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## Research Article

# Chromosomal Aberrations in Turkish Infertile Couples with Reproductive Problems

### Abstract

**Aim of the study:** Infertility is a relatively common health condition, affecting nearly 15% of all couples, and has been estimated that nearly 50% of infertility cases are due to genetic defects. Chromosomal aberrations (CAs) contribute to infertility and repeated miscarriage leading to reproductive failure in couples.

**Objective:** To determine the frequency and types of CAs in unexplained infertile couples with reproductive problems, and the association between clinical background and genetic abnormality.

**Materials and method:** This study was a retrospective analysis to examine the CAs and prevalence in 160 couples and 210 individuals with unexplained infertile problems, and 58 control cases. The samples were cultured routinely for the karyotype analysis using G banding.

**Results:** CAs were detected in 9.8% of total 530 infertile individuals, and in 12% of all 160 couples (320 individuals). In the control group, CAs were only found in 3.4% of 58 healthy volunteers. The 50.0% of these CAs was structural aberrations, and also numerical CAs was 50.0% in infertile individuals. Specifically, 47, XXY (Klinefelter syndrome-KS) karyotype was the most common. Aneuploidies were present in 1.1% of infertile individuals. Among numerical CAs; mosaic Turner, X chromosome mosaicism and interseks were detected only in one case for each numerical CA type. Reciprocal translocations were present in 0.8% of infertile individuals. The inversions and the other variants were present in 1.9% and 2.3% of infertile individuals, respectively. The incidence of abnormal karyotypes was higher in males than females.

**Conclusion:** The results suggest that CAs were a major cause of infertility in humans, and cytogenetic analysis should be strongly recommended for infertile individuals. The incidence of CAs in infertile men was 3-fold greater than reported in infertile women. These findings will could be used widely in the clinical genetics and will be an effective tool for genetic counseling and reproductive guidance.

## Introduction

The World Health Organization has described infertility as a health problem of global concern. One in seven couples experiences infertility or subfertility [1]. The most common-cause of infertility is simply unexplained and this accounts for about 20% of couples. Also, infertility can be hormonal, related to age, exercise, obesity or infectious disease; it can be immunological, psychological, result from surgery or blockage, or can be associated with defined abnormalities in the gametes [2]. It is difficult to assess accurately the genetic contribution to reduced fertility as most, if not all, of the above factors are likely to have a genetic component. However, infertility may be manifested in the progeny during gametogenesis. The genetic causes of infertility are varied and include CAs, single gene disorders and phenotypes with multifactorial inheritance. Constitutional CAs contribute to infertility leading to reproductive failure in married couples. Chromosome studies in married couples were performed in order to elucidate their infertility, spontaneous abortions and foetal wastage. The present study offers our contribution on the topic by a analysis of the prevalence of CAs in a population of infertile Turkish couples.

## Materials and Methods

The patients included in this study were retrospectively evaluated females and males, who possess a risk for infertility. Over the past 15 years in our laboratory, postnatal karyotyping was done in 160 couples and 210 individuals with unexplained infertility (total 530 infertile cases). The mean age of the women was 32 years (range 19–40), and that of the men was 36 years (range 26–60 years). The sex ratio (male/female) of the patients was 1.1. In control group (the healthy individuals with no reproductive problems), the mean age of the women was 34 years (range 19–45), and that of the men was 38 years (range 26–65 years). The sex ratio (male/female) of the patients was 1.1. The patients were recruited during the year 2003 from the Department of Obstetrics and Gynecology and the Departments of Urology, who postnatally possess a risk for infertility. The genetics diagnosis of the patients is made on the basis of a chromosomal analysis in Department of Medical Biology and Genetics, Faculty of Medicine, Çukurova University. The decision of the ethics committee is not necessary because the patients were sent for diagnosis by the clinicals. Metaphase chromosome preparations from peripheral blood were made according to the standard cytogenetic protocols. Fifty metaphases were analyzed in all the patients, but in cases

of abnormalities and mosaicism the study was extended up to 100 metaphases. All CAs were reported according to the current international standard nomenclature (ISCN, 2009).

## Results

A total of 530 individuals with infertility and 58 control groups were analyzed. The karyotype results were divided into two categories: the structural and numerical CAs was shown in **Table 1**. The karyotype results were normal in 90.2% of 530 infertile individuals. However, CAs were detected in 9.8% of total 530 infertile individuals, and in 12% of 160 couples (320 individuals).

