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Case Report

Pericentric inversion in chromosome 2(p11q13) in two cases

Figen Celep*, Ahmet Karagüzel

Karadeniz Technical University Faculty of Medicine Department of Medical Biology Trabzon/Turkey

Abstract. Pericentric inversion of chromosome 2 was detected in two cases with cytogenetic analyses. Chromosome analyses were performed on routinely cultured peripheral blood lymphocytes. Slides were processed for trypsin-Giemsa banding. This study, and data from the literature, suggests that the pericentric inversion of chromosome 2 is generally considered a benign familial variant without significant reproductive consequences. Generally, inherited phenotypic or developmental abnormality and, even in a rare de novo form, has been found to be benign. According to the literature, the implications for management in these cases are discussed.

Key words: Pericentric inversion chromosome 2

1. Introduction

Chromosomal inversions visible under the light microscope are a common class of human balanced structural rearrangement. The material between the two breakpoints reserves orientation, reinserts, and the breaks unite. If the inverted segment includes the centromere, the inversion is pericentric: if not, it is paracentric. The common inversions having a breakpoint within the heterochromatic regions of chromosome 1,9,16 and Y are considered to be variants, not abnormal chromosomes. A second group of apparently benign inversions are those having the breakpoint near the centromere of the long and short arm of chromosome 2, 3 and 10 (1-4).

Pericentric inversions generally do not cause problems in carriers unless one of the breakpoints has disrupted an important functional gene. However, they can be associated with reproductive difficulties and /or an increased risk of producing unbalanced gametes through crossing over between the normal and inverted homologues. As a general rule, genetic imbalance of the recombinant cases decreases while the probability of the crossover increases with larger inverted segment (4-6).

Inversion of chromosome 2 with breakpoints at p11 and q13 is the most common pericentric inversion with euchromatic breakpoints and is considered to be clinically benign, and which are also considered to be variants (4,5). Excluding these variants, inversions are uncommon rearrangements with an estimated frequency range from about 0.12-0.7 per thousand for pericentric forms and about 0.1-0.5 per thousand for paracentric inversions. It has been estimated that about 85-90% of inversions are inherited (2,6,9). When faced with an abnormal individual carrying this inversion, where the karyotypes of the parents are not accessible, one must consider the possibility that this rearrangement has arisen *de novo*. In this case, there may be regions of duplication or deficiency at the breakpoints. This may account for some of the variability of abnormal phenotypes identified with inv(2). A carrier of a pericentric inversion 2 obviously has an increased risk for reproductive wastage (4,7,10). This is indicated by an increase of the rate of spontaneous abortions and an increase of the rate of index patients ascertained because of previous miscarriages but do not increase the risk for unbalanced recombinant offspring. There was still a suggestion of an excess of cases among couples with reproductive failure and that their early abortions may in fact have been nonviable

*Correspondence: Assoc. Prof. Dr. Figen CELEP, Ph D
Karadeniz Technical University Faculty of Medicine
Department of Medical Biology
61080 Trabzon/TURKEY
Fax: 00 90 462 3252270
Tel: 00 90 462 3777941-7957
Mail: gencelep@yahoo.com

recombinants. Due to this uncertainty, reporting of such cases is important in order to enable this information to be used for genetic counseling in similar situations.

2. Case reports

Metaphase chromosome spreads were obtained from phytohemagglutinin-stimulated cultures of peripheral blood lymphocytes on the level of 400-500 bands. GTG-banded chromosome preparations were examined in a minimum of 20 metaphases for each patient and karyotyped for inversion (2) (p11q13).

Case 1: A 28-year-old woman was referred to our Cytogenetics laboratory for investigation of the cause of primary amenorrhea. In hormonal analysis, prolactine was 116 ng/ml (2.8-29.2 ng/ml) and pelvic ultrasonography was normal. The proband had a sister and two brother and they phenotypically were normal. The parent had unrelated and two stillbirths. Karyotypic analysis revealed that she was a carrier of a pericentric inversion of chromosome 2, inv(2)(p11q13). Parenteral chromosome analyses were not performed.

