Interstitial deletion on chromosome 14q in prenatal diagnosis

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INTRODUCTION

Interstitial deletions of the long arm of chromosome 14 involving the 14q31-32 region have been reported and well characterized in a low number of prenatal diagnosis (PND) cases. The genotype-phenotype correlation in pure deletion cases is not well established as it depends on the size of the deletion.

On ultrasound, those cases presented cardiac, cerebral, and genitourinary anomalies, diaphragmatic hernia, and/or UPD(14)like phenotypes. However, prenatal ultrasound findings may be irrelevant or relatively non-specific. This report intends to contribute to a better knowledge of the features associated to del(14q) in PND.

MATERIALS AND METHODS

We report the PND of a 33-year-old pregnant woman, who underwent chorionic villus sampling at 12 weeks of gestation after a positive combined 1st trimester screen. Rapid aneuploidy diagnosis was made by QF-PCR assay. The karyotype revealed a 14q interstitial deletion.

Amniocentesis was performed at 18 weeks of gestation to confirm the deletion and to exclude a confined placental mosaicism.

Microarray analysis was performed in order to accurately define the deletion breakpoints. The patient DNA sample was processed according to the Affymetrix manual “Agnostic Copy Number Assay Protocol P / N 703588 Rev. 3.” The detection of gain and/or loss of genetic material was carried out using the CytoScan 750k array (Affymetrix) with a total of 750436 markers (SNP 200 436/550 000 non-polymorphic), having the following analysis parameters were applied: for gains at least 25 markers in a 15SNP region; for losses at least 35 markers in a region of 75SNP and for detection of LOH (loss of heterozygosity) at least 50 markers in a region of 500kb.

In order to identify the parental origin of the deleted chromosome we proceeded to the segregation analysis of microsatellites from parents and proband. Informative STR markers were performed on the DNA extracted from the CVS sample and the parental bloods using STR markers D14S1246 [14q32.3], D14S503 [14q32.13], D14S5033 [14q32.13], and D14S512 [14q31.3]. Samples were amplified by PCR using FAM- and HEX-labeled primers (obtained from the NCBI UnSTS Database) and analysed by capillary electrophoresis using ABI Prism 3130xl Genetic Analyser (Applied Biosystem).

RESULTS

Cytogenetics analysis revealed a karyotype 46,XY,del(14)(q31q32.2)dn (Figure 1). Parental karyotypes were normal.

Rapid aneuploidy diagnosis by QF-PCR showed no evidence of trisomy 13, 18, and 21 and no aneuploidy of the sexual chromosomes.

Microarray analysis allowed to redefine the breakpoints accurate localization and the identification of a ~21Mb deletion [arr[GRCh37] 14q31.1q32.31(99117376_101568230)x1] encompassing 106 OMIM genes (17 non morbid genes) (Figure 2).

Informative STR markers showed a paternal origin of the del(14q) chromosome (Figure 3).

At 17 weeks of gestation the fetus presented abnormal fetal biometric parameters (occipitofrontal diameter, cephalic perimeter and abdominal circumference) on ultrasound. After counselling the couple opted for pregnancy termination. The post-mortem analysis revealed a moderately macerated fetus mainly at the brain region.

The fetus presented decreased biometry, low weight and low fetal size, facial dysmorphism (micrognathia), clinodactyly, clubfoot, overlapping fingers and short penis. In internal habitus he presented thymus hypoplasia, bladder hypoplasia, and horseshoe kidney (Table 1).

Table 1 - Prenatal ultrasonography (US)/TOP clinical findings (X : present; Ab : abnormal value) presents in del(14q) cases.

DISCUSSION

• A limited number of PND cases have reported deletions of the long arm of chromosome 14 involving the 14q31-32 region. Many of them are related with ring chromosomes 14.

• The genotype-phenotype correlation in PND pure interstitial del(14q) cases is not well established as it depends also on the deletions size and the breakpoints (Table 1).

• Furthermore, to our knowledge, interstitial del(14q) had not been reported so early in the gestation (11-12 weeks of gestation). In the present case the positive 1st trimester screen was related to the inverted ductus venous and low PAPP-A value.

• The observed genitourinary anomalies, biometry anomalies, and intrauterine growth restriction (IUGR) are in agreement with features described in the literature. Though even cardiac and cerebral anomalies have been reported, the analysis of this fetus cerebral status was not possible.

• The establishment of a phenotype-genotype correlation in the present case was difficult given the size of the deletion, which includes a large number of genes (106 OMIM genes in distict regions).

• Furthermore, the STR markers showed that the deleted region was of paternal origin and comprises the 14q32.2 imprinted region. The features associated to UPD(14)mat-like or Temple syndrome (TS) phenotype in PND are relatively non-specific, include IUGR and facial dysmorphism, which was also observed in this fetus. Skeletal anomalies (scoliosis, arthrogripsy), small hands and feet, and hypotonia have been also reported, mainly at 11-12.

• However, in the present case some unique features were detected, namely, clinodactyly, overlapping fingers, bilateral clubfoot, thymus hypoplasia and bladder hypoplasia (Table 1), possibly due to the absence of genes other than those located in the imprinted region.

• This work contributes to a better identification of additional features associated to del(14q) that can be present in PND.

REFERENCES

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