ANDROLOGY
Original Article

Evaluation of chromosomal abnormalities and Y-chromosome microdeletions in 1696 Turkish cases with primary male infertility: A single-center study

Taha Reşid Özdemir[1], Berk Özyılmaz[1], Özgür Çakmak[2], Özge Özer Kaya[1], Can Köse[3], Özgür Kırbıyık[1], Mehmet Zeynel Keskin[2], Altuğ Koç[1], Tuğba Zeyrek[3], Yaşar Bekir Kutbay[1], Kadri Murat Erdoğan[1], Merve Saka Güvenç[1]

Cite this article as: Özdemir TR, Özyılmaz B, Çakmak Ö, Kaya ÖÖ, Köse C, Kırbıyık Ö, et al. Evaluation of chromosomal abnormalities and Y-chromosome microdeletions in 1696 Turkish cases with primary male infertility: A single-center study. Turk J Urol 2020; 46(2): 95-100.

ORCID IDs of the authors:
T.R.Ö. 0000-0003-4870-6945;
B.Ö. 0000-0003-2654-3698;
Ö.Ç. 0000-0002-4618-9465;
Ö.Ö. 0000-0001-6731-2461;
C.K. 0000-0001-7351-7981;
Ö.K. 0000-0003-1333-2007;
M.Z.K. 0000-0002-9206-5586;
A.K. 0000-0002-8366-6806;
T.Z. 0000-0002-1427-6863;
Y.B.K. 0000-0002-9006-5072;
K.M.E. 0000-0003-0097-1424;
M.S.G. 0000-0001-8842-0381.

[1]Genetic Diagnostic Center, Health Sciences University, İzmir Tepecik Training and Research Hospital, İzmir, Turkey
[2]Department of Urology, Health Sciences University, İzmir Tepecik Training and Research Hospital, İzmir, Turkey
[3]Department of Histology and Embryology, Health Sciences University, İzmir Tepecik Training and Research Hospital, İzmir, Turkey

Submitted:
29.07.2019

Accepted:
06.11.2019

Available Online Date:
29.11.2019

Corresponding Author:
Taha Reşid Özdemir
E-mail:
dr.tahaoz@gmail.com

Available online at
www.turkishjournalofurology.com

ABSTRACT

Objective: The aim of this study was to determine the frequencies of chromosomal abnormalities and Y-chromosome microdeletions in Turkish cases with primary male infertility in a single center.

Material and methods: Chromosomal abnormalities and Y-chromosome microdeletions were investigated in 1696 cases with primary male infertility between 2012 and 2017. Karyotype analyzes and Y-chromosome microdeletions analyzes [azoospermia factor (AZF) regions] were performed in all cases by using standard cytogenetic methods and the multiplex polymerase chain reaction method, respectively.

Results: Chromosomal abnormalities were found in 142 cases (8.4%; 142/1696). Y-chromosome microdeletions were detected in 46 cases (2.7%; 46/1696). Y-chromosome microdeletions in the AZFc region were found in 20 of 46 cases (43%).

Conclusion: This study is one of the few were a large number of cases was studied in Turkey. It indicates that cytogenetic and Y-chromosome microdeletion studies should be conducted in cases with primary male infertility prior to selecting assisted reproductive techniques.

Keywords: AZF regions; chromosomal abnormalities; multiplex PCR; primary male infertility; Y-chromosome microdeletion.

Introduction

Infertility is affecting approximately 15% of all the couples attempting pregnancy in the general population. Male infertility is responsible for approximately 50% of the infertility cases. There are several factors that cause male infertility, such as endocrine disorders, varicocele, ejaculatory duct obstruction, testicular trauma, cryptorchidism, systemic diseases, genetic factors, etc. Chromosomal abnormalities, Y-chromosome microdeletions, and single gene defects are the most common genetic causes of male infertility.[1]

Chromosomal abnormalities could be detected as numerical or structural in sex chromosomes or autosomes (e.g. balanced translocations). Klinefelter syndrome (47,XXY) is the most common chromosomal abnormality causing male infertility. The second most common genetic cause are the Y-chromosome microdeletions.[2] There are several genes responsible for normal spermatogenesis in the azoospermia factor (AZF) region of the Y-chromosome. The AZF region has three non-overlapping loci named AZFa, AZFb, and AZFc. Microdeletions of the AZF genes are associated with oligozoospermia and azoospermia.