The 50% of these CAs was structural aberrations (translocations, inversions, the other variants), along with numerical CAs were 50%. Specifically, KS was the most common karyotype (in 3.2% of 17 cases, in 32.7% of CAs) among the infertile individuals (47,XXYx14; 47,XXY,inv(9)(p11;q12)x1; 47,Xi(Xq)Yx2). Aneuploidies were

present in 1.1% of all infertile individuals (in 11.5% of CAs) [46, XX, aneuploidy (8-10%) x4; 46,XY, aneuploidy (10-15%)x2]. Among numerical CAs, mosaic Turner, X chromosome mosaic and intersex were detected in a case [46,XX/45,X(25%); 46,XX/47,XXX(10%); 46,XX/46,XY(8%)]. Reciprocal translocations were present in 0.8% of all infertile individuals (in 7.8% of CAs) [46,XY,t(7;14)(q36;q22); 46,XX,t(X;22)(q26;q11); 46,XX,t(1;19)(q22;q13); 46,XY,t(13q;18q)]. The inversions and the other variants were present in 1.9% and 2.3% of the all infertile individuals (in 19.2% and 23.1% of CAs), respectively [46,XY,inv(12)(p13;q21); 46,XY,inv(9)(p11;q13)x4; 46,XY,inv(9)(p11;q12); 46,XX,inv(9)(p11;q13)x5; 46,XY,small(Y)x6; 46,XYqh+x5; 46,Xy,15p+]. The incidence of abnormal karyotype was higher in males than females. In the control group, CAs were only found in 3.4% of 58 healthy volunteers. The all of these CAs was structural aberrations; 46, XY, chtb(2q21), del(11)(q13-qter), 9qh+; 46,XY,chtb(12q13). The number of patients with CAs compared with the control group was significant (P=0.0001).

**Table 1:** Frequencies and distributions of the karyotypes in patients with infertile and in control group.

	The patient group			Control group	
Cytogenetic Category	Karyotypes	No. of cases	Frequency in anomalies (%)	Frequency in all cases (%)	Frequency in all controls (%)
Normal	46,XX or 46,XY	478		90.2	96.6
Abnormal	Numerical and structural chromosome abnormalities	52		9.8	3.4
	<b>Total</b>	<b>530</b>			<b>58</b>
<b>Abnormal</b>					
<b><u>NUMERICAL CHROMOSOME ABNORMALITIES</u></b>					
Klinefelter syndrome	47,XXY	14			
Klinefelter syndrome with isochromosome X long arm abnormalities	47,Xi(Xq)Y	2			
Klinefelter syndrome with inversion	47,XXY,inv(9)(p11;q12)	1	32.7	3.2	
Mosaic Turner or normal	46,XX/45,X (25%)	1			
X chromosome mosaics	46,XX/47,XXX (10%)	1			
Intersex mosaics	46,XX/46,XY (8%)	1			
Aneuploidies	46,XX,Anoploidy (8-10%)	4	11.5	1.1	
	46,XY,Aniploidy (10-15%)	2			
	<b>Total</b>	<b>26</b>	<b>50.0</b>	<b>4.9</b>	
<b><u>STRUCTURAL CHROMOSOME ABNORMALITIES</u></b>					
Resiprocal translocations	46,XY,t(7;14)(q36;q22)	1			46,XY,chtb(2q21), del(11)(q13-qter), 9qh+
	46,XX,t(X;22)(q26;q11)	1			
	46,XX,t(1;19)(q22;q13)	1			
	46,XY,t(13q;18q)	1			
	<b>Total</b>	<b>4</b>	<b>7.8</b>	<b>0.8</b>	46,XY,chtb(12q13)
Inversions	46,XY,inv(12)(p13;q21)	1			
	46,XY,inv(9)(p11;q13)	4			
	46,XY,inv(9)(p11;q12)	1			
	46,XX,inv(9)(p11;q13)	5			
	<b>Total</b>	<b>10</b>	<b>19.2</b>	<b>1.9</b>	
The other variants	46,XY,small(Y)	6			
	46,XYqh+	5			
	46,XY,15p+	1			
	<b>Total</b>	<b>12</b>	<b>23.1</b>	<b>2.3</b>	
	<b>Total</b>	<b>26</b>	<b>50.0</b>	<b>4.9</b>	<b>2</b>

