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A Fetus with 17p13.3 Deletion and 15q24.1q26.3 Duplication Derived from a Paternal Balance Translocation t (15; 17) (q24; p13)

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Abstract: *Background:* We present prenatal diagnosis of a 17p13.3 deletion and 15q24.1q26.3 duplication associated with paternal chromosome balance translocation, and to illustrate the importance of early diagnosis ultrasound showed fetal structural abnormality and reduce the birth defects. *Case presentation:* A primigravid woman who 25-year-old underwent amniocentesis at 24weeks of gestation because of the ultrasound showed the head structure abnormal of fetus. The routine test indicates that the fetus is normal in early pregnancy. Karyotype analysis showed 46, XN, -17, der (17)t (15; 17) (q24.1; p13.3), chromosome microarray analysis (CMA) detected a duplication on chromosome 15 and a deletion on chromosome 17 of fetus. Furthermore, the results of chromosome karyotype analysis indicated that the maternal karyotype is normal and the paternal karyotype is a balanced translocation of 46, XY, t (15; 17) (q24; p13), which inherited to the fetus. The pregnant woman decided to terminate the pregnancy after counseling. *Conclusions:* CMA is useful in prenatal to diagnose of fetal chromosomal abnormalities in pregnancy with ultrasound showed fetal abnormal structure, CMA can't detect balanced translocations, but can be found by karyotyping. The two methods are complement each other. In addition, for patients with balanced translocations, preimplantation genetic diagnosis may be an option, it not only relieves the pain of spontaneous abortion for patients but also avoids the birth of defective fetal.

Keywords: CMA, Prenatal Diagnosis, Karyotyping, Chromosome Balance Translocation

1. Introduction

The balanced translocation of chromosomal is one of the important causes of infertility and abortion. Balanced translocation is the most common chromosomal structural abnormality in humans. The incidence in infants is 0.16%-0.20% (1/625-1/500) [1]. The balanced translocations detected in Amniotic fluid karyotype analysis were mainly inherited from one parent, a few are new mutations. Usually the genetic type is balanced translocation in both parents, less some of them were diagnosed as carriers of balanced translocation before the prenatal diagnosis of amniotic fluid, some were confirmed by fetal karyotype analysis [2].

Here, we report one case of prenatal diagnosis of chromosome 17p13.3 deletion and 15q24.1q26.3 duplication derived from a paternal balance translocation t (15;17) (q24; p13) in a pregnancy with abnormal ultrasound results.

2. Case Presentation

A 25-year-old, gravida 1, woman went to went to our hospital for genetic counseling and prenatal diagnostic testing due to the bilateral lateral ventricles of the fetus were enlarged 1.2cm, and the posterior fossa was 1.3cm wide on prenatal ultrasound. Her husband was 26-year- old. The couple has a normal phenotype and no family history of genetic disease, the woman under ultrasonic monitoring and guidance through abdominal amniotic cavity punctur extract 30 mL of amniotic fluid e, 15 mL of which was used for cell culture to analyze karyotypes with traditional G-banding, and 15 mL for CMA

detection. CMA revealed a 2.16Mb of 17p13.3 deletion and 28.6 Mb of 15q24.1q26.3 duplication [arr [hg19]17p13.3 (525-2,158,383) x1, arr[hg19] 15q24.1q26.3 (73,768,298-102,429,040)x3] (Figure 1a and 1b). Cytogenetic analysis of the parents showed that the mother had a normal karyotype of 46, XX, and the father had a balanced translocation karyotype of 46, XY, t (15; 17) (q24; p13) (Figure 2a). The fetal karyotype revealed XN,-17, +der (17)t (15;17) (q24.1; p13.3) (Figure 2b), the abnormal chromosome 17 is inherited from the father's karyotype with a balanced translocation.

Figure 1. *The Result of Fetal CMA.*

a) The results showed that the 2.16 Mb deletion in 17p13.3 region, as indicated by the red box;
b) The results showed that the 28.6 Mb duplication in 15q24.1q26.3 region, as indicated by the blue box;
c) The deletionregion and the corresponding OMIM genes of Chromosome 17;
d) The duplication region and the corresponding OMIM genes of Chromosome 15; (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

