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Pericentric Inversion of Chromosome 9 in a non-consanguineous Couple with spontaneous abortions

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Abstract

The balanced pericentric inversion of chromosome 9, inv(9) despite being considered a normal variant has been frequently observed and reported in individual partners with spontaneous abortions. To the best of our knowledge, we report the first case of this chromosomal abnormality in both partners of a non-consanguineous marriage. This report highlights that inv(9) in both partners may be leading to unbalanced rearrangements in the fetus thereby leading to spontaneous abortions.

Keywords: Pericentric inversion, Chromosome, Spontaneous abortion

Introduction

Recurrent pregnancy losses (RPL) defined typically as 2 or more consecutive pregnancy losses can be attributed to various factors like uterine abnormalities, hormonal imbalance immunological disorders, infections and chromosomal anomalies etc. The frequency of chromosomal anomalies in couples with RPL is estimates to be 2-8%. The most common chromosomal anomaly is a balanced rearrangement, usually balanced reciprocal translocation or inversion (1-3).

Inversions may be pericentric (involving both arms of chromosome and the centromere) or paracentric (involving only one arm of the chromosome). Some common chromosomes where inversion have been reported are chromosome 1,3, 9, Y etc. While there are isolated cases on paracentric inversions, most inversions reported are pericentric inversions in chromosomes 1,2,3,5,9,10,16 and Y. The most common pericentric variants have been reported in chromosome 9 and Y and are usually considered non-pathological polymorphisms (4, 5).

The pericentric inversions in human chromosome 9 (inv(9)) involving the heterochromatic region and centromere reported in literature have different breakpoints. The most common breakpoints involving the heterochromatic region of chromosome 9 are inv(9)(p11q12), inv(9)(p11q13), or inv(9)(p12q13). In other words, chromosome 9 shows highest degree of structural variability. In normal population also, pericentric inversion 9 is observed in 1-3.57% individuals with varying incidence across different ethnic groups. The balanced inversion does not usually have phenotypic effect in heterozygote carriers so, it is usually considered as a normal variant (4-9). However there are some reports suggesting a correlation with outcomes is subsequent pregnancy (e.g. abortion or chromosomally unbalanced offspring) in couples with one partner harboring inv (9).

The carriers of this inversion are at a risk of producing abnormal gametes during meiosis that may lead to unbalanced offspring (9-11). It is usually considered that during pachytene stage of meiosis, there is circulized configuration between normal and inverted chromosome that may lead to abnormal and unbalanced gametes. These gametes may have duplication of the region outside the inversion segment or one arm of inverted chromosome along with deletion of the terminal segment on the other arm and vice versa. The recombinant chromosomes arising from this inversion may have duplicated or deficient regions distal to the breakpoints.

Pericentric inversions in chromosome 9 have usually been reported in single partner of the couple with history of RPL and incidence is similar to general population (2, 5, 8, 9). This has often led to confusion in clinical management of these couples. To the best of our knowledge, we present the first case of both partners of a non-consanguineous marriage having inv(9) resulting in RPL which highlights the importance of reporting these variants.

Material and methods

A non-consanguineous couple of Indian origin was referred to the Department of Cytogenetics, Clinical Reference Laboratory, SRL Limited, Gurugram for chromosomal analysis. The husband was 34 years old and his wife was 28 years old. They had a history of 2 first-trimester pregnancy losses.

About 5 ml of venous blood collected in sodium heparin was received for both partners separately. Cytogenetic analysis (karyotyping) was performed using standard protocols wherein chromosome preparations were obtained from 72 hours phytohaemagglutinin (PHA) stimulated cultures of peripheral blood lymphocytes (12). These chromosomal preparations were then subjected to GTG-banding and analysed using *ikaros* software (Metasystems). At least 20 metaphases were analysed at 550-band resolution according to The International System for Human Cytogenomic Nomenclature (ISCN 2020) (13).

Results

The chromosomal analysis in both partners revealed balanced inversion in chromosome 9 in all the cells analyzed. The karyotype of the wife was 46,XX,inv(9)(p12q13) (Figure 1) and the husband was 46,XY,inv(9)(p12q13) (Figure 2). Both

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revealed the common pericentric inversion in chromosome 9 with similar breakpoints.

