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Case Report

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Prenatal genetic diagnosis in a fetus with tetrasomy 18p from maternal trisomy 18p:a case report

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[Abstract]

Background Tetrasomy 18p syndrome is a very rare chromosomal disorder that is caused by the presence of isochromosome 18p.Most tetrasomy 18p cases are de novo cases,maternal origin trisomy 18p is a very rare condition.At present, only 4 cases of maternal origin trisomy 18p have been reported.This was the the fifth from maternal trisomy 18p,the mother has no apparent disease phenotype.**Case presentation** We hereby report a case of a fetus with normal ultrasound features,the Karyotyping and Single Nucleotide Polymophism array (SNP array) confirmed tetrasomy 18p.The mother and grandfather are phenotypically normal and healthy,but with trisomy 18p was confirmed by conventional karyotyping and SNP array.**Conclusions** We report a family with an 18p trisomic mother and grandfather,18p tetrasomic fetus,the mother and grandfather are phenotypically normal. The findings could provide a reference for the genetic counseling of trisomy 18p in the future.

[**Key words]** trisomy 18p ;tetrasomy 18p;Isochromosome 18p;prenatal diagnosis

Background

Tetrasomy 18p syndrome is a very rare chromosomal disorder with a prevalence of 1/140,000-180,000[1],and affects both genders equally. Tetrasomy 18p syndrome is associated with developmental delays and cognitive impairment, microcephaly, hypertonia, strabismus, scoliosis/kyphosis, and variants on brain MRI[1].Tetrasomy 18p is caused by the presence of isochromosome 18p,which consists of two copies of the short arm of chromosome 18. Isochromosomes are supernumerary chromosomes that are composed of two copies of the same arm on a chromosome.Isochromosome 18p is one of the most commonly observed

isochromosomes.Most isochromosome 18p cases are de novo,some cases are maternal origin.At present, only 4 cases of maternal origin trisomy 18p have been reported[2-5].In some articles, the molecular mechanism of isochromosome 18p has been discussed.The mechanism of isochromosome 18p may be related to maternal meiosis II nondisjunction and centromeric misdivision or U-shaped exchange[6-9.]In this study,We report a family with an 18p trisomic mother and grandfather,18p tetrasomic fetus,the mother and grandfather are phenotypically normal.

Case presentation

A 23-year-old woman was referred to the the Department of Medical Genetics at *Changsha hospital for maternal and child health care* for opinion counseling because of history of abnormal pregnancy at 17+4 weeks of gestation. Gravida 2,Induced abortion 1,In 2019, she as induced labor due to "fetal nuchal cystic hygroma" at 5+ months of gestation in another hospital, the hospital performed copy number variation sequencing (CNV-seq) on the fetal tissue,the CNV-seq revealed a 14.82Mb deletion of the 18p11.32p11.21 region and a 1.32Mb duplication of the 9q22.2.Subsequent amniocentesis was arranged, and 320 bands G-banding karyotype analysis of the cultured amniocytes revealed an unusual type of tetrasomy 18p : 47,XN,+i(18)(p10)(Fig.2A). Affymetrix CytoScan 750K SNP array on uncultured amniocytes revealed a 18.4Mb quadruple duplication of the 18p11.32p11.1 region(Pathogenic CNV) (Fig.3A).Afterwards,karyotyping and SNP array were performed on pregnant women, and karyotyping was performed on other members of the family.The mother's(Fig.1II_2)karyotype was 47,XX,del(18)(p11),+i(18)(p10)(Fig.2B), the result of SNP array was 18.4Mb duplication of the 18p11.32p11.1 region(Pathogenic CNV) and a 1.29Mb duplication of the 9q22.2(Uncertain significance CNV)(Fig.3B),the women the women was 158cm,44kg,her head circumference,face, lungs, heart, and abdomen,spine,limbs were normal.She graduated from junior middle school, mathematics was poor,and she used to work as a kindergarten teacher.The grandfather's (Fig.1I_1)karyotype was 47,XY,del(18)(p11),+i(18)(p10)(Fig.2C).He worked as a welder, and was also poor in calculation.The grandmother(Fig.1I_2) and aunt(Fig.1II_3) had normal karyotypes,they were phenotypically normal and healthy.(Fig.2DE).The fetus ultrasound was no abnormalities during this pregnancy.The women decided to terminate the pregnancy after genetic counseling.Unfortunately, no autopsy was performed on the induced fetus.

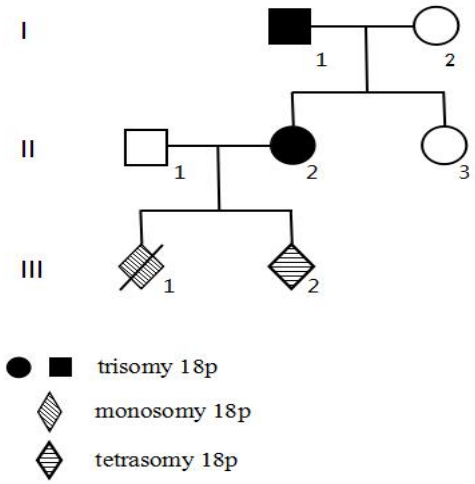

Fig.1:The pedigree.

