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X Chromosome Pericentric Inversion: Report of a Case with 46,X,inv(X)(p11.2q26) and a Mini-Review of the Literature

X Kromozomu Perisentrik Inversiyonları: 46,X,inv(X)(p11.2q26) Karyotipli Bir Olgunun Sunumu ve Literatürün Kısa Bir Derlemesi

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ABSTRACT

Pericentric inversions arise from double breaks on opposite arms of the chromosome, followed by 180° rotation and reintegration of the broken segment. Carriers of an inversion are mostly phenotypically healthy. However, they may have some clinical implications, including reproduction anomalies due to imbalanced gamete production. Here, we highlighted the phenotypical variability of X chromosome inversions by reporting a case. The female proband who had recurrent spontaneous abortions was admitted to the Medical Genetics polyclinic. After clinical evaluation, conventional Giemsa-banded karyotyping was performed. The result was 46,X,inv(X)(p11.2q26). Segregation analysis of the family members revealed that she inherited the pericentric inversion from her father and passed it on to her daughter. Detailed genetic counseling was provided to the family. The significance of X chromosome pericentric inversions in the literature was discussed with regard to their phenotypical relevance to enhance our understanding of clinical variability caused by chromosomal inversions.

Keywords: Pericentric inversions, X chromosome, habitual abortus, chromosome rearrangement

ÖZ

Perisentrik inversiyon; bir kromozomun zıt kolları üzerinde bulunan iki farklı bölgenin kırılması ve ardından bu kırık parçanın 180° dönerek yeniden aynı kromozoma birleşmesiyle oluşan kromozomal yeniden düzenlenmedir. İnversiyon taşıyıcıları sıklıkla fenotipik olarak sağlıklıdır. Ancak dengesiz gamet oluşumuna bağlı üreme bozukluklarının da dahil olduğu bazı klinik etkilenmeler görülebilir. Burada, oldukça nadir görülen kromozom X inversiyonuna sahip bir olgu sunulmuştur. Tekrarlayan spontan düşükleri olan kadın hasta Tıbbi Genetik polikliniğine başvurdu. Klinik değerlendirme sonrası, Giemsa-bantlama ile kromozom analizi gerçekleştirildi. Karyotip 46,X,inv(X)(p11.2q26) şeklinde raporlandı. Ailedeki segregasyon araştırıldığında, hastadaki perisentrik inversiyonun babasından kalıtıldığı ve hastanın yaşayan kız çocuğunda da mevcut olduğu görüldü. Aile bireylerine detaylı genetik danışma verildi. Olgumuzu, kromozomal inversiyonların yol açabileceği klinik çeşitliliği vurgulamak için literatürdeki X kromozomu perisentrik inversiyonlarının kısa bir derlemesiyle birlikte tartıştık.

Anahtar Sözcükler: Perisentrik inversiyon, X kromozomu, tekrarlayan düşükler, kromozom yeniden düzenlenmeleri

INTRODUCTION

Chromosome inversions are abnormal structural rearrangements arising from double breaks on the same chromosome followed by the segment between these breakpoints reversed and reattached. According to the localization of the breakpoints, there are two types of inversions: paracentric and pericentric. In paracentric inversions, both breaks occur on the same chromosome arm. In contrast, in pericentric inversions, which are more commonly observed, breaks are on the different sides of the centromere. Therefore, the inverted fragment includes the centromere. Inversions including the pericentric heterochromatin region on chromosomes 1, 9, 16, and Y are commonly regarded as polymorphisms. Breakpoints in these inversions are believed to be located in non-coding areas or repeat regions, causing them to be clinically benign. On the other hand, inversions that arise de novo and affect euchromatic regions may have direct health implications (1).

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Inversion of an autosomal chromosome is observed in approximately 1%-2% of the general population. The significance of the clinical outcome is expected to be correlated with the size of the inverted segment. However, X chromosome inversions are extremely rare, with an estimated incidence of 1/28,000-30,000 and their phenotypic implications are much more complicated (2).

Because of the conservation of the total genetic material, inversions are usually not associated with severe morphological effects; however, carriers may have reproduction issues, including infertility and recurrent pregnancy losses, because of gametes with an unbalanced karyotype. If one of the parents is known to be an inversion carrier, the risk of imbalanced gamete formation has been estimated as 5-10% and the risk of having offspring with malformations is around 1%. These risk ratios depend on the size of the inverted fragment. If the region distally located to the inversion is smaller, the clinical findings are expected to be less severe because of lower gene content (3). Here we describe a case with an X-chromosome pericentric inversion presenting with habitual abortus.

