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Unusual chromosomal rearrangements detected by FISH in patients at high genetic risk

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Abstract

Background: Genetic and chromosomal causes in particular are responsible for a large percentage of pregnancy losses during the first trimester of pregnancy. Among chromosomal abnormalities, balanced or unbalanced, structural aberrations are the least common in reproductive disorders. **The aim of the study:** To describe several types of unusual structural chromosomal aberrations diagnosed by FISH in patients at high genetic risk. **Materials and methods:** Two patients were referred to the cytogenetics laboratory of the National Center of Medical Genetics from infertility clinic in the province of Pinar del Rio. Two patients, from Sancti Spiritus and Isla de la Juventud, with high genetic risk due to repeated miscarriages and advanced maternal age were referred to the laboratory for pre-natal diagnosis. In the cytogenetic laboratory, conventional cytogenetic and FISH analyses were carried out. Conventional cytogenetic methods are used as the first tool in the diagnosis of chromosomal abnormalities. The FISH technique is used with VYSYS probes for specific labelling (LSI probes and CEP probes) of regions of chromosomes 5, 15, 13, 18, 21 and X, which completes the diagnosis. **Results:** In four women carrying structural rearrangements, the following chromosomal aberrations were detected: 47, XX,+ idic(15)(pter→q11.1::q11.1→ pter) .ish idic (15)(D15Z1++), 46,XX,t(13;21)(q22;q11.2), 46,XX,tas(18;21)(p11.3;q22.3) and 46,XY,inv(5)(p12q31.1). **Conclusion:** The present study is a demonstration of the importance of the FISH technology for the characterisation of subtle genomic aberrations causing reproductive disorders in female carriers. The effect of chromosomal aberrations, whether balanced or not, on the formation of altered germ cells that cause reproductive disorders has been discussed.

Keywords: reproductive disorders; FISH; translocations; inversions; carrier parents

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Introduction. During gestation, several genetic factors may predispose to early pregnancy loss and 3-5% of couples are known to experience recurrent pregnancy loss (RPL). The identification of causative genetic aberrations associated with RPL is a very broad field of research within medical genetics. [1]

Foetal chromosome abnormality is a significant cause of RPL, with aneuploidy (trisomy) being the main cause (45.0%) of miscarriages and fetal deaths, followed by monosomy X (9.6%) and triploidy (8.6%) [2, 3]. Structural abnormality (3.4%) are found in lower proportion within fetal anomalies [4]. In contrast, in prenatal diagnosis by amniocentesis (16-20 weeks of gestation), Mendez et al. found that up to 22% of structural chromosomal abnormalities (balanced or unbalanced) had made it to this stage of gestation, probably because the potential genomic imbalances they caused were relatively well tolerated [5, 6].

Individuals who carry a balanced chromosomal rearrangement may be at risk of having a child with intellectual and physical abnormalities due to unfavorable chromosome segregation during gamete formation. The imbalance is typically caused by trisomies or partial monosomies of the chromosomes involved in the structural aberration [7]. Sometimes these balanced rearrangements can be easily diagnosed under routine microscopy. In some cases, molecular methods such as FISH or microarrays may be necessary to accurately determine the type of rearrangement, breakpoints, duplicated or deleted segments, and potentially involved chromosomes due to the size or complexity of the aberration [8, 9].

The FISH technique, or fluorescence in situ hybridization, has been utilized in the field of science since the 1980s. It has many applications in the field of genetics, allowing the diagnosis of both congenital and acquired diseases. As a result, it is considered an invaluable diagnostic tool. [10, 11]

Material and methods. The cytogenetics laboratory of the National Center of Medical Genetics in Havana is a national reference laboratory for cytogenetic studies of patients at high genetic risk. Two patients were referred to the cytogenetics laboratory from infertility

clinic in the province of Pinar del Rio. Two patients, from Sancti Spiritus and Isla de la Juventud, with high genetic risk due to repeated miscarriages and advanced maternal age were referred to the laboratory for prenatal diagnosis.

First, patients were studied by conventional cytogenetics using GTG banding. If a conclusive diagnosis could not be reached then the FISH technology was applied.

Conventional cytogenetic analysis

1. Postnatal. Routine chromosome preparations were obtained by peripheral blood culture using standard protocols described in the AGT Cytogenetics Laboratory Manual [12]. It allowed chromosomal analysis and also FISH analysis on chromosomes.

