PRENATAL DIAGNOSIS IN A FETUS WITH FETAL GROWTH RESTRICTION AND A 4-COPY GAIN IN THE 15Q11.2Q13.1 REGION

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INTRODUCTION

Fetal growth restriction (FGR) is a common ultrasound finding in pregnancy that can result from maternal, fetal, placental, environmental factors, or their interaction, and its diagnosis is based on ultrasound screening[1]. This finding is associated with a significant increase in perinatal morbidity and mortality.

Copy number variants (CNV) in the 15q11.2q13.1 region are associated with recurrent microdeletion/microduplication syndromes, in which the phenotype depends on the parental origin of the CNV[2,3,4].

Case Report

Here we report the case of a healthy 32-year-old woman, who underwent an amniotic fluid sampling (AF), referred for prenatal diagnosis (PND) due to a fetal growth restriction (FGR) in prenatal screening.

RESULTS

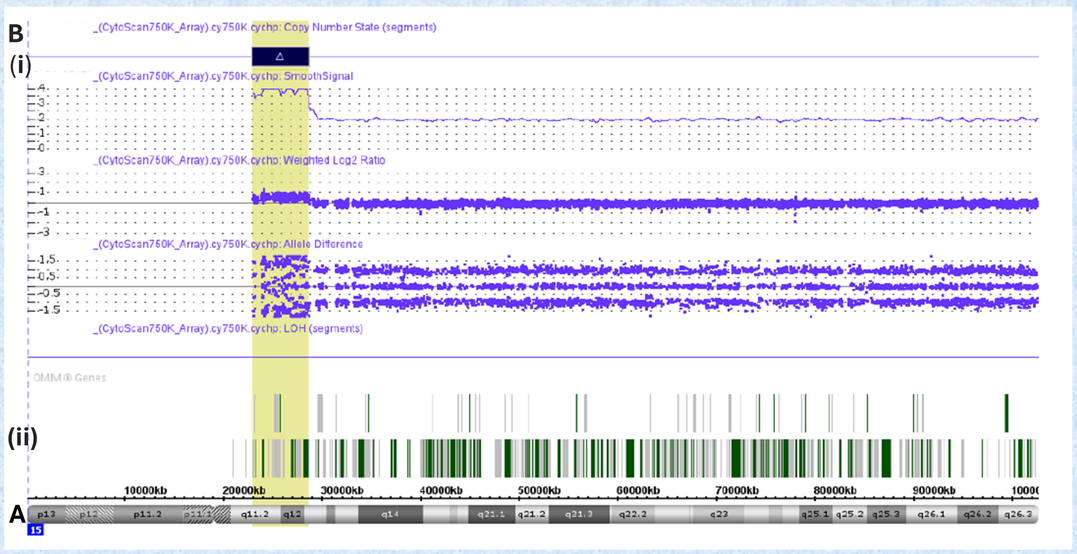
The RAD study revealed a normal result, in a XX fetus.

The CMA identified, in a female profile, a pathogenic gain of 4 copies, with 5.77 Mb, corresponding to the region 15q11.2q13.1 - arr[GRCh37 15q11.2q13.1(23693931-28526905)x4 (Figure 1).

The karyotype was established as mos47,XX,+mar dn[40]/46,XX[28] (Figure 2) showed a sSMC chromosome, with some degree of mosaicism in the sample. The karyotype of the parents was normal.

The MS-MLPA studied loci (*SNRPN* and *MAGEL2*) showed that the gain it was inherited maternally (Figure 3).

After genetic counseling, the parents decided to terminate the pregnancy.



METHODOLOGY

Rapid aneuploidy diagnostic test (RAD) using QF-PCR (Deviser®) was performed. Chromosomal *microarray* analysis (CMA) of the fetus was performed using the CytoScan 750K (Affymetrix®/Thermo Fischer®).

Karyotype was performed in the fetus and parents by standard techniques.

The methylation status was studied using the Methylation-Specific Multiplex Ligation-Dependent Probe Amplification (MS-MLPA) kit Salsa®M028-C1 PW/AS.

Figure 1. Karyotype showing thepresence of the sSNC (idic(15)) (red arrow).

Figure 2. SNP array profile for chromosomes 15. (**A**) Chromosome ideograms showing the gain (yellow area) region. **(B)** (**i**) Copy number state, smooth signal, copy number probe intensities (wieighted log2 ratio) and allele peak tracks indicating the the gain (blue box). (**ii**) Genes duplicated, being the OMIM genes in gray and morbid in dark green.