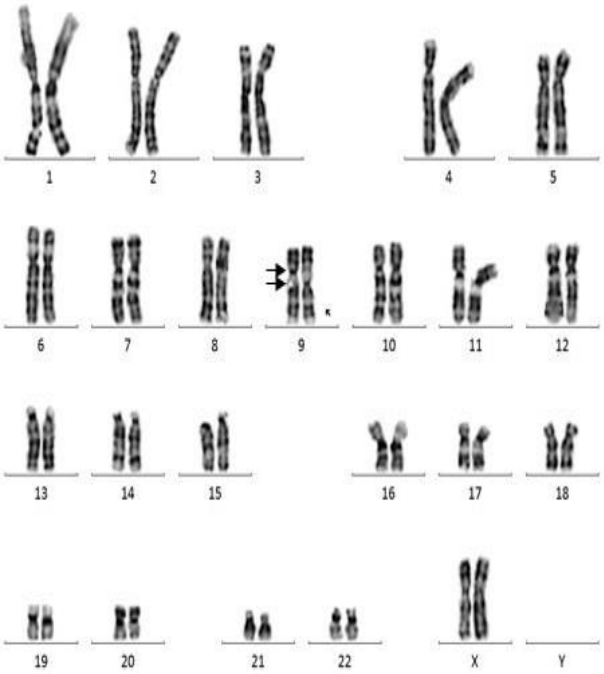

Figure 1. G-banded karyotype of female partner-46,XX,inv(9)(p12q13)

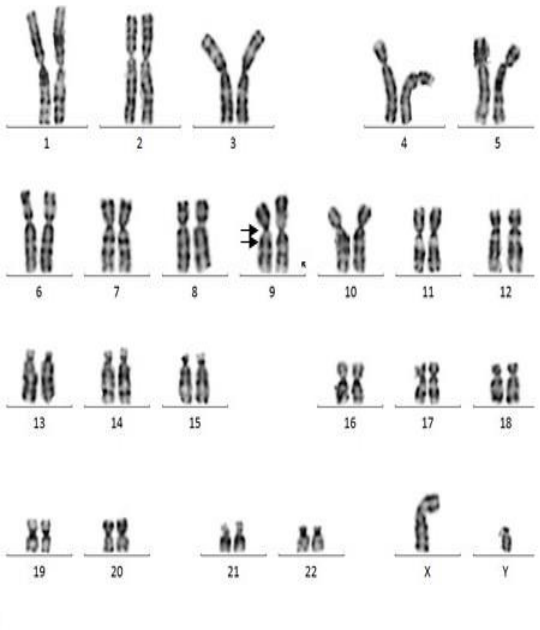

Figure 2. G-banded karyotype of male partner-46,XY,inv(9)(p12q13)

Discussion

The most common observation during cytogenetic analysis, an integral part of clinical management of RPL, is balanced rearrangements like balanced reciprocal translocations or inversions (1, 2).

One of the highly susceptible chromosomes to structural rearrangements is human chromosome 9 with variable breakpoints preferentially located in the 9p12 or 9q13-21 regions (8-10). It is however, challenging to differentiate these breakpoints inv(9)(p11q13) and inv(9)(p12q13) by cytogenetic analysis or karyotyping. The high frequency of variants involving this region is supposedly related to repetitive DNA sequences and homology of the 9p12 and 9q13 regions (9, 10).

These pericentric inversions in chromosome 9 have been reported in general population with variations among various ethnic groups and genders as well as partners of couples with reproductive failure. Some studies reported a significantly higher incidence in females

(3, 10). The incidence of observing inv(9) in partners of couples with history of RPL or BOH is 1-3% which according to some studies is similar to the general population (1,3). However, some studies highlight a possible relationship of inv(9) with infertility, RPL and poor outcomes of assisted reproduction treatment.

Some reports also associate inv(9) with infertility, miscarriages, sub-fertility, births defects, abnormal pregnancies like intrauterine growth retardation, psychiatric disorders, ectodermal dysplasia, azoospermia etc. The clinical significance of this abnormality in RPL is still debatable due to which a lot of confusion exists related to counseling and medical management of couple with a partner harboring this heteromorphic variant.

Although there are many reports of normal outcome in couples with one partner harbouring inv(9), there is a possibility of recombinant chromosomes in offsprings that may have either duplicate or deficient regions distal to breakpoints due to circulized configuration between normal and inverted chromosomes during meiosis. These may render non-viable zygotes or embryos thereby leading to pregnancy loss (7, 11, 14, 15)

The chromosome imbalance results from formation of recombinant chromosomes following a crossover event between the inversion and the normal homolog of the chromosome. Some studies estimated the risk of a child with an unbalanced chromosomal rearrangement as 1-10% if one of the chromosomes involved in meiosis had a pericentric inversion (4, 7, 9, 11).