2. Prenatal. Prenatal studies were performed by amniocyte culture at 16-20 weeks of gestation according to the protocols described in the TGA Cytogenetics Laboratory Manual [12] and adapted to the conditions of our laboratory.

FISH

VYSIS probes, specifically from ABBOT, were used to identify the rearrangements:

Supernumerary Marker Chromosome (SMC): LSI SRNPN spectrum green/CEP 15(D15Z1) spectrum red/ LSI PML spectrum orange probes or another variant of this probe with LSI SRNPN spectrum orange/CEP 15(D15Z1) spectrum green/ LSI PML spectrum orange for the detection of the critical region of PW/AS syndromes (Prader Willi-Angelman).

Aneuvision probe kits for α -satellite probes CEP 18 (p11.1-q11.1) labeled with SpectrumAqua fluorochrome, X (p11.1-q11.1) labeled with SpectrumGreen fluorochrome and Y (p11.1-q11.1) labeled with SpectrumOrange fluorochrome were used to identify chromosomes 18, X and Y.

Aneuvision probe kits for LSI probes 13 (13q14) labeled with SpectrumGreen fluorochrome and 21 (q22.13-q22.2) labeled with Spectrum Orange fluorochrome were used for the identification of chromosomes 13 and 21.

LSID5S23, D5S71 Spectrum Green/LSI EGR1 Spectrum Orange probes were used to

identify the regions of interest on chromosome 5.

For diagnosis, we relied on the computer program Cytovision version 3.9, Genus section (Applied Imaging, USA), which was used to capture and process images taken with Olympus microscopes (BX-51, Japan).

FISH molecular tests were performed according to the modifications applied in the laboratory based on the Aneuvision manufacturer's protocols.

Ethical aspects: In all cases, genetic counseling was provided to patients and informed consent was requested for the invasive sample collection procedure. Once the diagnosis was obtained, all unused samples were discarded. In the laboratory databases, each patient is assigned a code with which this work was performed, maintaining anonymity during

the processing of the information. The Ethical Committee for Scientific Research of the National Center of Medical Genetics approved the execution of this study.

Results

Case I

25-year-old woman, normal intellect, with fertility disorders due to multiple spontaneous abortions in the first trimester. Chromosomal study in peripheral blood detects a SMC. FISH study using the chromosome 15 probe to detect the PW/AS critical region showed that the SMC originated from chromosome 15 but did not comprise the PW/AS critical region (Fig. 1).

The FISH result was: 47, XX,+idic(15)(pter→q11.1::q11.1→pter).ish idic(15)(D15Z1++).

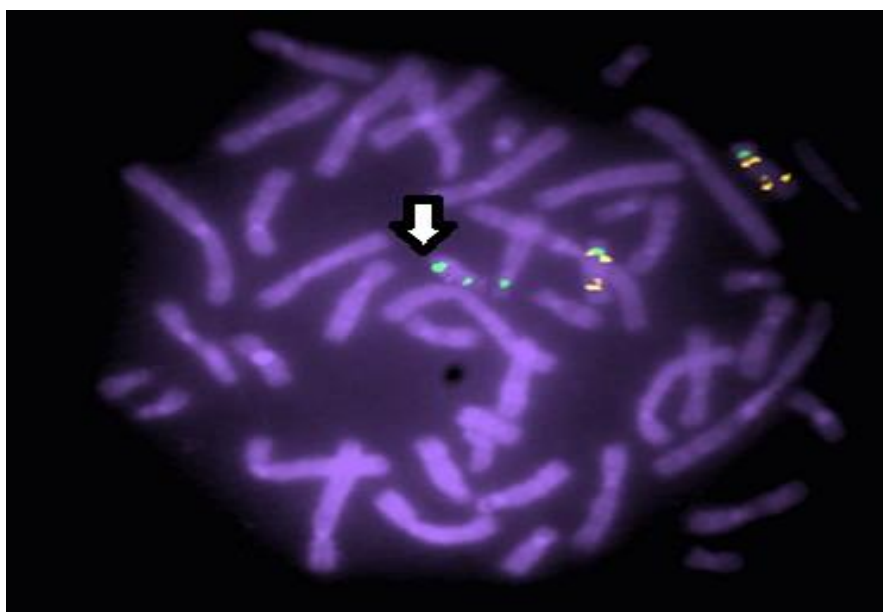


Fig. 1. SMC marked with an arrow. It has two centromeres towards its ends, it is a pseudo-isodicentric 15. Five centromeres (green), two q11-q13 regions and two q25 regions (yellow) are present in metaphase.

