

PRENATAL DIAGNOSIS OF MOSAIC RING CHROMOSOME 16

A RARE EVENT WITH UNCERTAIN PROGNOSIS



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INTRODUCTION

Ring chromosomes are rare cytogenetic findings (prenatal frequency ~ 0.0075%) often associated with an abnormal phenotype, depending of the chromosomal origin, genetic content and the presence of a mosaic. Supernumerary ring chromosome 16 [r(16)] is rarely observed and mosaicism makes the genotype/phenotype correlation difficult (1,2). We report a de novo mosaic r(16) detected during prenatal diagnosis in a woman referred for advanced maternal age. This case addresses the assay's limitations in the clarification of the genomic content of the ring chromosome.

MATERIAL AND METHODS

A 40-year-old woman was referred for prenatal diagnosis of chromosomal abnormalities and molecular rapid aneuploidy analysis (MRA) at 19 weeks of gestation, due to maternal age. Intrauterine growth restriction (IUGR) was observed later in the pregnancy. A ventricular sept defect was suspected at 21 weeks, however echocardiography was normal.

The karyotype was performed by standard methods. Chromosomal microarray analysis (CMA) on DNA obtained from long-term cultured amniocytes was processed according to the Affymetrix manual protocol Affymetrix® Cytogenetics Copy Number Assay P / N 703038 Rev. 3. Gains and/or losses of genetic material were analyzed using the array CytoScan 750K (Affymetrix®) with a total of 750,436 markers (200,436 SNP / 550,000 non-polymorphic), in order to identify/characterize the ring chromosome. Multiplex ligation-dependent probe amplification (MLPA) on an uncultured sample was used for MRA (Salsa® MLPA®Kit P95-A3 Aneuploidy) and a pericentromeric probe kit (Salsa® MLPA®Kit P181-A2 and P182-B1) for further identification/characterization of the ring chromosome. Fluorescence in situ hybridization (FISH) was also performed on metaphases obtained from cultured cells, using a probe which spans 16p13 region (Oncor inv(16) DNA Probe) and a probe on 16q23.1-q23.2 region (IGH/MAF Translocation, Dual Fusion Probe – Cytocell).

RESULTS

MRA for chromosomes 13,18, 21, X and Y was normal. Cytogenetic analysis revealed a mosaic pattern with two cell lines, and the karyotype was defined as 47,XX,+r[10]/46,XX[15] (Fig.1).

CMA did not detect genomic imbalances. MLPA with the pericentromeric probe kit showed a chromosome 16 gain, encompassing 16p11.2 and 16q11.2 regions, including the *TGFB111*, *AHSP*, *VPS35* and *ORC6* genes. FISH results revealed a signal for the inv(16) DNA probe (16p13 region) and absence of signal for the 16q23.1-16q23.2 probe (D16S3213-D16S3073) on the r(16) (Fig.2 A-B).

These results allowed us to partial characterize the r(16), as containing euchromatic material of both arms of chromosome 16 (regions 16p11.2-16p13 and 16q11.2), and include at least the *TGFB111*, *AHSP*, *VPS35* and *ORC6* genes (Fig. 3). This would lead to a mosaic partial trisomy 16.

Parental karyotypes were normal.

Fetal karyotype was redefined as: 47,XX,+r[10]/46,XX[15].ish r(16)(pcp16p13+,D16S3213-).rsa16p11.2(TGFB111,AHSP)x3,16q11.2(VPS35,ORC6)x3.arr[GRCh37](1-22,X)x2 dn After genetic counseling the couple opted to continue the pregnancy. At birth no major malformations were observed and a lower level of mosaic r(16) was observed in peripheral blood (13,3% vs 40% in amniotic fluid). At 4 months of age the child was clinically normal.

