et al reported the first KS patient.\(^3\) Since 1994, approximately 8 KS patients have been reported.\(^4-6\) However, none of them demonstrated causative genetic abnormalities. We report 2 KS patients in Taiwan with genetic survey, one of whom showed a novel c.10440+2, T>G mutation of the MLL2 gene, which has not been reported previously. The other patient showed 2 heterozygous mutations: c.13606C>T mutation (in exon 40) and c.13839+89dupTGACGT (IVS41+89dupGACGT). The c.13606C>T mutation causes an amino acid change of p.Arg4536X, which causes nonsense mutation.\(^2\) The parents of these 2 patients were normal and healthy; hence, we believe that the mutations were de novo.
Case Report

Case 1

A 4-year-old female patient was born at a gestational age (GA) of 38+ weeks with a birth body weight (BBW) of 3240 g and normal spontaneous delivery with an imperforate anus that underwent reconstruction. She experienced frequent upper airway infection and was hospitalised for bronchopneumonia and otitis media 3 times after birth. Growth retardation was noted in the first year with a body weight (BW) of 6 kg (third percentile) and body length (BL) of 65 cm (50th-75th percentile) at 5 months old and 7.5 kg (third percentile) at 1 year old. She was lost to follow-up for 2 years and returned to my clinic this year. A BL of 92.5 cm (<third percentile), BW of 13.5 kg (3rd-10th percentile), and head circumference of 47 cm were measured, and she is currently 4 years old. A developmental delay was noted. She could not sit until 1 year and 4 months old and could not walk until 1 year and 7 months old because of hypotonia. She could run and climb stairs with support at 3 years old. Currently, she can say only "papa" and "mama" and cannot form sentences. Physical examinations showed long palpebral fissures, high finger pads, and clinodactyly of the fifth fingers. A cleft palate and imperforate anus have been corrected by surgery. We arranged a cardiac sonography for her and revealed a dilated right ventricle, an atrial septal defect with a left-to-right shunt, 1.32 cm, and that the first branch of the innominate artery to the right subclavian artery was not visible. We also arranged a renal sonography for her and a left duplex of the collecting system was observed. On the basis of the aforementioned symptoms, we highly suspected that the patient had KS; hence, genetic testing was performed. From a sequence analysis of exon 1-54, this patient was found to exhibit heterozygous c.10440+2, T>G mutation of the MLL2 gene (Figure 1), and MLPA (Multiplex Ligation-dependent Probe Amplification) analysis detected no partial or whole gene deletions or duplications of the MLL2 gene. This is a novel mutation not documented in the literature. However, the mother was pregnant at GA of 10 weeks when the patient was diagnosed and for prenatal diagnosis, both the parents and the fetus received genetic testing (chorionic villus sampling for the fetus) and none of them have this mutation (Figure 1).

Figure 1 The Case 1 patient shows c.10440+2, T>G alteration of the MLL2 gene, which is a novel mutation.
Case 2

A 2-year-old male patient was born prematurely at a GA of 36 weeks with a BBW of 2430 g. Growth retardation was noted with a BW of 8 kg (<third percentile) at 1 year and 4 months old. Physical examinations showed long palpebral fissures, a high arched palate, eyebrows with sparse lateral third, large protruding ears, high finger pads, and long fourth toes with clinodactyly (Figure 2). A developmental delay was noted since birth. He could not sit and crawl until 1 year of age. He received rehabilitation since birth and is currently 2 years and 6 months old; he can now walk alone, pinch, throw objects over his head, use spoons, and build a tower of cubes. In addition, he exhibited auditory comprehension and the capability to communicate with peers. He was diagnosed with congenital heart disease with ASD (Atrial Septal Defect), VSD (Ventricular Septal Defect), PDA (Patent Ductus arteriosus), and severe coarctation of the aorta. Renal sonography showed a right horseshoe kidney and left small kidney. Brain echo showed ventricular dilatation. He had experienced seizures since birth with abnormal EEG (Electroencephalography) findings, but the seizures eventually ceased. We conducted a spine X-ray for him but found no abnormality. KS was suspected, and the MLL2 gene exhibited 2 heterozygous mutations: c.13606C>T mutation (in exon 40) and c.13839+89dupTGACGT(IVS41+89dupGACGT) (Figure 3).