Case II

38-year-old woman with two previous pregnancies, the first a normal girl and the second a boy with Down syndrome. In the third pregnancy, prenatal diagnosis was performed and 47 chromosomes were detected in the fetal

karyotype, the origin of one of them could not be identified by conventional methods (Fig. 2).

Chromosomal study of the mother showed an unusual, apparently balanced 13;21 translocation (Fig. 3).

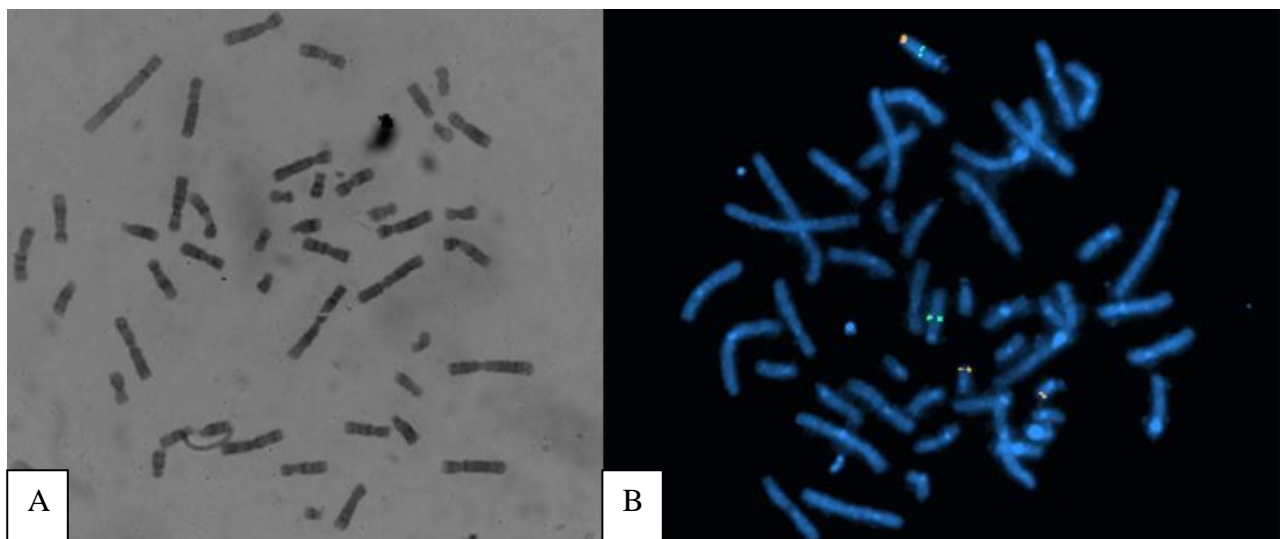


Fig. 2. A – Metaphase obtained from amniocytes during prenatal diagnosis, unidentified chromosome is indicated by the arrow. B – Fetal metaphase analyzed with FISH, using probes for the 13q14 region (green) and 21q22.13-q22.2 (yellow). Three signals were observed for the critical region of chromosome 21, one of them translocated to chromosome 13.

