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Short Communication

Prenatal diagnosis of 17q12 duplication and deletion syndrome in two fetuses with congenital anomalies

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ABSTRACT

Objective: The objective of this study was to characterize the genetic abnormalities in two fetuses with congenital anomalies in prenatal screening.
Materials and methods: The mother of Fetus 1 was 26 years old and had a second trimester serum screening that indicated the fetus was at low risk. The prenatal ultrasound and magnetic resonance imaging (MRI) at 28 weeks of gestation showed mild ventriculomegaly, microcephaly, and agenesis of the corpus callosum. The mother of Fetus 2 was 25 years old and also had a second trimester serum screening that indicated the fetus was at low risk. The prenatal ultrasound at 32 weeks of gestation showed the presence of hyperechogenic and enlarged kidneys with multicystic renal dysplasia bilaterally and a persistent left superior vena cava (PLSVC). Both pregnant women underwent cord blood samplings because of the abnormal imaging results. Karyotype analysis revealed normal results in the two fetuses. Chromosome microarray analysis (CMA) was then performed to provide genetic analysis of the cord blood and parental blood samples. Ultimately, the pregnancies were both terminated.
Results: CMA detected a 1.56-Mb duplication at 17q12 in Fetus 1 and a 1.93-Mb deletion of 17q12 in Fetus 2. Both the duplicated and deleted regions included the *HNF1B* and *LHX1* genes. Neither the duplication nor deletion was inherited from the parents.
Conclusion: This study is the first to report the prenatal diagnosis of a 17q12 duplication syndrome. Our results further confirmed that genes in this region, including *HNF1B* and *LHX1*, are essential for normal brain and kidney development, and also indicated some genes that may be associated with the cardiovascular abnormality. Combined with imaging examination, the use of CMA will improve the diagnosis of submicroscopic chromosomal aberrations in fetuses with congenital anomalies.

Introduction

Chromosome 17q12 deletions and duplications have been established to be associated with a wide range of clinical phenotypes with considerable variability in expressivity. Generally, a deletion of 17q12 is associated with renal cyst and diabetes syndrome [1–3], developmental delay [2–4], autism and schizophrenia [4–6], seizures [2,3], and less common phenotypes containing dysmorphic features [4,6], transient neonatal hypercalcemia [4], Mullerian aplasia [7,8], and congenital diaphragmatic hernia [9]. A duplication of 17q12 could result in developmental delay [2,3,10,11], structural abnormalities of the brain [2,3,10], cognitive impairment and behavioral abnormalities [3], epilepsy [2,10], and less common phenotypes including esophageal atresia [3,12], eye anomalies, cleft soft palate, sex reversal, cardiac defects, and Peters' anomaly [11]. Recently, Hendrix et al [9] and Chen et al [13] reported the prenatal diagnosis of 17q12 deletion syndrome in two fetuses. Here, we present our study on the prenatal diagnosis of a 17q12 duplication and deletion in two fetuses with ultrasound findings by chromosome microarray analysis (CMA).

Materials and methods

Clinical description

The mother (G1P0A0) of Fetus 1 was 26 years old and her second trimester serum screening indicated that the fetus was at low risk.

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The prenatal ultrasound at 28 weeks of gestation showed that the width of the bilateral lateral ventricles was 10 mm, the biparietal diameter was 59 mm, and the pericallosal artery took an abnormal course. Cardiac and urogenital systems were normal. To confirm the abnormality of brain structure, magnetic resonance imaging (MRI) was then performed and revealed that the width of the bilateral lateral ventricles was 12 mm, the biparietal diameter was 63.4 mm (the reference value at the 28th week was 72.5 ± 5.1 mm), and the corpus callosum was faintly visible. The mother had no significant medical, surgical, or family history. She received genetic counseling on the abnormal ultrasound and MRI findings and underwent cord blood sampling at the prenatal diagnostic center. The karyotype analysis revealed a normal female (46, XX).

The mother (G1P0A0) of Fetus 2 was 25 years old and her second trimester serum screening indicated that the fetus was at low risk. The prenatal ultrasound at 32 weeks of gestation showed the presence of persistent left superior vena cava (PLSVC), hyperechogenic and enlarged kidneys (right kidney measured 38 mm × 28 mm, left kidney measured 39 mm × 29 mm) with multicystic renal dysplasia bilaterally, and polyhydramnios (amniotic fluid index was 286 mm). The brain structure was normal. The mother had no significant medical, surgical, or family history. She received counseling and decided to undergo cord blood sampling. The karyotype analysis showed a normal male (46, XY).

