Genetic counseling for a prenatal diagnosis of structural chromosomal abnormality with high-resolution analysis using a single nucleotide polymorphism microarray

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Abstract

A 41-year old pregnant woman underwent amniocentesis to conduct a conventional karyotyping analysis; the analysis reported an abnormal karyotype: 46,XY,add(9)(p24). Chromosomal microarray analysis (CMA) is utilized in prenatal diagnoses. A single nucleotide polymorphism microarray revealed a male fetus with balanced chromosomal translocations on 9p and balanced chromosomal rearrangements, but another chromosomal abnormality was detected. The fetus had microduplication. The child was born as a phenotypically normal male. CMA is a simple and informative procedure for prenatal genetic diagnosis. CMA is the detection of chromosomal variants of unknown clinical significance; therefore, genetic counseling is important during prenatal genetic testing.

Introduction

Amniocentesis (AS) is a procedure for prenatal genetic diagnosis. Chromosomal microarray analysis (CMA) is utilized in prenatal diagnosis to detect chromosomal abnormalities that are not visible by conventional karyotyping. It is a high-resolution whole-genome screening. Herein, we describe a case lacking apparently severe phenotypic consequences that was detected in an amniotic fluid sample, differential diagnosis was conducted with Giemsa banded (G-Banding) and a microarray used for genome-wide screening.

Case Report

A 41-year old pregnant woman wanted to receive a first-trimester combined screening test at 15 gestational weeks. This screening was indicated because of parental anxiety due to advanced maternal age. Couples have an age-dependent risk for fetal aneuploidy, of which trisomy 21 is the most common form. There was no fetal pathological ultrasound finding or history of a fetus or child with a major congenital anomaly. The couple has two children that are phenotypically normal females (Figure 1).

From the amniotic fluid material, a karyotype analysis was performed at 16 gestational weeks. The samples underwent rapid aneuploidy testing for trisomies 21, 13, and 18 or for a monosomy X before conventional karyotyping, and the results were normal. There was no large structural chromosome anomaly present. A more detailed conventional karyotyping analysis reported an abnormal karyotype: 46,XY,add(9)(p24).

An abnormal karyotype can originate from parents that carry a balanced translocation or *de novo*; therefore, parental blood samples were collected. The parental standard chromosomal analysis showed a normal karyotype.

To further analyze the additional material of unknown origin, a CMA from the amniotic fluid was performed. A single nucleotide polymorphism (SNP) microarray revealed a male fetus with balanced chromosomal translocations on 9p and balanced chromosomal rearrangements, but another chromosomal abnormality was detected: arrXp22p22.13 (16,992,941-17,729,022)x2; Xp21.3(28,791,782-28,903,443)x2. The fetus had a *de novo* duplication that was 736 kb in size at p22.13 and a duplication that was 112 kb in size at p21.3. The 22.2 and Xp21.3 duplications have not been previously reported, and it is unknown whether they are considered pathogenic, benign, or of unknown significance compared to those in public National Institute of Child Health and Human Development (NICHD) databases. Translocations or deletions of Xp22.2 may cause Nance-Horan syndrome (NHS). NHS is an X-linked genetic disorder. Comparative mapping has identified the NHS gene to be localized in the Xp22.31-p22.13 region to a 15-18 cM interval between the loci DXS85 and DXS1226. Translocations or deletions of Xp21.3 are recognized as a possible cause of mental retardation. Microduplication may be more likely to identify differences that have uncertain significant clinical variations and incidental findings.

Unlike conventional karyotyping, CMA cannot detect balanced translocations. Therefore, we recommended the use of fluorescence *in situ* hybridization levels of resolution on microduplication. On the basis of these experiments, the parents decided to conduct no further management. The child was born a phenotypically normal male weighing 2,750 g at 37 gestational weeks. Routine karyotyping of child blood samples was not performed.

