Cytogenetic abnormalities and reproductive failures

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ABSTRACT

Abnormal reproductive outcomes, also defined as “reproductive failures” include a wide variety of problems as: infertility, pregnancy loss, abnormal pregnancy, birth defects, and childhood cancer. The cause of almost any reproductive abnormality can be the result of genetic and physiological events that occurred in mother, father and child.

Among reproductive failures causes, chromosomal changes are encountered quite frequently. In order to identify the cytogenetic causes potentially involved in the reproductive failures, we investigated 128 persons. From this, 102 were individual persons or partners in infertile couples, and the other 26 cases were members of 9 different families.

Short term cell cultures from peripheral blood, cell-cycle synchronization, standard methods for cytogenetic slides, conventional GTG and CBG banding techniques have been used for cytogenetic investigations.

Numerical and structural aberrations were identified in 14.7% of cases. Aneuploidy of sex chromosomes, deletion of short arms of Y and X chromosomes was identified mostly in mosaic form. In 5% of cases with spontaneous abortions pericentric inversion inv(9)(p12q13), was identified. A Robertsonian translocation t(13;14) was found in a Prader-Willi boy who inherited the cytogenetic abnormality from his healthy mother. Balanced inherited rearrangements were found in 5 families, maternally transmitted in 3 families, and of paternal origin in 2 families. Overall, 8 cases with normal phenotype proved to be carriers of balanced rearrangements.

Our results underline the importance of cytogenetic investigation in all instances of reproductive failures, to offer a well informed genetic counseling and improve the management of these cases.

Key words: cytogenetic abnormalities, reproductive failures, aneuploidy, translocation, azoospermia, primary amenorrhea

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INTRODUCTION

Human reproduction may be considered the most important demographic phenomenon, because only by it functions a healthy society is insured and maintained. Reproductive failures include a wide variety of problems as: infertility, pregnancy loss, abnormal pregnancy, birth defects, childhood cancer and are more common than many people realize. Yearly, millions of conceptions are lost in the first trimester of gestation all over the world, millions of couples who want to have children are infertile, up to 10% of newborns have low birth weight, or are born with some major birth defects affecting the health and viability of the individual. The psycho-social and medical costs of reproductive abnormalities are inestimable, yet their causes are not well understood. It is very difficult to establish a specific cause of a reproductive abnormality, because it can be the result of genetic and physiological events that occurred in mother, father, or child. Each of the reproductive failures is generated by different molecular or cellular mechanisms, which means different ways for investigation, diagnosis and treatment. Establishing the specific cause of reproductive failure is not a simple task, and many cases remain classified as “unexplained infertility” (1,2). It is well documented that chromosomal abnormalities are involved in first trimester spontaneous abortions. Cytogenetic evaluations of these specimens have revealed an overall incidence of chromosomal abnormalities of 50–70% (3,4,5,6).

Many question marks arise when we try to establish a relationship between cytotogenetic changes and reproductive failures. Constitutional chromosomal abnormalities with great risk to be transmitted to offspring are rare, but their discovery is of crucial importance in prevention of spontaneous abortion and recurrent miscarriage (7). Among couples with two or more abortions ~ 4.7% include a carrier of a balanced structural abnormality (7,8). In such cases, the therapeutic measures to enhance fertility are worthless and even contraindicated for patients carrying balanced chromosomal abnormalities, because the consequence can be delivery of children with serious genetic abnormalities. In change, de novo numerical abnormalities is the most common cause of spontaneous abortions, in particular autosomal trisomies for chromosomes 13, 14, 15, 16, 21 and 22, followed by monosomy X (6,9,10).

For the most common trisomies it has been shown that the incidence of chromosomal abnormalities decreases with the gestational age (9), in such a manner that in stillborns it is ~ 6% (11,12) and in live births 0.6% (12). This pattern of negative selection against chromosomal abnormalities between implantation and birth operates mainly during the pre-implantation period. In fact, autosomal monosomies are rarely found in spontaneous abortions and are thought to be responsible for preclinical abortions (3,6,9). This mechanism of natural selection may also operate during preimplantation embryogenesis, with a progressive loss of abnormal embryos at specific stages in early development, through developmental arrest and degeneration of abnormal embryos.