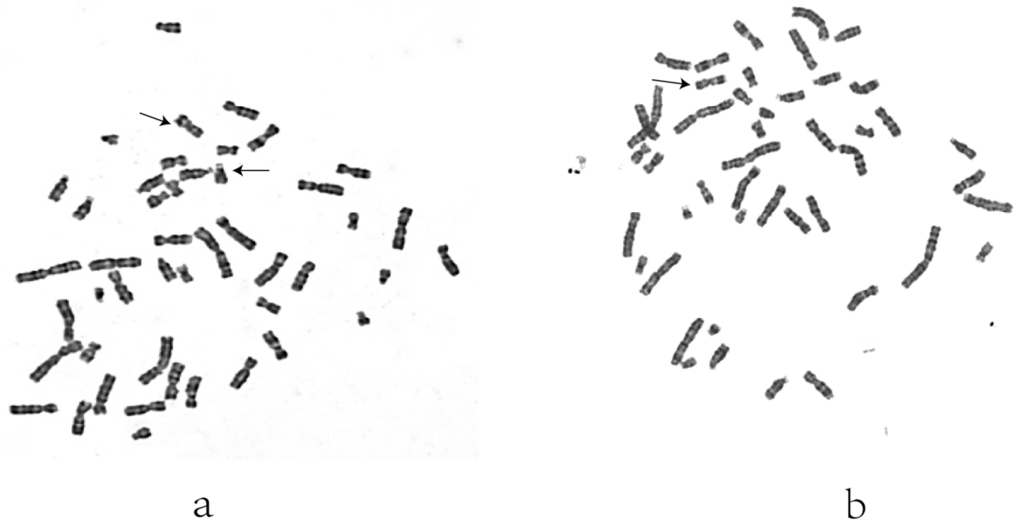

Figure 2. *The Results of Karyotype Analysis.*

a) The fetal paternal karyotype was 46, XY, t (15; 17) (q24; p13)
b) The fetal karyotype was XN,-17,+der (17) t (15; 17) (q24.1; p13.3)

The CMA result of this case showed an approximate 2.16Mb deletion in 17p13.3. This deletion region involved 30 OMIM genes, such as *CRK*, *YWHAE*, *PAFAH1B1* et al, which contains key areas of Miller-Dieker syndrome, Decipher, ISCA, ClinGen, OMIM and CAGdb databases showed that patients with this deletion region have clinical manifestations: abnormality of the heart, intellectual disability, developmental delay, epilepsy, lissencephaly, microcephaly, ataxia, myopia and short toe. The deleltion of this region is clearly pathogenic. The other result showed an approximate 28.6 Mb duplication in 15q24.1q26.3. The duplication region contained 143 OMIM genes, such as *LINGO1*, *MTHFS*, *KIF7*, *CHD2*, *NR2F2*, *IGF1R* et al. Moreover, 15q26 region of overgrowth syndrome in the Decipher database was included, and patients with this syndrome showed craniofacial abnormalities, craniosynosus, renal abnormalities, etc., and databases such as CAGdb, ISCA, and Clinvar and related literature also showed that patients with this region duplication had mild to moderate mental retardation, craniofacial abnormalities, and macacephaly. Table 1 shows the different evidence provided by different databases.

Ultimately, the parents chose to terminate the pregnancy at 31 gestation weeks after genetic counseling.

Table 1. *Results of The Evidence Found in Each Database in This Case.*

Databases	Search result	
ClinGen	Query dose-sensitive genes: *CRK, PRPF8, HIC1, YWHAE et al*.	Query dose-sensitive genes: *LINGO1, MTHFS, KIF7, CHD2, NR2F2, IGF1R et al*.
UCSC Decipher OMIM	Exploit the OMIM and Decipher databases to obtain the results of the patient containing the fragment related to the 17p13.3 region and the gene information contained in the fragment.	Exploit the OMIM and Decipher databases to obtain the results of the patient containing the fragment related to the 15q24.1q26.3 region and the gene information contained in the fragment.
NCBI	Query related literatures with deletion region of the 17p13.3.	Query related literatures with duplication region of the 15q24.1q26.3.
ISCA CAGdb	Suggest that this similar region is pathogenic, and list the clinical manifestations: short stature, abnormal brain development (No gyri or megacephaly), special facial features, mild to moderate developmental retardation, intellectual disability, congenital heart disease, epilepsy etc.	Suggest that this similar region pathogenic, and list the clinical manifestations: mild-to-moderate mental retardation, craniofacial abnormalities, craniosynostosis, megacephaly, and renal abnormalities etc.

3. Discussion

This woman underwent amniocentesis at 28 weeks of gestation due to abnormal ultrasound and confirmed by prenatal diagnosis that the fetus with an unbalanced reciprocal translocation is inherited from the carrier father who had a karyotype of 46, XY, t (15; 17) (q24; p13).