The cytogenetic analysis (karyotype) and Y-chromosome microdeletion tests are useful to determine appropriate assisted reproductive techniques (ART) such as the intracytoplasmic sperm injection (ICSI) and fertilization (IVF) techniques. Therefore, in this study, it was

Turk J Urol 2020; 46(2): 95-100
DOI:10.5152/tud.2019.19156

aimed to investigate the types and frequencies of both chromosomal abnormalities and Y-chromosome microdeletions in 1696 Turkish cases with primary male infertility to provide accurate and reliable genetic counseling before attempting ART.

Material and methods

Patients

This study included 1696 cases with primary male infertility who were referred to the Genetic Diagnostic Center between 2012 and 2017. All cases' records were examined. All cases had primary infertility, and none had obstructive azoospermia. The approved this study as a retrospective study , and informed consent was not obtained from all participants**.** The data were collected from the records of patients.

Main Points:

- Male infertility is responsible for approximately 50% of the infertility cases. Y-chromosomal microdeletions [azoospermia factor (AZF) regions] are the most common genetic cause of human male infertility after Klinefelter syndrome (47,XXY).
- The AZFa or AZFb microdeletion has more severe effects than AZFc. Assisted reproductive techniques (ART) treatments are not successful in cases with a complete deletion of AZFa or AZFb regions. Cases with AZFc microdeletions have approximately a 50% chance of sperm retrieval by testicular sperm extraction (TESE), and children can be conceived by intracytoplasmic sperm injection (ICSI). The family with Y-chromosomal microdeletion should be informed that there may be a male offspring with suspected external genitalia or mixed gonadal dysgenesis. Therefore, preimplantation genetic diagnosis (PGD) and/or prenatal genetic diagnosis should be offered to the couple. If a couple has a male offspring, it may be worthwhile to have their son's semen checked early in puberty and to cryopreserve sperm if any sperm are found. However, a family have options to avoid male offspring transmission include PGD and the transfer of female embryos.
- Most of the autosomal chromosomal abnormalities can be diagnosed at birth, but most sex chromosome abnormalities (except Turner syndrome) are not revealed clinically until puberty. It is assumed that the conceptions with unbalanced chromosomal abnormalities are being lost very early as unrecognized pregnancies (infertility) or later during gestation. In balanced chromosomal structural rearrangements, fetal karyotyping (chorionic villus biopsy or amniocentesis) or PGD is recommended for families who are planning pregnancy.
- This study is one of the few that involved a large number of cases from this field in Turkey. Chromosomal abnormalities were detected in 140 of 1696 cases (8.3%). The most common chromosomal abnormalities were found in sex chromosomes (76.4%; 107/140). Y-chromosome microdeletions were detected in 45 of 1696 cases (2.6%). The AZFc region was found as the most affected site (44.4%; 20/45).
- Karyotyping and the Y-chromosome microdeletion test should be carried out to provide appropriate genetic counseling and to determine an appropriate treatment in males with primary infertility.

Cytogenetic analysis

The karyotypes of all cases were studied in cultured peripheral blood lymphocytes using conventional method. At least 20 metaphase fields were analyzed after staining by trypsin-G banding techniques. The karyotype results were written according to the International System for Chromosome Nomenclature Guidelines.

Y-chromosome microdeletion analysis

After genomic DNA samples were obtained, screening of AZF deletions was performed with the multiplex polymerase chain reaction (PCR) method using a ChromoQuant AZF PCR kit (CyberGene AB, Solna, Sweden) according to the protocol supplied with the kit. It relies on the PCR amplification of sequence-tagged sites in the AZFa (sY84, sY86), AZFb (sY127, sY134), and AZFc (sY254, sY255, sY160) regions and control regions (SRY, ZFX/ZFY) on the Y-chromosome. PCR products were analyzed using an ABI PRISM 3500 DNA analyzer (Applied Biosystems, Foster City, CA, USA). Data were analyzed with the GeneMapper Software (Applied Biosystems, Foster City, CA, USA).

