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[1,2,3,4,5,6]. However, prenatal ultrasound findings may be irrelevant or relatively non-specific[7,8].

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 "Affymetrix® Cytogenetics Copy Number Assay Protocol P / N 703038 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 been applied: for gains at least 25 markers in a 150kb region; for losses at least 35 markers in a region of 75kb and for detection of LOH (loss of heterozigoty) at least 50 markers in a region of 5000kb.

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 D14S1426 (14q32.2), D14S306 (14q21.1), D14S553 (14q32.13), and D14S128 (14q31.3). Samples were amplified by PCR using FAM- and HEX-labeled primers (obtained from the NCBI UniSTS 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 redefined the breakpoints accurate localization and the identification of a ~21Mb deletion (arr[GRCH37] 14q31.1q32.31(79917376_101568230)x1) encompassing 106 OMIM genes (17 morbid genes)9 (Figure 2).

Informative STR markers showed a paternal origin of the del(14) 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 counseling 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 kidneys (Table 1).

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

Reference/cases	A1	A2	A3	B	C	D	E	F	G	H	I	J
Breakpoints	q31.1 q32.31			q31.3-qter	q31.1 q31.3	q24.2 q32.11	q32	q32.2	q32.2	q22-q32	q32-qter	q24.3 q32.1
Size deletion Mb)	21			19	-	17	-	-	-	-	-	-
Origin	pat			pat	mat	-	pat	pat	mat	-	-	-
USS weeks	11+4	17	19	20	30	30				30,33	27	16-20
Combined 1st trim. screen	Ab											
Fetal Size/IUGR/birth weigth		x	x				x	x		x		
Biometric parameters		x	x				x					
Polyhydramnios									x		x	
Neonatal hypotonia				x			x	x		x		
Bilateral dilation of the ventricles											x	x
Abn. facial profile/dysmosphism			x			x TOP		x	x			
Micrognathia			x						x			
Ductos venosus inverted	x											
Congenital heart defects				x								
Narrow/Small bell-shaped thorax									x			
Thymus hypoplasia			x									
Stomach location						x						
Diaphragmatic hernia						x						
Horseshoe kidneys			x									
Dilation of the bladder												x
Mild bilateral hydronephrosis												x
Bladder hypoplasia			x									
Mild pyelectasis					x 30w							
Genitourinary abnormalities				x								
Abnormal external genitals			x								x	
Diastasis recti									x			
Arthrogryposis				x								
Scoliosis				x								
Cervical abnormalitie				x								
Hyperextensible joints				x								
Clinodactyly			x									
Abnormal hands position/clamped						x TOP						
Fingers position											x	
Overlapping fingers			x									
Small hands and feet							x	x		x		
Bilateral clubfoot			x									

A1 - Present study at 11+4 weeks ; A2 – present study at 17weeks; A3- Present study at TOP ≈ 18-19 weeks;
B- Chen (Features related to monosomy 14q), 2013; C- Gimelli, 2013; D- Sleurs, 2012; E- Severi, 2015(literature review)
F- Hosoki, 2009; G – Watanabe, 2015; H- UNIQUE, 2011(review); I – Mertens, 2000 J- Ochi, 1998

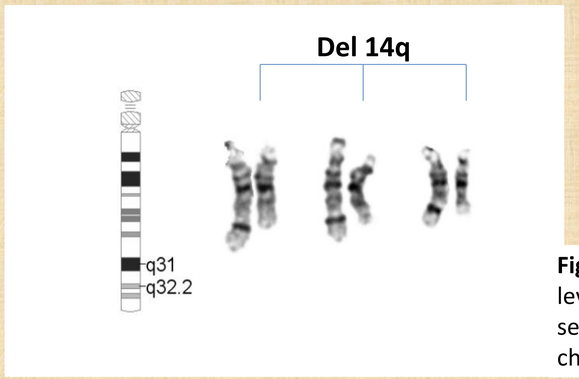

Figure 1 - Ideogram of chromosome 14 (700-band level ISCN) and partial metaphases showing several chromosomes 14 pairs; the abnormal chromosomes del 14q are indicated.

