

A Rare Case of Pericentric Inversion, Inv (21) (p12;q22) in Repeated Pregnancy Loss: A Case Report

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Abstract

Pericentric inversions are among the most frequent chromosomal rearrangements with a frequency of 1-2%. There is no phenotypic effect in the majority of pericentric inversion heterozygote carriers, when it is a balanced rearrangement. However, miscarriages, infertility and/or chromosomally unbalanced offspring can be observed in carriers of a pericentric inversion. This is a case of pericentric inversion of one chromosome 21: inv (21) (p12; q22) in repeated pregnancy loss. A couple was referred for cytogenetic examination due to idiopathic miscarriages. The proband proved to be a carrier of chromosomal inversion and her partner's karyotype was found to be normal. The karyotype of the proband is 46, xx, inv (21) (p12; q22). This abnormal karyotype is reported as a probable reason of miscarriage in the investigated couple. The risk of further miscarriages and the risk of a progeny with abnormal karyotype are rather high. Therefore, amniocentesis for finding the chromosomal abnormality as a prenatal diagnosis are proposed for the patient if future pregnancy does not lead to miscarriage.

Keywords: Miscarriage; Pericentric inversion of chromosome 21.

Introduction

The frequency of pericentric inversions among the commonest chromosomal rearrangements is 1-2%.¹ Pericentric inversions result from a two-break event which occurs between the short (p) and the long arms (q) within the chromosome followed by a 180° rotation of the intercalary segment. There is no phenotypic effect in the majority of pericentric inversion heterozygote carriers with balanced rearrangement. However, miscarriages, infertility and/or chromosomally unbalanced offspring can be observed in carriers of a pericentric inversion.² Carriers of such rearrangements are at risk. During meiosis, in order to produce a percentage of abnormal gametes with duplication of the region outside the inversion segment on one arm of the inverted chromosome and deletion of the terminal segment on the other arm, and vice versa, it will end up with duplicated/ deficient recombinant chromosomes distal to the breakpoints.²

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Here, we report a female who carries a unique pericentric inversion of one chromosome 21: inv (21) (p12; q22). This abnormal karyotype was ascertained after three miscarriages.

Case report

A consanguineous couple with a relative of first cousin was referred to the Genetic Research Center, Yazd, Iran, due to repeated pregnancy loss. The woman had three miscarriages after 6-9 weeks of pregnancy. They have had one healthy boy with normal karyotype. The family pedigree was prepared according to Rimoin et al.³ (Fig. 1)

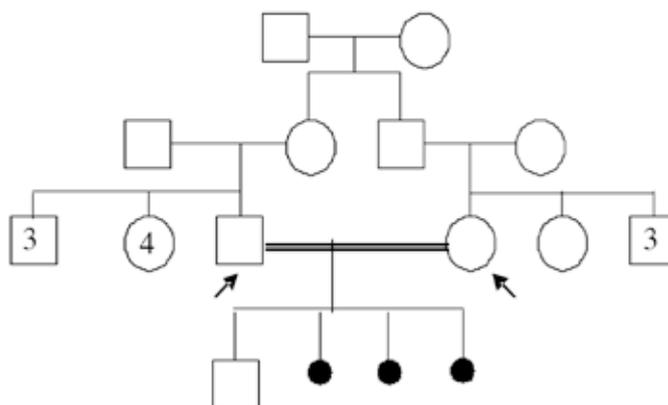


Figure 1: Family pedigree.

The husband was a 40-year-old man with normal sperm analysis⁴ and normal karyotype. The 29 year-old woman had normal fertility evaluation (normal ovarian reserve and hysterosalpingography in ovulatory cycles with abnormal karyotype. Her biochemical tests were also normal. Cytogenetic examination was performed on blood lymphocytes with a resolution of ~550. Separated peripheral blood lymphocytes were suspended in a RPMI 1640 medium invitrogen supplemented with 10% foetal calf serum (FCS), 1% Gentamicin and 1% L-glutamine. The lymphocytes were stimulated by phytohemagglutinin.

The culture was synchronized by the addition of Colcemid at 72 hrs. Cells were grown and then fixed according to the standard cytogenetic procedure.⁵ The karyotypes were analyzed by the use of a conventional banding technique (GTG). Analysis of 25 metaphase cells showed a pericentric inversion of one chromosome 21, with the breakpoint in the short arm at 21p12 and in the distal

region of long arm at 21q22: 46, xx, inv (21) (p12; q22) in all cells (Fig. 2) while, she was phenotypically normal. Unfortunately, her karyotypes were not available also, no cytogenetic study was performed in abortions' material.