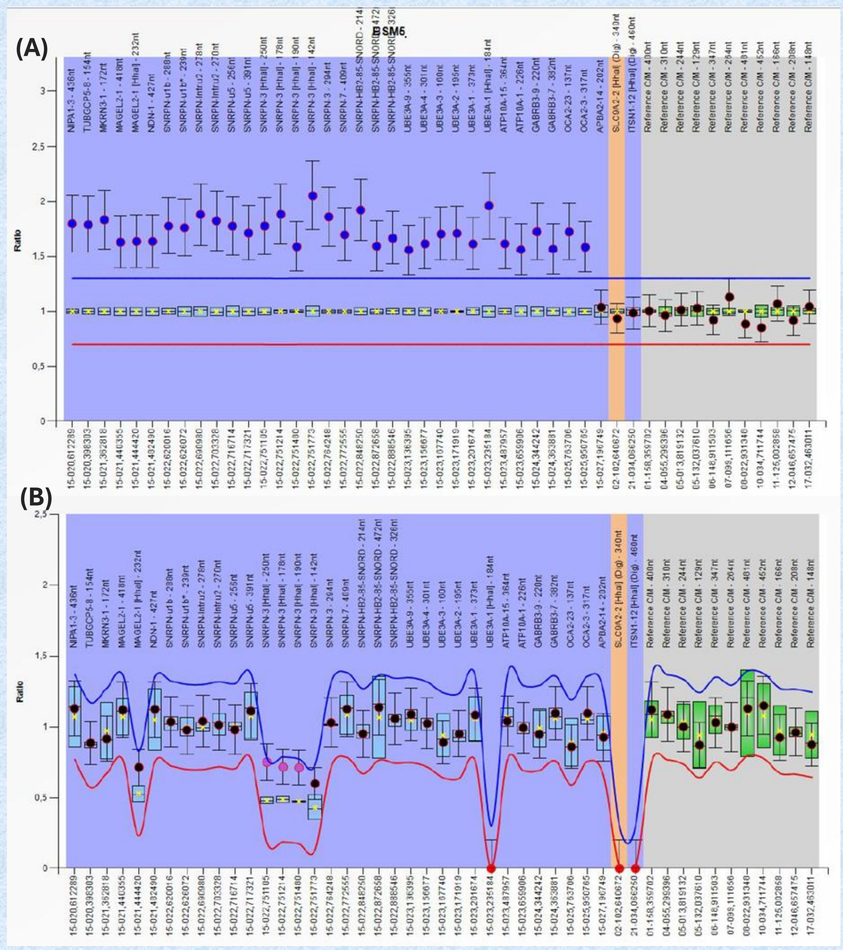


Figure 3. MS-MLPA results. **(A)** Copy number: abnormal result showing a gain of the 15q11 region. (**B)** Methylation status: abnormal result showing an after-digestion methylation ratio of 0.7, indicating the presence of two maternal alleles and one paternal allele.

DISCUSSION

- The detected CNV is a recurrent known microduplication, and some authors characterized it as a recognizable “15q11-q13 duplication syndrome”[5] or “15q duplication syndrome” (dup15q)[6]. The phenotype is dependent on the parental origin of the duplication[2,3].

- As the outcome of the CNV in the study region are depended on the origin of the affected allele the methylation status was studied, and revealed a maternal origin.

- The additional copy (or copies) of 15q11.2 q13 most commonly arise by one of two mechanisms: (1): an interstitial 15q11.2q13.1duplication that leads to trisomy for 15q11.2q13.1; and (2) an isodicentric 15q11.2q13.1 supernumerary chromosome (namely idic(15)) typically comprising two additional copies of 15q11.2q13.1 and resulting in tetrasomy for 15q11.2q13.1[3,6]. In the present case, the karyotype reveals the presence of a sSMC compatible with an isodicentric chromosome.

- In 15q11q13 duplications the most affected individuals have a duplicated chromosome maternally derived, whereas if the CNV has paternal origin is often associated with a normal phenotype, and although some patients have developmental delays and behavioral disturbances, most cases are rarely symptomatic[2,4,7].

- When it has maternally origin “maternal 15q duplication syndrome (maternal dup15q)” has a severe outcome characterized by hypotonia, developmental and motor delays, intellectual disability, language delay, autism spectrum disorder (ASD), and epilepsy including infantile spasms[2,3,6,8]. It is likely that increased maternal gene dosage in 15q11q13 causes abnormal development and function of brain[7,9,10].

- Most cases with a maternal isodicentric 15q11.2-q13 (or “inv dup(15) syndrome”) supernumerary chromosome are typically more severely affected than those with an interstitial duplication[3,5,6,10]. In maternal idic(15) penetrance is 100%[3]. However, severity varies even among individuals who have increased dosage by the same genetic mechanism and that results in different phenotypes[3,6]. Clinical diagnosis, due the variable expressivity of the phenotype, should be addressed on a case-by-case basis in a combination with a molecular diagnosis and clinical outcome.

- In prenatal diagnosis, few cases have been described in the literature. NIPT, increased risk for Down syndrome, tetralogy of Fallot and FGR were referred in microduplications[2,11,12], with FGR being one of the ultrasound abnormalities reported when the abnormality is of maternal origin[2].

- In maternal idic(15) the risk to future pregnancies is presumed to be low. However, couples may wish to consider prenatal testing, as risk may be slightly greather than in the general population due to the possibility of maternal germline mosaicism. The majority of inv dup(15) is of maternal origin, and seems to be associated with advanced maternal age[5,10].

- This case reinforces the importance of the combined use of cytogenetic and molecular cytogenetic technologies, such as karyotyping, MS-MLPA, and CMA, which play a key role in identifying the origins and genetic make up of sSMC. Knowledge of the molecular mechanisms have important implications for disease management, genetic counseling, and testing of at-risk family members.

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