Some of the following instances where chromosomal abnormalities may be identified are: women with primary amenorrhea, infertile males, in aborted tissues, in couples with recurrent abortions, in parents of children with congenital malformations and in children with congenital malformations.

The indication for genetic exploration has to be made before deciding the beginning of some form of treatment; thus the patients carrying a chromosomal abnormality will not be exposed to an unacceptable genetic risk. The carriers of balanced chromosomal abnormalities have not phenotypic manifestations, making them unidentifiable until reproduction age.

Reproduction failure can be absolute (infertility, spontaneous abortions, and still-births) and relative (congenital malformation, genetic syndromes, mental retardation).

Infertility affects ~10%-15% of couples who attempt pregnancy, thus representing an extensive phenomenon. The prevention and the control of reproductive failures begin with the study of etiology and necessitate multidisciplinary investigations. Among these, cytotogenetic investigations are very useful, because infertility can be caused by a chromosomal abnormality. Over 600 types of chromosomal abnormality have been discovered and their incidence in humans has been evaluated. In this study, the results of cytotogenetic investigations performed in cases with absolute or relative reproduction failures, are presented.

CASES

In order to identify the cytotogenetic changes potentially involved in reproductive failures, we investigated 128 persons.
In this study we included 47 infertile couples plus other 8 individual infertile cases (6 women and 2 men), and 26 cases from 9 families with chromosomal abnormalities. All patients were referred to the Medical Genetic Laboratory from “Victor Babes” National Institute and to Filantropia Hospital, for absolute or relative reproductive failures and/or for investigation of children with syndromic or idiopathic mental retardation. Participating families gave informed consent, according to the new bioethical rules.

**METHODS**

Chromosomes were prepared from peripheral blood cultures following standard procedures. Fixed cytogenetic preparations were obtained after short term (72h), phytohemagglutinine-stimulated cultures. GTG and CBG banded slides were used for analysis. All cytogenetic studies were performed by analyzing at least 30 GTG-banded metaphases, using Nikon and Zeiss microscopes. For image processing, LUCIA and Metasystems Karyotyping Softwares were used.

**RESULTS AND DISCUSSIONS**

The patients have been grouped in three categories: couples, individuals, and families. All couples investigated were non-consanguineous. Also the children have non-consanguineous, healthy parents.

- **COUPLES**
  
  In Table 1 are synthesized the results obtained in 94 cases out of 47 couples having absolute or relative reproductive failures. Eighty percent of investigated couples were considered in the group of absolute reproductive failures because they had recurrent abortions, infertility or had stillborns.

  The karyotype was normal in 35 of the investigated couples (28 with absolute reproductive failure and 9 with children with congenital malformation/mental retardation). In the remaining 12 couples, one partner presented structural or numerical chromosomal changes. In our study group, females are predominantly bearing cytogenetic abnormality (9 females:3 males). None of the couples had both partners affected by a cytogenetic anomaly.

  **Pericentric inversion involving chromosome 9** was detected in 4 of 10 cases with cytogenetic changes in the group of couples with absolute reproductive failures (3 women and one man) (Figure 1, 2). In our study, pericentric inversion involving chromosome 9 was detected in 4.2% of total number of 94 infertile persons.

![FIGURE 1](gtg-banded-male-karyotype.png)
who had presented two or more spontaneous abortions due to indeterminate causes (13). The control group was made up of 384 individuals. The chromosomal studies have included GTG, CBG, NOR and high resolution banding. Ten couples (representing 8.3%) had major chromosome aberrations and 33 couples (representing 27.5%) showed a polymorphic chromosome 9. Pericentric inversion involving 9q region was detected in 9.1% of the couples and in 1.3% of the samples from the control group. In all cases, the breakpoints were located in euchromatic region, confirming the cytogenetic cause of early recurrent abortions. The origin was maternal in 80% of cases. The research results of the authors have indicated a correlation between pericentric inversions of chromosome 9 and recurrent abortions.