Results

Chromosomal abnormalities were detected in 140 of 1696 cases (8.3%) with primary male infertility (Table 1). The most common chromosomal abnormalities were found in sex chromosomes (76.4%; 107/140). The others were autosomal translocations (19.3%; 27/140) and autosomal inversions (4.3%; 6/140). The most common chromosomal abnormality was found as the Klinefelter syndrome (47,XXY) in 75 of 140 cases. The second was found in 11 cases as 47,XYY.

Y-chromosome microdeletions were detected in 45 of 1696 cases (2.6%). The AZFc region was found as the most affected site (44.4%), followed by AZFb+c (31.1%), AZFa+b+c (11.1%), AZFa (8.9%), and AZFb (4.5%) regions. Abnormal karyotypes were found in 11 of 45 cases (24.4%) with Y-chromosome microdeletions (Table 2).

Discussion

Chromosomal abnormalities are associated with male infertility. The frequency of cytogenetic aberrations has been estimated as 2.1%–28.4% among infertile men.[3] In our series, abnormal karyotypes were found in 140 cases (8.3%). There are several reports from Turkey covering this subject.[3-5] The incidence rates in these studies were 11.2%, 1.6%, and 4.8%, respectively.

Table 1. Chromosomal abnormalities observed in 1696 cases with primary male infertility

Karyotype	Number
Normal (46,XY)	1556 (91.7%)
Abnormal	140 (8.3%)
Abnormal Karyotypes	
47,XXY	75
47,XYY	11
47,XY,+mar	5
45,XY,rob(13;14)(q10;q10)	5
46,XX (SRY+)	4
45,XY,rob(13;21)(q10;q10)	3
46,XY,t(1;2)(q21;q35)	2
46,X,del(Y)(q11.2)	2
46,X,del(Y)(q11.2)[80]/45,X[20]	2
46,XX (SRY-)	1
46,X,derY	1
46,X,inv(Y)(p11q11)	1
46,XY[60]/47,XY,+mar[40]	1
46,XY[52]/45,X[48]	1
45,X[94]/46,XY[6]	1
46,XY[50]/46,XX[40]/45,X[10]	1
47,XXY[84]/46,XY[16]	1
45,XY,rob(13;15)(q10;q10)	1
45,XY,rob(14;21)(q10;q10)	1
46,XY,t(1;5)(p32;q12)	1
46,XY,t(1;6)(q21;p23)	1
46,XY,t(1;19)(qter;p13.1)	1
46,XY,t(2;3)(p10;q10)	1
46,XY,t(2;3)(p22;q27)	1
46,XY,t(3;7)(p12;p21)	1
46,XY,t(3;12)(p21.1;q24)	1
46,XY,t(3;14)(q11.2;q11.2)	1
46,XY,t(4;21)(q12;q22)	1
46,XY,t(6;7)(p25;q22)	1
46,XY,t(9;13)(q21;q21)	1
46,XY,t(10;20)(q22;q13.3)	1
46,XY,t(11;22)(q23;q11)	1
46,XY,t(11;22)(q24;q12)	1
46,XY,t(12;22)(q23;p11.2)	1
46,XY,inv(1)(p13.1q23)	1
46,XY,inv(1)(p22q25)	1
46,XY,inv(1)(p34.3q23)	1
46,XY,inv(6)(p23q23)	1
46,XY,inv(12)(p11.2q13)	1
46,XY,inv(17)(p13q22)	1

Table 2. Karyotypes observed in 45 cases with Y-chromosome microdeletions

Y-chromosome microdeletion type	Number	Karyotype
AZFc	20	46,XY
AZFb+c	8	46,XY
AZFb+c	2	46,X,del(Y)(q11.2)[80]/45,X[20]
AZFb+c	1	46,X,del(Y)(q11.2)
AZFb+c	1	46,X,derY
AZFb+c	1	46,XY[52]/45,X[48]
AZFb+c	1	45,X[94]/46,XY[6]
AZFa+b+c (SRY+)	4	46,XX
AZFa+b+c (SRY-)	1	46,XX
AZFa	4	46,XY
AZFb	2	46,XY

Sex chromosome abnormalities are the most common cause of chromosome-related infertility. In this study, abnormal karyotypes were detected in sex chromosomes in 107 of 140 cases (76.4%). Klinefelter syndrome is the most common genetic cause of infertility in men. It is associated with severe failure of spermatogenesis. In our study, the 47,XXY karyotype was found as the most frequent chromosome abnormality in 75 of 140 (53.5%) cases. In Klinefelter syndrome, it has been shown that there is a possibility to retrieve sperm by testicular sperm extraction (TESE). These cases can be good candidates for ICSI and preimplantation genetic diagnosis (PGD).[6]