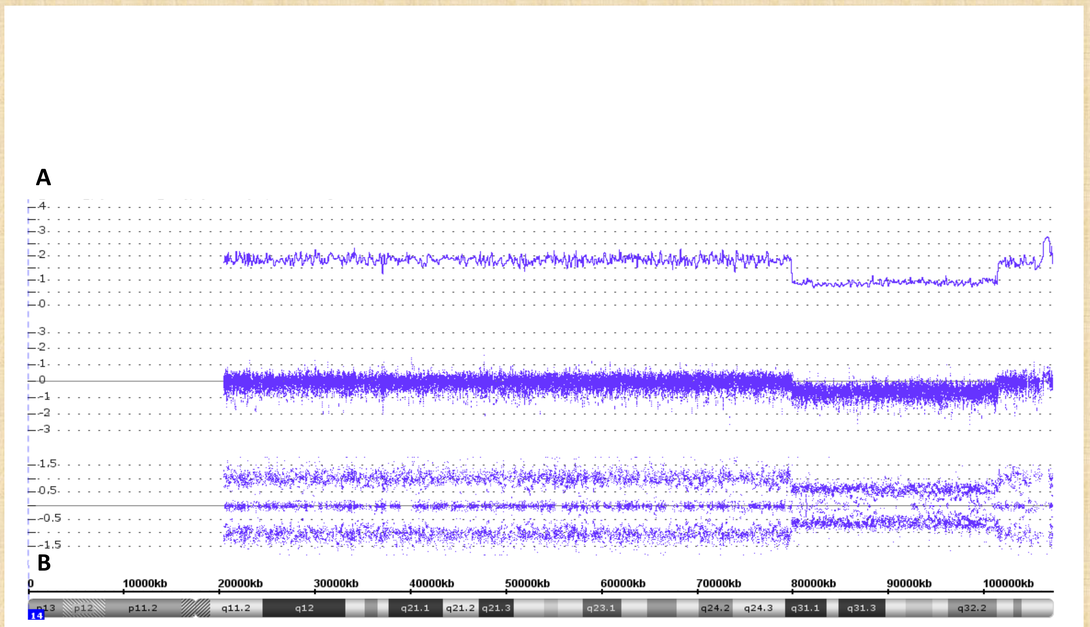

Figure 2 - SNParray profile for chromosome 14. (**A**) Smooth signal is represented in the upper track, copy number probe intensities (log_2 ratio) in the middle and allele peak tracks below indicating a loss at 14q31.1-q32.31 region; (**B**) Chromosome 14 ideogram showing the deleted region.

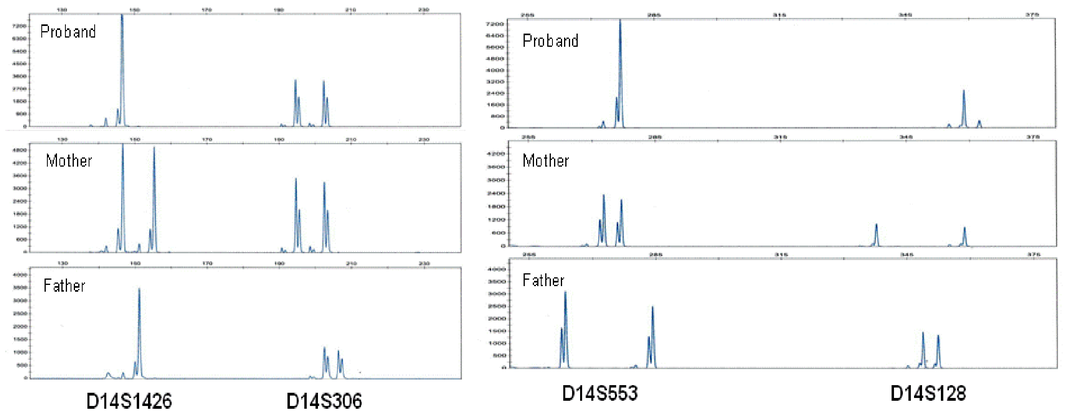

Figure 3 – Electropherograms of 14q markers. Informative markers D14S1426 (14q32.2), D14S553 (14q32.13), and D14S128 (14q31.3) show only one maternal allele, indicating a paternal origin of the del(14) chromosome; D14S306 (14q21.1) is located outside the deleted region.

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 venosus 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[1,2,8,10]. Even though cardiac and cerebral anomalies have been reported, the analysis of this fetus cerebral status was not possible[1,5].
- 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 distinct 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, arthrogryposis), small hands and feet, and hypotonia have been also reported, mainly at birth[5,8,11,12].
- However, in the present case some unique features were detected, namely, clinodactyly, overlapping fingers, bilateral clubfoot, thymus hypoplasia and bladder hypoplasia (Table I), 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

1-Ochi, H et al, 1998, *Obstet. Gyneco.*, 92(4 Pt 2):685-6.
2-Mertens, DJ et al, 2000, *Genet. Couns.*, 11(4):341-6.
3-Sleurs, E & Janssens, S, 2012, *Ultrasound Obstet.Gyneco.*, 40 (Suppl.1):171-310.
4-Gimelli, S et al, 2013, *J Appl. Genetics., 54:361-365.*
5-Chen, CP et al, 2013 *Gene*, 516:132-137.
6-Watanabe, T et al, 2015, *J. Obstet. Gynaecol. Res.*, 41(7):1133-6.
7-Goto, M et al, 2017, *Am. J. Med. Genet.*, Part A 170A:2483-2485.
8-Severi, G et al, 2016, *Am. J. Med. Genet.*, Part A 170A:162-169
9--https://decipher.sanger.ac.uk/search?q=chr14%3A79917376-101568230#genes/results
10- UNIQUE, 2011, *rarechromo.org* ,14q deletions between 14q22 and 14q32.
11- Ioannides, Y et al, 2014, *J. Med. Genet.*, 51:495-501.
12-Hosoki, K et al , 2009, *J. Pediatr.*, 155(6):900-903.