Case Report

First Case of Prenatal Diagnosis and Characterization by SNP Arrays of an Interstitial de Novo 6p 12.3-21.2 Duplication

Turrado Sánchez E1*, Miguez Álvarez L1, Solar Vilariño I1, Ariza Cobas M1, Alfonso Somoza G1, Barros Angueira F2 and Macía Cortiñas M1

1Department of Gynecology and Obstetrics, Santiago de Compostela University Hospital Complex, Spain
2Galician Public Foundation for Genomic Medicine, Santiago de Compostela University Hospital Complex, Spain

Abstract

In this paper we present the first case of prenatal diagnosis in a 20-week-old fetus, without apparent ultrasound abnormalities, of an interstitial “de novo” 6p 12.3-21.2 duplication with a size of 13 Mb. The chromosomal abnormality was discovered prenatally by karyotype and then characterized using SNP arrays in amniotic fluid cells. The clinical characteristics described for this type of alteration are: low birth weight, psychomotor retardation, prominent forehead, thin and sparse hair, microcephaly due to craniosynostosis, flat occiput, microstomia, thin lips, malformed, low-set ears and thin and sparse hair, heart disease, hemangiomas and proteinuria. Unlike the cases published so far, which were all diagnosed postnatally, no major morphological abnormalities were observed from ultrasound exams or fetal autopsy. This fact is probably related to the gestational age at diagnosis (20 weeks), an age at which the most frequent clinical characteristics described in the literature have not yet developed. This is the first case of an interstitial “de novo” 6p 12.3-21.2 duplication diagnosed prenatally and characterized at the molecular level. Our observation emphasizes the importance of using SNP arrays for prenatal diagnosis, even in cases where the ultrasound screening is normal.

ABBREVIATIONS

IVF: In vitro Fertilization; ICSI: Intracytoplasmic Sperm Injection; QF-PCR: Quantitative Fluorescence Polymerase Chain Reaction

INTRODUCTION

Since 1971, when Therkelsen et al. reported the presence of a partial trisomy of 6p in four members of the same family, about 40 cases have been described with partial duplication of the short arm of chromosome 6. All cases have been described in born individuals; there is no review of duplication in the field of prenatal diagnosis. In most of these cases, trisomy was due to reciprocal translocations; thus, they also presented partial monosomies or trisomies of the other chromosome involved in the translocation [1]. Moreover, at present, not many cases have been described as being “de novo” cases [1-4].

Partial trisomy 6p is considered a recognizable syndrome by many authors [5-7]. The most frequently cited anomalies in pregnancies carried to term are: low birth weight, psychomotor retardation, prominent forehead, thin and sparse hair, microcephaly due to craniosynostosis, flat occiput, microstomia, thin lips, malformed, low-set ears, heart disease, hemangiomas and proteinuria. Ocular problems such as microphthalmia, blepharophimosis, strabismus and nystagmus [1,8-12] have also been described.

We describe the first case of prenatal diagnosis by amniocentesis of a de novo 6p 12.3-21.2 duplication in a patient undergoing in vitro fertilization (IVF) with Preimplantation Genetic Screening for aneuploidies of the transferred embryo. Further molecular analysis of fetal DNA was performed using SNP arrays to characterize the duplication.

CASE PRESENTATION

39-year old woman, 5 pregnancies (1 vaginal live birth delivery and 4 first-trimester miscarriages). She undergoes an
IVF treatment with ICSI with preimplantation genetic screening for chromosomes 13, 18, 21 and sex chromosomes.

The ultrasound exams were absolutely normal. The karyotype of the patient and her partner is normal and there is no data of interest in the family history. The amniocentesis was performed at 16+6 weeks of gestation as a result of the screening test performed on the implanted embryo.

Cytogenetic analysis detected a small, extra DNA area on the short arm of chromosome 6. Molecular analysis confirmed the anomaly, which was characterized as an interstitial duplication of the short arm of chromosome 6. The analysis of peripheral blood of the parents suggests that this is not a feature inherited from the parents and its compatibility with a normal phenotype cannot be confirmed.

The patient was informed about the findings and the known data on the phenotypic pattern associated with this type of alteration and she decided to request voluntary interruption of her pregnancy, as allowed by the legislation in force.

The fetus and placenta were sent to the Pathological Anatomy Unit for analysis. The fetal and placental autopsies show a fetus with female sexual characteristics, with a weight of 452.4 grams and physical and organic measurements consistent with the gestational age of 21 weeks. Generalized organic immaturity consistent with estimated gestational age. No agenesis, internal or external deformities, or malpositions are evident. Placenta of 196.5 g, 14 cm in diameter with a small hematoma in the maternal face without any other abnormalities. Development consistent with 2nd trimester gestation. Umbilical cord with 3 vascular structures (2 arteries and 1 vein) without signs of funisitis or other alterations (image 3).

