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RECURRENT MISCARRIAGE IN A NOVEL TRANSLOCATION 7; 9 CARRIERS WITH NO INFERTILITY

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Abstract

A balanced translocation between the short arm of chromosome 7 and the long arm of chromosome 9 was observed in a pedigree of three carriers (proband, his daugther and first cousin). In this study, the proband and first cousin have no infertility problems, they had phenotypically normal progeny but shows recurrent miscarriage. Cytogenetic analysis of metaphase chromosomes was performed, the karyotype of the proband carrier was determined as 46, XY, t(7;9)(7pter→7p12;9qter→9q34::7p12→7qter). The study of this family is important because to our knowledge there have not previous report with the same translocation, and it has been transmitted through generations. In conclusion, the most striking finding was the non-existence of unbalanced offspring after detecting a structural chromosome abnormality in the parents. To understand the cytogenetic and clinical significance of this case the authors discuss the possible causes of recurrent miscarriage. Detection of chromosomal abnormalities in spontaneous abortion materials is very important to clarify the causes of loss of pregnancy. The evaluation of the incidence of segregation products of balanced translocation in sperm nuclei of carriers can be evaluated by FISH, using the proper combination of probes, and will give patients more accurate genetic advice and helps to personalize the reproductive risk in male carriers of balanced translocation 7:9.

Introduction

Recurrent miscarriage (RM) is a common problem in reproductive medicine. Couples who have two or more miscarriages are at increased risk of a structural chromosome abnormality in one of the partners. Translocation and inversion carriers are usually phenotypically normal, but meiotic segregation errors can lead to miscarriage, stillbirth or birth of a child with major congenital defects and severe mental handicaps [1-3]. A balanced structural chromosome abnormality is found only in 2–6% of couples with RM [1-3]. The probability of a child with an unbalanced chromosomal abnormality in carrier couples with RM is estimated to be below 1% [4, 5]. The risk of an unbalanced fetus varies according to the type of rearrangement and the chromosomes involved.

Couples with a balanced rearrangement with a high risk of recurrent miscarriage usually have a low risk of an unbalanced ongoing pregnancy, which is in contrast with the risk of 25 or 50% of affected offspring in monogenic disorders [4].

Here, we report a pedigree of three members with the t(7;9)(7pter→7p12;9qter→9q34::7p12→7qter), with no reduction of fertility. To our knowledge there have not previous report with the same translocation.

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Clinical findings

A couple, a 35-year-old man and a 32-year-old women, were referred by cytogenetics consultant because the woman had three pregnancies resulting in two normal infants and one spontaneous abortion. The chromosomal status of this abortion was not investigated. The couple were interviewed and evaluated to identify both personal and medical histories of clinical abnormalities. Informed consent, medical history, clinical evaluations, echocardiographic scanning, biochemical tests, and genetic analysis were obtained from the participants.

The couple had no abnormal symptoms and the physical examinations showed both to be phenotypically normal, including their reproductive systems. No family history of congenital anomalies or sterility was determined from either the husband or wife. In total, we recruited information of 54 subjects from these family networks of Gypsies in San Luis, Argentina, with complex genealogical relationships.

There was paternal family history of consanguinity and hereditary diseases (thalassemia).

Relationships between the parents are of two types: close, as between first or second cousins, and non-existent, as in mixed marriages. There are three consanguineous marriages between first cousins (I-1 with I-3; I-2 with I-4 and II-7 with II-8) and two consanguineous marriages between second cousins (III-8 with III-9 and III-12 with III-13). Moreover, the patrilineal relatives show recurrent miscarriage. There was thirteen spontaneous abortions occurred at irregular times, in different members of the family, and suggested a possible chromosomal problem, since there was no evidence of any uterine abnormality or any other underlying disease during the pregnancies. None of the matrilineal relatives exhibited consanguinity or miscarriage (**Figure 1**).

