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Original Article

Investigation of the relationship between reproductive disorders and chromosomal abnormalities in a large-scale, single-center 10-year retrospective study

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ABSTRACT

Objective: Chromosomal changes are an important cause of reproductive disorders. This study investigated the chromosomal changes and prevalence of pathologies in individuals admitted to our Genetic Evaluation Center over a 10-year period due to a reproductive disorder.
Materials & Methods: The chromosomal findings of 4345 individuals with reproductive disorders who applied to our Genetic Evaluation Center at Akdeniz University in Antalya, Turkey between 2011 and 2021 were retrospectively evaluated.
Results: In this study, an abnormal karyotype was found in a total of 138 individuals (87 males and 51 females). Although the incidence of this abnormal karyotype varied among the diseases in the reproductive disorder subgroups, it was most frequently seen in azoospermia (17.0%). Of the 138 abnormalities, 75 were numerical and 54 were structural. The remaining 9 abnormalities consisted of 6 sex reversals and 3 patients with both numerical and structural anomalies. Additionally, the X chromosome was the chromosome most frequently involved in these abnormalities, being observed in 40.6% of patients.
Conclusion: This 10-year, single-center study involved one of the largest case series in the literature to investigate the subtypes of reproductive disorders and their chromosomal relationship. Although the importance of chromosome analysis has been deemphasized, it is still recommended for use by the guidelines and, as the results of this study demonstrate, is still a highly effective method in the investigation of reproductive disorders. Furthermore, chromosome analysis of individuals diagnosed with a reproductive disorder is also very important in the practice of the increasingly utilized preimplantation genetic diagnosis (PGD).
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Introduction

Reproductive disorders are pathologies that affect reproductive function in humans and lead to infertility or the failure of a pregnancy. There are a number of reasons that give rise to reproductive disorders, including inflammatory diseases, endocrine dysfunction, infectious diseases, genital abnormalities, gametogenesis or implantation failures, and erectile or ejaculatory problems.

A major subgroup of reproductive disorders is infertility. Infertility is defined as the inability of a couple to conceive despite having regular, unprotected sexual intercourse for at least one year [1]. Studies have reported that 8–12% of couples worldwide are affected by infertility at the reproductive age [2]. In low-income countries throughout much of the world, infertility rates are even higher, reaching upwards of 30% [3].

Another subgroup of reproductive disorders is miscarriage, which is seperated into two groups based on frequency of occurrence: spontaneous abortion (loss of a pregnancy without outside intervention before 20 weeks of gestation) [4] and habitual abortion (defined as 3 or more spontaneous abortions) [5].

Genetic factors are an important underlying cause of many reproductive disorders, and can occur at the gene-level or result from chromosomal aberrations. The causes of chromosomal abnormalities include numerical anomalies (Klinefelter syndrome, Turner syndrome),

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structural anomalies (chromosomal translocations: both reciprocal and Robertsonian), and sex reversals (XX males, XY females) [6].

The most widely studied reproductive disorder subgroup from a genetic and chromosomal standpoint, is infertility. The rate of chromosomal abnormalities among individuals with infertility has been reported from 1.05% to 17% [7, 8] The wide range of difference in this rate is due to the general concept of infertility and the different subgroups that fall under this concept. Therefore, the ratio of chromosomal abnormality varies in different studies with respect to the different types of reproductive disorders that are included. Indeed, habitual abortion patients have been observed to show chromosomal abnormalities at a rate of 4–8% [9], primary amenorrhea patients at 13.22% [10], and 3.95% of couples had one partner carrying a chromosomal abnormality in a study that involved couples referred for assisted reproductive techniques [11].It should not be forgotten that the frequency of chromosomal disorders seen in reproductive disorders and infertility in the population may show regional differences [12].

To better manage the impact of reproductive disorders and/or unexplained infertility, it is extremely important to first try to understand the type and nature of the chromosomal abnormality and underlying cause. This way, a more effective genetic counseling approach can be provided for the patient and allow for potential treatment.

This study investigated the karyotypes and chromosomal abnormalities of patients who applied to our genetic evaluation center over a 10-year span with a diagnosis of a reproductive disorder. Although there are many studies in the literature that report on the chromosomal basis of reproductive disorders and infertility, there are no other recent studies from Turkey or the Mediterranean region that include a patient group as large as the one included here.

Materials & methods

Patients

This retrospective study was conducted on 4345 patients with reproductive disorders who visited the Center for Genetic Disorder Evaluation at Akdeniz University Hospital in Antalya, Turkey between January 2011 and December 2021. This study was approved by the local Clinical Research Ethics Committee (16.02.2022/17)) of Akdeniz University.

In our study, we classified the patients according to their primary admission causes, which in turn led us to evaluate these patients according to specific subgroups of reproductive disorders. Since spontaneous and habitual abortions comprised such a large portion of the participants, they were evaluated as two separate groups. For the purposes of this study, spontaneous abortions meant the spontaneous end of a pregnancy before 20–24 weeks of gestation, while habitual abortions were defined as the loss of three or more pregnancies, according to RCOG 2011 guidelines [13, 14]. Furthermore, those patients who were referred to our center after failures in assisted reproductive technologies, regardless of the cause of their reproductive disorder, made up another large subgroup. Two other subgroups included patients with the congenital absence of a uterus and/or vagina [15] and patients with azoospermia, respectively. Also included was a small group of patients with primary amenorrhea and a small group of patients with secondary amenorrhea [16]. And, finally, patients who were referred to us with a diagnosis of unexplained infertility, also referred to as idiopathic infertility, were placed in another subgroup. For the patients with unexplained infertility, no cause could be found to explain their reproductive problem [17].

