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Association of Pericentric Inv(12)(p11.2q14) with Infertility and Recurrent Miscarriages: Case Report and Literature Review

Perisentrik inv(12)(p11.2q14)'nin İnfertilite ve Tekrarlayan Düşüklerle İlişkisi: Vaka Örneği ve Literatür Taraması

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ABSTRACT

Infertility, reported in 15% of the couples who want to have children, is an important worldwide health problem. Recurrent miscarriage, observed in 15–25% of pregnancies, is another important health issue affecting millions of couples in the world. Despite many genetic factors have been associated with infertility or recurrent miscarriages especially in recent years, the genetic and epigenetic factors underlying these problems are mostly unknown. Most of the pericentric inversions do not affect phenotypes of the individuals carrying balanced rearrangements. However, the pericentric inversions may cause chromosomally unbalanced sperm/ovum during the meiotic crossover leading to infertility or recurrent miscarriages. In this case report, we report a familial pericentric inv(12)(p11.2q14) in eight individuals with infertility or recurrent miscarriages in three different families.
Keywords: Infertility; recurrent miscarriages; pericentric inversion; inv(12)(p11.2q14).

ÖZ

Çocuk sahibi olmak isteyen çiftlerin %15'inde görülen infertilite, tüm dünyada önemli bir sağlık sorunudur. Gebeliklerin %15-25'inde gözlenen tekrarlayan düşükler, dünya genelinde milyonlarca çifti etkileyen bir diğer önemli sorundur. Özellikle son yıllarda infertilite ya da tekrarlayan düşüklüklerle pek çok genetik faktör ilişkilendirilmiş olsa da, bu sorunların altında yatan genetik ve epigenetik faktörlerin çok büyük kısmı henüz bilinmemektedir. Perisentrik inversiyonların çoğu, taşıyıcı bireylerin fenotipini etkilemez. Bununla birlikte mayoz bölünmenin krosing over aşamasında hatalara neden olabilen perisentrik inversiyonlar infertiliteye veya tekrarlayan düşüklere yol açabilir. Bu olgu sunumu çalışmasında, üç farklı aileden sekiz bireyde tespit ettiğimiz pericentric inv(12)(p11.2q14)'ün infertilite ve tekrarlayan düşüklerle ilişkisi üzerinde durulmuştur.
Anahtar kelimeler: İnfertilite; tekrarlayan düşükler; perisentrik inversiyon; inv(12)(p11.2q14).

INTRODUCTION

Infertility is a disease defined by the failure of achieving a pregnancy after one year or more of regular unprotected sexual intercourse (1). Recurrent miscarriage is defined as 3 or more consecutive clinical pregnancy losses before 20 weeks of gestational age (2). Despite many genetic factors have been associated with infertility or recurrent miscarriages especially in recent years, the genetic and epigenetic factors underlying these problems are mostly unknown (3). When a chromosome breaks at two points, occasionally the region of chromosome among the breaks rotates 180° before reinserted to the same chromosome (1). This event is called as inversion, which is one of the mutations at the chromosomal level. First evidence of inversion was published by Alfred Sturtevant in 1921 (4). Most of the pericentric inversions do not affect phenotypes of the individuals carrying balanced rearrangements. However, the pericentric inversions may cause chromosomally unbalanced sperm/ovum during the meiotic crossover leading to infertility or recurrent miscarriages (5). Here, we report a familial pericentric inv(12)(p11.2q14) in eight individuals with infertility or recurrent miscarriages in three different families (Figure 1). Informed written consents for the publication of clinical details and images were obtained from the patients.

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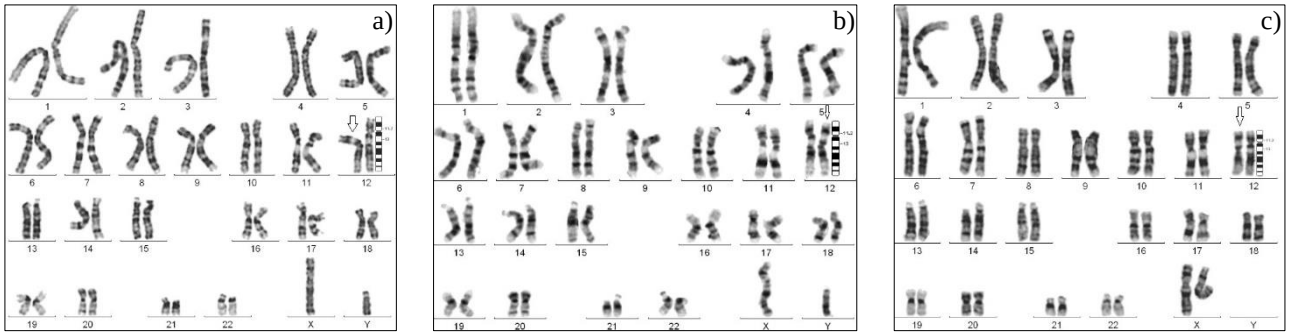

