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ORIGINAL ARTICLE

Characterization of a balanced complex chromosomal rearrangement carrier ascertained through a fetus with dup15q26.3 and del5p15.33: case report

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Abstract
Complex chromosomal rearrangements (CCRs) are structural aberrations involving more than two chromosomes which rarely appear in individuals with normal phenotypes. These individuals report fertility problems, recurrent miscarriages, or congenital anomalies in newborn offspring as a consequence of either meiotic failure or imbalanced chromosome segregation. A CCR involving chromosomes 5, 15, and 18 was discovered in a phenotypically normal man through a fetus with congenital malformations and partial trisomy of chromosome 15 and monosomy of chromosome 5. Ultrasound examination at 20 weeks of gestation showed severe oligoamnios and hydrothorax. Prenatal cytogenetic analysis and array comparative genomic hybridization (array-CGH) revealed a female fetus with dup15q26.3 and del5p15.33. We diagnosed the CCR using three-color fluorescence in situ hybridization (three-color FISH), and a balanced CCR using array-CGH and FISH was diagnosed in the paternal karyotype. The father is a carrier of a balanced translocation 46,XY,t(5;15;18)(p15.31;q26.3;p11.2). Due to the complexity of these rearrangements the diagnosis is difficult and the reproductive outcome uncertain. Reporting such rare cases is important to enable such information to be used for genetic counseling in similar situations and help estimate the risk of miscarriage or of newborns with congenital abnormalities.

Keywords: *Chromosomal abnormalities, abortion*

Report

Complex chromosomal rearrangements (CCRs) are defined as structural abnormalities involving more than two chromosomes with at least three breakpoints and the exchange of genetic material between two or more chromosomes (de Vree et al., 2009). They can occur in patients who are mentally retarded or have multiple congenital abnormalities or in phenotypically normal individuals with the birth of a malformed child or fetus, repeated miscarriages, or reproductive disorders (Gardner & Sutherland 2004). Hitherto, more than 255 patients with CCR are reported in the literature (Pellestor et al., 2011). CCRs can be divided into familial and de novo. Familial CCRs represent 1/3 of all cases (Pai et al., 1980).

The advent of molecular cytogenetic techniques has greatly improved the characterization of complex rearrangements. New technologies involve the use of FISH and microarray to uncover cryptic rearrangements located near the breakpoints. They have indicated that many CCRs may harbor a more complex rearrangement not detectable by routine cytogenetics (Pellestor et al., 2011). The feasibility of preimplantation genetic diagnosis (PGD) of embryos in couples with CCRs by FISH strategies has also been demonstrated (Escudero et al., 2008).

Here we report the diagnosis of a recombinant balanced paternal CCR involving three chromosomes and three breakpoints using a combination of molecular cytogenetic techniques.

The parents were a 32-year-old woman and a 31-year-old man, healthy and non-consanguineous. The familial reproductive history fails to show major or minor malformations or repeated miscarriages. The couple had a previous miscarriage. Both pregnancies were achieved spontaneously.

Prenatal diagnosis on amniotic cells was performed at the 20th week of gestation after a routine ultrasound

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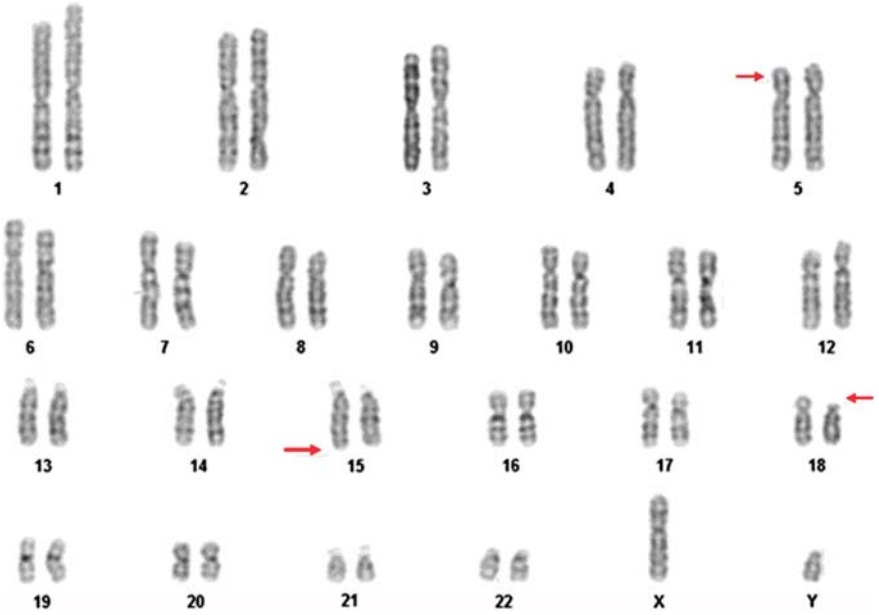

Figure 1. G-banded karyotype of father. The karyotype was 46,XY,t(5;15;18)(p15.31;q26.3;p11.2).