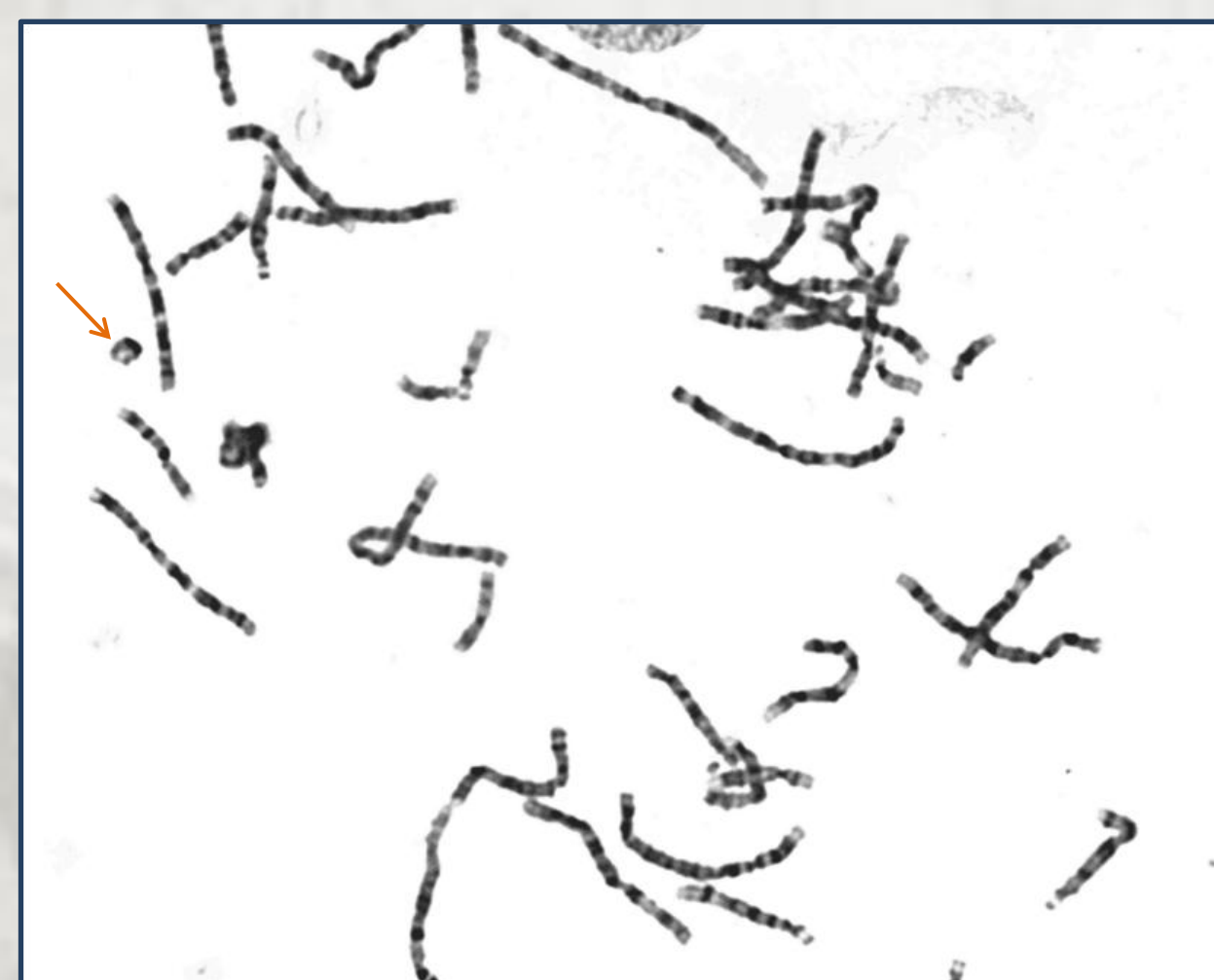


Fig.1 G-banded partial metaphase showing the ring chromosome 16 (arrow).