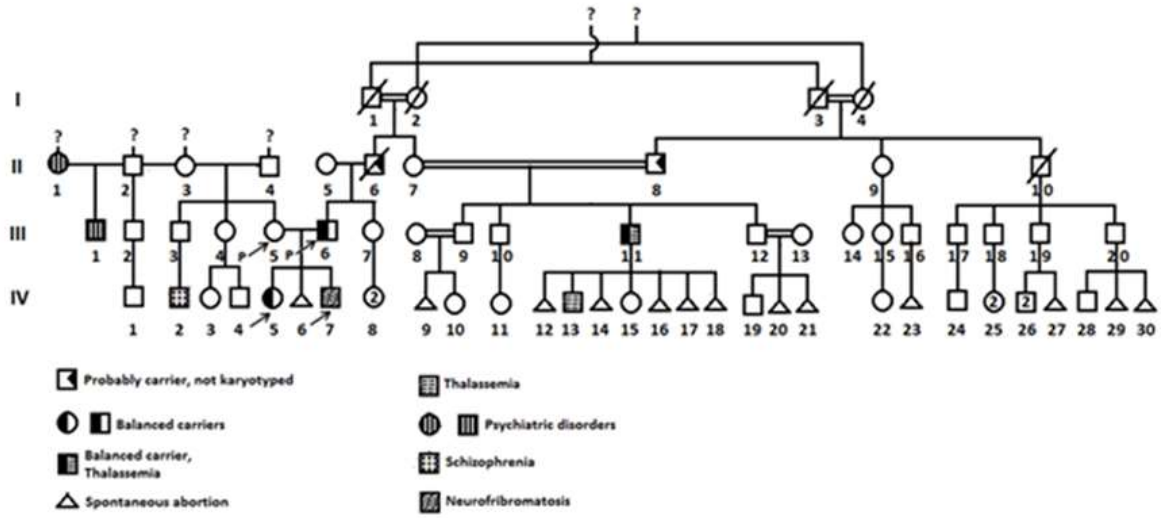

Figure 1: Pedigree of the family. The woman has a normal karyotype and the man is carrier of a balanced translocation. Only these family members were tested.

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Cytogenetic characterization

Chromosome analysis in the couple was performed on peripheral blood lymphocytes according to standard techniques. Metaphase spreads were prepared for G banding and high-resolution staining. The wife had normal karyotype both by G banding and high-resolution staining (data not shown). However, metaphases from the husband revealed a balanced translocation between the short arm of chromosome 7 and the long arm of chromosome 9**:** 46,XY,t(7;9)(7pter→7p12;9qter→9q34::7p12→7qter) in 30 metaphases analyzed (karyotype described according to ISCN 2009) (**Figure 2**).

Because of the paternal rearrangement karyotype was performed in the two normal children of the couple, revealing a balanced translocation in the girl (IV-5) with normal phenotype and normal karyotype in the boy (IV-7). No other members of the family were available for cytogenetic investigation in our lab. However, previous karyotype of III-11 was done. In this family the translocation, probably, has been transmitted through three generations (**Figure 1**).

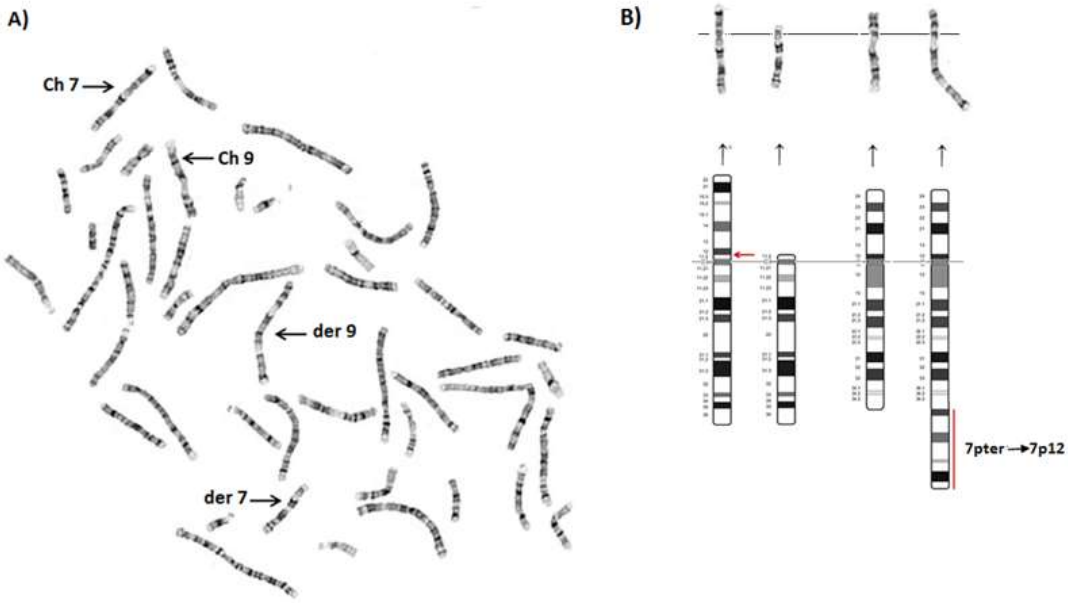

Figure 2. A) Routine G banded karyotype of the man, 46,XY,t(7;9)(7pter→7p12;9qter→9q34::7p12→7qter). B) Partial chromosome 7 karyotype is shown with the arrow indicating where the breakpoint in chromosome 7 occurred.

