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Case Report

A fetus with Kabuki syndrome 2 detected by chromosomal microarray analysis

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Abstract: Background: Kabuki syndrome is a rare multiple congenital anomaly syndrome characterized by distinct facial features, intellectual disability, cardiovascular and musculoskeletal abnormalities, persistence of fetal fingertip pads, and postnatal growth deficiency. Currently, the diagnosis mainly depends on clinical manifestations and genetic testing. To date, there is no report on the identification Kabuki syndrome in fetuses using chromosomal microarray analysis (CMA). Case presentation: A fetus was identified with growth retardation and cardiovascular abnormality on color Doppler ultrasonography; however, non-invasive prenatal testing (NIPT) revealed a low risk and G-banding karyotyping revealed no abnormal karyotype detected. CMA identified a 1.3 Mb deletion on the X chromosome (Xp11.3) containing *KDM6A*, *DUSP21*, *MIR222, MIR221* and *CXorf36* genes. The fetus was diagnosed with Kabuki syndrome 2, and labor was induced. In addition, CMA detected a 1.3 Mb deletion in the chromosome Xp11.3 in the mother, which contains 5 genes namely *KDM6A*, *DUSP21*, *MIR222, MIR221* and *CXorf36*, while no chromosomal abnormality was identified in the father. Conclusions: We report a fetus with Kabuki syndrome 2 detected using CMA. It is strongly recommended that CMA be included in prenatal diagnosis in fetuses with growth retardation, cardiovascular and musculoskeletal abnormalities revealed by routine Color Doppler ultrasonography.

Keywords: Kabuki syndrome, ultrasound abnormality, chromosomal microarray analysis, *KDM6A* gene

Introduction

Kabuki syndrome, also known as Kabuki make-up syndrome or Niikawa-Kuroki syndrome, is a multiple congenital anomaly syndrome characterized by distinct facial features, intellectual disability, cardiovascular and musculoskeletal abnormalities, persistence of fetal fingertip pads, and postnatal growth deficiency [1]. As a rare disease, the incidence of this disorder is estimated to be 1 per 30,000 to 40,000 births [2]. Currently, the diagnosis mainly depends on the identification of infantile hypotonia, developmental delay and/or intellectual disability, in combination with typical dysmorphic features and/or genetic tests of *KMT2D* or *KDM6A* mutations [3]. Here, we report a fetus with Kabuki syndrome detected by chromosomal microarray analysis (CMA).

Case presentation

A 29-year-old pregnant woman, G2P1, at a gestational age of 24 + 6 weeks was admitted to our hospital on May 31, 2019. Color Doppler ultrasonography measured a biparietal diameter of 4.97 cm (**Figure 1A** and **1B**), an occipitofrontal diameter of 6.82 cm, a head circumference of 18.66 cm (**Figure 1A** and **1B**), an abdominal circumference of 17.35 cm (**Figure 1A** and **1C**), a femur length of 3.70 cm (**Figure 1A** and **1D**), a humerus length of 3.38 cm (**Figure 1A** and **1E**), and a transverse cerebellum diameter of 2.50 cm, indicating a fetal developmental delay. In addition, color Doppler ultrasonography displayed aberrant right subclavian artery (**Figure 1F**), dot-like strong echoes of the left and right ventricles (**Figure 1G**), small-interior-diameter aortic arch isthmus (**Figure 1H** and **1I**), and undetectable gall bladder. The pregnant woman reported a regular menstrual cycle, a natural smooth pregnancy, and she had no special discomfort, no history of smoking or alcohol consumption, no family history of fetal anomaly, and no history of viral infections. The woman denied oral administration of specific medications during the pregnancy. During the second trimester of pregnancy,