I1:grandfather,I2:grandmother,II2:mother,II3:aunt

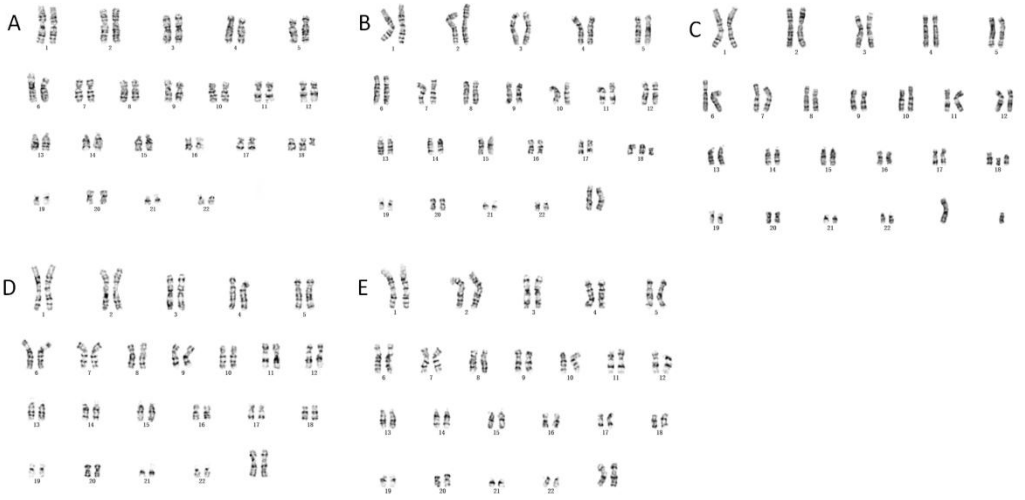

Fig.2 The results of karyotype.

A The fetal amniotic fluid sample showed a abnormal karyotype:47,XN,+i(18)(p10)；

B The mother peripheral blood sample showed a abnormal karyotype:47,XX,del(18)(p11),+i(18)(p10)；

C The grandfather peripheral blood sample showed a abnormal karyotype:47,XY,del(18)(p11),+i(18)(p10);

D The grandmother peripheral blood sample showed a normal karyotype:46,XX；

E The aunt peripheral blood sample showed a normal karyotype:46,XX.

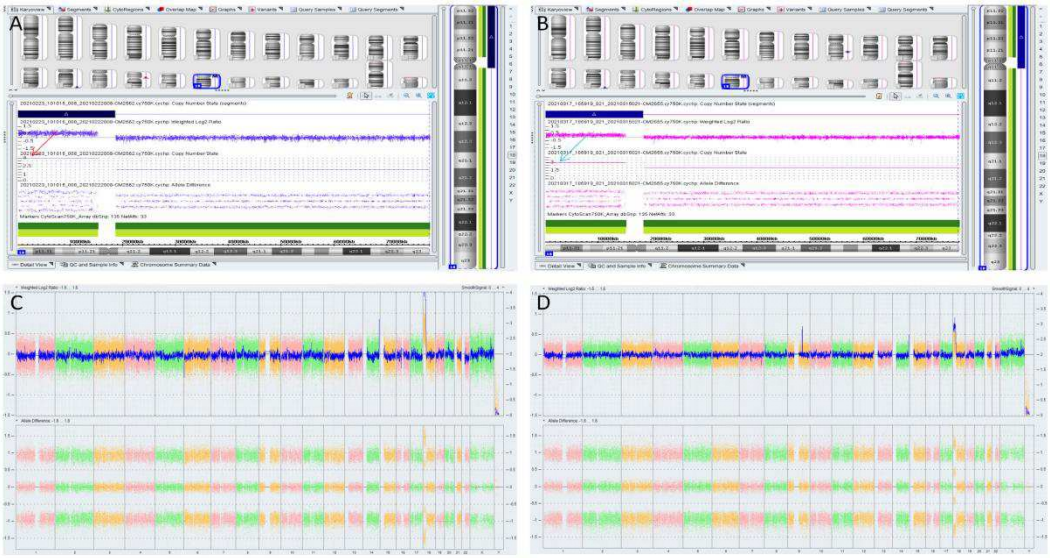

Fig.3 The results of SNP array.

AC The fetal amniotic fluid sample SNP array revealed a 18.4Mb quadruple duplication of the 18p11.32p11.1 region(red arrow);

BD The mother peripheral blood sample SNP array revealed a 18.4Mb duplication of the 18p11.32p11.1 region(Pathogenic CNV) (blue arrow)and a 1.29Mb duplication of the 9q22.2(Uncertain significance CNV).