Discussion

We have described a male carrier ascertained through his wife's spontaneous abortion and patrilineal history of multiple miscarriage. Karyotype of the two normal children of the couple, revealing a balanced translocation in the girl with normal phenotype and normal karyotype in the boy.

In the present case, the male carrier, 46,XY,t(7;9)(7pter→7p12;9qter→9q34::7p12→7qter), did not have primary infertility.

Balanced translocations can be transmitted through the generations, and a high incidence of recurrent miscarriage was observed in the pedigree presented in this study.

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Recurrent miscarriage (RM) is a common problem in reproductive medicine. Couples who have had two or more RM are at increased risk of a structural chromosome abnormality in one of the partners. Structural chromosomal abnormalities mainly consist of reciprocal translocations (61%), Robertsonian translocations (16%), pericentric inversions (8%) and paracentric inversions (8%). Other structural chromosomal abnormalities are rare **[3]**. The incidence of balanced structural chromosome abnormalities is 0.7% in the general population and increases to 2.2% after one miscarriage, 4.8% after two miscarriages and even 5.2% after three miscarriages **[1-3]**. Low maternal age and a history of recurrent miscarriages in siblings or parents increase the probability of carrier status.

The risk of carrier status is estimated based on the maternal age at second miscarriage, a history of three or more miscarriages, and a history of two or more miscarriages in a brother or sister of either partner or in the parents of either partner **[3]**.Products of conception with an unbalanced structural chromosome abnormality can lead to miscarriage, stillbirth or birth of a child with major congenital defects and severe mental handicaps **[1-3]**. The probability of a child with an unbalanced chromosomal abnormality in carrier couples with RM is estimated to be below 1% **[4, 5]**

The risk of having a handicapped child with an unbalanced karyotype depends on the type of translocation, and on the sex of the transmitting parent **[6-8]**. Generally a 5–10% risk of a live-born child with multiple congenital abnormalities is mentioned in cases of carri **[8]**. Given a 5–10% risk figure of a live-born child with multiple congenital handicaps, in our study population seven live-born children with multiple congenital handicaps would be expected (10 pregnancies in carriers, III-6 and III-13, multiplied by 0.075). But, beside cases with Neurofibromatosis (IV-9) and Thalassemia (IV-14), most probably unrelated to the parental carrier status, in our study population no children with unbalanced karyotype were born out of a total number of 10 pregnancies. Our results are in agreement with the study of **[9]**in forty-one couples with carrier status of a structural chromosome abnormality where no unbalanced offspring were born out of a total number of 43 pregnancies.

Finally, the risk that parents will bear offspring with an unbalanced chromosome complement depends, apart from the sex of the carrier and type of rearrangement as stated above, on the method of ascertainment **[10]**. The frequencies of unbalanced translocations at prenatal diagnosis in subsequent pregnancies are much higher when a family is ascertained through prior full-term unbalanced progeny than when they are ascertained through repeated miscarriage: 19.8 versus 4.8% for maternal carriers; 22.2 versus 1.4% for paternal carriers **[11]** and 20.8 versus 3.4% for both maternal and paternal carriers **[12]**. In our study, the type of rearrangement, t (3;7)(3q29::7q22), the sex of the carriers (male) and the repeated miscarriage observed in this family, could be the cause of no offspring with an unbalanced chromosome complement.

In our study, the incidence of abnormal pregnancy outcome in the paternal family (13/29 miscarriage) suggests a higher risk of producing embryos with chromosomal anomalies formed during meiotic mal-segregation of parental chromosomes in our case.