Chromosome17p13.3 deletion syndrome [Online Mendelian Inheritance in Man (OMIM) 247200] due to haploinsufficiency of one or more genes on 17p and is autosomal dominant disorders. And it is characterized by classic lissencephaly, microcephaly, narrow forehead, prominent occiput, downward slanting palpebral fissures, cardiac malformations, growth retardation, and mental deficiency with seizures and EEG abnormalities, hypoplastic male extrenal genitalia [3]. The 17p13.3 deletion observed obviously a terminal deletion (due to the nature of the unbalanced translocation). Deletions that are associated with MDS can range from 0.1 to 2.9 Mb in size. The critical deleted region which about 2.76 Mb in size and included at least 30 RefSeq genes, the key genes of which are *PAFAH1B1* (formerly *LIS1*), *YWHAE*, *CRK*. Deletion of or mutation in the *PAFAH1B1* (OMIM: 601545) to cause the lissencephaly because point mutations have been identified in this gene in isolated lissencephaly sequence [4]. *YWHAE* (OMIM: 605066) is the brain expressed gene, which deleted to contribute to the brain malformation [5], *CRK* (OMIM: 164762) is a candidate gene for the growth restriction that is typically seen [6].

The reports of 15q24 duplication are relatively few. Lacro et al [7] first reported a duplication of 15q22.1-qter and a deletion of 13q32.3-qter in an abortus with an omphalocele and a cephalic defect in neural tube closure. One reported a female infant with anencephaly carried the duplication of 15q24-q26.3 [8]. The other reported that one case with a duplication of 15q24.2-q26.2 associated with anencephaly and neural tube defect (NTD) [9]. This case had a 28.6 Mb duplication of 15q24.2q26.2, which including the key genes of *LINGO1*, *MTHFS*, *KIF7*, *CHD2*, *NR2F2* and *IGF1R*. *LINGO1* (OMIM 609791) is located at 15q24.3 and encodes *LINGO1* (or LRRN6A) protein. One reported a family with 15q24 microduplications including *LINGO1* with a broad clinical spectrum such as developmental delay, dysmorphic features and autistic traits [10]. *MTHFS* (OMIM 604197) is located at 15q25.1 and encodes 5, 10-methenyltetrahydrofolate synthetase. *MTHFS* polymorphisms have been related to congenital malformations such as congenital heart defects and non-syndromic cleft lip and palate [11]. *KIF7* (OMIM 611254) is located at 15q26.1 and encodes kinesinfamily member 7. The mutations of *KIF7* in individuals is related to hydrolethalus and acrocallosal syndromes, two multiple malformation disorders with overlapping features that include brain abnormalities, cleft palate and polydactyly [12]. *CHD2* (OMIM 602119) is located at 15q26.1 and encodes chromodomain helicase DNA-binding protein 2, and expressed in the heart, forebrain, extremities, and facial and dorsal regions during embryonic development [13], mutations of *CHD2* are related to autosomal dominant childhood-onset epileptic encephalopathy [14, 15]. *NR2F2* (OMIM107773) is located at 15q26.2, which expressed in the developing fetal several structures of heart (atria, coronary vessels, and aorta). Rare Variants in NR2F2 Cause Congenital Heart Defects in Humans [16]. *IGF1R* (OMIM147440) mapping on the 15q26.3 chromosome, is necessary for for normal embryonic and postnatal growth. Both the increased or

decreased *IGF1R* gene expression play a role in the etiology of neurological and gonadal disorders. In the previously 96 published cases of chromosome 15q duplication, the prominent features in patients with chromosome 15q duplication such as neurological disorders congenital cardiac defects, typical facial traits and gonadal abnormalities [17].

The result of fetal karyotype is 46, XN,-17,+der (17)t (15; 17) (q24.1; p13.3), the abnormal chromosome 17 is inherited from the father's karyotype with a balanced translocation of 46, XY, t (15; 17) (q24; p13), the short arm end of chromosome 17 of fetus was increased, which was inherited from abnormality chromosome 17 of the father. The short arm of chromosome 17 itself was missing, but a part of chromosome 15 was added, which were confirmed on two clinical and molecular methods as being derived from paternal balanced chromosomal rearrangements. The case contained two CNVs were clearly pathogenic, and this couple chose to terminate the pregnancy after genetic counseling.

The father had a balanced translocation of non-homologous chromosome 15 and 17, later follow-up early spontaneous abortion 2 times, the couple is advised to Preimplantation genetic diagnosis (PGD) was performed directly to avoid deformity the birth of a fetus. Balanced translocations of chromosomes 15 and 17 are rare.

4. Conclusion

In this study, prenatal diagnosis techniques (karyotype and CMA) were used to discover the chromosomal abnormalities of the fetus and avoid the birth of the defective baby. In addition, this study also shows that CMA and karyotype complement each other and can provide more accurate diagnosis and genetic counseling than using only one method. In addition, for patients with balanced translocations, preimplantation genetic diagnosis may be an option to reduce the occurrence of birth defects.

Founding

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Authors Contributions

Study concepts: YD; Study design: YD, SW; CMA analysis: YZ; Karyotyping: SW; Data analysis and interpretation: YX, YZ; Manuscript preparation: JL, HY. All authors read and approved the final manuscript.

Conflict of Interest

The authors have no conflicts of interest relevant to this article.

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