Figure 1. Karyotypes of the three patients included into the study. The Inv(12) chromosomes marked with arrow. a) The karyotype of the patient with recurrent miscarriages in family 1, b) The karyotype of the case with infertility in family 2, c) The karyotype of the patient with infertility in family 3

CASE REPORT

Family 1

A couple with a history of recurrent miscarriages was referred to the Medical Genetics Department of Istanbul Medical Faculty at Istanbul University for cytogenetic evaluation. The husband was a 35-year-old healthy male and the wife (proband) was a 32-year-old female. The couple experienced four intrauterine fetal deaths before the 18th week of pregnancy and had a healthy three years old girl. The wife had 8 phenotypically normal siblings. The husband had a normal karyotype (46, XY), although the wife's karyotype was 46, XX, inv(12)(p11.2q14). Further karyotype analysis for her parents and 4 siblings demonstrated that her mother and her three siblings had normal karyotypes, however, her father and her brother had the same balanced chromosomal inversion. Moreover, the brother carrying the same inversion had an extra Y chromosome (47, XYY, inv(12)(p11.2q14)) and he had two healthy girls. There was not any miscarriage or infertility history in proband's family.

Family 2

The second family had also infertility problem. The proband was a 33-year-old man with a history of four years of primary infertility. His wife was apparently healthy. The patient and his wife were not consanguineous. The proband had one unmarried sister and his parents had no history of miscarriage or infertility. Both testes of the case are located in the scrotum with a normal volume. Semen analysis of the proband revealed azoospermia. His endocrine hormone levels were within normal limits: Follicle-Stimulating Hormone (FSH) was 3.6 IU/L (normal range 1.2–12.4 IU/L); Luteinizing hormone (LH) was 5.12 IU/L (normal range 1.7-8.6 IU/L); testosterone was 2.5 ng/mL (normal range 2.3-8 ng/mL). Y microdeletion analysis of the proband demonstrated that there was no microdeletions on azoospermia factor regions (AZFa, AZFb and AZFc) of the Y chromosome. Karyotype analysis was carried out for the proband, his parents, and his sister. His karyotype was 46, XY, inv(12)(p11.2q14). The mother and the sister had a normal 46, XX karyotype, however, the proband's father had the same inversion with the proband; 46, XY, inv(12)(p11.2q14).

Family 3

The third family had infertility history. The proband was 36-year-old male with infertility. His wife was a healthy 33-years-old female. Proband's basal endocrine hormone levels were normal: FSH was 11.71 IU/L; LH was 8 IU/L; and testosterone was 3.5 ng/mL Semen analysis of the proband revealed azoospermia. Y microdeletion analysis showed that there was no microdeletions on Y chromosome. His mother was his father's cousin (consanguineous). He had a 30-years-old, unmarried brother. There wasn't any miscarriage history of his mother and there was no person with miscarriage or infertility history among his relatives. Karyotype of the proband was 46, XY, inv(12)(p11.2q14) and his brother had the same inversion. Chromosome analysis could not be carried out for proband's parents since they were dead.

DISCUSSION

There are two kinds of inversions: 1) Paracentric inversions that do not contain the centromere with the breakpoints present on the same arm of the chromosomes and 2) pericentric inversions, which include the centromere with the breakpoints found on distinct arms of the chromosomes (6). During the meiosis, loop formation occurs in order to the pairing of normal homologous chromosome and the inverted chromosome. This event may give rise to abnormal gametes with duplicated and deleted chromosome regions (7). In general, the patients with chromosomal inversions are phenotypically normal, however there is an increased risk (estimated 6.1% for de novo abnormalities) for neurodevelopmental disorders or developing congenital anomalies for these patients (8). Chromosomal inversions are usually associated with infertility, intellectual disability (ID) and ovarian failure (8). Sperm segregation studies demonstrated that the size of the inverted chromosomal segment is important for the occurrence of unbalanced gametes throughout the meiosis. The inverted segment being more than 100 Mbp may affect reproductive fitness of the carriers significantly (9). Balanced chromosomal rearrangements including inversions may only be detected by karyotype analysis, however small alterations on chromosomes may not be clarified by this valuable method due to its low resolution (nearly 5-10 Mb) (8). The breakpoints of the inversion can exist in a vital region of the DNA coding sequences and the inversion can directly disrupt or change gene expression of adjacent genes by dividing regulatory elements from the corresponding coding sequences. Furthermore, some inversions can lead to additional consequence of the predisposition to copy number alterations and chromosomal translocations (10).

