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Prenatal diagnosis of a complex chromosomal rearrangement involving five chromosomes

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Summary

The present authors report an exceptional complex chromosomal rearrangement involving five chromosomes. Cytogenetic analysis of cultured amniocytes revealed a unique karyotype of 46,X,t(X;13;9)(q13;q14;p22),t(3;6)(p13;q23) in 35/35 cultured amniocytes. Microarray-based comparative genomic hybridization (aCGH) revealed two microdeletions on chromosome Xq13.1-q13.2 and 13q14.2-q21.1 respectively. This study demonstrates the feasibility of using aCGH for prenatal diagnosis, especially in detecting subtle chromosomal abnormalities in high risk pregnancies.

Key words: Karyotype analysis; aCGH; Reciprocal translocation; Prenatal diagnosis.

Introduction

Conventional karyotyping on prenatal cells yields lower band resolution than on blood cells, making detection of subtle abnormalities more difficult or not detectable by even blood karyotype [1]. These very small changes are often called microdeletions and microduplications. They cannot be seen down the microscope but can still disrupt growth and development [1]. Microarray-based comparative genomic hybridization (aCGH) compares a fetus's DNA with a control DNA sample and identifies differences between the two sets of DNA. In this way, deletions or duplications (imbalances) in the fetus's DNA can be identified. From this, the gene content of any such imbalance can be established. Therefore, aCGH allows the detection of microdeletions and microduplications that are over 1 kb [2, 3].

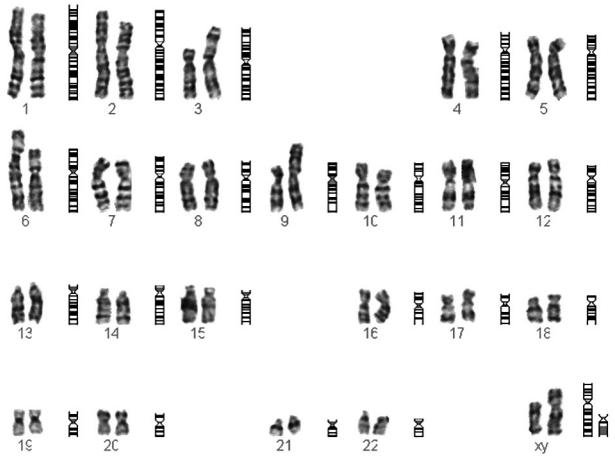

Figure 1. — Karyotype of 46,X,t (X;13;9) (q13;q14;p22), t(3;6) (p13;q23).

Case Report

A 38-year-old primigravid woman underwent amniocentesis at 20 weeks of gestation because of her advanced maternal age. Banding cytogenetic analysis of cultured amniocytes revealed a karyotype of 46,X,t(X;13;9)(q13;q14;p22),t(3;6)(p13;q23) in all (35/35) cells (Figure 1). However, parental karyotypes were normal. This pregnancy was conceived naturally. Her husband was 42 years of age. This couple had attempted to become pregnant for two years. Routine pregnancy examinations including height, abdominal circumference, fetus heart rate, fetal movement, and blood tests were normal. Ultrasound scan at 23 weeks of gestation showed talipes equinovarus (also called club foot) on both feet of the fetus (Figure 4). However the couple was willing to continue the pregnancy if no other defects were to be found.

To identify potential microdeletions or microduplications of the fetal chromosomes that might harmful to the fetus, the authors performed aCGH on the DNA extracted from uncultured amniocytes using commercial arrays as previously described [4]. Two microdeletions were detected by the aCGH analysis. One was on chromosome Xq13.1-q13.2 or arr Xq13.1q13.2 (71,699,190-71,820,393)x1 (Figure 2). The other was on chromosome 13q14.2-q21.1 or arr 13q14.2q21.1 (48,706,590-57,520,639)x1 (Figure 3).

Percutaneous umbilical cord blood sampling (PUBS) was performed at 26 weeks of gestation. PUBS showed a rare karyotype of 46,X,t(X;13;9)(q13;q14;p22),t(3;6)(p13;q23) in 50/50 cord blood lymphocytes. An aCGH analysis on uncultured cord blood lymphocytes revealed the same results as previously observed in the aCGH analysis using the uncultured amniocytes. In contrast,

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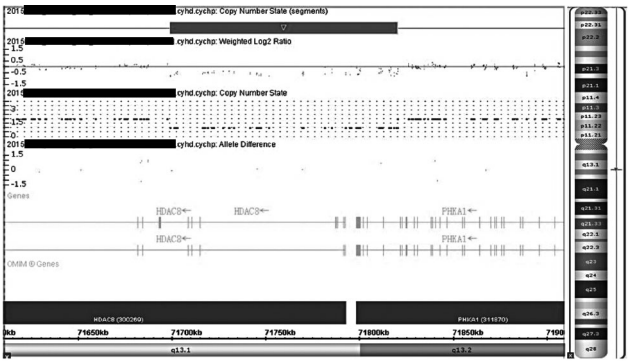


Figure 2. — Xq13.1q13.2 (71,699,190-71,820,393) x1, 121kb.