Another structural modification identified by us, in a female who had two spontaneous abortions, was a pericentric inversion affecting chromosome 7 (Figure 3). The karyotype of the case is: 46,XX,inv(7)(p11q32), and it is the first reported case bearing such a structural abnormality in connection with reproductive failures. Even though, having into account the size of inverted region, we can speculate that it could be the main cause of early recurrent abortions in this case.

Numerical mosaics of sex chromosomes were identified in 5 cases: 4 females and one male with absolute reproductive failures. In addition, one of the females with numerical mosaics had a deletion of the short arm of X chromosome in 6.3% of investigated cells. The partial deletions of short arm of the X chromosome are known to be compatible with fertility in some cases but they could induce a significant ovarian insufficiency, with Turner signs or gonadal dysgenesis in other cases.

Vjatkina et al. (14) reported the case of a family in which the mother (54 years) and two daughters (27 years) with short stature but without other Turner syndrome features had the same chromosomal anomaly. In their study, 46,X,del(X), non-mosaic karyotype was established by standard cytogenetic techniques and FISH with (Xp21.1) locus-specific DNA probe. By reverse chromosomal banding technique (RBA) was established that abnormal X chromosome was always late replicating in all examined cells. One of the two sisters had a 8 months old daughter with 46,XX normal karyotype. The other one was pregnant and prenatal.

The chromosome heteromorphism involving pericentromeric region of chromosome 9 has been associated to early recurrent abortions, even though, results and opinions about the clinical significance of pericentric inversions remain contradictory (13).

Martelli & al. (2001) have performed cytogenetic investigations of 120 unrelated couples who had presented two or more spontaneous abortions due to indeterminate causes (13). The control group was made up of 384 individuals. The chromosomal studies have included GTG, CBG, NOR and high resolution banding. Ten couples (representing 8.3%) had major chromosome aberrations and 33 couples (representing 27.5%) showed a polymorphic chromosome 9. Pericentric inversion involving 9q region was detected in 9.1% of the couples and in 1.3% of the samples from the control group. In all cases, the breakpoints were located in euchromatic region, confirming the cytogenetic cause of early recurrent abortions. The origin was maternal in 80% of cases. The research results of the authors have indicated a correlation between pericentric inversions of chromosome 9 and recurrent abortions.

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One of the 3 males with karyotype modifications in our study had a deletion of the short arm of chromosome Y, which may correlate with sterility in this case. In the development of the male sex, the presence and the integrity of the Y chromosome is decisive, because it contains SRY gene and many other genes involved in spermatogenesis (15).

Cytogenetic investigation was also recommended in couples with relative reproductive failures, for history of dysmorphic children, genetic syndromes or idiopathic mental retardation. In 2 of these couples chromosomal anomalies were found in one partner.

In the first couple, father exhibited normal karyotype, but the mother had a centric balanced translocation, which resulted in a hypodiploid karyotype 45,XX,t(13;14).

The second couple had a history of three perinatal unexplained deaths. The karyotype of female partner showed numeric mosaics of sex chromosomes: 45,X(6,2%)/46,XX,del(Xp)(6,3%)/46,XX(87,5%).

- INDIVIDUALS

Beside 47 couples, another 8 adults were investigated: 6 women with absolute reproductive failures (3 with primary amenorrhea) and 2 men with azoospermia. The data are presented in the Table 2.

The clinical diagnosis of the 6 female patients was infertility, recurrent abortions, and primary amenorrhea. The male patients were azoospermic.

Only one of the 3 women with primary amenorrhea had a mosaic karyotype with X monosomy in 85% of the cells. In this case, the etiology of infertility is cytogenetically justified. The other two females with primary amenorrhea showed normal karyotypes.

One of the women with history of spontaneous abortions, had 7 recurrent miscarriages and a mosaic karyotype: 45,X[10]/46,XX[40]. A non-mosaic 46,XX karyotype was found in one of the cases with azoospermia, by GTG and CBG banding.