Some of the apparently balanced chromosomal translocations or inversions can be familial, which may lead to discordant phenotypes in patients with the same chromosomal abnormality in the family. The interpretation and counseling of these chromosome abnormalities is extremely challenging due to the deficiency of routine techniques and the scarcity of publications (11). For instance, in the family 1, although the proband with familial inv(12) had four early pregnancy losses, there wasn't any miscarriage in her parents. Furthermore, the proband's parents had eight phenotypically normal children. In family 2 and family 3, although the probands' parents had not experienced any recurrent miscarriage or infertility problem, the probands were azoospermic men. A number of mechanisms have been proposed to explain how familial balanced chromosome abnormalities including inversions may lead to discordant phenotypes in carriers. One of them is the presence of complex chromosomal rearrangements or submicroscopic imbalances. The second one can be functional homozygosity because of the gene disruption by the rearrangement of one allele and unmasking of a recessive gene mutation on the allele inherited from the normal parent. The disruption of imprinted genes could be one of the other possible mechanisms. The position effect of the genes existing near the break points and reduced penetrance could be the other important mechanisms about discordancy (11). It has been suggested that if the patients have a neurodevelopmental disorder or congenital anomaly then especially the putative candidate genes in the break regions of the chromosome should be investigated with Next-Generation Sequencing (NGS) methods (8). The knowledge about possible functional effects of familial inversions on infertility or miscarriage is still limited. Unfortunately, until now, a few number of inversions have been studied in detail in humans. It should also be noted that the location of the inversion breakpoints within complex repeated chromosomal segments makes it difficult to analyze them. For this reason, the inversions have been overlooked for a long time (10).

The inversions have rarely been reported as an additional chromosomal abnormality. To our knowledge, inv(12) have previously been reported in five cases as an additional abnormality. It has been described in a patient with trisomy 21 and a familial pericentric inversion (12)(p13q13) (12). In a different study, a familial inv(12) has been found in a girl. Her karyotype was 46, XX, inv(12)(p13q22) / 47, XX, i(Xq),inv(12)(p13q22) (13). In another study, a familial inversion (12)(p13q13) was identified in a girl with Down Syndrome (14). A paracentric inversion inv(12)(q15q24) (15) and a centric inversion inv(12)(p10p13.3) have been described in two different patients with Klinefelter syndrome (16). In the family 1, proband's brother carrying inv(12) had an extra Y chromosome. To the best of our knowledge, coexistence of the inv(12) and extra Y chromosome was first shown in our report. Considering the previous and our cases, inv(12) seems to be associated with numerical chromosome abnormalities.

To date, pericentric inversion 12 have been reported in twelve families in seven studies (Table 1). In one study, it has not been reported whether the inv(12) is familial or de novo (22). In the current study, we report three familial pericentric inv(12). Literature findings and our study demonstrate that the pericentric inv(12) mostly occurred as familial chromosome abnormalities. No viable fetus or child was reported with unbalanced chromosome 12 derived from balanced pericentric inv(12) in parents. In none of the twelve families in those seven studies, the pericentric inv(12) has not been associated with infertility. However, we report two infertility patients with familial inv(12) in current study. The proband experienced recurrent miscarriage in family 1 and infertile probands having this abnormality in family 2 and family 3 might be evidences that the pericentric inv(12) may cause recurrent miscarriages and infertility.

Table 1. Previous studies reporting pericentric inv(12) as familial chromosome abnormality

	Break point	NF	Carriers	Family History	Rf
Previous Studies	inv(12)(p13q11)	1	Father and two children	Advanced maternal age	18
	inv(12)(p13;q11) inv(12)(p13;q13)	2	Two patients in different families	NA	12
	inv(12)(p11.2q13)	1	15 carriers out of 44 individuals in one 8 generation family	A previous stillborn child	19
	inv(12)(p11.2q13)	2	Two patients in two different families	Routine chromosome analysis	17
	inv(12)(p11q13)	2	Two different cases. One of them had paternal inversion and the other had maternal inversion	NA	20
	inv(12)(p13q13)	3	25 carriers out of a total number of 52 persons examined in three families	Family 1: a previous child with Down's syndrome Family 2: A preterm delivery and two late abortions Family 3: advanced paternal age	14
	inv(12)(p12.3q14)	1	A Child and her father	Advanced maternal age	21
	inv(12)(p12q12)	*	NA	Infertility	22
Current Study	inv(12)(p11.2q14)	1	A wife, her father and her brother had the same inversion	Recurrent Miscarriages The brother of the wife carrying the same inversion had an extra Y chromosome	F1
	inv(12)(p11.2q14)	1	A male patient and his father had the same inversion	Infertility	F2
	inv(12)(p11.2q14)	1	A male patient and his brother had the same inversion	Infertility	F3