Conventional chromosomal analysis

Chromosome analysis was performed using conventional methods according to standard protocol [18].

Data analysis and statistics

During data analysis, polymorphic variants were considered to be normal karyotypes and not included. Statistical analyses were performed with SPSS 23.0 software, and all data was automatically rounded to two digits after the decimal point.

Results

Demographic evaluation

In this study, cytogenetic analysis was performed on a total of 4345 patients: 2261 male (52%) and 2084 female (48%) (Fig. 1a). The median age at the time of karyotype analysis was found to be 34 years for male patients and 31.8 years for female patients (Fig. 1c).

Among the reasons why patients were included in the study group, spontaneous abortions (the majority of whom were admitted to our center after two miscarriages), were the most common (37.9%), followed by habitual abortions (23.4%) and the inability to get pregnant while using assisted reproductive Technologies-ART (17.5%) (Table 1). When all of the patients were divided according to male and female, abortions and ART failure were the two leading causes of referral for both genders due to the fact that many patients were investigated as couples (Fig. 2b). When males were considered on their own, azoospermia (14.8%) and unexplained infertility (11.3%) were found to be the leading male factors. Among females, unexplained infertility (11.9%) and the congenital absence of the uterus and/or vagina (CAUV) (3.6%) were the most common causes for inclusion in the study group (Table 1).

In terms of relationship status, 85.3% of the patients were couples (1847 men and 1859 women, 3706 total), and most of them applied together as a couple, while 14.7% of the patients applied individually (Fig. 1b). The number of individual men (414) was almost double the number of individual women (225). While there wasn't a significant difference in the median age at the time of application between couples (33) and individual patients (32.6), there was a significant difference between these two groups in terms of chromosomal abnormality. Karyotype analysis revealed that 11.3% of individual patients displayed a chromosomal abnormality, while a chromosomal abnormality was found in just 1.8% of couples. Furthermore, spontaneous abortion was the main cause of evaluation in couples (41.6%), whereas azoospermia was the main cause among individual patients (49.8%).

Out of 4345 patients, a total of 138 (3.2%) were diagnosed with an abnormal karyotype, 87 of which were male and 51 female. Therefore, of the patients with a chromosomal abnormality, 63.05% were male and 36.95% were female. Based on gender, 3.84% of males were found to have a chromosome abnormality, while 2.44% of female patients had an abnormal karyotype.

Additionally, 17.0% of the patients who were referred to our center with a diagnosis of azoospermia had an abnormal karyotype, while 9.3% of patients diagnosed with CAUV had a chromosomal abnormality (Table 2). These two indications for cytogenetic evaluation, azoospermia and CAUV, had a higher probability of a chromosomal abnormality compared to the median range of chromosomal abnormalities (3.2%) for all types of reproductive disorders. The reproductive disorders and their percentages of karyotype abnormality were as follows: unexplained infertility (3.0%), ART failure (2.2%), and spontaneous and habitual abortions (1.6%).