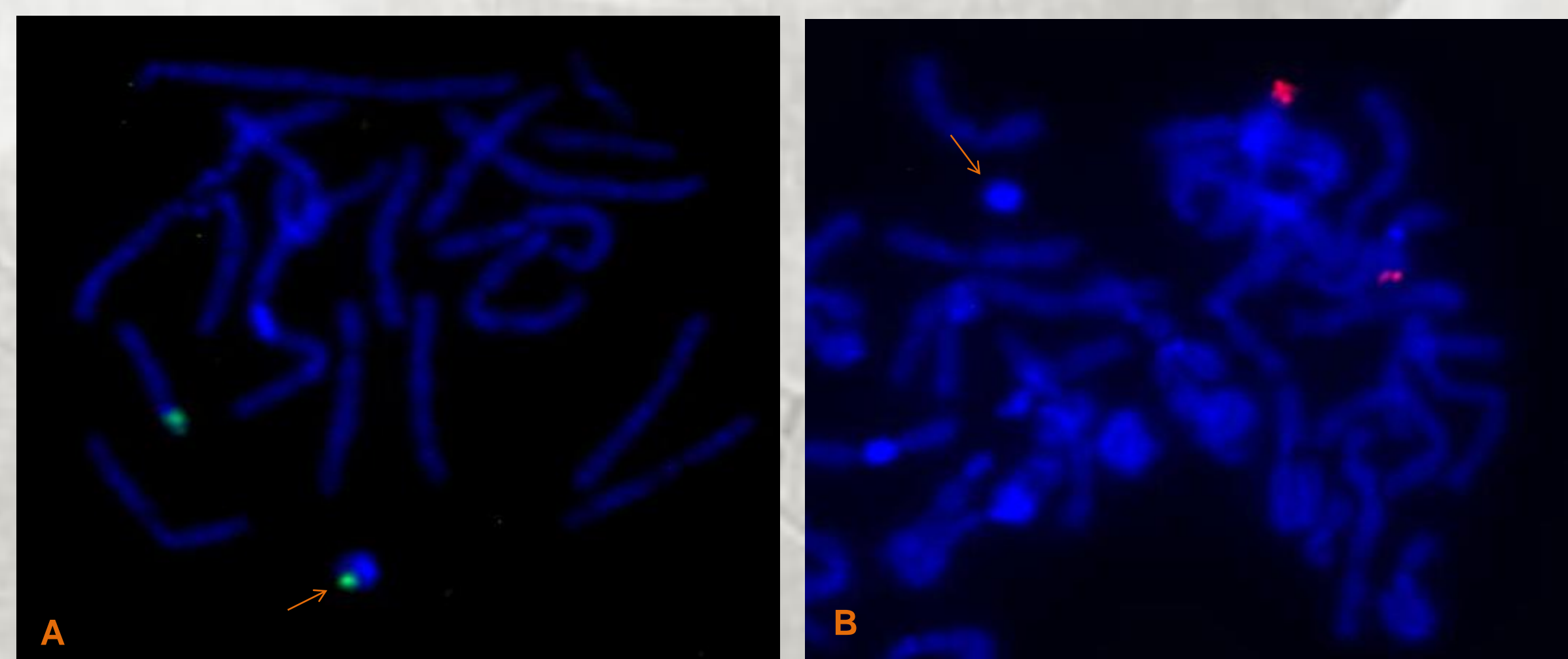


Fig. 2 – FISH analysis. (A) Pcp16p13 showing the presence of signal on the ring chromosome (arrow), which confirms the presence of part of 16p13 region; (B) 16q23.1-16q23.2 probe showing the absence of signal on the ring chromosome (arrow), which confirms the absence of the 16q23.1 region.

