



## Discordance for Cri du Chat Syndrome in a dichorionic–diamniotic twin pregnancy



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### ABSTRACT

We report on the prenatal diagnosis through array CGH of a dichorionic–diamniotic (DC/DA) twins discordant for Cri du Chat Syndrome. Structural anomalies on one of the twins lead to amniotic fluid sampling, which revealed a partial deletion on the short arm of the chromosome 5. Selective feticide of the affected twin was performed at 34 + 1 weeks' and elective Cesarean section at 37 + 2 weeks. Postnatal cytogenetic analysis confirmed pre-natal genetic findings.

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### 1. Introduction

Cri du Chat Syndrome (CdCS), is a genetic disease resulting from a deletion of variable size on the short arm of chromosome 5, OMIM#123450, with an incidence rate that ranges from 1:15.000 to 1:50.000 live-births.

Main clinical features include low weight at birth, high-pitched monochromatic cat like cry, microcephaly, hypotonia, variable degree of psychomotor and mental retardation, abnormal dermatoglyphics, round face and dysmorphic facial features among others. Although not very frequent, this syndrome can also encompass cardiac, neurological and renal abnormalities that aggravate the vital prognosis.

Almost 80% of cases arise as de novo deletion, while 12% result from unbalanced segregation of parental translocations, and less than 10% are associated with cytogenetic rare aberrations [1].

Prenatal diagnosis of CdCS is rare, especially in cases with de novo deletions. In this regard, the prenatal diagnosis is performed more frequently among patients with a known parental 5p translocation diagnosed in the context of a previous CdCS child.

### 2. Case Report

A 32-year-old nulligravida, without relevant medical history, pregnant with a DC/DA twin pregnancy after an in vitro fertilization cycle, showed biochemical markers at 13 + 4 weeks' gestation within normal

range and low risk for chromosomal abnormalities in the first trimester screening test. However, in the morphologic ultrasound a fetal growth discordance was detected, motivating the transfer of the patient to our center at the 24 weeks' gestation, where this finding was confirmed. In addition, a unilateral renal dysplasia was observed in the small fetus, together with a mild dilation of the cavum septum pellucidum as well as a fetal head and femur length biometries below the 5th percentile, abnormalities confirmed in subsequent examinations. Amniotic fluid sampling of both sacs was performed at the 25 + 1 weeks, which revealed a terminal deletion on the short arm of chromosome 5 (46XY,?del(5)(p13)) of the abnormal fetus (Fig. 1) and euploid karyotype of the healthy twin (46XX). Molecular analysis through array CGH (*qChip Pre® v1.1 Complete*. Quantitative Genomics Medicine Laboratories, S.L.) confirmed a distal 5p deletion of considerable size (~26,7 Mb), ranging from 5p15.33 to p14.1 (Fig. 1). Karyotype of both progenitors was also studied, excluding parental chromosomal rearrangements.

Genetic counseling provided with a detailed prognosis of this syndrome, and accordingly selective termination of the abnormal fetus was offered, and later approved by the Ethics Committee.

At the 33 + 2 weeks, the selective feticide was performed successfully by transabdominal injection of intracardiac potassium chloride in the anomalous fetus under ultrasonographic guidance, after completing fetal lung maturation of the healthy fetus. In subsequent examinations, a flattening in the growing curve of the healthy fetus was observed, placing fetal biometry down to the 16th percentile. Elective Cesarean section was performed at 37 + 2 weeks, with the birth of a girl small for her gestational age (2390 g), APGAR score 9/10/10, arterial and venous umbilical cord pHs of 7.34 and 7.35,

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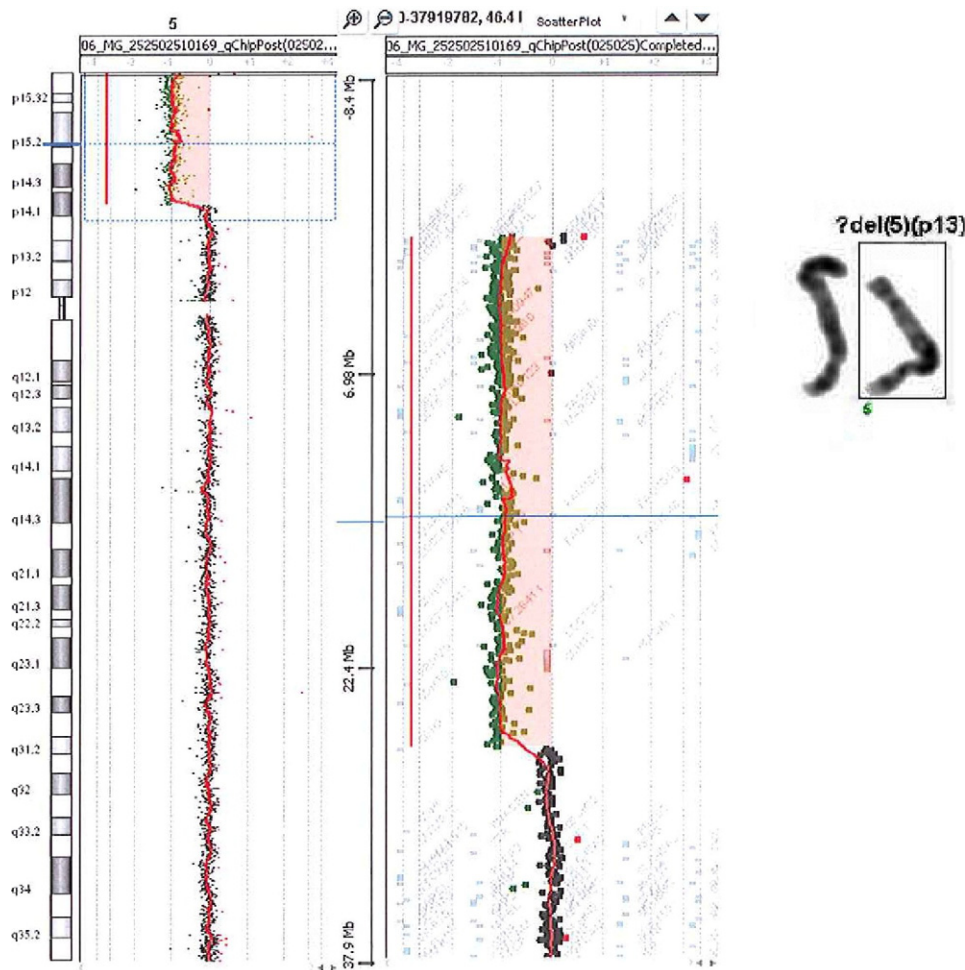