scan showed a fetus with severe oligoamnios and hydrothorax. The woman was advised to have an amniocentesis. Chromosome analyses were carried out on amniotic fluid cells using standard cytogenetic techniques with G-banding and array comparative genomic hybridization (array-CGH) (qChip Pre v1.1 ®). Array-CGH detected three CNVs: a 5p terminal deletion (~7.3 Mb) 5p15.33p15.31 (131.946–7.511.976); a 15q terminal duplication (~1.46 Mb) 15q26.3 (98.741.098-100.201.137); and a 15q deletion (~569 Kb) 15q11.2 (20.199.602-20.769.096). Terminal 5p deletion contains more than 40 RefSeq genes (including some OMIM genes: SDHA, SLC6A19, TERT, SLC6A3, NDUFS6) and is associated with cri-du-chat syndrome (OMIM 123450). Terminal 15q duplication contains more than 15 RefSeq genes and partially overlaps with a previously described region associated with a characteristic phenotype (15q overgrowth syndrome) (Tatton-Brown et al., 2009) and must be considered as of unknown significance. Interstitial 15q deletion between breakpoints BP1 and BP2 contains four evolutionarily conserved genes (TUBGCP5, CYFIP1, NIPA1, and NIPA2) that are not imprinted and must be considered as a susceptibility region to neurocognitive impairment (Burnside et al., 2011; Sempere et al., 2011). The couple decided to terminate the pregnancy. After legal consent, the procedure was carried out with no complications, and the patient was discharged the day after the abortion.

Chromosome analyses from parental peripheral blood lymphocytes of the parents using standard

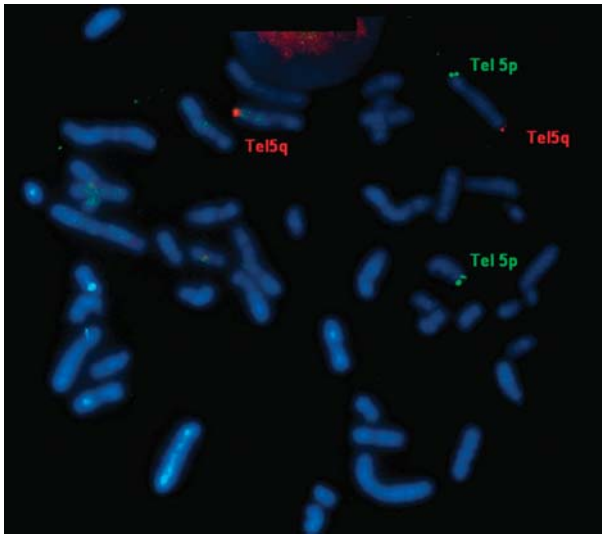

Figure 2. FISH of the translocated chromosomes of the father's karyotype. FISH metaphase shows the derivative chromosome with only one signal on Tel 5p and Tel 5q.

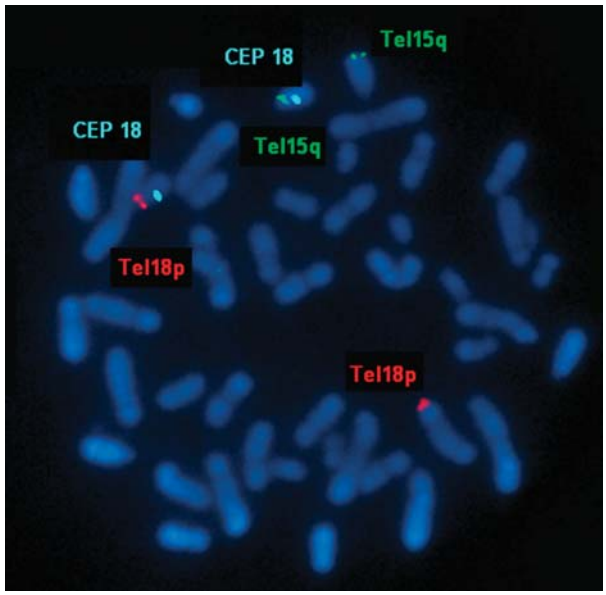

Figure 3. FISH of the translocated chromosome of the father's karyotype. FISH metaphase shows the two derivative chromosomes with one signal Tel 15q and CEP 18 and one signal Tel 18p.

techniques with G-banding were first performed in another cytogenetic center. A chromosomal analysis of the mother showed a normal 46,XX karyotype, whereas that of the father showed a karyotype of 46,XY, t(5;18) (p15.31;p11.2). Surprisingly, this result disagreed with the prenatally detected partial monosomy 15. A second karyotype was performed again in another cytogenetic center in order to compare the father's karyotype and the result was 46,XY, t(15;18) (q26.2;p11.2). After these discordant results, three-color FISH was performed using probes involved in both traslocations. In one, we hybridized lymphocyte cells from the father with two subtelomeric probes on chromosome 5 (Tel5p Spectrum Green Vysis ® and Tel5q Spectrum Orange Vysis ®) (Figure 2) in order to show a translocation between the chromosome 5 and another chromosome. We found one signal Tel5p hybridized in a D chromosome. In the other, we hybridized lymphocyte cells from the father with three probes: two on chromosome 18 (CEP 18 Spectrum Aqua Vysis ® and Tel18p Spectrum Orange Vysis ®) and one on chromosome 15 (Tel15q Spectrum Green Vysis ®) in order to show a traslocation between chromosomes 15 and 18. We found CEP18 and Tel15q on the same chromosome and one signal Tel18p hybridized in a B chromosome (Figure 3). According to these results we could conclude that the father's karyotype was 46,XY,t(5;15;18) (p15.31;q26.3;p11.2) (Figure 1).

Genetic counseling for families with CCR is not easy because the risk of imbalances probably differs with the nature of the rearrangement, as well as the number of chromosomes and the number of underlying breakpoints involved. The reproductive risks seem to be very specific for each carrier and the precise prevalence has been impossible to establish until now mainly due to the lack of appropriate technology. For prenatal diagnosis, the genetic counseling of balanced CCRs can greatly benefit from the use of microarray technologies for the potential detection of the most likely imbalances which would otherwise go undetected.

Declaration of interest: The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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