In this study, autosomal chromosomal abnormalities were detected as balanced translocations and inversions in 33 of 140 (23.6%) cases. Balanced autosomal translocation and inversion carriers generally have a normal phenotype, but the failure of spermatogenesis is frequently seen because translocations can damage the structure of important genes related to spermatogenesis.[7] Similarly, in inversions, recombination that may occur during the gamete formation may lead to the genetically defective gametes and, subsequently, unbalanced embryos. This could result in repeated IVF failures or repeated pregnancy loss.[8]

Y-chromosomal microdeletions (AZF regions) are the most common genetic cause of human male infertility after Klinefelter syndrome.[5] The Y-chromosome microdeletion screening is a crucial test to provide appropriate genetic counseling and to determine appropriate ART in male infertility with azoospermia and severe oligozoospermia. Therefore, it should be routinely performed. In our study, Y-chromosome microdeletion was detected in 2.6% of cases (45/1696). There were several studies that reported different incidence rates in Turkey. However, most

Turk J Urol 2020; 46(2): 95-100
DOI:10.5152/tud.2019.19156

of them consisted of a limited number of cases. Sargın et al.[4] found Y-chromosome microdeletion in 2 of 60 cases (3.3%). In another study, the frequency was found as 1.3% (1 in 80 cases) by Balkan et al.[3] Furthermore, Akin et al.[5] detected microdeletions in AZF regions in 7 of 187 cases (3.7%). Küçükaslan et al.[9] identified the frequency of Y-chromosome microdeletions as 9.6% (11 of 115 cases). The other study was performed by Taga et al.[10] These authors determined the frequency of Y-chromosome microdeletion as 6.3% (4/63). Yet another study that had a large number of cases was carried out by Akınsal et al.[11] They performed the Y-chromosome microdeletion test in 1616 infertile males. They detected it in 3.3% of cases (54/1616). Similarly, our study was one of the few studies that had a large number of cases in Turkey. Their result was close to our result (2.6%; 45/1696).

AZFa, AZFb, and AZFc are different regions with several genes that play a role in human spermatogenesis. The size and region of Y-microdeletions may differ from each other. The majority of Y-microdeletions occur in the AZFc region (80%) followed by AZFb (1%–5%), AZFa (0.5%–4%), and AZFbc (1%–3%).[12] In our study, the most frequently affected region was found in the AZFc region (44.4%), followed by AZFb+c (31.1%), AZFa+b+c (11.1%), AZFa (8.9%), and AZFb (4.5%). The frequency in the AZFa region was found to be higher than in the literature. The complete deletion of the AZFa+b+c region is most probably related to an abnormal karyotype such as 46,XX male or iso (Y).[13] Likewise, we revealed the karyotype as 46,XX in five cases. The SRY locus was not detected in 1 of 5 cases. In the general population, the incidence of 46,XX males is low. The most of them have the SRY gene. They have normal genitalia but are infertile.[5] In our study, abnormal karyotypes were found in 11 of 45 cases (24.4%) with Y-chromosome microdeletions (Table 2). All cases with AZFa, AZFb, and AZFc microdeletions had a normal karyotype. On the other hand, 6 of 14 cases with the AZFb+c microdeletion and all of cases with the AZFa+b+c microdeletion had an abnormal karyotype.

The diagnosis of Y-chromosome microdeletion is important to identify therapeutic options. As a rule, the AZFa or AZFb microdeletion has more severe effects than AZFc. ART treatments (TESE, ICSI) are not successful in cases with a complete deletion of AZFa or AZFb regions. Therefore, TESE should not be recommended in these cases. On the other hand, the cases with AZFc microdeletion have a variable histological and clinical phenotype. In general, residual spermatogenesis is present in AZFc microdeletions. These cases have approximately a 50% chance of sperm retrieval by TESE, and children can be conceived by ICSI.[12]