## Discussion

The genetics of infertility is very complex. Clearly the hope is that a greater understanding of the genetic control of infertility. Difficulties with reproduction have been associated with cytogenetic abnormalities, and CAs are relevant causes of human infertility. In the present study, retrospective analysis of cytogenetic results in 530 unexplained infertile individuals revealed constitutional CAs in 12% of all infertile couples and 9.8% of all infertile individuals. The 50% of these CAs was carriers of numerical aberrations, and 50% were carriers of structural (Table 1). The frequencies of CAs was higher in the infertile individuals than in the control group ( $p=0.0001$ ). Our results consistent with the previous studies [3,4]. Therefore, cytogenetic analysis can be strongly recommended in infertile individuals. Infertility is thought to be male related in about half of infertile couples, but this often-quoted figure is poorly documented. In our cases, the sex ratio (male/female) of the individuals was 1.1. This means that male infertility accounts for approximately 50% of infertility among couples. Just as, according to the World Health Organization, male factor infertility accounts for an estimated half of all infertile cases. Whereas, in our study the incidence of CAs in infertile men was 3-fold greater than reported in infertile women. Thus, most authors have observed that CAs are far more common among infertile men than in women with infertility [5]. The most frequent chromosome-related causes of infertility are sex CAs. Male infertility occurs because of various factors, including those of environmental and genetic origin. Approximately, 5-10% of the men with unexplained infertility associated with azoospermia/oligozoospermia and/or anomalies of sperm morphology/motility have CAs, mostly gonosomal but also autosomal [6].

Among infertile men, the most frequent cytogenetic findings are 47, XXY and 47,XXY/46,XY. We also identified KS and variants in 17 males (3.2%), which accounted for the majority of the abnormalities (in 32.7% of CAs). In the previous studies, among patients with CAs, KS is the most frequent cause of infertility, affecting nearly 4% of infertile men [7,8]. The prevalence of KS is 0.1-0.2% in the general population [9], 3.1-4% in infertile male, and 11% in azoospermic men [10]. Thus, KS is the most common chromosomal aneuploidy leading to male infertility [9], and our study reconfirmed this conclusion. At the same time, X-chromosome deletions are usually sporadic, although familial cases have been reported. Deletions affecting the short arm of the X chromosome at band p11.2 result in ovarian failure in about half of women, and the other half experience menstrual irregularities. We identified two males with a variant KS, and trisomy Xq resulting from an isochromosome Xq [47,Xi(Xq)Y], and reviewed the cases of this 47,X,i(Xq),Y reported in the literature [10,11]. It has been shown by observations on other structural anomalies of X chromosomes that the presence of additional material of Xq causes azoospermia and hormonal imbalance in males [12,13].

Ninety percent of women with 45,X or with 45,X mosaicism with 46,XY, 46,XX, 47,XXX, or 46,iXq cell lines present with primary amenorrhea and lack of pubertal development. However, low-frequency mosaicism seems to be a frequent and underestimated due to failure in assisted reproduction [14]. It is uncertain whether carriers of gonosomal mosaic have any risk for having an abnormal

child. The risk is probably negligible for the majority of fertile individuals with a low level of sex chromosome mosaicism, but there seems to be an increased risk for repeated abortions [15]. Actually, Persson et al. [16], suggested that the recent finding of sex chromosome aneuploidies in fetuses conceived after ICSI might be due to a high rate of undetected Klinefelter mosaicism carriers. We also detected one female with mosaic Turner syndrome (TS) (46,XX/45,X). The karyotype 45,X/46,XX accounts for roughly 15% of TS cases, and the other mosaic karyotypes contribute to TS cases to a lesser degree [17]. Two to three percent of 45,X women and 10-15% of women with mosaic 45,X undergo normal pubertal development and menarche but are highly likely to undergo secondary amenorrhea [19,20]. In present study, the addition of one than one X chromosome (46,XX/47,XXX) was also found in one female. Most 47,XXX females are of normal weight, height and mental function, have normal pre-pubertal development and are fertile but have an early onset of menopause at about 30 years of age compared with the average of about 50 years of age [20]. Mosaicism occurs in approximately 10% of cases and can occur in many combinations such as 46,XX/47,XXX or 47,XXX/48,XXXX, or in combinations including TS cell lines such as 45,X/47,XXX or 45,X/46,XX/47,XXX [21]. However, we diagnosed a very rare infertile male because of the 46,XX/46,XY mosaicism. This suggests that the gonosomal mosaic carriers are infertility. It is generally held that almost all hermaphrodites are infertile, however, a study observed spermatogenesis in a hermaphrodite and a chimeric infertile male with a 46,XX/46,XY karyotype [22]. Increased dosage of genes that escape X inactivation accounts for clinical features and individuals with four or more X chromosomes have been reported. Severity of symptoms increases in proportion with the number of X chromosomes. The rate of chromosomal gains and losses can lead to aneuploidy was termed chromosomal instability. The common aneuploidy observed in 1.1% of our patients, occurring in 8-15% of metaphases. Although, the degree and spectrum of aneuploidy varies considerably among infertility. Patients with seminal anomalies could be affected by improper meiotic recombination and increased sperm chromosome aneuploidy. The infertile patients had an increased frequency of disomy for chromosomes 1, 13, 14, 18, 21, X and Y disomy compared with controls [23,24].