Discussion and conclusions

Tetrasomy 18p syndrome is a rare type of chromosomal syndrome with phenotypic heterogeneity. Almost all patients have global developmental delay and dysmorphic features, followed by abnormal brain MRI (63%) and feeding difficulties (56.1%),central hypotonia (49.6%), acquired microcephaly (47.7%), strabismus (45%), cryptorchidism (17.4%), scoliosis/kyphosis(37%), recurrent otitis media (34.6%), congenital heart disease (23.7%), seizure (21.5%),etc.[10-11].Due to the lack of specific morphologic features of tetrasomy 18p syndrome, a prenatal ultrasound diagnosis of tetrasomy 18p syndrome is very diffificult with absence of malformations. Therefore,ultrasound combined with prenatal genetic testing is an effective method for diagnosis of tetrasomy 18p syndrome. In this article,prenatal diagnosis was done for the women due to history of abnormal pregnancy.There was no obvious abnormality in early ultrasound,it may be due to the early gestational age, the limitations of ultrasound detection, and some malformations were not found. The women decided to terminate the pregnancy after genetic counseling.Unfortunately, no autopsy was performed on the induced fetus,and we cannot add partial phenotype.

Tetrasomy 18p is caused by the presence of isochromosome 18p,which consists of two copies

of the short arm of chromosome 18. Most isochromosome 18p cases are de novo,some cases are maternal origin.Taylor et al[2]reported a mother with trisomy 18p syndrome and a child with monosomy 18p syndrome,a child with tetrasomy 18p syndrome. The mother was normal phenotype, though height was 152.4 cm and weight was 34.0 kg.Moreover, Takeda et al[3]described a phenotypically normal mother with a karyotype 47,XX,del(18)(pter→p11.21),+i(18p), and two tetrasomy 18p syndrome daughters;Abeliovichet al[4]reported a female was diagnosed as a mosaic with a karyotype 46,XX,+i(18p)[2]/46,XX[58],with a normal intelligence and completed secondary school education,she transmitted the abnormal chromosome 18 to the offspring ,her daughter was confirmed to be tetrasomy 18p syndrome.Boyle J et al[5]reported tetrasomy 18p syndrome in two maternal half-sisters,the mother has normal phenotype, and the karyotypes and FISH of peripheral blood and skin fibroblast were normal. The authors speculated that is was likely to be caused by maternal gonadal mosaicism.The four cases of tetrasomy 18p syndrome were maternal origin, and all the mothers have no apparent disease phenotype. In this study, the women has no obvious abnormal phenotype, except for poor mathematics,which was basically consistent with the previously reported.In addition, this study analyzed the karyotypes of other family members,and confirmed that grandfather transmitted the two abnormal chromosome 18 to the offspring,one of which is the deletion of the short arm of chromosome 18, and the other is the isochromosome 18p.The grandfather has no obvious abnormal phenotype, except for poor computing skills.The grandfather had seven brothers and sisters, none of them had a history of abnormal pregnancy. It is speculated that the two abnormal chromosome 18 were de novo. The mechanism of the isochromosome 18p was through misdivision of the centromere or a U-type exchange during mitotic or meiotic division [8].

In this article, the woman's first fetal tissue was confirmed monosomy 18p syndrome by genetic test.Unfortunately, the parents did not do genetic testing to identify the source of the abnormality chromosome 18.She came to our hospital for prenatal diagnosis due to history of abnormal pregnancy.Both the amniotic fluid karyotype and SNP array indicated tetrasomy 18p syndrome.At the same time, it was confirmed that the mother and grandfather had isochromosome 18p.In theory,the female germ cells can produce normal gametes, isochromosome 18p gametes, or deletion of 18p gametes, or contain the above two types and three types of gametes at the same time.Combining the above gametes with normal gametes can give birth to normal karyotype

fetuses or fetuses with the same karyotype as the mother, but also may lead to spontaneous abortion, embryo suspension or give birth to fetuses with abnormal chromosomes.Therefore,prenatal diagnosis or preimplantation genetic diagnosis are recommended for the next pregnancy to reduce the risk of birth defects.

To sum up,we report a family with an 18p trisomic mother and grandfather,and 18p tetrasomic fetus,the mother and grandfather is phenotypically normal. The findings could providea reference for the genetic counseling of trisomy 18p in the future.

Abbreviations

SNP array Single Nucleotide Polymophism array

CNV-seq copy number variation sequencing

Declarations

Ethics approval and consent to participate

The study protocol has been approved by the Changsha hospital for maternal and child health care.

Consent for publication

Parental consent was obtained for the publication of this case report.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LanPing Hu collected clinical data from the family. SiYuan LinPeng,Xiufen Bu,XuanYu Jiang performed genetics experiments on the family and the controls.Can Peng and Xiufen Bu conducted the bioinformatics analysis. Can Peng and ShiHao Zhou designed and supervised the study. Can Peng drafted the manuscript. Jun He and Xiufen Bu revised the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

Not applicable to this article as no datasets were generated or analysed during the current study.

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