There are several possibilities for a higher incidence of abnormal pregnancy outcome in our case. At the pachytene stage, the normal and abnormal chromosomes 7 and 9 may associate as a tetravalent (**Figure 3**). This configuration is relatively symmetrical, which may favour alternate segregation over adj-1 and adj-2 modes, and will rise to many possible combinations of rearranged chromosomes in the embryos. The unbalanced results of 3:1 and 4:0 segregations are most likely to produce much greater genotypic imbalance and are expected to be nonviable, with most or all resulting in early pregnancy lost. The only combination that are likely to produce viable progeny, however, are the normal, the balanced carrier, and those having an additional or missing copy of 7p12 to 7pter (adjacent-1), leading to partial pure trisomy 7p12 → 7pter or partial pure monosomy 7p12 → 7pter, respectively.

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Figure 3. Theorical pachytene configuration. Synapsis of t(7p12;9q34) and pairing of the homologous segment between the abnormal chromosome 7 and chromosomes 7 and 9.

Nevertheless, in this family no children were born out with trisomy 7p or monosomy 7p. Trisomy 7p12→7pter is characterized by multiple congenital anomalies including facial dysmorphism, prominent low set ears, micrognathia, anti-mongoloid palpebral fissures and psychomotor retardation **[13, 14]**; and monosomy 7p12→7pter where the more prominent features include plagioturricephaly, osseous defects of the parietal bones, short fingers, proximally implanted thumbs microphthalmia, congenital heart defect, and hydronephrosis **[15]**.

The unbalanced results of 3:1 and 4:0 segregations are likely to produce genotypic imbalance and would be expected that were the cause of the recurrent miscarriage observed in this family.

The only viable progeny are the normal and the balanced carrier who were product of alternate segregation (2:2) at the pachytene stage. Although the models of meiotic segregation for translocation require equal proportions of complementary segregants, which result from all types of recombination events, this phenomenon of equal segregant proportions has not been documented. To date, there is no clear explanation why it has not seen equal segregant proportions; some authors have discussed the possibility of differences between the frequencies of complementary products, which could result from the viability of the spermatocytes and spermatids according to their chromosomal contents, and could represent evidence for the preferential selection of certain segregants **[16]**. Although in our study, the male t (7;9)(7q21::9q34) carrier (III-6) have not been examined at the level of the meiotic segregation patterns of spermatozoa, we can infer that the another male carrier (III-11) had similar meiotic segregation patterns as well as only phenotypically normal progeny, spontaneous abortions and no children with partial trisomy or monosomy 7p12 to 7pter.

During meiosis, translocation carriers can produce unbalanced gametes, as stated above, through 4 modes of segregation: adjacent I, adjacent II, :3:1 and 4:0. Many male carriers with a balanced translocation have a decreased number of gametes, and these gametes may have an unbalanced chromosomal constitution **[17]**. Studies on live-born

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offspring or fetuses do not provide accurate information about meiotic segregation, since lethal segregations are lost through spontaneous abortions. Thus, the true mechanisms responsible for structural rearrangement at segregation remain unknown. Data obtained directly by cytogenetic analysis of sperm from men having balanced translocations should lead to a better understanding of abnormal segregation products and mechanisms. The development of chromosome-specific probes now permits the use of fluorescence in situ hybridization (FISH) to study cells at interphase. The application of FISH using different probe combinations appears to be a reliable, sensitive, and rapid method of establishing the segregation patterns for specific chromosomes in sperm. Sperm-chromosome studies by the multicolor FISH technique appear to be of special value in determining the chromosomal constitution of sperm nuclei in translocation carriers. There have been only a limited number of cases reported using the FISH technique.

The similar segregation profiles for the same translocation, compared with those very divergent profiles of the other cases of studied translocations that were published in the literature, confirm that the risks of meiotic imbalances vary primarily according to the characteristics of the chromosomes involved in the rearrangement and the breakpoint position. For these reasons, it is important to carry out the proposed study because, to our knowledge, there have not previous report with the same translocation. In addition, this study will enable us to explain the behavior of segregation patterns and the mechanism for this type of translocation in carriers and their effects on reproduction.

In conclusion, the most striking finding was the non-existence of unbalanced offspring after detecting a structural chromosome abnormality in the parents.

Detection of chromosomal abnormalities in miscarriage materials is very important to clarify the causes of loss of pregnancy, but they do not provide accurate information about meiotic segregation, since lethal segregations are lost through spontaneous abortions. Thus, the evaluation of the incidence of segregation products of balanced translocation in sperm nuclei of carriers can be evaluated by FISH, using the proper combination of probes, and will give patients more accurate genetic advice and helps to personalize the reproductive risk in carriers of balanced structural chromosomal aberrations.

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Competing interest

The authors declare no competing interests

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