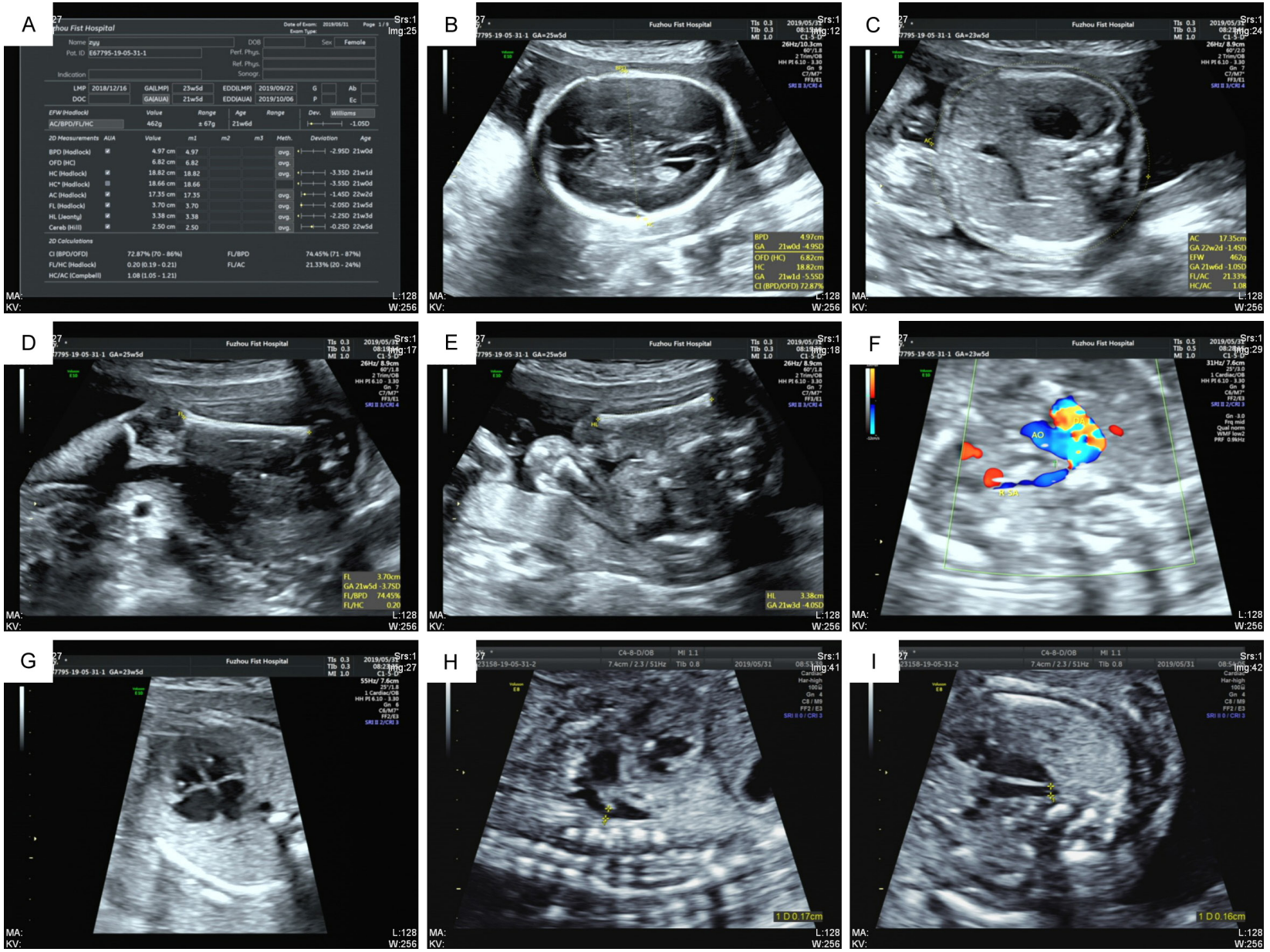
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Figure 1. Color Doppler ultrasonographic findings of a fetus at gestational age of 24 + 6 weeks. A. Measurement of fetal growth parameters using color Doppler ultrasonography; B. Biparietal diameter and head circumference; C. Abdominal circumference; D. Femur length; E. Humerus length; F. Vagus of the right subclavian artery (AO, aorta; DA, ductus arteriosus); G. Strong echoes of the left and right ventricles; H. Transverse section of the interior diameter of aortic arch; I. Longitudinal section of the interior diameter of aortic arch.

non-invasive prenatal testing (NIPT) revealed a low risk.

On June 7, 2019, approximately 30 mL of amniotic fluid was collected by ultrasound-guided transabdominal puncture for conventional chromosomal G-banding karyotype analysis and CMA with the BioChip Detection System of Affymetrix GeneChip following the manufacturer's instructions (Zhejiang Biosan Biochemical Technologies Co., Ltd.; Hangzhou, China). G-banding karyotyping revealed a 46, XN karyotype, with no abnormal karyotype detected, and CMA identified a 1.3 Mb deletion on the X chromosome (Xp11.3) (arr [hg19] Xp11.3 (44,559,776-45,879,273) × 0) containing *KDM6A*, *DUSP21*, *MIR222, MIR221* and *CXorf36* genes (**Figure 2A**). The fetus was therefore diagnosed with Kabuki syndrome 2. After careful consideration, the pregnant woman and her family decided to terminate pregnancy. Labor was induced and a male infant was delivered on July 13, 2019.