The total incidence of numeric and structural cytogenetic changes established in 102 infertile cases is 14.7%.

- FAMILIES

Cytogenetic investigations were extended to family members, in order to establish the de novo or inherited nature of the abnormalities identified in our study group. So, a total of 26 persons were investigated in 9 families (Table 3).

Family 1: cases 1/1, 1/2, and 1/3 in table 3.

In this family the investigation started from a child (proband) with a mosaic karyotype with two cellular lines: 45,X/46,X,isonic(Y)(qter → p11.2::p11.2 → qter) (16). The child was 11 year-old when recommended for karyotype examination, because of ambiguous genitalia and Turner stigmata. The rearrangement has been diagnosed by GTG (Figure 4) and CBG banding methods and fluorescent in situ hybridization (FISH). Cytogenetic investigations were extended to parents with the aim to establish if the abnormal Y chromosome has been inherited or it is de novo. Both parents revealed normal karyotype, so that, the structural abnormality of Y and mosaic karyotype of the proband proved to be de novo. In the meantime, the couple got a healthy son, with normal karyotype.

### Table 2. Cytogenetic findings in individual cases with reproductive failures

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Karyotype formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>27 y</td>
<td>F</td>
<td>Infertility</td>
<td>46,XX</td>
</tr>
<tr>
<td>2.</td>
<td>33 y</td>
<td>F</td>
<td>7 spontaneous abortions</td>
<td>Mosaic: 45,X[10]/46,XX[40]</td>
</tr>
<tr>
<td>3.</td>
<td>36 y</td>
<td>F</td>
<td>2 spontaneous abortions</td>
<td>46,XX</td>
</tr>
<tr>
<td>4.</td>
<td>19 y</td>
<td>F</td>
<td>Primary amenorrhea</td>
<td>46,XX</td>
</tr>
<tr>
<td>5.</td>
<td>23 y</td>
<td>F</td>
<td>Primary amenorrhea</td>
<td>Mosaic: 45,X[42]/46,XX[8]</td>
</tr>
<tr>
<td>6.</td>
<td>25 y</td>
<td>F</td>
<td>Primary amenorrhea</td>
<td>46,XX</td>
</tr>
<tr>
<td>7.</td>
<td>44 y</td>
<td>M</td>
<td>Azoospermia</td>
<td>46,XY</td>
</tr>
<tr>
<td>8.</td>
<td>28 y</td>
<td>M</td>
<td>Azoospermia</td>
<td>46,XY</td>
</tr>
</tbody>
</table>

F= female; M= male
Family 2: cases 2/1, 2/2 and 2/3 in Table 3.

The proband (P) was a male case investigated for Prader-Willi syndrome (PWS). PWS is a neurodegenerative disorder, characterized by mental retardation, short stature, poor motor skills, weight gain, underdeveloped sex organs, mild mental retardation and learning disabilities. The critical region for PWS has been established to 15q11-q13. In a majority of cases (~70%) the mechanisms responsible for PWS is a deletion occurring in the critical region of paternally derived chromosome 15. In almost 25% of cases, unimaternal disomy generates the same phenotype. The remaining cases are due to other mechanisms (mutation, deletion in other regions). In our case, GTG banding was used to reveal the microdeletion on the long arm of chromosome 15q. Surprisingly, we found that, instead 46 chromosomes, his karyotype was 45,XY,t(13;14). The Robertsonian translocation t(13;14) was found also in the proband’s healthy mother, while his father showed a normal karyotype. The balanced translocation t(13;14) maternally inherited is not involved in Prader-Willi syndrome. The couple has another normal girl. The translocation is inherited and could be at risk of recurrence.

Family 3: cases 3/1, 3/2 and 3/3, table 3.