This risk or probability of pregnancy loss or progeny with chromosomal imbalance may increase if both the chromosomes involved during meiosis have inv(9), which is probably the scenario in the current couple where both partners harbour inv(9). The meiotic outcomes may include alteration of expression of important functional genes, loss or duplication of these genes or even aneuploidy, thereby, rendering the zygote or embryo non-viable. This is similar to a case of consanguineous couple with molar pregnancies where both partners harboured inv(9) (15).

To the best of our knowledge, we report the first case of a non- consanguineous marriage with a recurrent pregnancy loss where both partners harboured inv(9). Since the cytogenetic analysis was not available for the products of conceptions in the current case, it is difficult to explain if there was chromosome imbalance due to gametes with recombinant chromosomes or an aneuploidy that rendered the fetus non-viable thereby resulting in RPL. Further follow up like prenatal diagnosis in future pregnancies is essential to establish the correlation. The present case still reiterates the importance of cytogenetic analysis in both partners of a couple with a reproductive disorder like infertility, RPL etc. or even opting for assisted reproductive technologies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

Author contributions

All authors made substantial contributions to the processing, analysis, interpretation and manuscript preparation.

Ethical issue

This retrospective study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate

Informed consent has been taken from all patients who have participated in this study.

References

1. Sheth J F, Liehr T, Kumari P, et al. Chromosonal abnormalities in couples with repeated fetal loss: An Indian retrospective study. Indian Journal of Human Genetics. 2013; 19(4):415-422.
2. Srebniak M, Wawrzkiewicz A, Wiczkowski A, et al. Cytogenetic abnormalities in couples with a history of primary and secondary recurrent miscarriage: a Brazilian Multicentric Study. Journal of Matern Fetal Neonatal Med. 2020; 33(3):42-4448.
3. Janani R.P, Muruga A, Santhiya T.S. Chromosomes Abnomalities among Recurrent Spontaneous Abortions Cases. Journal of Biomedical and Pharmacology. 2015; 9(1):349-356.
4. Xie X, Li F, Tan W, Tang J. Analysis of the clinical features of pericentric inversion of chromosome 9. Journal of International Medical Research. 2020;48(9):1-9.
5. Nonaka T, Takahashi M, Nonaka C, Takakuwa K. The analysis of chromosomal abnormalities in patents recurrent pregnancy loss, focusing on the prognosis with inversion of chromosome 9. Journal of Reproductive Medicine and Biology. 2019.
6. Jeong YS, Kim YB, Yu EJ. De Novo Pericentric Inversion of Chromosome 9in Congenital Anomaly. Journal of Yonsei Medicine. 2010; 51(5):775-780.
7. Muthuvel A, Ravindran M, Chander A, Subbian C. Pericentric inversion of chromosome 9 causing infertility and subsequent successful in vitro fertilization. Journal of Nigerian medical. 2016; 57(2):142-144.
8. Wang R, Yu Y, Wang Q, Jaing Y, et al. Clinical features of infertility men carrying a chromosome 9 transloction. Journal of Open Medicine. 2019; 14:854-862
9. Mozdarani H, Meybodi M.A, Karimi H. Impact of pericentric inversion of chromosome 9 (inv(9)(q11q12)) on infertility. Journal of Human Genetics. 2007; 13(1): 26-29.
10. Merrion K, Maisenbacher M. Pericentric inversion (Inv) 9 Variant – reproductive risk factor or benign finding? Journal of Assisted Reproduction and Genetics. 2019; 36: 2557-2561.
11. Liang S, Yang J, Wu H, Teng X, Duan T. Effects of chromosome 9 inversion on IVF/ICSI: A 7-year retrospective cohort study. Journal of Molecular Genetics and Genomic Medicine. 2019;7:856.
12. Roulston D, Beau MML: Cytogenetic analysis in peripheral blood lymphocytes. In: The AGT Cytogenetics Labor Manual, Third edition, The Association of Genetic Technologists, Barch MJ, Knutsen T, Spurbeck ed, Lippincott-Raven Publishers, Philadelphia (1997).
13. ISCN 2020: An International system for Human Cytogenomic nomenclature, McGowan-Jordan, Simons, Schmid. ed. Karger (2020).
14. Kumar M, Thatai A, Chapadgaonkar S.S, Homozygosity and Hetrozygosity of the Pericentric Inversion of Chromosome 9 and Its Clinical Impact. Journal of Clinical and Diagnostic Research. 2012 ; 6(5) : 816-820
15. Abdalla M.E, El-Kharadly N.R. Pericentric inversion chromosome 9 in a Consanguineous Couple with Molar Pregnancies and Spontaneous Abortions. Journal of Lab Medicine 2012; 43:5.