Case 2: A 29-year-old woman was referred after having experienced two microinjection and abortuses. She was discovered to have the same pericentric inversion, inv(2)(p11q13). Chromosome analysis of parental peripheral blood cells demonstrated normal karyotypes. Chromosome analysis of abortuses had not performed.

3. Discussion

Reorientation of a sequence of genetic material apparently does not influence its function, and breakage and reunion at most sites do not cause an abnormal phenotype. However, with *de novo* inversions not presenting one of the common variant forms an about 9.4% risk for abnormalities, has been reported, which is 6 to 7% above the background risk (3,9). Most pericentric inversions involve breakpoints centromeric heterochromatin of chromosome 1, 9, and 16. These inversions are generally inherited and considered clinically insignificant heteromorphisms, as their breakpoints are in repetitive, non-coding sequencec (2). In contrast, inversions with euchromatic breakpoint, when they occur *de novo*, are sometimes associated with abnormalities as there is the potential for gene distruption or position effect (8,11,12).

Pericentric inversion of chromosome 2 is also relatively common, accounting for 14% of all pericentric inversions and the most common breakpoints are p11q13 (6,7,13). A specific abnormal phenotype has not been found in balanced carriers of inv (2) (p11q13). This inversion is not linked to an increased risk of livebirth, mental retardation and/or congenital abnormalities, but a twofold risk of recurrent miscarriage (1,3,5,7-10,13-16). But, there was no direct phenotypic consequences and is considered a polymorphic variant (2,6-8).

In the Ferfouri's study, it is claimed that risk of recurrent miscarriage associated with inv (2) (p11q13) is close to 0.3%, far from the doubled risk described in the literature. Because miscarriage risk in the general population ranges from 10-20%, they considered that the additional 0.3% increased risk linked to inv (2) (p11q13) is minor and, confirmed that inv (2) (p11q13) is probably a chromosome variant not associated with a particular risk of malsegregation or miscarriage. According to Ferfouri et al, genetic counseling could be modified, and amniocentesis and chorion villus sampling are not necessary. Because the risk of miscarriage is higher (0.5-1%) for these invasive procedures than for inv (2) (p11q13) (10).

In a study of inv(2) (p11q13) cases was supported that, there was a suggestion of an excess number of cases among couples with reproductive failure and that their early abortions may in fact have been nonviable recombinants (13). This was followed by another report suggesting an increased risk for carriers of pericentric inv(2) for recurrent miscarriage twice that of the general population (7). However, MacDonald et al. claimed that the inversion of chromosome 2 was small and benign. It was further stated that for these aberrations, which were not *de novo*, such inversions should be treated as a normal variant segregating within the pedigrees (8). Richter et al. presented a familial pericentric inversion 2 resulted in two unbalanced recombinant offspring. The inverted segment in this case was very large with breakpoints at 2p25 and 2q35 with the recombination resulting in partial deletion 2p25→2pter and partial duplication 2q35→2qter (17). Four cases are reported of interstitial deletion (2) (p11.2p13) (18-21), and two had known de novo deletions (20,21), but only one of them was associated with paternal inv(2) (p11.2q13) (18). The other report had a direct duplication of chromosome 2 (p12→p21) (22). Also, Ferfouri et al. studied pericentric inversion segregation and interchromosomal effect on sperm carrier inv 2 and suggested that inv(2) (p11q13) is probably a chromosome variant not associated with a

particular risk of malsegregation or miscarriage (10).

In this report, we have presented two cases having inversion of chromosome 2. The first patient had primary amenorrhea and, the second was related to recurrent miscarriage. The association of pericentric inversion of chromosome 2 and miscarriage and primary amenorrhea do not immediately imply a causative role. It is obvious that there were inversion 2 cases with miscarriage and unbalanced offspring in the literature, but it had not observed any case with amenorrhea. To our knowledge there is no direct evidence to support this as a common mechanism in such cases. We believe that reporting is important these cases as clinically and cytogenetically. We suggest that further monitoring offspring of couples in which one of the members has the generally considered innocuous inv (2) (p11.2q13) should be considered. However, at this point, it seems premature to recommend prenatal diagnosis for couples in this situation.

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