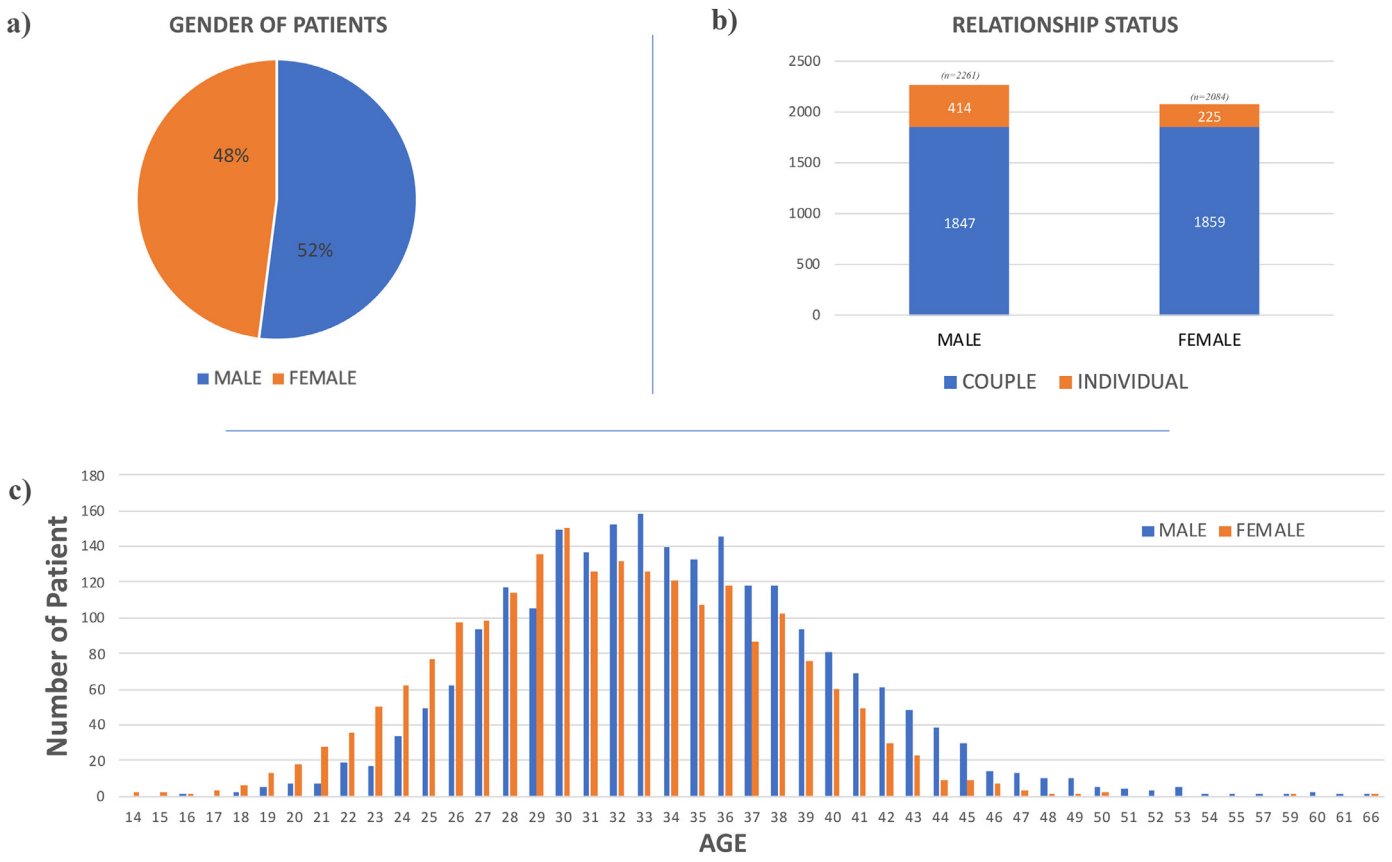


Fig. 1. Demographic characteristics of the patients a) Gender Ratio b) Relationship Status c) Age Distribution of the Patients.

The content of chromosomal irregularities

The total count of numerical and structural chromosomal anomalies were found to be close to each other. Among all of the 138 abnormalities, 75 were numerical (54.3%), 54 were structural (39.1%), 6 were sex reversals (4.3%) and 3 were male patients with both numerical and structural anomalies (2.2%).

The X chromosome was found to be the chromosome most commonly involved in abnormalities, appearing in a total of 40.6% (n = 73) of the patients. Chromosomes 13 and 14 were the next most frequent, appearing in an equal number of anomalies at n = 12 each (Fig. 2a).

Sex chromosome abnormalities (n = 81), the most common karyotype abnormality among the patients, comprised 45% of all abnormalities found in this study (Fig. 2a).

When patients with chromosomal irregularities were evaluated in terms of known clinical entities, the karyotypes of 43.5% of patients were found not to be related to any known syndrome. Of the remaining 56.5% of patients whose karyotypes were related to a known syndrome, 53 had Klinefelter syndrome (52 regular and mosaic Klinefelter patients and one Klinefelter patient with inv6) (38.4%), 11 had Mosaic Turner syndrome (10 patients had only numerical anomalies and one patient had mosaic isodicentric chromosome Y formation with Turner syndrome) (8.0%), 8 had Triple X syndrome (5.8%) and 6 had sex reversals (4.3%) (Fig. 2c) (Table 3).

Excluding Klinefelter syndrome, chromosomal translocations were the most commonly observed abnormalities among patient karyotypes (males (n = 21) and females (n = 23)), while the second most commonly observed abnormality differed for each gender, with mosaicisms (n = 15, 8 Mosaic Turner, 6 mosaic Triple X Syndrome and one low-level mosaicism of 45,X) for females and inversions (n = 7) for males (Fig. 2c) (Table 3).

Aberrations with only numerical anomalies

Among all of the chromosomal abnormalities, numerical abnormalities without profound structural changes accounted for 54.3%

Table 1
The reasons for admission of patients to the study and the frequency of these reasons according to gender.

REPRODUCTIVE DISORDERS	FREQUENCY IN MEN *N (%)*	FREQUENCY IN FEMALE *N (%)*	FREQUENCY IN GENERAL GROUP *N (%)*
	N = 2261	*N = 2084*	*N = 4345*
Spontaneous Abortion	804 (35.6)	841 (40.4)	1645 (37,9)
Habitual Abortion	497 (22)	519 (24.9)	1016 (23,4)
ART Failure	369 (16.3)	393 (18.9)	762 (17,5)
Unexplained Infertility	256 (11.3)	247 (11.9)	503 (11,6)
Azoospermia	335 (14.8)	0 (0)	335 (7,7)
CAUV	0 (0)	75 (3.6)	75 (1,7)
Primary Amenorrhea	0 (0)	7 (0.3)	7 (0,2)
Secondary Amenorrhea	0 (0)	1 (0)	1 (0)
Ovarian Insufficiency	0 (0)	1 (0)	1 (0)