To investigate the cause of the fetal chromosome with the 1.3 Mb deletion, peripheral blood samples were collected from the fetus' parents and subjected to CMA on July 17, 2019. CMA detected a 1.3 Mb deletion in the chromosome Xp11.3 region (arr [hg19] Xp11.3 (44,566,542-45,879,273) × 1) in the fetal mother, which contained 5 genes of *KDM6A*, *DUSP21*, *MIR222, MIR221* and *CXorf36* (**Figure 2B**), while no chromosomal abnormality was identified in the father. These testing suggested that the fetal chromosome with the deletion was inherited from his mother.

This study was reviewed and approved by the Ethics Review Committee of Fuzhou Municipal First Hospital (approval number: FZSY-2019-00345). Written informed consent was obtained from the fetus's parents following a detailed description of the study purpose. All experimental procedures were performed in accordance with the Declaration of Helsinki, international and national laws, regulations and guidelines. The fetus's parents involved in this study agreed to publish related demographic and clinical features.

Discussion

Kabuki syndrome is a rare, inherited disorder and there are two major genetic subtypes, including *KMT2D*-associated, autosomal-dominant Kabuki syndrome 1 (approximately 80%) and *KDM6A*-associated, X-linked-dominant Kabuki syndrome 2 (approximately 6%) [2]. Currently, this disorder is identified by clinical manifestations and genetic testing [3]. Hereby, we report a fetus with Kabuki syndrome 2 as revealed by CMA, which is effective to detect 50 to 100 bp microdeletions and microduplications [4].

In this study, color Doppler ultrasonography displayed postnatal growth deficiency and cardiovascular abnormalities in a fetus, and CMA detected a 1.3 Mb deletion in the chromosome Xp11.3 region containing *KDM6A*, *DUSP21*, *MIR222, MIR221* and *CXorf36* genes. *DUSP21*, which encodes a member of the atypical dual specificity phosphatases that are implicated as major modulators of critical signaling pathways and therapeutic targets [5], has shown an important role in maintaining the proliferation of hepatocellular carcinoma (HCC) cells and may be a target for the treatment of human HCC [6]. Both *MIR222* and *MIR221* genes are located on chromosome Xp11.3 region, and *MIR222/MIR221* have been identified as oncogenes or tumor suppressor genes, depending on the cancer type, a modulator of response to cancer chemotherapy, predictors for prognosis in multiple human cancers, and therapeutic tools to mediate resistance or sensitivity to chemotherapeutics [7]. CXORF36, a FAM69 protein family member restricted to vertebrates which has no predicted conserved active site aspartate, is assumed to be a pseudokinase that may interfere with signaling by other FAM69 proteins in a dominant negative fashion or a highly atypical kinase [8], and the *CXorf36* gene is involved in autism spectrum disorders and mental retardation [9].