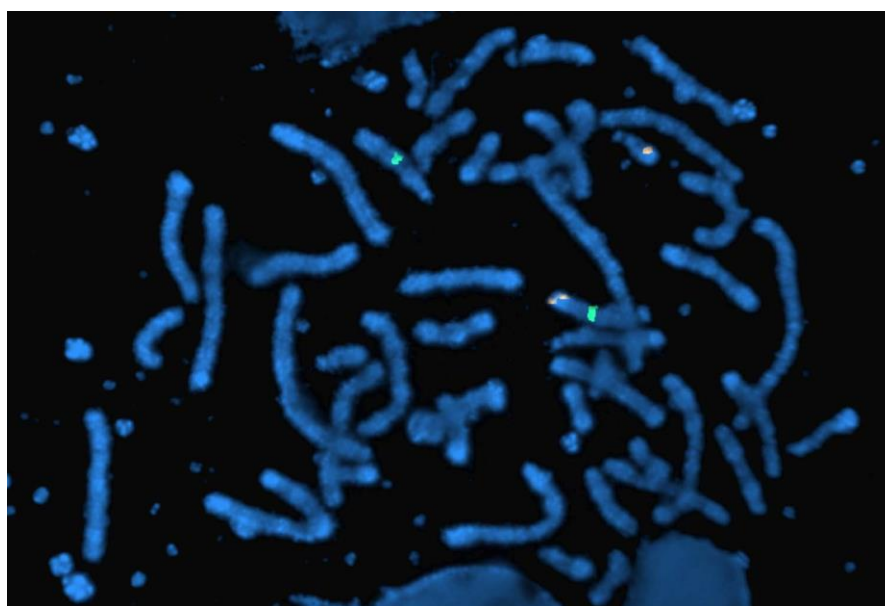


Fig. 3. The critical region of chromosome 21 (21q22.13-q22.2) is observed to be translocated to the 13q end of the maternal chromosome.

Once the FISH results (mother and fetus) were analyzed, conventional chromosome reanalysis led to the conclusion that the maternal karyotype was: 46,XX,t(13;21)(q22;q11.2). The fetal karyotype is due to a 3:1 segregation of maternal gametes: 47,XY,t(13;21)(q22;q11.2)mat+21. The couple decided to continue the pregnancy. The child was born but died at 11 months old. A subsequent study of the healthy girl showed that she carried the same rearrangement as the mother.

Case III

A 32-year-old woman with recurrent pregnancy losses. In conventional chromosome analysis, a rare chromosomal structure is detected, which is assumed to be a possible translocation of a chromosome 18 and a chromosome 21, since those two chromosomes are missing in the analyzed metaphases. FISH was performed with probes of chromosomes 21, 13, 18 and X to confirm this hypothesis (Fig. 4).

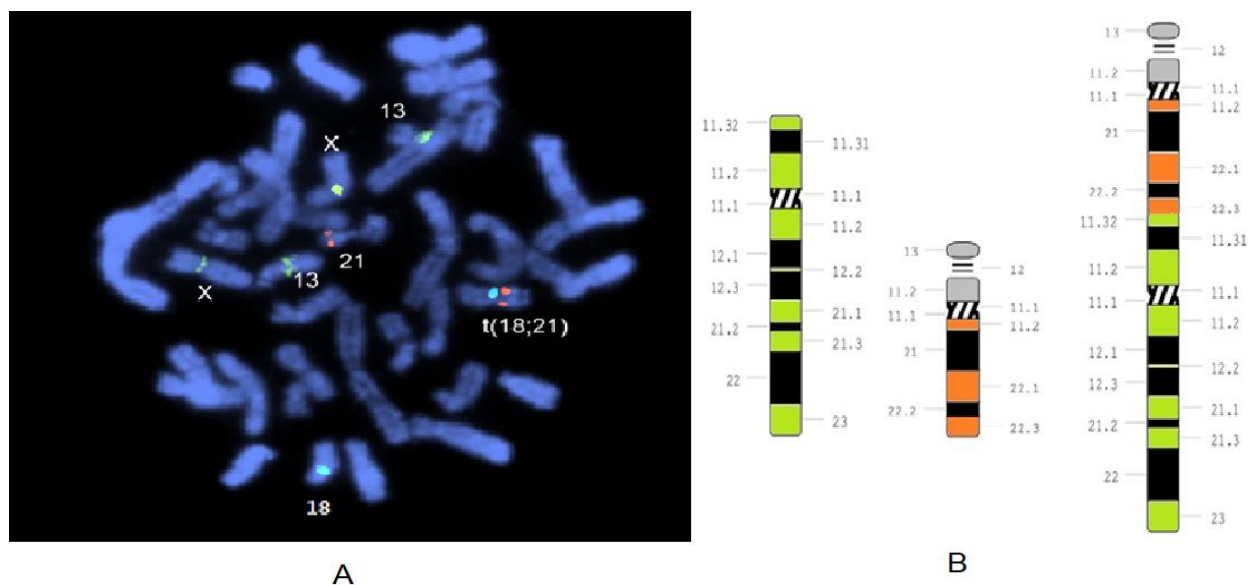


Fig. 4. A – Metaphase with labeling of chromosomes 21 (red),13(green),18 (aqua) and X (light green). The 18;21 translocation is observed. The 21qter region binds to the 18pter forming an apparent dicentric structure. B – Translocation ideogram 18;21. Karyotype: 46,XX,tas(18;21)(p11.3;q22.3)

Case IV.