In present study, specifically inversions among the autosomal variations were the most common karyotypes (in 19.2% of CAs and in 10 cases) among the structural CAs. These inversions may be associated with a typical molecular break points, which ultimately leads to infertility. Both paracentric and pericentric inversions of a variety of chromosomes have been associated with male infertility [25]. We found unusual breakpoints in our patients with the pericentric inversion of chromosome 9 and 12. The pericentric inversion of chromosome 12 has never been mentioned in the literature in association with the birth of a recombinant offspring. However, prenatal diagnosis was recommended. Whether autosomal pericentric inversion is a possible threat to male fertility is unclear, but it has been assumed so by some authors [26]. The localization of breakpoints on chromosome 12 may lead to the cloning of fertility-susceptibility genes. In the present study, inversion of chromosome 9 [inv(9)] seems to be involved more often than the other chromosomes, and were involved in 1.7% of the patients. The inv(9) is the most

common reciprocal translocation in the general population and the prevalence of *inv(9)* varies with ethnicity. Most of *inv(9)*s observed do not give rise to any specific phenotypic abnormalities.

An increased incidence of reciprocal translocations are found in infertile men as compared to newborns. Translocations can remain without clinical consequences as long as they are balanced, without loss or gain of genetic material and do not interrupt an important gene. Mau et al. [27], found an 18-fold increase in 150 couples were told that the genetic risk for translocation study. Different authors have shown that male sterility is often associated with reciprocal translocations. Sperm karyotyping studies of over 30 reciprocal translocation carriers have demonstrated that 19–77% of spermatozoa are chromosomally unbalanced, and an average of about 50% are chromosomally abnormal [28]. Meiotic studies have shown that a translocation can result in spermatogenetic arrest or impairment [29]. In our patients we found reciprocal translocation carriers (0.8%). These translocations were concluded that the interchromosomal effect of these translocations may be associated with a typical molecular break points, which ultimately leads to infertility. The most interesting finding in these translocations was the involvement of chromosome regions 7q36, 14q22, Xq26, 22q11, 1q22 and 19q13. Azoospermic men demonstrate an incidence of these translocations that is approximately nine times higher than in control populations [30].

We found balanced X-autosome translocation [t(X;22)(q26;q11)] in a female. The genetic risk for the couple in our study was difficult to estimate. The possibilities of segregation are similar to those in reciprocal translocations in autosomes. Translocations involving the X chromosome and an autosome are rare [31]. For women, the phenotypic effects depend on the breakpoint and the status of inactivation of the X chromosomes. If the derivative X is active in all cells and the breakpoint does not interrupt a functional gene, about half have a normal phenotype and half have ovarian failure. In general, those with ovarian failure have breakpoints within the Xq13-q26 region. The breakpoints on the X chromosome vary widely in X; autosome translocations. The most common autosomes involved include chromosomes 15, 21 and 22. The pericentromeric regions of these chromosomes are predisposed to pairing with the X chromosome. Just as, we also found X-autosome translocation breakpoints within the Xq26 and 22q11 regions in one case.

Pericentric inversions, deletions, dicentric Y chromosomes, and ring Y chromosomes have been associated with azoospermia. One of the most common genetic damage of male infertility is Y chromosome microdeletions, which often result in azoospermia or oligozoospermia. Y chromosome infertility is inherited in a Y-linked manner. Because, males with Y chromosome deletions and microdeletions are infertile, and estimated at one in 2000 to one in 3000 males. We found the small Y in 1.1% of the males. These small Y have been associated with chromosome deletions and microdeletions of the long arm of the Y chromosome, it might lead to reduced fertility in males.

## Conclusions

We found the CAs frequencies surprisingly high in infertile couples and individuals with reproductive problems. The pericentric

inversion of chromosome 12 is a new finding. Therefore, we suggest that chromosomal analysis should be performed routinely in both males and females of infertile couples. The incidence of CAs in infertile men was 3-fold greater than reported in infertile women. These findings could be used widely in the clinical genetics and will be an effective tool for genetic counseling and reproductive guidance.

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