The proband is a 34 year-old man and he was referred for karyotype examination because his wife had seven recurrent pregnancy losses. Both partners of the couple were investigated. In the carrier’s karyotype a balanced rearrangement consisting in a pericentric inversion inv(5) (pter→q12) has been revealed. His wife exhibited normal karyotype. After seven spontaneous abortions, the eighth pregnancy resulted in a healthy son who inherited the pericentric inversion inv(5) from his father (Figure 5), followed by another 3 miscarriages. The balanced rearrangements of the chromosome 5 proved to be transmitted, but the carriers are at significant risk of recurrence.

Family 4: cases 4/1, 4/2, 4/3 and 4/4 in Table 3.

A constitutional balanced translocation t (3; 5) has been identified by chance in a 72 year-old woman who requested a cytogenetic exam as a completion of essential thrombocytaphernia diagnosis. Instead what we expected, we had an unbelievable surprise: the presence of translocation t(3;5) both in the bone marrow cells and in peripheral blood lymphocytes. So, the rearrangement was constitutional, without any apparent connection with the carrier’s disease. We extended cytogenetic investigations to the offspring: one daughter and 2 grandchildren of different sex. The proband’s daughter and granddaughter inherited the balanced translocation t(3;5), while the grandson showed a normal karyotype (17). Regarding the fertility

FIGURE 4. Mosaic karyotype 45,X[90]/46,X,idic(Y)[10]. Hypodiploid karyotype on the left (A) and pseudodiploid karyotype, on the right (B); GTG banding.
issue, the proposita had a single daughter who was treated for infertility. The proband’s grand-daughter and grandson fertility potential is not assess due to their young age. The translocation has been proved to be maternally transmitted for three generations (Figure 6). Constitutional chromosomal abnormalities with great risk to be transmitted to offspring are rare, but their discovery is of crucial importance in prevention of spontaneous recurrent miscarriage.

**Family 5:** cases 5/1, 5/2 and 5/3 in table 3.
Three members of this family were investigated. The reason for karyotype recommendation of the proposita was infertility: she has a history of four early pregnancies losses. Her karyotype exhibited a balanced translocation t(15;18) inherited from her mother who carried the same translocation (Figure 7). As in the case of other balanced rearrangements, the carriers in this family are healthy but they are at high risk of recurrence for spontaneous abortions.

**Family 6:** cases 6/1 and 6/2, Table 3.
The family includes a couple with a history of 6 recurrent abortions. The male partner proved to be a carrier of a balanced translocation t(5;13) (Figure 8). Vertical investigations were not further possible. The balanced change generates an increased risk of reproductive failure.

**Family 7:** cases 7/1, 7/2 and 7/3, Table 3.
The starting point for the cytogenetic investigation was a 7 month-old child with mental retardation and dysmorphic features, bearing a deletion 1q42 (Figure 9). He is the second child of the family, the first born being healthy. This case does not fit in a certain syndrome. The 1q 42 deletion has been reported in another 4 cases up to the present; the ventricular enlargement and brachicephaly are the only shared features; the rest of the clinical signs are particular to our case. In both parents, the karyotype was normal, confirming the de novo nature of this abnormality.

**Family 8:** cases 8/1, 8/2 and 8/3, Table 3.
The start point of investigation was a dysmorphic girl (macro-cranium and micrognathism) aged 5 years and a half. In addition, she was mentally retarded (consisting mostly in language dysfunctions). Chromosome studies revealed an interstitial deletion within band 3q22 of the long
arm of chromosome 3 (Figure 10). Cytogenetic investigation extended in both of her parents showed normal karyotypes. The abnormality seems to be de novo. Interstitial deletions of the long arm of chromosome 3 are rare cytogenetic abnormalities and the relatively small