40-year-old woman with history of infertility. A prenatal diagnosis is carried out due to the advanced age of the mother. Prenatal ultrasound at 22 weeks' gestation revealed an increased nuchal fold (7.1 mm) and intrauterine growth retardation in the fetus, and later a heart defect (ventricular septal defect). In the fetal karyotype, a chromosome 5 with an altered GTG banding pattern was observed, though it was not possible to determine the nature of this rearrangement. The FISH test is

performed with chromosomal probe 5 used for the detection of Cri-du-Chat syndrome (Fig. 5). After analyzing the FISH results and in light of the altered GTG banding pattern observed, it was concluded that the fetal karyotype was 46,XY,inv(5)(p12q31.1). The couple decides to terminate the pregnancy. Chromosomal analysis of both parents reveals a pericentric inversion of chromosome 5 in the mother, similar to that in the fetus.

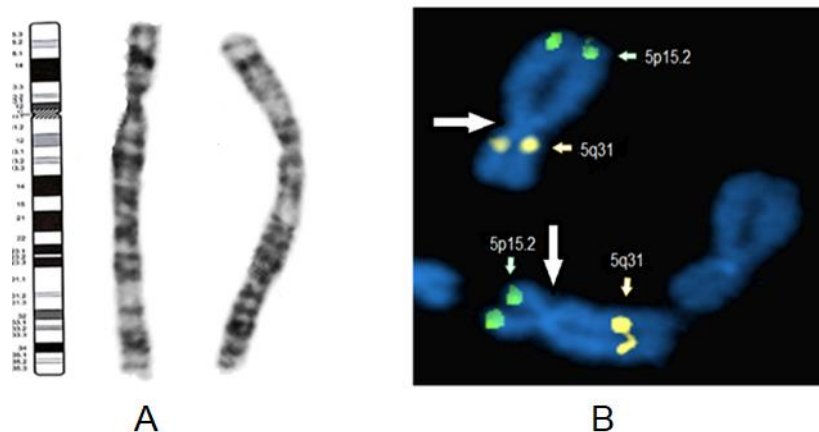


Fig. 5. A – Chromosome 5, GTG banding. B – Chromosome 5 labeling on the short arm (5p12.1) is green and on the long arm (5q31.1) is yellow. The inferior chromosome 5 shows normal labeling

with correct centromere localization. Chromosome 5 above shows a pericentric inversion. Note the change in centromere position (arrow), now closer to 5q31.

Discussion. The FISH technology has been used internationally to discover the genetic causes of neurodevelopmental disorders [13, 14], aberrations involved in cancer development [15, 16], and many other applications. In the present study we demonstrate the application of this technique for studies of reproductive disorders.

Although structural chromosomal aberrations are among the least common, they are widely implicated in reproductive disorders and are high risk factors for recurrent miscarriage, birth of affected children with malformations and/or dysmorphic features, and intellectual disability [7]. This study describes four cases with these types of aberrations, each of which will be discussed.

SMC from chromosome 15

A study by Liehr and Weise reported 41 marker chromosomes in 30,510 infertility patients and detected an overall rate of 0.125% of sSMC carriers. They found 36/21,841 (0.165%) male and 2/9,165 (0.022%) woman sSMC carriers. [17]

Between 25-50% of all SMC originate from chromosome 15. Most of them result from inversion duplication of 15 (inv dup (15)) or also called pseudo isochromosome 15 (psu dic(15;15) with an incidence of 1 in 30,000 cases. [18, 19]

When SMC involves only the inversion and duplication of 15 from the centromere to the q11.1 band, neurodevelopmental disorders are generally not present, this is explained because in this region there are no genes involved, that is, it is composed of the centromeric and pericentromeric heterochromatin of chromosome 15, which is a highly repetitive DNA. [20, 21, 22]

In this case, the carrier is not intellectually disabled, but has fertility problems. According to several literature reports, the presence of inv dup (15) can interfere with the process of meiosis during gametogenesis. SMC can lead to disruption of the correct pairing of homologous chromosomes causing aneuploidy, which is known as the interchromosomal effect. [23, 24, 25]

In this case a centromeric region of a chromosome other than 15 appears marked in green, this is due to some kind of polymorphism of the repetitive DNA region of the centromere of this acrocentric chromosome that causes it to be marked with the D15Z1 probe. This event has also been reported by other authors. [26]

Reciprocal Translocations

Reciprocal chromosomal translocations (RCTs) are the most frequent structural rearrangements in humans. The incidence of these translocations is estimated at 1 in 712 live births, and the frequency at the time of prenatal diagnosis is even higher, approximately 1 in 250 pregnancies. [27]