Siffroi et al.[14] showed that most of the spermatozoa obtained from males with Y-chromosome microdeletions were nullisomic for sex chromosomes. This result demonstrated the potential risk for Turner's syndrome (45,X) and other sex chromosome mosaicisms in the offspring. The family should be informed that there may be a male offspring with suspected external genitalia or mixed gonadal dysgenesis. Therefore, PGD and/or prenatal genetic diagnosis should be offered to the couple. On the other hand, Patsalis et al.[15] screened for Y-chromosome microdeletions in patients with a mosaic 46,XY/45,X karyotype with sexual ambiguity and/or Turner stigmata. They found a high incidence (33%) of AZFc deletions. These data suggested that some Y-chromosome microdeletions were associated with a Y-chromosomal instability, which may lead to the formation of the 45,X cell lines. Therefore, a karyotype analysis should be performed in males with Y-chromosome microdeletions.

In addition, the risk of gonadoblastoma is increased in phenotypic females with the 46,XY/45,X mosaicism. Moreover, for those patients with a male phenotype and external testes, the risk of neoplasm is not as high, but frequent physical and ultrasound examinations are recommended.[16]

On the other hand, the defective Y-chromosome will be inherited by the male offspring. Thus, there is a risk of conceiving a son with impaired spermatogenesis. He would very likely suffer infertility similar to his father. However**,** some males with a Y-chromosome microdeletion show sperm production early in life, which is lost later on. For example, Chang et al.[17] reported an azoospermic 63-year-old man with a AZFc (DAZ genes) deletion. He had five children from when he was 25 to 38 years of age. His four sons had the Y-chromosome microdeletion, and the three of them were oligospermic or azoospermic (tested ages 24–37). Therefore, if a couple has a male offspring, it may be worthwhile to have their son's semen checked early in puberty and to cryopreserve sperm if any sperm are found. However, a family have options to avoid male offspring transmission include PGD and the transfer of female embryos.

A Y-chromosome microdeletion test is recommended to the male relatives of the AZFc cases or those with partial AZFb or AZFa deletions. Conversely, this is not recommended in case of complete AZFa, AZFb, AZFbc, or AZFabc deletions, because such deletions are generally incompatible with sperm production.[12]

The structure of chromosomal abnormalities, whether they are balanced or unbalanced, is important in genetic counseling. Structural chromosomal changes can occur from a displacement of chromosomal regions with (unbalanced) or without (balanced) loss or duplication of genetic material. Balanced structural rearrangements may pass through multiple generations of a family without detection. Because they are phenotypically healthy individuals. These families are investigated usually due to the presence of infertility, multiple spontaneous pregnancy

losses, and/or clinically abnormal family members. Balanced chromosomal rearrangements do not usually lead to a phenotypic effect because all the genomic material is present. Rarely, clinically abnormal phenotype can be occurred even carrying balanced chromosomal rearrangement. It is important to distinguish here between truly balanced rearrangements and those that appear balanced cytogenetically but are really unbalanced at the molecular level. Therefore, a molecular test such as microarray should be performed in such a case. There is also the possibility that a gene may be affected and cause mutation due to chromosome breaks. It can lead to a significant phenotypic effect. In such cases, whole-genome sequencing can be performed to examine the nature of apparently balanced rearrangements. A karyotype analysis is recommended for family members in terms of balanced rearrangements. Balanced structural rearrangement carriers are likely to produce a significant frequency of unbalanced gametes. Therefore, they have an increased risk of having abnormal offspring with unbalanced karyotypes. The risk can range between 1% and 20%.

One of the structural chromosomal abnormalities is a translocation that includes the exchange of chromosome segments between two chromosomes. There are two main types of translocation: reciprocal and nonreciprocal. Reciprocal translocations usually involve only two chromosomes, and the total chromosome number is 46. Balanced reciprocal translocations are usually without the phenotypic effect. However, they are associated with a high risk for unbalanced gametes and abnormal progeny, like other balanced structural rearrangements. Nonreciprocal translocations are Robertsonian translocations. They are the most common type of chromosome rearrangement observed in humans and involve two acrocentric chromosomes (ch13, 14, 15, 21, 22) that fuze near the centromere region with loss of the short arms (p-arm). Such translocations have 45 chromosomes, including the translocation chromosome. rob(13;14) and rob(14;21) are relatively common. Although a carrier of a Robertsonian translocation is phenotypically normal, there is a risk for unbalanced offspring. The risk depends on the particular Robertsonian translocation and the sex of the carrier parent. Carrier females in general have a higher risk for transmitting the translocation to an affected child. The main clinical significance of this type of translocation is that a Robertsonian translocation carrier involving chromosome 21 is at risk of producing a child with Down syndrome.