<table>
<thead>
<tr>
<th>Family no.</th>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Diagnosis/position in genealogic tree</th>
<th>Karyotype formula</th>
<th>Inheritance pattern</th>
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<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>11 y</td>
<td>F/M</td>
<td>Turner S, ambiguous genitalia/Proband</td>
<td>Mosaic 45,X[90]/46, idic(Y)(p11qter)(10)</td>
<td>de novo</td>
</tr>
<tr>
<td>2</td>
<td>37 y</td>
<td>F</td>
<td>Healthy, fertile woman/Proband's mother</td>
<td>46,XX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>35 y</td>
<td>M</td>
<td>Healthy, fertile man/Proband's father</td>
<td>46,XY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17 y</td>
<td>M</td>
<td>Prader-Willi S/Proband</td>
<td>45,XY,t(13;14)</td>
<td>Inherited</td>
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<tr>
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<td>38 y</td>
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<td>Healthy woman/Proband's mother</td>
<td>45,XY,t(13;14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>40 y</td>
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<td>Healthy man/Proband's father</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>33 y</td>
<td>M</td>
<td>Infertile man/Proband</td>
<td>46,XY,inv(5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>34 y</td>
<td>F</td>
<td>7 spontaneous abortions / Proband's wife</td>
<td>46,XX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>new-born</td>
<td>M</td>
<td>Healthy infant/Proband's son</td>
<td>46,XY,inv(5)</td>
<td>Inherited</td>
<td></td>
</tr>
<tr>
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<td>72 y</td>
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<td>Essential thrombocytopenia/Proposita</td>
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<tr>
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<td>41 y</td>
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<td>46,XX,t(3;5)</td>
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<tr>
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<td>18 y</td>
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<td>46,XX,t(3;5)</td>
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<tr>
<td>4</td>
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<td>M</td>
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<td>46,XY</td>
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<tr>
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<td>46,XX,t(15;18)</td>
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<tr>
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<td>M</td>
<td>Healthy man/Proposita's partner</td>
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<tr>
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<td></td>
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<tr>
<td>3</td>
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<td>M</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>4 y</td>
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<td>del(3)(q22)</td>
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<tr>
<td>2</td>
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<td>32 y</td>
<td>M</td>
<td>Proposita's father</td>
<td>46,XY</td>
<td></td>
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</tr>
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</table>

F = female; M = male
dismorphic features was considered a deletion in the long arm of chromosome 3, band 23. Our case does not fit in the BPES syndrome neither by phenotype nor by deleted band on chromosome 3.

**Family 9: cases 9/1, 9/2, 9/3**

The investigation started from a new-born girl with dysmorphic feature suggesting cranio-oculo-facio-skeletal syndrome: microcephaly, craniostenosis, eye malformations (severe microphthalmia with bilateral cataract), left hand polydactyly, and bilateral renal malformations. Cytogenetic examination showed free trisomy 13 in 100% of the analyzed cells, confirming thus the diagnosis of Pattau syndrome. Both parents exhibited normal karyotypes. The couple conceived a second normal child.

Among the structural chromosomal changes whose pattern of inheritance has been followed in a limited number of families, in our study: five were balanced (reciprocal translocation, inversion) and three were unbalanced (isochromosome, deletion). Only balanced abnormalities were found to be inherited: – on maternal line: t(3;5) [three successive generations]; t(15;18) and t(13;14) for two successive generations each;– paternally transmitted: pericentric inversion, inv(5). This chromosomal anomaly is frequently reported in reproductive failure (19). From a total of eight abnormalities investigated in our families group, three were "de novo".

**CONCLUSION**

The results of this study underline the necessity of a full-scale preconceptional, preimplantational and prenatal diagnosis in all cases with reproductive failures, for the following reasons:

- Twelve from 102 persons with different forms of infertility exhibited a chromosomal anomaly microscopically visible as balanced or unbalanced rearrangement, extra or lost material – causing infertility, pregnancy loss, abnormal pregnancy, birth defects, syndromic or idiopathic mental retardation.

- The preventive role of identification and characterization of chromosomal abnor-
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malities must not be underestimated both in those cases already experiencing reproductive failures, and in non-symptomatic carriers.

- The risk of recurrence is absent for de novo cases (del 3q22 and 1q42) and is high for those inherited ones. Balanced translocations and inversions are identified frequently at adult age, because they don’t generate abnormal phenotype.

- The chromosomal aberrations cannot be corrected or cured!

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References