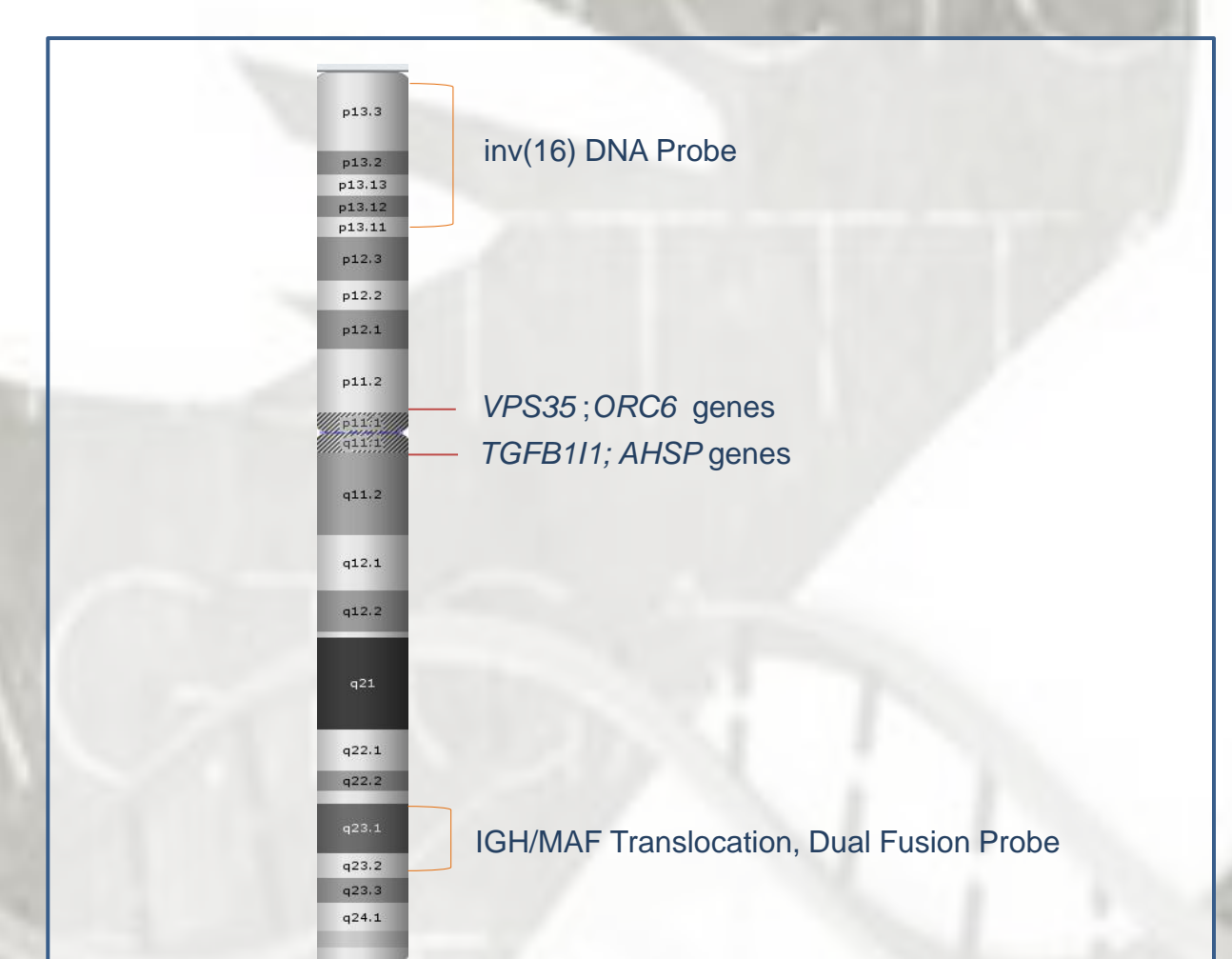


Fig. 3 – Chromosome 16: regions where the genes identified by MLPA and the probes used by FISH studies are located.

DISCUSSION

The presence of a supernumerary ring chromosome derived from an autosomal is a rare event with difficult prognosis of fetal outcome, and it is often associated with a high risk of abnormal phenotype (3,4).

Although no specific phenotype has been correlated with overexpression of the *TGFB111*, *AHSP*, *VPS35* and *ORC6* genes, submicroscopic rearrangements in the 16p11.2 region have been associated with neurodevelopmental disorders (5). On the other hand, individuals with microduplication in 16p11.2 and normal development have been also described (6,7). Duplications involving the 16p13 region have been described in individuals with cardiac abnormalities, seizures, and development delay (5,6).

The knowledge of the type of genetic material involved proves to be critical for prediction of clinical outcome. However the identification of the genetic content, especially by CMA, is hindered by the presence of mosaicism. Therefore the lack of a refined characterization of this type of genomic imbalances continues to pose a challenge in genetic counseling, in a prenatal setting.

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Conflicts of interest: The authors have no conflicts of interest to declare.