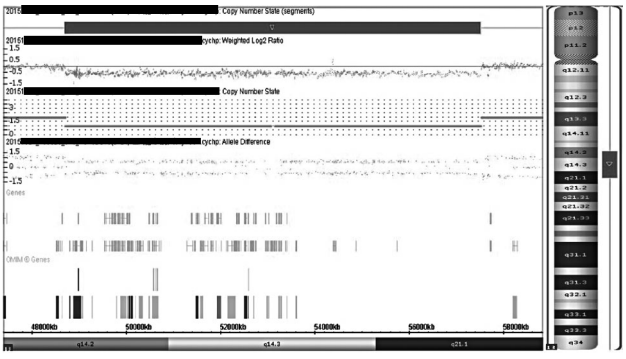
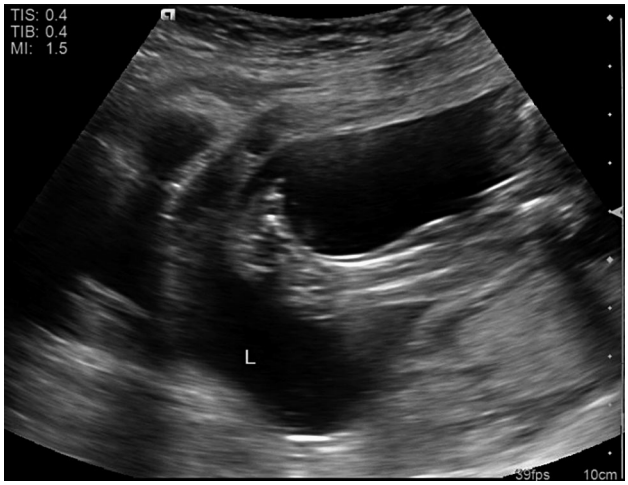


Figure 3. — 13q14.2q21.1 (48,706,590-57,520,639) x1, 8.8Mb.



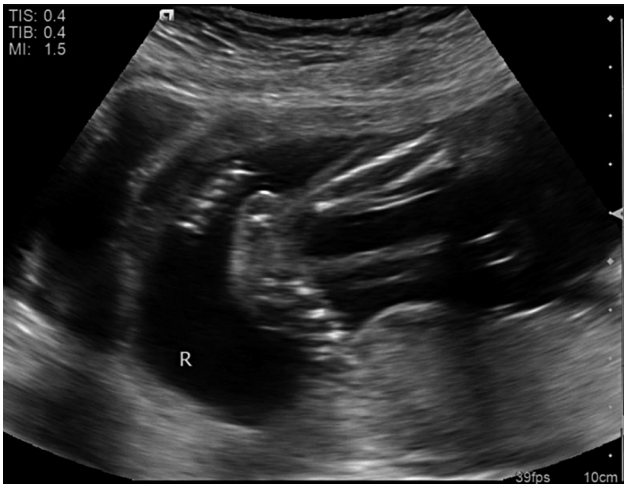


Figure 4. — Ultrasonography showing talipes equinovarus on both sides.

Figure 5. — Autopsy showing talipes equinovarus on both sides.

aCGH analysis of the parental blood revealed no pathogenic microdeletions or microduplications suggesting these microdeletions were *de novo.* After genetic counseling, termination of pregnancy was performed at parent's request at 28 weeks of gestation. A female fetus was delivered vaginally after medical induction with prostaglandins. The fetus showed talipes equinovarus on both feet (Figures 4 and 5). No other malformations (i.e., congenital heart disease, craniofacial anomalies) were observed during autopsy.

Discussion

Diagnostic amniocentesis for the prenatal detection of genetic defects has rapidly established itself as a powerful tool for genetic counseling [5, 6]. Conventional full karyotyping has a resolution of between 5 and 10 Mb and requires a skilled cytogenetic analyst to report results [7]. It also requires cultured cells and this process can take between ten and 21 days [7]. Microarray-based aCGH has a resolution of 10 to hundreds of kb in size, which is well below the level of discrimination of the conventional full karyotyping [8]. In addition, it uses DNA extracted from uncultured cells, which significantly reduces the turnaround time for reporting results [8]. For these reasons, aCGH appears to be an attractive alternative to traditional karyotype analysis.

In the present case, the authors reported an exceptional complex chromosomal rearrangement involving five chro-

mosomes. With aCGH analysis, they detected two *de novo* microdeletions that are rarely reported. One was on chromosome Xq13.1-q13.2 carrying a deletion of 121kb including gene HDAC8 and PHKA1. Mutations in HDAC8 may cause the rare multisystem disorder Cornelia deLange syndrome (CdLS) characterized by somatic defects and mental retardation [9]. Mutations in PHKA1 may myasthenia, amyotrophy and spasm [10]. Since females have two X chromosomes, not 100% of them will be actually affected with these mutations. In the present case, no such phenotypes were detected during autopsy.

The other microdeletion was on13q14.2 q21 carrying a deletion of 8.8 Mb including a few important functional genes. For example, retinoblastoma is due to haploinsufficiency of the retnoma susceptibility of RB1 gene located at 13q14.2 [11]. Individuals with mutation or deletion of RB1 gene are at high risk for retinoblastoma. These patients are also at high risk of osteosarcomas and pinealoblastomas [11]. Another important gene in this region is protocadherin 8 (PCDH8-17). PCDH8-17 is thought to function in signaling pathways and cell adhesion in a central nervous system-specific manner [12]. Therefore, misregulation of PCDH8-17 expression gene could affect neuron communication, thus inducing mental retardation. A woman carrying a fetus with a deletion of 12.87Mb in 13q14.2q21.2 found at 22 weeks of gestation was previously reported. Autopsy showed cranio-facial dysmorphism with dolichocephalia, hypertelorism, interorbital crease, large nose, large and malformed ears, retrognatia, short neck, and pre-frontal edema. Physical examination showed a single palmar crease and clinodactyly on the left hand fifth finger [13]. In the present case, the fetus was delivered with talipes equinovarus on both sides. No other malformations (i.e., congenital heart disease, craniofacial anomalies) were observed during autopsy.

Conclusion

The authors reported an exceptional complex chromosomal rearrangement involved five chromosomes combined with two *de novo* microdeletions. They demonstrated the feasibility of using aCGH for prenatal diagnosis, especially in detecting subtle chromosomal abnormalities in high-risk pregnancies.

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