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Discussion

AS is the most commonly applied invasive diagnostic test used to obtain fetal cells for prenatal cytogenetic studies. It is a simple and informative procedure for prenatal genetic diagnosis. G-banded karyotype as the first-tier test is increasingly utilized for genetic evaluation. If an abnormal karyotype analysis is reported, sample karyotyping of routine parental blood samples is performed, and a microarray for genome-wide screening is necessary for the evaluation of clinical significance. The obvious advantage of a whole-genome microarray analysis over conventional karyotyping is the improved sensitivity of the method for detecting significant abnormalities in the genome because of the high resolution of the method.[1,2] CMA, which includes SNP and comparative genomic hybridization (CGH) testing, is a method of measuring gains and losses of DNA throughout the human genome. It is a type of high-resolution whole-genome screening that can identify major chromosomal aneuploidies as well as the location and type of specific genetic changes that are too small to be detected by conventional karyotyping. With SNP arrays, only fetal DNA is hybridized to the array platform, and the presence or absence of specific known DNA sequence variants is evaluated by signal intensity to conduct a genome-wide copy number analysis. Major abnormalities in the chromosome structure can include translocations, deletions, gene inversions and gene duplications. The biggest challenge presented by CMA

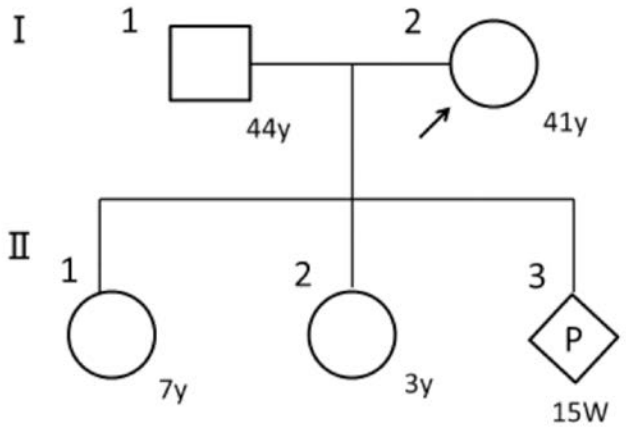

Figure 1. Pedigree of this family.

is the detection of chromosomal variants of unknown clinical significance. These are responsible for most of the genetic variations in populations and are generally not associated with clinical diseases.[3] The decision regarding further management and the pregnancy in many cases is based on diagnostic genetic tests. The potential for complex results and the detection of clinically uncertain findings identified by prenatal testing can result in substantial patient anxiety.

Genetic counseling is recommended based on the results of the standard cytogenetic procedure during prenatal genetic counseling when phenotypes must be predicted. Truly balanced rearrangements and low-level mosaicisms are generally not detectable by arrays, but these are relatively infrequent causes of abnormal phenotypes.[4] When balanced rearrangements are detected prenatally by karyotype analysis, the parents are usually tested, and if a *normal* parent carries the same rearrangement, counseling offers reassurance. However, if the rearrangement is *de novo*, counseling can be very difficult because an estimated 6.1% of fetuses with *de novo* balanced translocations will show some characteristics or abnormal symptoms.[5] Therefore, new techniques such as CGH-arrays and SNP-arrays provide new opportunities for more precise diagnostic procedures and the subsequent integration of the obtained results into genetic counseling. Thus, it is important to make a correct determination of when and how to apply such procedures.

In this case, after genetic counseling, the couple decided to continue the pregnancy; no facial dysmorphism or neuropathy was noted in the infant at birth or at the 1-year follow-up. This report further supports the necessity of integrating genetic counseling with diagnostic and clinical procedures such as the use of CMA in cases with abnormal karyotypes. Additionally, our case helps provide prognostic information regarding microduplications in general.

Conclusions

CMA provides new opportunities for more precise diagnostic procedures and the subsequent integration of the obtained results into genetic counseling. Thus, it is important to correctly determine when and how to apply such procedures because CMA is the detection of chromosomal variants of unknown clinical significance.

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