Prenatal diagnosis of 45,X/46,X,dic(X;18) mosaicism: a case report

Dongying Wang
Yiwu Maternity and Child Health Care Hospital

Ke Wu
Quzhou Maternity and Child Health Care Hospital

Yuanzhen Zhu
Yiwu Maternity and Child Health Care Hospital

Junying He (✉️ 754299058@qq.com)
Quzhou Maternity and Child Health Care Hospital

Case Report

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Abstract

Background:

A dicentric chromosome is an abnormal chromosome with two centromeres on the same chromosome. They are rarely identified in genetic conditions. Robertsonian translocations (ROBs) involving acrocentric chromosomes (13, 14, 15, 21, and 22) are most frequently generate the dicentric chromosomes. In this report, we described a phenotypically abnormal fetus with mosaic karyotype 45,X/46,X,dic(X;18). This was a rare type of dicentric chromosome X, which has not been reported.

Case presentation: At 16 weeks of gestation, A 39-year-old pregnant woman (gravida 2, para 1) was referred to the center of prenatal diagnosis for genetic counseling. The fetal ultrasonography indicated ventricular septal defect (VSD), pulmonary stenosis, cystic hygroma colli (CHC), choroid plexus cyst, and bilateral hydronephrosis. Subsequently, amniocentesis was performed, the G-banding karyotype analysis of the fetal sample showed a rare type of mosaicism of 45,X,dic(X;18)(p11.2;p11.2)[31]/45,X[26]. Single nucleotide polymorphism array (SNP array) (Affymetrix CytoScan 750K Array, Santa Clara, California) revealed arr[GRCh37]18p11.32p11.21(136228_15181208)x1-2 (Pathogenic); arr[GRCh37]Xp11.22q28(52705315_155233098)x1-2 (Pathogenic). After genetic counseling, the parent chose to terminate the pregnancy.

Conclusions: We report a prenatal case of 45,X,dic(X;18)(p11.2;p11.2)[31]/45,X[26] mosaicism with multiple congenital anomalies. The C-banding analysis showed dicentric chromosome X. This was a rare type of dicentric chromosome X, which has not been reported. Our case report added the descriptive information on this fetus and could provide a reference for genetic counseling.

Background

A dicentric chromosome is an abnormal chromosome with two centromeres on the same chromosome. They are rarely identified in genetic conditions, but the occurrence of dicentric chromosomes in cancer cells is a well-recognized event. It has been reported that dicentric chromosomes are a specific biomarker of radiation exposure. Dicentric chromosomes are mainly (up to 80%) happened between acrocentric chromosomes. Robertsonian translocations (ROBs) involving acrocentric chromosomes (13, 14, 15, 21, and 22) are most frequently generate the dicentric chromosomes. In this report, we described a phenotypically abnormal fetus with mosaic karyotype 45,X/46,X,dic(X;18). This was a rare type of dicentric chromosome X, which has not been reported.

Case Presentation

A 39-year-old pregnant woman (gravida 2, para 1) was referred to the center of prenatal diagnosis at Yiwu maternity and child health care hospital for genetic counseling. At 16 weeks of gestation, the fetal
ultrasonography indicated ventricular septal defect (VSD), pulmonary stenosis, cystic hygroma colli (CHC), choroid plexus cyst, bilateral hydronephrosis (Fig. 1). Subsequently, amniocentesis was performed, and the fetal sample was detected by single nucleotide polymorphism array (SNP array) analysis, G-banding karyotype analysis with a band resolution of 400 bands and C-banding karyotype analysis. The G-banding karyotype analysis revealed a rare type of mosaicism of 45,X,dic(X;18)(p11.2;p11.2) [31]/45,X[26] (Fig. 2). The C-banding analysis showed dicentric chromosome X (Fig. 3). The chromosomal microarray analysis (CMA) using SNP-array (Affymetrix CytoScan 750K Array, Santa Clara, California) revealed arr[GRCh37]18p11.32p11.21(136228_15181208)x1-2 (Pathogenic); arr[GRCh37]Xp22.33p11.22(168552_52154982)x1 (Pathogenic); arr[GRCh37]Xp11.22q28(52705315_155233098)x1-2 (Pathogenic). The pregnant woman was informed of the results of genetic tests. After genetic counseling, the woman decided to terminate the pregnancy at 20 weeks of gestation.