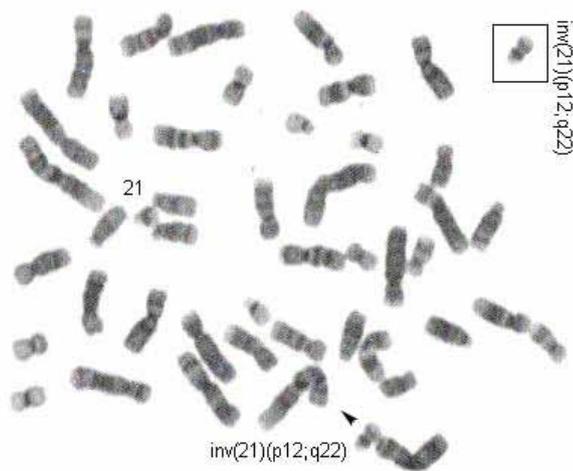


Figure 2: Pericentric inversion of one chromosome 21, with the breakpoint in the short arm at 21p12 and in the distal region of long arm at 21q22: 46, xx, inv (21) (p12; q22) in all cells.

Discussion

In this study, we report a woman who carries a unique pericentric inversion of one chromosome 21: inv (21) (p12; q22). This abnormal karyotype was diagnosed after three miscarriages. The first case of pericentric inversion of one chromosome 21 was reported by Gray et al.⁶ Since then, at least 15 cases of this inversion have been reported.⁷⁻¹⁶ The low frequency of inverted chromosome 21 described in the literature is probably due to the small size of the chromosome.¹ In all cases previously reported, with the exception of two case ascertained after four miscarriages and another case was diagnosed by infertility,^{12,16} while our patient was ascertained after three miscarriages, other cases were referred for Down's syndrome in offspring resulting from mitotic recombination in the inverted segment. These patients had inherited the rec(21) dup(21q), leading to a partial trisomy of chromosome 21.

In fact, pairing in meiosis constitutes the main problem in inversion heterozygosis. An odd number of crossover events (during the pachytene stage of meiosis I) within the inversion segment can lead to two monocentric recombinants with reciprocal duplications/ deficiencies in the gametes, ending up in a risk of inheriting such an imbalance when conception occurs.

Hence, the offspring of the reported patient carries such risk of imbalance in the inverted chromosome 21. It has been shown that the risk of recombination depends on the location of breakpoints and on the rearranged chromosomes. Several studies have demonstrated that the more distal the breakpoints, the higher the risk.^{17,18} This is because of the fact that the imbalance is smaller, thus more compatible with life, and that the probability of crossover will be higher in the inverted segment. Moreover, the risk of a live born child with a recombinant is higher when the

carrier is ascertained through the birth of an affected individual than through miscarriage or infertility. In one study, the authors estimated that the risk of recombination in patients with an inversion of one chromosome 21 is close to 10%.⁹

In our patient, the breakpoint on the long arm is more distal than those reported in the literature. Hence, the inverted segment is larger in our patient, leading to a higher risk of recombination.

For genetic counseling, the main concerns are related to the phenotypical consequence of a child inheriting chromosomal abnormality derived from the paternal or maternal inv (21). It is known that a deletion or a duplication of the region distal to p12 in an acrocentric chromosome does not lead to any phenotypic effect. On the other hand, the presence of an abnormal phenotype (mental retardation and/or malformations) is not always present in patients with partial trisomy or monosomy of the distal region of the long arm of chromosome 21(21q22.3qter).¹⁹ In humans, the problem of genetic counseling of inversion carriers and risk estimation is very difficult to resolve. With respect to the probability of chromosomal abnormality in the future progeny of our patient therefore; amniocentesis is proposed for the patient if the pregnancy does not lead to miscarriage in order to find chromosomal abnormality in a child as a prenatal diagnosis.

Conclusion

The abnormal karyotype is reported as a probable reason for miscarriage in the investigated couple. The risk of further miscarriages and the risk of a progeny with abnormal karyotype are rather high. Therefore, amniocentesis for finding the chromosomal abnormality as a prenatal diagnosis are proposed for the patient if future pregnancy does not lead to miscarriage.

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