METHOD

Cytogenetic analysis

The genetics laboratory performed a QF-PCR (quantitative fluorescence polymerase chain reaction) within 24 hours to rule out the most common numerical abnormalities of chromosomes 13, 18, 21, X and Y.

In parallel, a cytogenetic analysis was performed using long-term cultured suspension cells present in the amniotic fluid. The cells studied were fibroblasts. Chromosomal analysis was performed by means of conventional cytogenetic techniques using a G-band staining technique with Wright’s stain with 400/550 bands per haploid set. The observed karyotype is described according to the nomenclature of ISCN (2013).

A total of 29 complete metaphases from two different origins of cell culture were analyzed.

Molecular analysis

The DNA was extracted from the cultured amniotic fluid cells. Due to the small size of the visible area involved in the karyotype, a whole genome analysis of genetic alterations was performed using the Affymetrix CytoScan HD SPN arrays to characterize the observed area. The data was analyzed with the chromosome analysis software (Affymetrix), which offers a practical average resolution of 400 Kb.

RESULTS

The result of the QF-PCR exam of chromosomes 13, 18, 21 and sex chromosomes indicated a normal chromosomal sex fetus for the analyzed chromosomes.

In the cytogenetic analysis, an extra small area on the p-arm was observed in chromosome 6. The chromosome formula observed was 46, XX, der (6) add (6) (p12) (Figure 1). The karyotype of the parents was normal, which suggested a “de novo” abnormality.

The result obtained in the characterization by arrays was: arr 6p21.2p12.3 (37,871,430-50,837,217)x3. A 6p12.3-21.2 duplication of 13 Mb of position 37,831,000 to 50,837,000 of the short arm of chromosome 6 (Figure 2) was observed.

DISCUSSION

The importance of this case is that it is the first prenatal diagnosis of interstitial 6p 12.2-21.2 duplication characterized by SNP arrays. Furthermore, it is a de novo acquired mutation, given that both parents showed normal karyotype, unlike most of the cases published in which the parents carry translocations.

There are no references in the literature to prenatally diagnosed 6p partial trisomy; however, 6p partial trisomy in live births is considered a well-known syndrome with widely described clinical characteristics. The presence of trisomy in individuals with normal phenotype has never been observed.

Table 1 compares the different phenotypes described so far in the literature for this alteration.

In our case, no morphological abnormalities were found in
the autopsy. However, the most commonly reported anomalies: postnatal growth retardation [8,12], psychomotor retardation, attention deficit hyperactivity disorder [8,9] are alterations that occur during postnatal development. Other alterations previously described in the literature, though they can be detected by prenatal ultrasound, usually develop at later gestational stages: craniosynostosis [1,8,11], which rarely develops before the third trimester; restricted intrauterine growth [10,12], micrognatia [1,9,12], which is difficult to diagnose in these weeks since the jaw greatly develops from week 20 onwards and postnatally; therefore, in our case, early diagnosis prevented this type of alteration from occurring.

With regard to the genotype, based on the cases reported in
the literature on partial trisomy 6p, it follows that the duplication of the different regions of 6p may lead to similar phenotypes. However, until now there has been great heterogeneity and sometimes inaccuracy in determining the breakpoints involved in the reorganization. Therefore, it is difficult to define the genes that contribute to the different phenotypes found. Knowledge of the genes involved in specific phenotypes may provide useful information for diagnosis and genetic counseling, as well as more personalized management and monitoring of patients. The characterization by arrays is important to establish a more precise correlation between phenotype and genotype in order to provide adequate genetic counseling to families.

This case helps to underline the importance of the use of new array technologies to define and characterize unbalanced chromosome abnormalities even in cases such as ours, in which the results of the ultrasound screening are normal.

REFERENCES


Table 1: different phenotypes described so far in the literature for this alteration.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated alterations</td>
<td>Monosomy 9pter-9p24</td>
<td>Trisomy 6p24 y sSMC(11)</td>
<td>Paternal UPD(6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Age at the last assessment</td>
<td>4.5 months</td>
<td>16 months</td>
<td>7 and 4 months</td>
<td>5 years</td>
<td>2 and 8 months</td>
<td>2 and 10 months</td>
</tr>
<tr>
<td>Prominent forehead</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Broad nasal bridge</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Prominent/smooth nasolabial fold</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thin upper lip</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Down-turned corners of mouth</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Ear abnormalities</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thick lips/large forehead</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>IUIGR</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Postnatal growth retardation</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Developmental retardation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Cardiac abnormalities</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Genital abnormalities</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Distal contractures</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Attention deficit/ Hyperactivity</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
<td>-</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Other</td>
<td>Trigonocephaly</td>
<td>Cerebellar hypoplasia, ventricular elongation, blepharophimosis, corneal opacity, choanal atresia, inguinal hernia</td>
<td>Clinodactyly, pectus excavatum</td>
<td>Hypoplasia of right kidney, nystagmus, strabismus</td>
<td>Diabetes</td>
<td>Blaschko's lines</td>
</tr>
</tbody>
</table>


