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

Murat KAYA1

Ömer Faruk KARATAŞ2

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


Anahtar kelimeler: İnfertilite; tekrarlayan düşüklüer; perisentrik inversion; 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.
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, XXY, 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 normal: FSH was 11.71 IU/L; LH was 8 IU/L; and testosterone was 3.5 ng/mL. Y microdeletion 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 de novo or familial (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

<table>
<thead>
<tr>
<th>Break point</th>
<th>NF</th>
<th>Carriers</th>
<th>Family History</th>
<th>Rf</th>
</tr>
</thead>
<tbody>
<tr>
<td>inv(12)(p13q11)</td>
<td>1</td>
<td>Father and two children</td>
<td>Advanced maternal age</td>
<td>18</td>
</tr>
<tr>
<td>inv(12)(p13q11)</td>
<td>2</td>
<td>Two patients in different families</td>
<td>NA</td>
<td>12</td>
</tr>
<tr>
<td>inv(12)(p11.2q13)</td>
<td>1</td>
<td>15 carriers out of 44 individuals in one 8 generation family</td>
<td>A previous stillborn child</td>
<td>19</td>
</tr>
<tr>
<td>inv(12)(p11.2q13)</td>
<td>2</td>
<td>Two patients in two different families</td>
<td>Routine chromosome analysis</td>
<td>17</td>
</tr>
<tr>
<td>inv(12)(p11q13)</td>
<td>2</td>
<td>Two different cases. One of them had paternal inversion and the other had maternal inversion</td>
<td>NA</td>
<td>20</td>
</tr>
<tr>
<td>inv(12)(p13q13)</td>
<td>3</td>
<td>25 carriers out of a total number of 52 persons examined in three families</td>
<td>Family 1: a previous child with Down's syndrome</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Family 2: A preterm delivery and two late abortions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Family 3: advanced paternal age</td>
<td></td>
</tr>
<tr>
<td>inv(12)(p12.3q14)</td>
<td>1</td>
<td>A Child and her father</td>
<td>Advanced maternal age</td>
<td>21</td>
</tr>
<tr>
<td>inv(12)(p12q12)</td>
<td>*</td>
<td>NA</td>
<td>Infertility</td>
<td>22</td>
</tr>
</tbody>
</table>

Current study

<table>
<thead>
<tr>
<th>Break point</th>
<th>NF</th>
<th>Carriers</th>
<th>Family History</th>
<th>Rf</th>
</tr>
</thead>
<tbody>
<tr>
<td>inv(12)(p11.2q14)</td>
<td>1</td>
<td>A wife, her father and her brother had the same inversion</td>
<td>Recurrent Miscarriages</td>
<td>F1</td>
</tr>
<tr>
<td>inv(12)(p11.2q14)</td>
<td>1</td>
<td>A male patient and his father had the same inversion</td>
<td>The brother of the wife carrying the same inversion had an extra Y chromosome</td>
<td>F2</td>
</tr>
<tr>
<td>inv(12)(p11.2q14)</td>
<td>1</td>
<td>A male patient and his brother had the same inversion</td>
<td>Infertility</td>
<td>F3</td>
</tr>
</tbody>
</table>

*: 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
Consent: Informed written consents for the publication of clinical details and images were obtained from the patients.

Competing interests: No competing interests were disclosed.

Grant information: The authors declared that no grants were involved in supporting this work.

REFERENCES