Fig. 1. Detail of molecular karyotype with the terminal deletion on 5p: Arr 5p15.33p14.1(131,946–26,885,727)x1,(XY)x1.

respectively, and subsequently the birth of a stillborn that showed significant signs of soaking.

### 3. Discussion

In the literature, the prenatal diagnosis of CdCS cases is uncommon, precisely because of the lack of specific sonographic signs and biochemical marker that suggest this syndrome. Hence, the majority of cases are detected unexpectedly after performing a karyotype analyses when seeking other chromosomal alterations that would be more commonly observed. Several authors have reported alterations in the levels of maternal serum beta-human chorionic gonadotrophin (Beta-hCG), either low [2] or elevated [3], while others have described morphologic sonographic alterations, that either way lead to the performance of a karyotype.

In the case presented herein, the diagnosis by karyotype was performed because of a restriction in the fetal growing curve together with renal and neurological anomalies, although levels of maternal serum Beta-hCG in the first trimester were within normal range. Through cytogenetic molecular analysis, we were able to detect and describe accurately a deletion in the short arm of the chromosome 5 that encompassed the regions 5p15.33 to p14.1.

In this regard, the introduction of cytogenetic molecular analysis has offered the possibility to identify certain critical regions within 5p, and has led several authors to define a correlation genotype–phenotype, by describing concrete regions associated with certain clinical features, such as the typical cry, speech delay,

microcephaly, facial dysmorphism, and most importantly mental retardation [4,5].

In this context, the use of array CGH has offered an exceptional accuracy at detecting gain or loss in genetic material [6,7], with higher resolution and efficiency than standard cytogenetics. Interestingly, Zhang et al. [6] through array CGH, were able to detect more accurately the location of genes involved in the typical cry, facial features and speech delay, and refined the genotype–phenotype correlation. Additionally, they described three chromosomal regions that influence in different ways the level of mental retardation (MR) (MRI to III), assigning a dominant role to MRI, whose deletions have been associated to moderate level of mental retardation. Deletions restricted to either MR II or MR III in their proximal part to MRI have been described to produce either mild forms of mental retardation or no discernible phenotype at all, respectively. However, as the deletion of MRI extended progressively into MR II and MR III the severity of the mental retardation was dramatically aggravated [6]. Individualizing this information in the case presented herein, the deletion described encompassed bands 5p15.33 to p14.1, where not only the regions for speech, cry and facial features are confined, but also regions for MRI to III, aggravating the prognosis of the affected twin. To a certain extent, this accurate information that array CGH may offer in terms of prognosis is rather relevant in clinical practice, and could provide thereby a more individualized genetic counseling to the progenitors.

Another relevant question to address is the adequate timing to perform a selective feticide in a twin pregnancy discordant for a fetal anomaly. In cases of lethal malformations expectant management could be a safe alternative. However, when selective feticide is considered, the

main limiting variable is the chorionicity, in terms of the technique and its inherent adverse events. In fact, the absence of placental anastomoses in dichorionic pregnancies reduces the incidence of complications, although the risk of preterm delivery remains intact.

To date, there is no consensus about the optimal gestational age at which to perform this procedure in order to avoid fetal loss or extreme prematurity of the healthy fetus. Experts recommend performing the selective feticide as early as possible, since the risk of miscarriage increases considerably after the 16 weeks. However, when the discordant congenital defect is detected after 24 weeks, the performance of the selective feticide after 30 weeks, when legally feasible, and individualizing the exact timing according to the maternal cervical conditions, could be an alternative in order to reach optimal perinatal outcomes, by reducing pregnancy loss and extreme prematurity [8].

#### Funding Sources

None.

#### Conflicts of Interest

None declared.

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