Two unusual translocations are described, the first 46,XX,t(13;21)(q22;q11.2) in a pregnant woman who already had a normal girl and a boy with Down syndrome. The fetus had a 3:1 segregation of the exchange trisomy type, in which the two derived chromosomes, der(21) and der(13) plus the maternal chromosome 21 segregate into one of the oocytes, forming a fetus with trisomy 21 during fertilization. It is likely that in this woman there were silent recurrent miscarriages due to adjacent type 1 or 2 segregations where there will be partial monosomies of chromosomes 13 and 21 [28]. Cohen et al. in a review of 1159 families carrying translocations found that the proportion of chromosomally unbalanced offspring was 71% with adjacent segregation type 1, 4% with adjacent segregation 2, 22% with tertiary trisomy/monosomy and 2.5% with trisomy Exchange [29].

Each couple and rearrangement involved must be analyzed on a case-by-case basis. Thus, taking into account the chromosomes and chromosomal segments involved in this case, it is possible to explain the conception of the child with trisomy 21. The 3:1 segregation in any of its variants will make the birth of the baby more feasible. Partial or total trisomies, 21 or 13, that form after fertilization are compatible with subsequent life and development.

The other translocation to be analyzed 46,XX,tas(18;21)(p11.3;q22.3) is more unusual. This rare translocation, in which the two complete chromosomes and their two centromeres are involved, represents one of the exceptional events of formation of a constitutional dicentric, which does not involve acrocentric chromosomes, and which is stable in the different cell divisions. Few such cases have been reported in the literature [30, 31].

Presumably, this stability is achieved by inactivation of one of the two centromeres, but this is only a hypothesis that the authors have not been able to corroborate. In this case, both adjacent segregations will give disomic gametes that may produce trisomy 21 or 18. In 3:1 segregation, double trisomies 13 and 18 would occur. In these cases, the percentage of reproductive disorders is high (miscarriages, children with malformations, neonatal deaths, etc.).

Dicentric chromosomes are rarely reported as constitutional events and usually cause severe phenotypic disorders in carriers [30, 32]. On the other hand, in the case that we have reported, the patient only had disturbances in the reproductive sphere.

Chromosome 5 pericentric inversion

Chromosomal inversions are usually balanced events and have been shown to be inherited in 85-90% of cases [33, 34]. The study of inversions is clinically relevant in part because they can lead to recombinant chromosomes in gametes, which could cause serious problems in offspring [34].

In the present case, it appears that the fetus inherited the same translocation as the mother. In theory, he should have been phenotypically normal. At the microscopic level, it is impossible to detect subtle deletions or duplications that may occur at breakpoints when an inversion is transmitted from a parent to its offspring, and this risk increases when the inversion occurs *de novo* [35].

Webb et al. report the case of a family carrying an inv(15)(p11q13) for three generations; when the inversion was passed from mother to child, a deletion in the critical region for Angelman syndrome occurred and the child developed this condition. This small deletion

could only be diagnosed by molecular methods [36]. On the other hand, a boy with Prader-Willi syndrome, whose grandmother and father were carriers of inv(15)(p11q12), had a deletion in 15q12, as reported by Kähkönen et al. [37]

In the case reported in this paper, one of the sites involved is the 5q31 locus. Literature reports show that *de novo* deletions in this region can cause the so-called PURA-Related Developmental and Epileptic Encephalopathy syndrome [38]. Cardiac anomalies may be present in 11.2% of these patients, as was detected prenatally in our case [38].

Unfortunately, in our case, molecular methods could not be used to detect a possible deletion at the breakpoints of chromosome 5. Another possibility could be that the inversion of this family is actually balanced and that the child's phenotypic conditions are due to a mutation elsewhere in his genome or to some epigenetic phenomenon not elucidated in our study.

Limitations: The lack of diagnostic methods such as SNP microarrays has made it impossible to detect possible microdeletion-duplications which in some cases would have complemented the results obtained by the FISH method.

Conclusion. The present study is a demonstration of the importance of the FISH technology for the characterisation of subtle genomic aberrations causing reproductive disorders in female carriers. The effect of chromosomal aberrations, whether balanced or not, on the formation of altered germ cells that cause reproductive disorders has been discussed.

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Conflict of interests

The authors have no conflict of interest to declare.

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