One of the other structural chromosomal abnormalities is an inversion. In inversions, two breaks occur in a single chromosome, and then, they are reconstituted with the segment between the breaks inverted. Inversions are two types: paracentric, in which two breaks occur in one arm (p- or q-arm), and pericentric, in which breaks occur in each arm (p- and q-arm). Carrier with an inversion does not have an abnormal phenotype because it is a balanced rearrangement. But this is important for the progeny. There is a risk for unbalanced offspring in a carrier of either type of inversion. The risk is very low in paracentric inversion and is between 5% and 10% in pericentric inversion.[18]

Most of the autosomal chromosomal abnormalities can be diagnosed at birth, but most sex chromosome abnormalities (except Turner syndrome) are not revealed clinically until puberty. It is assumed that the unbalanced conceptions are being lost very early as unrecognized pregnancies (infertility) or later during gestation. In balanced structural rearrangements, fetal karyotyping (chorionic villus biopsy or amniocentesis) or PGD is recommended for families who are planning pregnancy. When the carrier parent is an apparently phenotypically normal healthy individual, and the breakpoints appear to be identical to those seen in the fetus, it is likely to be a benign change without untoward consequences. On the other hand, if one parent is a carrier of a structural rearrangement seen in unbalanced form in the fetus, the consequences for the fetus may be serious.

In conclusion, karyotyping and the Y-chromosome microdeletion test should be carried out to provide appropriate genetic counseling and to determine an appropriate treatment in males with primary infertility. In this respect, our study is one of the few that involved a large number of cases from this field in Turkey.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Izmir Tepecik Training and Research Hospital (Date: 21.03.2018, No: 2018/2-3).

Informed Consent: Written informed consent was not obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – T.R.Ö., B.Ö., Ö.K., A.K., Y.B.K., C.K., Ö.Ç.; Design – T.R.Ö., B.Ö., Ö.Ö.K., K.M.E., M.S.G., T.Z., M.Z.K.; Supervision – T.R.Ö., B.Ö., Ö.K., A.K., Y.B.K., C.K., Ö.Ç., Ö.Ö.K., K.M.E., M.S.G., T.Z., M.Z.K.; Resources – T.R.Ö., B.Ö., Ö.K., A.K., Y.B.K., C.K., Ö.Ç., Ö.Ö.K., K.M.E., M.S.G., T.Z., M.Z.K.; Materials – T.R.Ö., B.Ö., Ö.K., A.K., Y.B.K., C.K., Ö.Ç., Ö.Ö.K., K.M.E., M.S.G., T.Z., M.Z.K.; Data Collection and/or Processing – T.R.Ö., B.Ö., Ö.K., A.K., Y.B.K., C.K., Ö.Ç., Ö.Ö.K., K.M.E., M.S.G., T.Z., M.Z.K.; Analysis and/or Interpretation – T.R.Ö., B.Ö., Ö.K., A.K., Y.B.K, Ö.Ö.K., K.M.E., M.S.G.; Literature Search – T.R.Ö., B.Ö., Ö.K., A.K., Y.B.K., C.K., Ö.Ç., Ö.Ö.K., K.M.E., M.S.G., T.Z., M.Z.K.; Writing Manuscript – T.R.Ö., B.Ö., Ö.K., A.K., Y.B.K., C.K., Ö.Ç., Ö.Ö.K., K.M.E., M.S.G., T.Z., M.Z.K.; Critical Review – T.R.Ö., B.Ö., Ö.K., A.K., Y.B.K., C.K., Ö.Ç., Ö.Ö.K., K.M.E., M.S.G., T.Z., M.Z.K.