Discussion

We report 2 patients with clinical manifestations of KS, which is diagnosed by the presence of mutations of the MLL2 gene. KS is a rare, multiple malformation disorder characterised by a distinctive facial appearance, cardiac anomalies, skeletal abnormalities, immunological defects, and mild to moderate mental retardation.2 A genotype-phenotype correlation was performed (Fisher's exact test) by comparing patients with pathogenic MLL2 mutations to those without. Patients with likely pathogenic nonsense or missense MLL2 mutations were typically more severely affected (mean "MLL2–Kabuki score" of 6.1) compared with the patients without MLL2 mutations (mean "MLL2-Kabuki score" of 4.5).7 The 2 cases in this study showed facial features with long palpebral fissures, everted lower eyelids, large dysplastic ears, arched eyebrows with sparse lateral one third, a flat nasal tip, and a high arched palate. Extremity features including persistent fetal pads and clinodactyly were also observed. After adding renal and heart problems, an MLL2-Kabuki score of 6 was calculated for the 2 cases. Based on the aforementioned symptoms, the 2 cases were severely affected. The birth weight and length of both patients were normal and their growth delay started early during the first year of life; this was consistent with the finding of Niikawa et al (1988).1

Figure 2  (a) The Case 2 patient exhibits typically large protruding ears and arched eyebrows. (b) Clinodactyly is also apparent.
In Case 1, recurrent airway infection and otitis media were noted; in some previous reports, immunological dysfunction including hypogammaglobulinemia and thrombocytopenic purpura have been described. Because of the increased incidence of immune abnormalities in children with KS, serum immunoglobulin levels should be determined at the time of diagnosis for children older than 1 year. The c.10440+2, T>G alteration of the \textit{MLL2} gene is a novel mutation and is pathogenic (2 strong pathogenicity: PS2+PS4) according to ACMG standards and guidelines. Segregation analysis was completed by paternity and maternity confirmation and prenatal diagnosis. These results confirmed its de novo. We found that the Case 1 patient exhibited many typical and considerably more severe clinical abnormalities compared with the Case 2 patient, including cardinal facial features, an imperforate anus, a duplex of the renal collecting system, a cardiac septal defect and artery anomalies, growth retardation with poor weight gain, a developmental delay, and frequent infection. Based on the aforementioned findings, the new mutation may cause severe clinical manifestations. Although Case 2 showed 2 heterozygous mutations of the c.13606C>T mutation (in exon 40) and c.13839+89dupTGACGT (IVS41+89dupGACGT) had typical facial features, developmental delay, and renal abnormalities, no gastrointestinal problems or frequent airway infection was observed. In addition, through rehabilitation, he showed substantial improvement in his development and hence we may predict a more favorable prognosis for him. The c.13839+89 dupTGACGT (IVS41+89dupGACGT) mutation is likely benign (1 strong and 1 supporting: BS4+BP5) according to ACMG standards and guidelines. So we may speculate that the c.13606C>T mutation or c.13839+89 dupTGACG (IVS41+89dupGACGT) indicates a mild phenotype no matter they exist alone or together. Case 2 received more regular follow-up and rehabilitation. This may explain his better prognosis when compared with Case 1. Although Fisher's exact test is one of the way to evaluate the severity of their phenotype but the items of the test are mainly according to the appearance (major or minor anomalies). So when we evaluate the prognosis of the patients, we also have to take growth, development, infection frequency, nutrition status and environmental factors into consideration.

\textbf{Figure 3} The Case 2 patient shows 2 heterozygous mutations: c.13606C>T mutation (in exon 40) and c.13839+89dupTGACGT (IVS41+89dupGACGT).
Disclosure

The authors declare no conflict of interest.

References