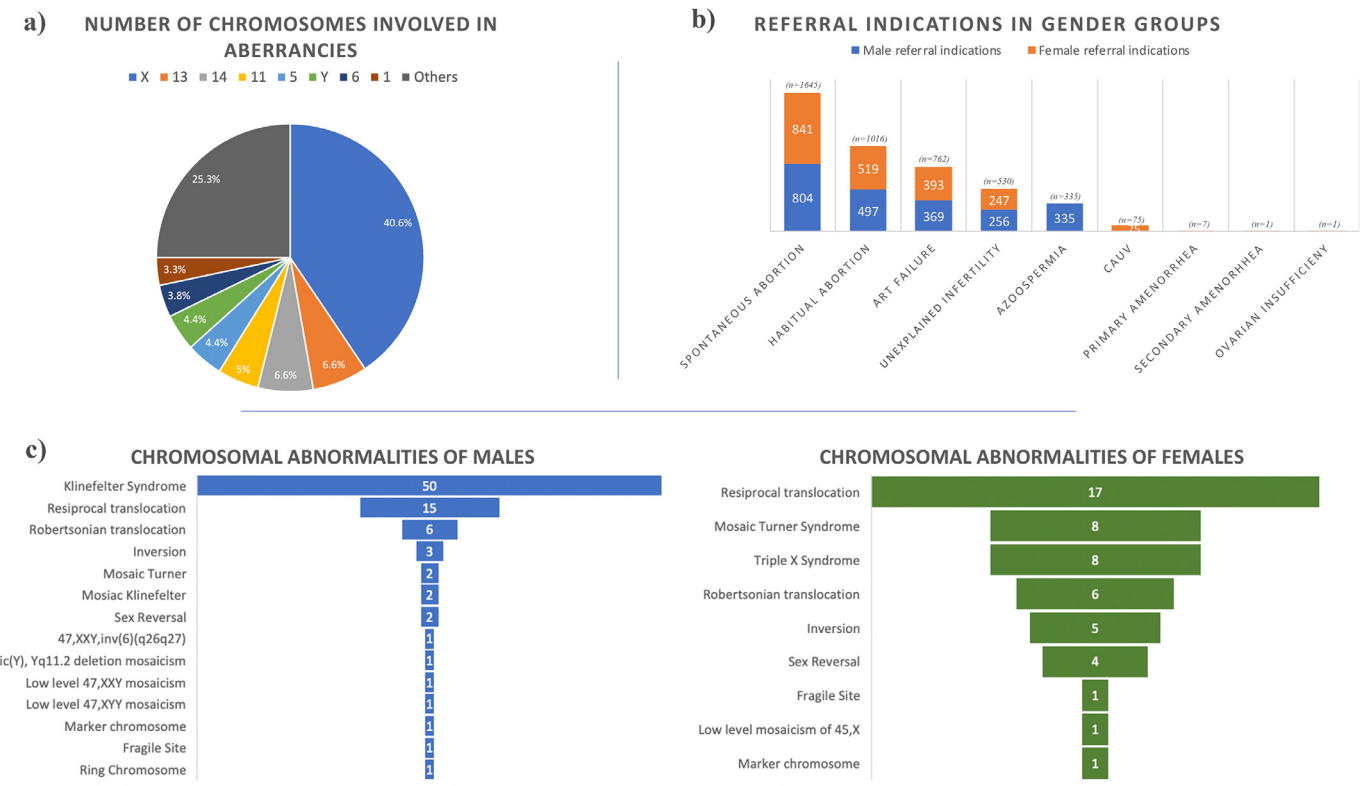


Fig. 2. Chromosomal abnormality and corresponding referral indication distribution of the patients a) Number of Chromosomes Involved in Aberrancies c) Referral Indications in Gender Groups c) Chromosomal Abnormalities in Gender Groups.

(n = 75) of the total. The numerical abnormalities found in this study consisted mostly of sex chromosome disorders (n = 73), with 52 total Klinefelter syndrome patients (regular and mosaic), 10 Mosaic Turner patients, 8 patients with Triple X syndrome, and three low-level mosaicism patients with the karyotypes mos 45,X[3]/46,XX[47], mos 47,XY+Y?[3]/46,XY[47] and mos 47,XXY[2]/46,XY[48] were not diagnosed as syndromic. There were two additional patients with marker chromosomes and the origin of these could not be determined.

As the predominant karyotype observed across the study group, Klinefelter syndrome (47XXY, all male phenotype, as would be predicted), was also the most commonly observed numerical abnormality. Out of all Klinefelter patients, only two were chromosomally mosaic, one of which was mos 47,XXY[48]/46,XY[2] the other mos 48,XXXY[4]/47,XXY[43]/46,XY[3].

Mosaic Turner syndrome was the second most frequent numerical abnormality. Of the 10 Mosaic Turner patients, 8 were females and 2 were males. The karyotypes of patients who displayed a male phenotype were 45,X[15]/46,XY[75] and 45,X[25]/48,XXYY[1]/46,XY[19]. All other Turner patients with the female phenotype had 45,X/46,XX mosaicism. There were no classical Turner syndrome patients who applied to the clinic with a diagnosis of a reproductive disorder.

The next most frequently observed numerical abnormality was Triple X syndrome. Among the 8 triple X syndrome patients, 6 were chromosomally mosaic, with only one having tetrasomy X mosaicism, 47,XXX[1]/48,XXXX[1]/46,XX[48]. The other two Triple X patients had 47,XXX karyotype.