CMA

Because the routine chromosome analysis revealed normal karyotypes, a CytoScan 750K array (Affymetrix Inc, Santa Clara, CA, USA)was used for CMA for each of the two fetuses. Parental blood samples from each set of parents were also obtained for the microarray analysis. The procedures for DNA digestion, amplification, segmentation, labeling, and hybridization with the arrays were performed according to the manufacturer's standard protocols (Affymetrix Inc, Santa Clara, CA, USA). The results were analyzed using Chromosome Analysis Suite software. For the interpretation of the data, the following public databases were used: database of genomic variants (DGV; http://projects.tcag.ca/variation/), Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources (DECIPHER; http://decipher.sanger.ac.uk/), Online Mendelian Inheritance in Man (OMIM; http://www.omim.org), and University of California Santa Cruz (UCSC; http://genome.ucsc.edu/, hg19). Confirmation of the copy number variations (CNVs) identified was performed by real-time polymerase chain reaction.

Results

The CMA of Fetus 1 revealed a *de novo* 1.56-Mb duplication at 17q12 containing 15 OMIM genes (chromosome position: 34822465-36378678, UCSC hg19). Fetus 2 had a *de novo* 1.93-Mb deletion at 17q12 encompassing 21 OMIM genes (chromosome position: 34477479-36404104). Neither the duplication nor deletion was inherited from the parents. Fig. 1 shows the duplicated and deleted regions and the involved genes in the two fetuses. We offered detailed genetic counseling to the couples and informed them of the variable phenotypes of the 17q12 microdeletion/microduplication syndrome. Ultimately, both couples chose to terminate the pregnancies.

Discussion

We present our findings on the prenatal diagnosis of a 17q12 duplication in a fetus with cerebral ventriculomegaly and agenesis of the corpus callosum and of a 17q12 deletion in a fetus with

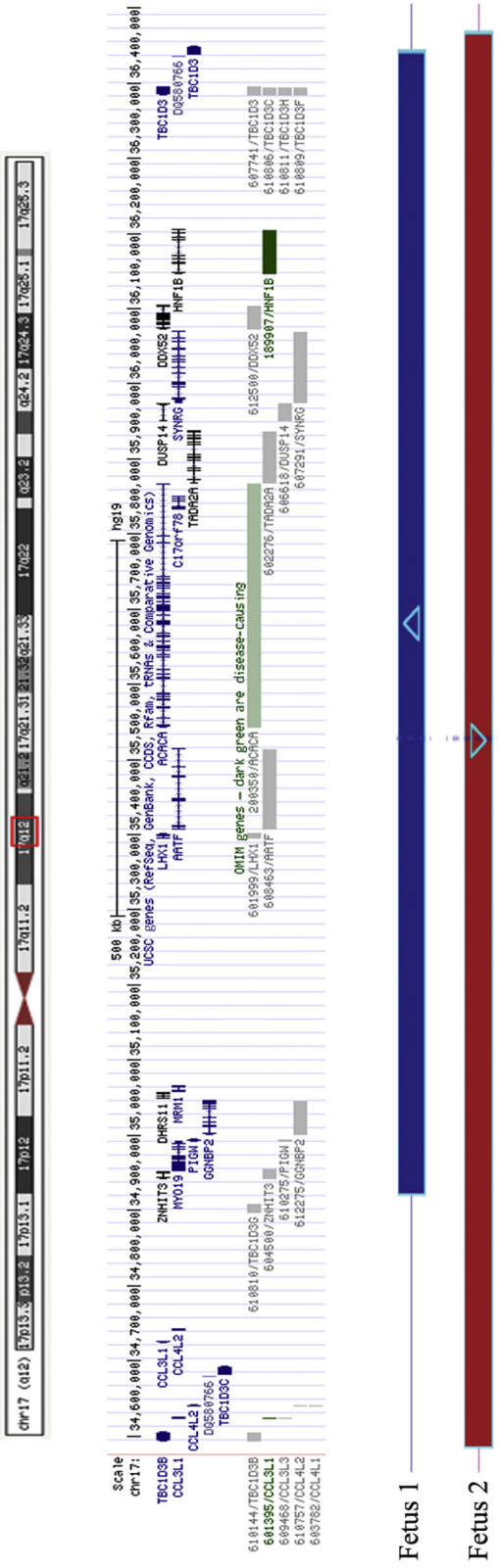

Fig. 1. Microarray profile of chromosome 17 showing the duplicated and deleted region and the corresponding UCSC and OMIM genes. Fetus 1 with a duplication is depicted in blue, and Fetus 2 with a deletion is shown in red. OMIM = Online Mendelian Inheritance in Man; UCSC = University of California Santa Cruz.