Case Presentation

A 35-year-old female patient was admitted to the medical genetics polyclinic with a complaint of recurrent pregnancy losses (in November 2021). She had five spontaneous pregnancies. The first two resulted in two healthy children who were born during the term. However, the next three pregnancies resulted in an abortion at 5, 7, and 7 weeks, respectively. She had no other health complaints, and there was no consanguinity. Physical examination revealed a mild/moderate symmetrical short stature (measured height was 158 cm). Her husbands evaluation revealed no symptoms or findings. To understand the etiology of the habitual abortus, karyotype analysis from peripheral blood was performed on both spouses. Metaphase chromosomes obtained from peripheral blood lymphocyte cultures were evaluated using high-resolution G-banding techniques; using the Leica Biosystems imaging system (IL, USA). At least 10 karyotypes at the 450-600 band resolution level were analyzed, and at least 50 metaphase cells were counted in each specimen. Results were reported according to the International System for Human Cytogenetic Nomenclature 2020 (ISCN-2020). While her husband's karyotype was normal; the patient had a pericentric X chromosome inversion, described as 46,X,inv(X)(p11.2q26) (Figure 1, 2). To perform a segregation analysis, a conventional cytogenetic investigation was performed on the parents, two brothers, and both offsprings of the patient. It was shown that the proband's father and daughter were also carriers of the X chromosome inversion, and the other family members had normal karyotypes. No individual with a recombinant chromosome was observed in the family (Figure 3). Appropriate informed consent was obtained from the family members for sharing their and their children's data.

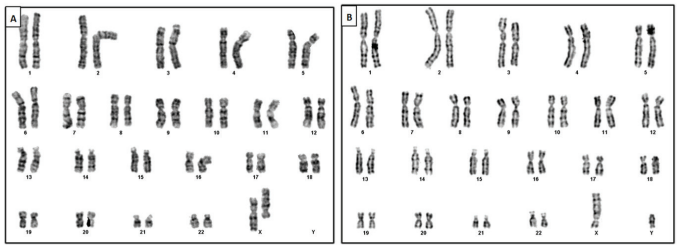

Figure 1. Karyotypes of two patients. Metaphase chromosomes from cultured lymphocytes were banded using conventional G-banding techniques and then arranged into homologous pairs. (A) The proband's karyotype is 46,X,inv(X)(p11.2q26)pat. (B) Karyotype of the proband's father is 46,Y,inv(X)(p11.2q26).

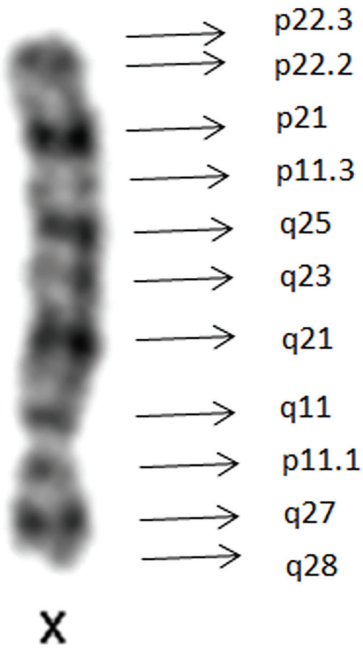

Figure 2. The figure depicting the X chromosome pericentric inversion. Breakpoints are located at p11.2 and q26.

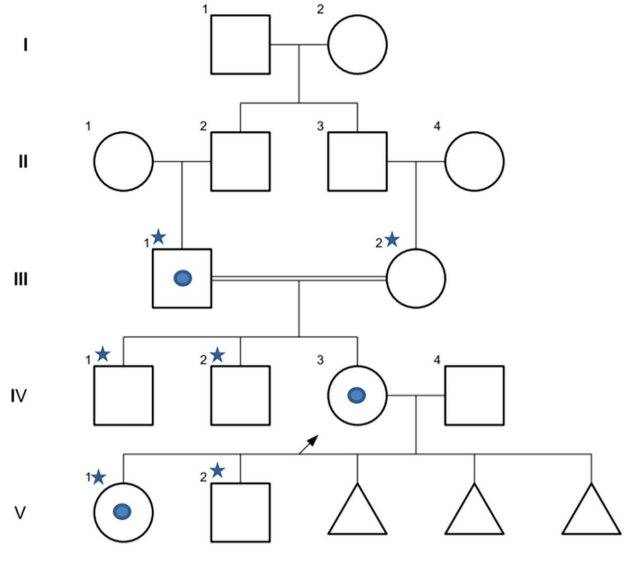

Figure 3. Pedigree of the proband's family. Individuals for whom cytogenetic evaluations are available are indicated using an Asterix. Males are represented by squares and females by circles. Triangles represent miscarriages. The blue dots depict individuals who harbored pericentric X chromosome inversion.