Numerical anomalies not consisting of gonosomes were seen in two patients (one male and one female) with marker chromosomes. The male patient displayed the mos 47,XY,+mar[3]/46,XY[47] karyotype and the female patient had a 47,XX,+mar karyotype. Both were referred to our center after ART failure.

Aberrations with only structural anomalies

Only structural anomalies comprised 39.1% of all abnormal karyotypes in this study. The structural anomalies (n = 54) observed were mainly translocations of autosomal chromosomes (n = 44).

Table 2
Distribution of chromosomal abnormalities according to reason for patient admission to the study. *The prevalence of chromosomal abnormalities in each subgroup according to the cause of admission.

REPRODUCTIVE DISORDERS	TOTAL (N = 138)	PREVALENCE*	NUMERICAL (N = 75)	STRUCTURAL (N = 54)	NUMERICAL AND STRUCTURAL (N = 3)	SEX REVERSAL (N = 6)
Azoospermia	57	17.0%	50	4	2	1
Spontaneous Abortion	26	1.6%	5	21	–	–
ART Failure	17	2.2%	5	11	–	1
Habitual Abortion	16	1.6%	2	14	–	–
Unexplained Infertility	15	3.0%	10	4	1	–
CAUV	7	9.3%	3	–	–	4
Primary Amenorrhea	–	0%	–	–	–	–
Secondary Amenorrhea	–	0%	–	–	–	–
Ovarian Insufficiency	–	0%	–	–	–	–

Table 3
The chromosomal abnormalities observed in the patients.

	CHROMOSOMAL ANOMALIES	PATIENT NUMBER
Klinefelter (~37.7%)	**47,XXY**	**50**
	mos 47,XXY[48]/46,XY[2]	**1**
	mos 48,XXXY[4]/47,XXY[43]/46,XY[3]	**1**
Mosaic Turner (~7.2%)	mos 45,X/46,XX	8
	mos 45,X[15]/46,XY[75]	1
	mos 45,X[25]/48,XXYY[1]/46,XYqh-[19]	1
Triple X(~5.8%)	**mos 47,XXX/ 46,XX**	**5**
	47,XXX	**2**
	mos 47,XXX[1]/48,XXXX[1]/46,XX[48]	**1**
Sex Reversal(~4.3%)	46,XY female	4
	46,XX male	2
Low level mosaicisms, non-syndromic (~1.4%)	**mos 47,XXY[2]/46,XY[48]**	**1**
	mos 45,X[3]/46,XX[47]	**1**
Reciprocal Translocations (~23.2%)	46,XY,t(1:11:8)(q25;q14;q13)	1
	46,XX,t(1;4)(p34;q35.1)	1
	46,XX,t(1;18)(p10;p10)	1
	46,XX,t(2;6)(p13.1;p23)	1
	46,XX,t(2;7)(q10;q10)	1
	46,XX,t(3;10)(p21;q24.3)	1
	46,XX,t(3;13)(p21;q27)	1
	46,XX,t(3;5)(q21;q31.1)	1
	46,XX,t(4;6)(q11;q11)	1
	46,XX,t(5;6)(q35.3;q25.1)	1
	46,XX,t(5;8)(q15;q22.3)	1
	46,XX,t(5;19)(p15.3;q13.3)	1
	46,XX,t(6;7)(q23.3;q32)	1
	46,XX,t(9;13)(q22.3;q12.3)	1
	46,XX,t(11;22)(q24.2;q13.1)	1
	46,XX,t(12;15)(q13;q22.3)	1
	46,XX,t(15;17)(q24.1;p11.2)	1
	46,XX,t(11;22)(q23;q11.2)	1
	46,XY,t(1;12)(q44;p13)	1
	46,XY,t(1;17)(p32.3;q11.2)	1
	46,XY,t(2;3)(p13;q27)	1
	46,XY,t(2;5)(q23;q15),t(11;14)(q23;q24.1)dn	1
	46,XY,t(3;11)(q26.2;q23.3)	1
	46,XY,t(5;8;)(q13;p23.1)	1
	46,XY,t(6;16)(q21;q12,1)	1
	46,XY,t(8;16)(q22.3;q24)	1
	46,XY,t(8;17)(q11.2;q23.1)	1
	45,XY,t(9;14)(q24,3;q11.2)	1
	46,XY,t(11;14)(q14.2;q11.2)	1
	46,XY,t(11;17)(q13;q23)pat	1
	46,XY,t(11;22)(q23.3;q11.2)	1
	46,XY,t(12;14)(q15;q24.3)	1
Robertsonian Translocations (~8.7%)	**45,XX,der(13;14)(q10;q10)**	**3**
	45,XX,derdic(13;14)(p11.2;p11.2)	**2**
	45,XX,der(14;21)(q10;q10)	**1**
	45,XY,der(13;14)(q10;q10)	**2**
	45,XY,der(13;22)(q10;q10)	**1**
	45 XY,derdic(13;14)(p11.2;p11.2)	**1**
	45,XY,derdic(13;22)(p11.2;p11.2)	**1**
	45,XY,derdic(22;22)(p11.2;p11.2)	**1**
Inversions (~5.8%)	46,XX,inv(1)(q25.3q31.2?)	1
	46,XX,inv(5)(p14.2p13.2)	1
	46,XX,inv(6)(p21.31p23)	1
	46,XX,inv(7)(q11.2q31)	1
	46,XY,inv(5)(q12.1q35.1)mat	1
	46,XY,inv(8)(p11.1p23.1)	1
	46,XY,inv(11)(p13q23.3)	1
	46,XX,inv(16)(p11.1p11.2)	1
Complex/Others; (~5.8%)	**mos 46,XY,fra(16)(q22)[15] /46,XY[35]**	**1**
	mos 46,XX,fra(16)(q22)[6]/46,XX[14]	**1**
	mos 47,XY,+Y?[3]/46,XY[47]	**1**
	47,XX,+mar?	**1**
	mos 47,XY,+mar[3],46,XY[47]	**1**
	47,XXY,inv(6)(q26q27) (Klinefelter)	**1**
	mos 45,XY,−21[52]/46,XY,dic r(21)[4]/46,XY,r(21)(p13q22.3),1qh+,9qh+[44]	**1**
	mos 45,X[46]/46,X,idic(Y)(q11.2)[2] /46,XY,del(Y)(q11.2)[2] (Mosaic Turner)	**1**