Discussion And Conclusion

Chromosome 18p deletion syndrome (OMIM#146390), also known as monosomy 18p, is a rare type of chromosomal syndrome with phenotypic heterogeneity. The clinical manifestations of 18p deletion syndrome include cardiac abnormalities (VSD, pulmonary stenosis, tetralogy of Fallot, mild aortic valve abnormality), neurologic abnormalities (seizures, hypotonia, holoprosencephaly), short stature, intellectual disability, holoprosencephaly, hypoplastic pituitary stalk, septo-optic dysplasia, isolated scoliosis, facial dysmorphism, genitourinary abnormalities, gastrointestinal abnormalities, hearing loss, pituitary abnormalities, ophthalmologic abnormalities. The prevalence is estimated to be about 1:50,000 live-born infants. Over one hundred individuals with 18p deletion syndrome have been reported, but rare cases (about ten cases) have been described in prenatal diagnosis. It has been reported that the fetuses with a pure 18p deletion could present with severe hydronephrosis, holoprosencephaly, tetralogy of Fallot, reduced head circumference, increased nuchal translucency, craniofacial abnormalities and premaxillary agenesis. The CMA result of our case showed that about 68% of fetal cells have a deletion of the 15.0Mb segment on chromosome 18p11.32-p11.21, which overlapped the 18p deletion syndrome and contained a total of 57 OMIM genes including a critical gene TGIF1 (OMIM*602630). The heterozygous mutations/deletions of TGIF1 gene are associated with autosomal dominant holoprosencephaly 4 (OMIM #142946). This fetus didn't show holoprosencephaly, fetal ultrasonography indicated VSD and bilateral hydronephrosis, which were reported in literature. The clinical phenotypes and severity of a patient may vary with the proportion of abnormal cells and their distribution in the tissue.

The CMA result of our case showed that the fetus had a 51.9Mb deletion in the Xp22.33-p11.22 region of the X chromosome, which contained 264 OMIM genes such as SHOX (OMIM*312865).

The short-stature homeobox (SHOX) gene is located on in the pseudoautosomal region 1 (PAR1) of the X (Xp22.33) and Y (Yp11.3) chromosomes. It plays a particularly important role in various short stature
conditions and disturbed bone development. SHOX has a clear haploinsufficiency effect. SHOX deficiency are associated with Léri-Weill dyschondrosteosis (LWD) (OMIM#127300) and isolated short stature (ISS) (OMIM#300582). In the absence of a family history of short stature, SHOX haploinsufficiency related diseases are rarely diagnosed before late childhood. Li et al reported that only 62.5% (5/8) fetuses of SHOX haploinsufficiency were presented with short long bones by prenatal ultrasound. Ultrasound examination of our case at 20 weeks indicated that long bone measurements were in the normal range.

The last abnormal CMA result of our case showed that about 28% of fetal cells had a 102.5Mb deletion in the Xp11.22-q28 region, which contained not only the centromere heterochromatin region of chromosome X, but also all the long arm of chromosome X and part of Xp11.22-p11.1. It contains 471 OMIM genes such as COL4A5 (OMIM*303630), MECP2 (OMIM* 300005), etc. COL4A5 gene has been reported to be associated with X-linked dominant Alport syndrome 1 (ATS1) (OMIM#301050). Large deletions and nonsense mutations of COL4A5 gene are associated with the highest risk of adult focal segmental glomerulosclerosis and progression to ESRD by the age of 25. Pathogenic variants or deletions in the MECP2 gene have been reported to be associated with X-linked dominant Rett syndrome (OMIM#312750), which is characterized by delayed language development, seizures, autism, absence of speech and intellectual disability.

In our report, we described a phenotypically abnormal fetus with mosaic karyotype 45,X/46,X,dic(X;18). This was a rare type of dicentric chromosome X, which has not been reported. Our case report added the descriptive information on this fetus and could provide a reference for genetic counseling.

**Abbreviations**

SNP array: Single nucleotide polymorphism array; CMA:chromosomal microarray analysis; CNV: Copy number variants; VSD:Ventricular septal defect; CHC:Pulmonary stenosis

**Declarations**

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**Author contributions**

Ke Wu drafted the manuscript. Ke Wu and Dongying Wang revised the manuscript. Yuanzhen Zhu collected clinical data from the family. Dongying Wang and Yuanzhen Zhu performed the genetic experiments on the family. Ke Wu conducted the bioinformatics analyses. Junying He designed and supervised the study. All authors read and approved the final manuscript.

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**Availability of data and materials**

All data generated and analyzed during this study are included in this published article.

**Ethics approval and consent to participate**

The study protocol has been approved by Yiwu Maternity and Child Health Care Hospital.

**Consent for publication**

Consent of the members of the family was obtained for the publication of this case report.

**Competing interests**

The authors declare that they have no competing interests.

**References**


Figures
Figure 1

The fetal ultrasonography (at 16 weeks of gestation). (A) ventricular septal defect (VSD) (B) pulmonary stenosis (C) cystic hygroma colli (CHC) (D) choroid plexus cyst (E) bilateral hydronephrosis
Figure 2

The G-banding karyotype of 45,X,dic(X;18)(p11.2;p11.2)

Figure 3

The C-banding karyotype of dic(X;18)(p11.2;p11.2)
Figure 4

The results of SNP array analysis. (A) The fetal sample SNP array revealed a mosaic loss of 15.0 Mb of 18p11.32p11.21 region; (B) The fetal sample SNP array revealed a mosaic loss of 102.5 Mb of Xp11.22q28 and a 52.0 Mb deletion of Xp22.33p11.22 region.