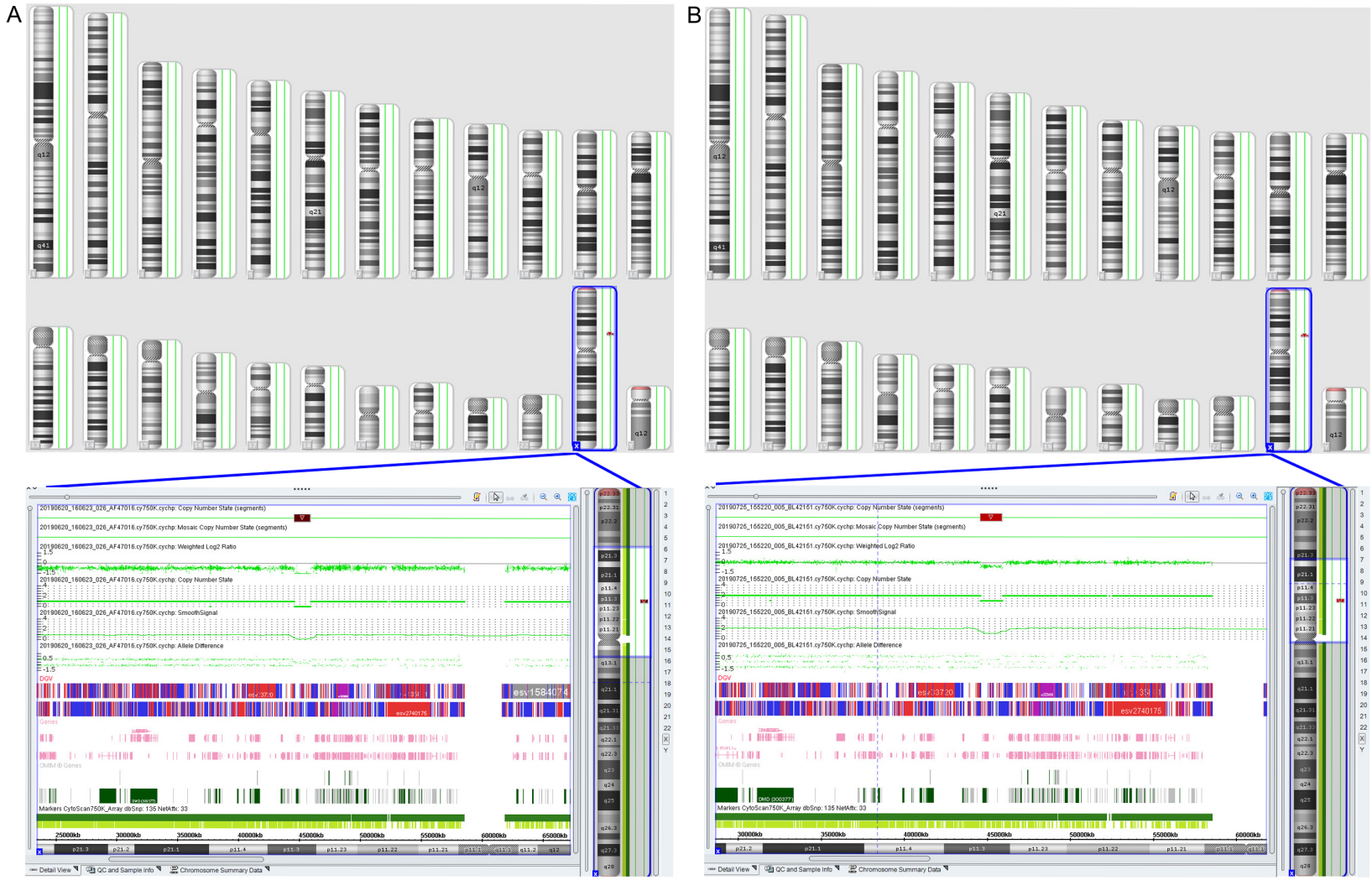

Figure 2. Chromosomal microarray analysis (CMA). A. CMA detects a 1.3 Mb deletion on the X chromosome (Xp11.3) containing *KDM6A*, *DUSP21*, *MIR222, MIR221* and *CXorf36* genes in the fetus; B. CMA detects a 1.3 Mb deletion in the chromosome Xp11.3 region in the mother, which contains 5 genes of *KDM6A*, *DUSP21*, *MIR222, MIR221* and *CXorf36*.

KDM6A, a histone demethylase gene located on the chromosome Xp11.3 region, is accepted as a tumor suppressor gene [10]. Previous studies have demonstrated that *KDM6A* is a causative gene of Kabuki syndrome 2 [11], and *KDM6A* plays critical roles in craniofacial, heart, and brain development [12]. In this study, the fetus was diagnosed with Kabuki syndrome 2 by ultrasound findings and CMA. To investigate the origin of the fetal chromosomal abnormality, the fetal parents' blood samples were collected for genetic testing using CMA, and a 1.3 Mb deletion was detected in the chromosome Xp11.3 region in the mother, which contained *KDM6A*, *DUSP21*, *MIR222, MIR221* and *CXorf36* genes, while no chromosomal abnormality was found in the father. The data suggested that the fetal chromosomal deletion was inherited from his mother.

In summary, this fetus had Kabuki syndrome 2, detected using CMA. It is strongly recommended that CMA be included in prenatal diagnosis in fetuses with growth retardation and cardiovascular and musculoskeletal abnormalities revealed by routine Color Doppler ultrasonography, which may provide valuable information for prenatal diagnostic consultation and a decision on pregnancy termination.

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Disclosure of conflict of interest

None.

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