Of the 44 translocation patients, 23 were female and 21 were male. There were 32 reciprocal and 12 Robertsonian translocations, and these also had nearly the same ratio between gender groups.

Among the 32 reciprocal translocations, 17 were observed in female patients and 15 in males. Twenty-four of the patients with reciprocal translocations came to the clinic due to habitual and spontaneous abortions, while 4 came with ART failure, 3 with azoospermia, and one with unexplained infertility. Chromosome 11 was found to be the most common chromosome involved in reciprocal translocations (n = 8). There were even two patients who displayed translocations involving the same chromosomes. One of these was 46,XY,t(11;14)(q14.2;q11.2), while the other patient had the double translocations 46,XY,t(2;5)(q23;q15),t(11;14)(q23;q24.1)dn. Both of these patients had a clinical diagnosis of azoospermia.

When Robertsonian translocations were evaluated in terms of referral indications, four were referred with ART failure, four with spontenous and habitual abortions, three with unexplained infertility, and one with azoospermia. As is common with Robertsonian translocations, chromosomes 13 (n = 10) and 14 (n = 9) were involved. The most common Robertsonian translocation, observed in 5 patients, was der(13;14)(q10;q10).

In patients who only displayed chromosomal inversions (n = 8), 4 were female and 4 were male. Their referral indications were mainly habitual and spontaneous abortions (n = 5), followed by two with ART failure, one with unexplained infertility.

A rare chromosomal abnormality encountered in our patient series was 46,XY,t(1:11:8)(q25;q14;q13) (Fig. 3). In this patient, it was observed that in addition to a history of spontaneous abortion, there was also hearing loss.

Numerical and structural anomalies

There were three patients who had both a numerical and a structural anomaly in their karyotypes. One of these patients was a male with azoospermia, and had a mosaic ring chromosome 21 and monosomy 21 with the karyotype 45,XY,−21[52]/46,XY,dic r(21)[4]/46,XY, r(21)(p13q22.3)[44]. The karyotype of another patient who applied to our center with azoospermia was a isodicentric chromosome Y formation in "mos 45,X[46]/46,X,idic(Y)(q11.2)[2] /46,XY,del(Y)(q11.2)[2]" without classical Turner syndrome symptoms. Our third case, who had both structural and numerical anomalies, came to our center with the diagnosis of unexplained infertility. It was observed that this patient had the karyotype "47,XXY,inv(6)(q26q27)", which consists of an extra X chromosome and the inversion of the 6th chromosome.

Sex reversals

Six patients displayed a normal karyotype but it did not match their gender identification. Two were 46,XX males and the others were all 46,XY females. All of the female phenotype sex reversal patients were referred to the clinic with a diagnosis of congenital absence of uterus and/or vagina.

Discussion

In this study, we analyzed a large number of karyotype anomalies from a wide variety of patients (both individuals and couples) that were referred to our genetic evaluation center with a diagnosis of either a reproductive disorder or infertility. No other study of such magnitude, and across such a long time span, has ever been