DISCUSSION

Pericentric inversions occur after two breaks are formed at each side of a centromere of a chromosome, which in turn causes that segment to be reversed 180° and reattached afterward. While autosomal chromosomal inversions are quite common, X chromosome inversions that may have a wide variety of clinical implications are rarely seen (4). In the literature, the most commonly identified breakpoints of the short arm of the X chromosome are the p11, p21, and p22 banding regions, whereas breakpoints located in the q arm are highly variable. Duckett and Young (5) reported a short-statured case with a recombinant X chromosome caused by maternal pericentric inversion in 1988. Cytogenetic analysis revealed the mother's karyotype as 46,X,inv(X)(p11.2q26); the same as our index patient. She was described as healthy; however, she had two first-trimester miscarriages and one daughter with a recombinant X chromosome (5). Because of the retained balance of the genetic material, carriers of an inversion are usually phenotypically healthy. However, it is difficult for the inverted chromosome to align during meiosis in germ cells. Because of an unequal crossing-over, the inversion carrier's reproductive potential can be affected. The possible gametes are the normal gamete, the one with the inverted X chromosome, and two different types of recombinant gametes; one with trisomy for the distal portion of the short arm and monosomy for the distal part of the long arm and one with monosomy of the distal portion of the short arm and trisomy of the distal part of the long arm. In the literature, females with an inverted X chromosome are associated with infertility, recurrent first-trimester pregnancy losses, and the birth of a child with genetic abnormalities (6). In this study, it is shown that the proband inherited the inverted X chromosome from her father and passed it on to her daughter. She had habitual abortus in the early weeks of pregnancy, which was consistent with the literature. According to the report of Mattei et al. (7), the Xq13-->26 critical region should be uninterrupted to preserve normal ovarian function. Our patient had this segment intact; therefore, her regular menstruation periods and spontaneous pregnancies can be regarded as supporting evidence for this hypothesis. Phenotypic implications of inversion carriers depend on the localization of breakpoints. In the literature, X-chromosome inversions have been associated with severe oligospermia. Ge et al. (6) reported two brothers with oligospermia whose karyotypes were 46,Y,inv(X)(p22.3;q22). This fracture site affects the Xp22::Xpter pseudoautosomal region 1 (PAR1), where homologous recombination of X and Y chromosomes occurs during meiosis in spermatogenic cells, causing severe oligospermia (6). In this study, breakpoints were not located in the PARs, and the proband's father had no difficulty having children. In the literature, a serious hemophilia A phenotype was also reported in a male proband whose karyotype was 46,Y,inv(X),(p11.21;q28)mat; this was caused by the interruption of the factor 8 gene localized in Xq28 region (1). In this case, the breakpoints excluded Xq28; therefore, inversion carriers had no bleeding disorder findings. Duchenne muscular dystrophy (DMD) is the largest known human gene encoding the dystrophin protein and is localized in the Xp21.2 region. Loss-of-function variations of this gene cause progressive DMD clinic. Approximately one-third of the patients additionally have an intellectual disability with an unclear mechanism. Tran et al. (8) reported a DMD case with an intellectual disability whose karyotype was 46,Y,inv(X)(p21.2;q28). The researchers found that the KUCG1 gene in the Xq28 region may be the cause of the disability through discontinuation. Family members in our study were evaluated for muscular disease or mental deficiency, and no symptoms or findings were revealed. In 2017, Wu et al. (9) defined a patient with inv(X)(p21q13) karyotype who had hypohidrotic ectodermal dysplasia. The EDA gene causing X-linked hypohidrotic ectodermal dysplasia, which is characterized by hypotrichosis, hypohidrosis, and hypodontia, is localized in the Xq13.1 region. Because of pericentric X chromosome inversion, interruption of this gene resulted in the phenotype (9).

The aforementioned studies clearly show that carriers of X chromosome inversions have phenotypic variability, depending on the breakpoints of the inversion. To estimate possible clinical features, it is crucial to define the inverted chromosomal regions and the genes localized at the breakpoints. Then, one must evaluate the correlation between these data and the clinical findings of the patient. A detailed evaluation is also important to predict any symptoms that might occur in the offspring. In the family we investigated, the carriers of the inversion were phenotypically healthy, and another case in the literature, which shares the same breakpoints. No family members were observed to harbor a recombinant X chromosome. However, the spontaneous abortions might have happened because of the recombinant X chromosome, through an intrauterine death. Because they have only one X chromosome, male embryos with nullisomic X chromosome fragments may not be able to develop or they might be expected to undergo abortion.

Detailed genetic counseling was given to the family, along with information about possible gamete production. It was emphasized that pregnancy losses could be due to this inversion. Clinical follow-up for inversion carriers is recommended for any future inversion-associated findings. Considering that future pregnancies can result in abortions or genetic abnormalities, the family was informed about preimplantation genetic testing and prenatal diagnosis techniques.

X chromosome inversions are very rarely observed in the general population, and inversion carriers are mostly phenotypically healthy. However, the interrupted genes localized at the breakpoints can cause a wide variety of clinical findings. One should keep in mind this variability when giving genetic counseling or when approaching a patient.

Ethics

Author Contributions

Concept: E.G., B.O.A., A.G.Z., M.S.Y., Design: E.G., B.O.A., A.G.Z., M.S.Y., Data Collection or Processing: E.G., B.O.A., A.G.Z., M.S.Y., Analysis or Interpretation: E.G., B.O.A., A.G.Z., M.S.Y., Literature Search: E.G., B.O.A., A.G.Z., M.S.Y., Writing: E.G., B.O.A., A.G.Z., M.S.Y.

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