Turk J Urol 2020; 46(2): 95-100
DOI:10.5152/tud.2019.19156

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Vogt PH. Molecular genetics of human male infertility: from genes to new therapeutic perspectives. Curr Pharm Des 2004;10:471-500. [CrossRef]
2. Plaseska-Karanfilska D, Noveski P, Plaseski T, Maleva I, Madjunkova S, Moneva Z. Genetic causes of male infertility. Balkan J Med Genet 2012;15(Suppl):31-4. [CrossRef]
3. Balkan M, Tekes S, Gedik A. Cytogenetic and Y chromosome microdeletion screening studies in infertile males with Oligozoospermia and Azoospermia in Southeast Turkey. J Assist Reprod Genet 2008;25:559-65. [CrossRef]
4. Sargin CF, Berker-Karaüzüm S, Manguoğlu E, Erdoğru T, Karaveli S, Gülkesen KH, et al. AZF microdeletions on the Y chromosome of infertile men from Turkey. Ann Genet 2004;47:61-8. [CrossRef]
5. Akin H, Onay H, Turker E, Ozkinay F. Primary male infertility in Izmir/Turkey: a cytogenetic and molecular study of 187 infertile Turkish patients. J Assist Reprod Genet 2011;28:419-23. [CrossRef]
6. Vernaeve V, Staessen C, Verheyen G, Van Steirteghem A, Devroey P, Tournaye H. Can biological or clinical parameters predict testicular sperm recovery in 47,XXY Klinefelter's syndrome patients? Hum Reprod 2004;19:1135-9. [CrossRef]
7. Zhang H, Wang R, Li L, Jiang Y, Zhang H, Liu R. Clinical feature of infertile men carrying balanced translocations involving chromosome 10: Case series and a review of the literature. Medicine (Baltimore) 2018;97:e0452. [CrossRef]
8. Yapan C, Beyazyurek C, Ekmekci C, Kahraman S. The Largest Paracentric Inversion, the Highest Rate of Recombinant Spermatozoa. Case Report: 46,XY, inv(2)(q21.2q37.3) and Literature Review.Balkan J Med Genet 2014;17:55-62. [CrossRef]
9. Küçükaslan AŞ, Çetintaş VB, Altıntaş R, Vardarlı AT, Mutlu Z, Ulukuş M, et al. Identification of Y chromosome microdeletions in infertile Turkish men. Turk J Urol 2013;39:170-4. [CrossRef]
10. Taga S, Leventerler H, Tuli A, Ürünsak İF, Arıdoğan İA, Erçelen N, et al. Determination of Y Chromosome Microdeletions in Infertile Men at Cukurova Region in Turkey. Cukurova Med J 2013;38:723-33.
11. Akınsal EC, Baydilli N, Dündar M, Ekmekçioğlu O. The frequencies of Y chromosome microdeletions in infertile males. Turk J Urol 2018;44:389-92. [CrossRef]
12. Krausz C, Hoefsloot L, Simoni M, Tüttelmann F; European Academy of Andrology; European Molecular Genetics Quality Network. EAA/EMQN best practice guidelines for molecular diagnosis of Y-chromosomal microdeletions: state-of-the-art 2013. Andrology 2014;2:5-19. [CrossRef]
13. Lange J, Skaletsky H, van Daalen SK, Embry SL, Korver CM, Brown LG, et al. Isodicentric Y chromosomes and sex disorders as byproducts of homologous recombination that maintains palindromes. Cell 2009;138:855-69. [CrossRef]
14. Siffroi JP, Le Bourhis C, Krausz C, Barbaux S, Quintana-Murci L, Kanafani S, et al. Sex chromosome mosaicism in males carrying Y chromosome long arm deletions. Hum Reprod 2000;15:2559-62. [CrossRef]
15. Patsalis PC, Sismani C, Quintana-Murci L, Taleb-Bekkouche F, Krausz C, McElreavey K. Effects of transmission of Y chromosome AZFc deletions. Lancet 2002;360:1222-4. [CrossRef]
16. Powell CM. Sex Chromosomes, Sex Chromosome Disorders, and Disorders of Sex Development. Gersen SL, Keagle MB, editors. The Principles of Clinical Cytogenetics. 3rd ed. Newyork: Springer; 2013.p.175-212. [CrossRef]
17. Chang PL, Sauer MV, Brown S. Y chromosome microdeletion in a father and his four infertile sons. Hum Reprod 1999;14:2689-94. [CrossRef]
18. Nussbaum RL, McInnes RR, Willard HF. Principles of Clinical Cytogenetics and Genome Analysis. Nussbaum RL, McInnes RR, Willard HF, editors. Genetics in Medicine. 8th ed. Philadelphia: Elsevier; 2016.p.57-74.