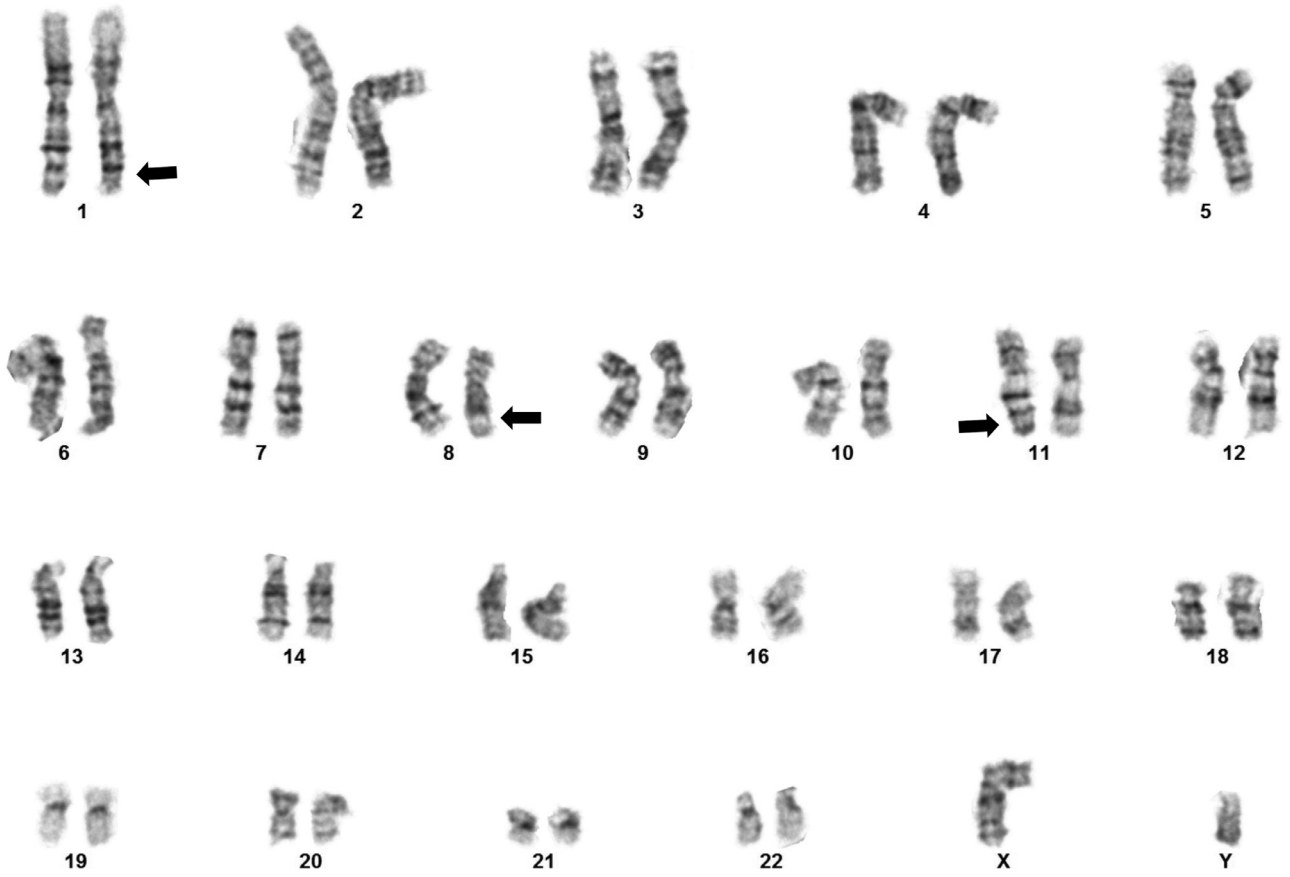


Fig. 3. The karyogram of the patient with the 46,XY,t(1:11:8)(q25;q14;q13) translocation.

conducted in Turkey or the Mediterranean region. Here we compare and discuss our results with those from studies that were carried out in different countries and geographic locations throughout the world.

In previous studies, the rate of karyotype anomalies in patients with reproductive disorders and infertility ranged from 2.37% [8] to 18.5% [19]. In our study, this rate was found to be 3.2%. Considering that we did not include heteromorphisms as anomalies, this low rate can be explained by the fact that our genetic evaluation center offered easy accessibility to patients with reproductive disorders and infertility throughout the local geographic region, and so included a large number of cases.

Among the patients, those with azoospermia and CAUV had a chromosomal abnormality rate higher than the mean rate of all reproductive disorder patients combined (3.2%). Azoospermia had the highest rate of chromosomal abnormality at 17.0%, while CAUV had the second highest rate at 9.3% (Table 2). As in another study, men with azoospermia had the highest incidence of chromosomal abnormalities among infertile patients [20]. This may also explain why the total percentage of karyotype abnormalities among males (3.9%) was higher than among females (2.4%). Furthermore, while CAUV patients would be expected to have a normal karyotype, this group showed low-level mosaicism involving the X chromosome.

A review of the literature revealed that our study is the first and only from a single center to evaluate the chromosomal abnormality rate in CAUV patients on such a large scale. This is partially due to the fact that the plastic surgery department at our university is the leading center of uterine transplantation (UTx) in Turkey, and so our center had the chance to evaluate many CAUV patients, including the first-ever uterus transplantation from a multiorgan donor [21].

The numerical and structural chromosomal abnormalities observed in our study were further divided into syndromic and non-syndromic groups. Most of the numerical abnormalities were syndromic aberrancies, and all of these were predictably sex chromosome abnormalities. With a total of 53 patients, Klinefelter syndrome was the most common cytogenetic diagnosis among patients with reproductive disorders. Indeed, Klinefelter syndrome accounted for 80.7% of karyotype abnormalities observed among azoospermia patients. The rate of Klinefelter syndrome has been reported at 64%, indicating that the X chromosome is important when evaluating the karyotypes of azoospermia patients [22]. Another well-described sex chromosome abnormality known to alter reproductive function is Turner syndrome. All of the Turner syndrome patients in our study had varying levels of mosaicism, including three who displayed a normal male phenotype. The absence of non-mosaic Turner patients in our study is likely due to the fact that these patients are usually diagnosed with the syndrome at an early age, and so would not be referred to our evaluation center for genetic testing with a reproductive disorder as adults.