*: It has not been mentioned whether this inversion is de novo or familial in this patient, NF: Number of the affected family in the studies, Rf: Reference, NA: Not available (This information was not found in the article), F1: Family 1, F2: Family 2, F3: Family 3

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REFERENCES

1. Kamel RM. Management of the infertile couple: an evidence-based protocol. Reprod Biol Endocrinol. 2010;8:21.
2. El Hachem H, Crepaux V, May-Panloup P, Descamps P, Legendre G, Bouet P-E. Recurrent pregnancy loss: current perspectives. Int J Womens Health. 2017;9:331-45.
3. Hyde KJ, Schust DJ. Genetic considerations in recurrent pregnancy loss. Cold Spring Harb Perspect Med. 2015;5(3):a023119.
4. Sturtevant AH. A case of rearrangement of genes in Drosophila. Proc Natl Acad Sci U S A. 1921;7(8):235-7.
5. Tayebi N, Khodaei H. A rare case of pericentric inversion, Inv (21) (p12;q22) in repeated pregnancy loss: A case report. Oman Med J. 2011;26(6):441-3.
6. Naseeb S, Carter Z, Minnis D, Donaldson I, Zeef L, Delneri D. Widespread impact of chromosomal inversions on gene xxpression uncovers robustness via phenotypic buffering. Mol Biol Evol. 2016;33(7):1679-96.
7. Luo Y, Xu C, Sun Y, Wang L, Chen S, Jin F. Different segregation patterns in five carriers due to a pericentric inversion of chromosome 1. Syst Biol Reprod Med. 2014;60(6):367-72.
8. Utami KH, Hillmer AM, Aksoy I, Chew EG, Teo AS, Zhang Z, et al. Detection of chromosomal breakpoints in patients with developmental delay and speech disorders. PLoS One. 2014;9(6):e90852.
9. Anton E, Vidal F, Egozcue J, Blanco J. Genetic reproductive risk in inversion carriers. Fertil Steril. 2006;85(3):661-6.
10. Puig M, Casillas S, Villatoro S, Cáceres M. Human inversions and their functional consequences. Brief Funct Genomics. 2015;14(5):369-79.
11. Aristidou C, Koufaris C, Theodosiou A, Bak M, Mehrjouy MM, Behjati F, et al. Accurate breakpoint mapping in apparently balanced translocation families with discordant phenotypes using whole genome mate-pair sequencing. PLoS One. 2017;12(1):e0169935.
12. Prieto F, Badia L, Asensi F, Moya A, Figuera MJ. Pericentric inversions of chromosome 12 in two families. Hum Genet. 1981;57(2):131-3.
13. Varela M, Wang N, Cerrillo M. Prenatal diagnosis of a 46,XX,inv(12)pat/47,XX,i(Xq),inv(12)pat. Hum Genet. 1987;75(1):93-4.
14. Haagerup A, Hertz JM. Pericentric inversion of chromosome 12; a three family study. Hum Genet. 1992;89(3):292-4.
15. Singh RP. Klinefelter's syndrome with a 47,XXY, inv (12) (q15q24) karyotype. Clin Genet. 1981;19(3):188-90.
16. Silahtaroglu AN, Hacihanefioglu S, Güven GS, Cenani A, Wirth J, Tommerup N, et al. Not para-, not peri-, but centric inversion of chromosome 12. J Med Genet. 1998;35(8):682-4.
17. Voiculescu I, Barbi G, Wolff G, Steinbach P, Back E, Schempp W. Familial pericentric inversion of chromosome 12. Hum Genet. 1986;72(4):320-2.
18. Kim HJ, Levy J, Roguero W, Iu B, Wallach RC. Prenatal detection of pericentric inversion of chromosome 12. Diagn Gynecol Obstet. 1980;2(3):231-4.
19. Poulsen H, Mikkelsen M, Holmgren G. Peri- and paracentric inversions in chromosome 12: prenatal diagnosis and family study. Prenat Diagn. 1981;1(1):35-42.
20. Kleczkowska A, Fryns JP, Van den Berghe H. Pericentric inversions in man: personal experience and review of the literature. Hum Genet. 1987;75(4):333-8.
21. Uehara S, Tanigawara S, Takeyama Y, Okamura K, Yajima A. A family with pericentric inversion of chromosome 12. Jpn J Hum Genet. 1994;39(1):201-4.
22. Ghorbel M, Baklouti-Gargouri S, ElGhazel H, Zribi N, Ben Abdallah F, Cherif M, et al. Pericentric inversion of chromosom 12 [Inv (12) (p12q12)] associated with idiopathic azoospermia in one infertile Tunisian man. Biochem Biophys Res Commun. 2013;432(3):472-4.