In our study group, translocations comprised the greatest number of structural anomalies, and were grouped as either reciprocal or Robertsonian. Two of our patients had a reciprocal translocation of t (11; 22)(q23;q11.2), which is a frequently observed translocation that leads to an increased risk for miscarriages, subfertility in males, and chromosomally unbalanced offspring [23]. The breakpoints in our patients (2p13, 3p21, 5q15, 8q22.3, 11q23, 17q23, 22q11.2) that were involved in more than one translocation could be further evaluated in terms of reproductive disorders and infertility. Some of the breakpoint regions seen in our study are known to include genes important for sex determination and spermatogenic growth. For example, one of the breakpoint regions, 17q11.2, that was observed in a male patient with the karyotype 46,XY,t(1;17)(p32.3;q11.2), has been associated with poor sperm function [24]. Likewise, a region on 6q21 observed in the karyotype 46,XY,t(6;16)(q21;q12.1) of one of our patients, includes the gene ARMC2, which has been associated with spermatogenic failure-38 in OMIM [25]. It has been reported that this breakpoint is involved in male fertility problems [26]. Additionally, one of our patients had the breakpoint region 9p24.3 with the karyotype 45,XY,t(9;14)(q24,3;q11.2). This region includes the gene DMRT1, which encodes a male-specific transcriptional regulator and is involved in sex determination and differentiation [27]. Finally, in a case of ours, we observed a rare occurrence in the form of a double translocation of t(2;5)(q23;q15),t(11;14)(q23;q24.1). As can be seen, the chromosomal regions that might contain genes involved in sexual development and gametogenesis are important breakpoints for the cytogenomic evaluation of reproductive disorders.

Robertsonian translocations are common structural rearrangements, and can lead to an increased risk of reproductive failure due to the formation of trivalent structures during meiosis [28]. As in previous studies, the majority of our patients with Robertsonian translocations had the karyotype der(13;14)(q10;q10) [29]. It is known that carriers of Robertsonian translocations have an increased risk for reproductive disorders such as infertility, azoospermia and spontaneous abortions [30]. Studies have shown that about 1.6% of infertile male patients carry a Robertsonian translocation [31]. In our study, this rate was 0.3% of the total group and 0.8% of the unexplained infertility subgroup among male patients.

Inversions are another common structural abnormality seen in karyotypes associated with reproductive problems. In the inversion group, the breakpoint 6p21 was once again observed in a patient with the karyotype 46,XX,inv(6)(p21.31;p23). This region was also the focus of a study which investigated the pericentric inversions of chromosome 6 and fertility problems [26]. There was one pericentric inversion patient in our study who was diagnosed with habitual abortions. This result might support the idea that pericentric inversions are more likely to be linked to repeated spontaneous abortions than paracentic inversions [26].

There were also some rare entities among the structural anomalies in our study. For example, two patients were both carriers of a fragile site on the long arm of chromosome 16. Despite the fact that fragile sites are not believed to have a phenotypic effect, a review of the literature found one patient who was diagnosed with infertility and had a fragile site on 16q22 [32]. Another extremely rare abnormality found in the karyotype of one of our patients was a ring formation of chromosome 21. In a previously published study of ours, we reported this anomaly in association with spermiogram anomalies, such as azoospermia and cryptozoospermia [33].

When examined in terms of planning a genetic counseling approach, it is clear that chromosomal analysis is critical for patients with azoospermia, as that group had the highest prevalence of chromosomal abnormalities in our study (17.0%). CAUV had the second highest prevalence rate (9.3%), and so for this reason we believe that chromosomal analysis should be performed in the determination of transplant candidates, especially centers where uterine transplant planning will be carried out. Although chromosomal analysis is no longer highly recommended in spontaneous abortion patients, according to our data the prevalence of chromosomal abnormalities in spontaneous abortion (1.6%) is the same as in habitual abortion. Therefore, based on our data, patients who had a spontaneous abortion might also benefit from chromosomal analysis, as it is both cost effective and provides a psychological relief to the patient and their family members because they will not need to wait for another miscarriage before learning that they do not have any chromosomal abnormality.

Lastly, two prior publications on chromosomal abnormalities among patients diagnosed with reproductive problems in Turkey reported chromosomal abnormality rates of 2.6% to 9.8%, respectively [34, 35]. In another study on recurrent first trimester abortions in Turkey, the chromosomal abnormality rate was found to be 8.7% [36]. A number of factors could explain the difference between these rates and ours (3.2%), including variation in sample size, inclusion criteria and geographical variability.

Conclusion

In order to enrich the literature and help improve the decision-making process of the clinician, it will be useful to bring together and analyze large-scale, single-center case series, such as ours, from different regions of the world. Such a broad range of data would greatly aid the ability of clinicians to administer the proper method of assisted reproductive technologies, such as in-vitro fertilization (IVF) or intra-cytoplasmic sperm injection (ICSI), to allow for the prevention of chromosomally unbalanced progeny and recurrent miscarriage cases by using methods such as PGD. Although cytogenetic analysis has been replaced in some areas by advanced technologies, such as array comparative genomic hybridization (aCGH), it is still useful for investigating reproductive disorders and remains the best option for laboratories without access to these newer techniques.

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