Original Article

# Frequency of Y Chromosome Microdeletions Among Iranian Infertile Men with Azoospermia and Severe Oligozoospermia: A Meta-analysis

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## Abstract

**Background:** While multiple factors can contribute to male infertility, genetic factors, such as chromosomal disorders or Y-chromosome microdeletion, are responsible for about 10% of male infertility. Considering the role of Y-chromosome microdeletions in men with oligozoospermia who volunteer for *in vitro* fertilization (IVF), the prevalence of such microdeletions in each particular community needs to be exactly determined. Hence, the present study attempted to analyze the available literature on the frequency of chromosome microdeletion among Iranian infertile men.

**Methods:** In the first stage, a systematic search was performed on international and Iranian databases including PubMed, Scopus, Web of Science, IranMedex, MEDLIB, and Scientific Information Database in order to extract all relevant studies published until December 1, 2014.

**Results:** According to the literature review and meta-analysis process, Y chromosome microdeletions were present in about 12.1% (95% CI, 6.5-21.5) of Iranian infertile men with azoospermia and severe oligozoospermia.

**Conclusion:** Because of the presence of Y-chromosome microdeletion in at least 12% of Iranian infertile men, it is necessary all the IVF centers, implement this Y-chromosome microdeletion screening tests in the work-up of male infertility.

**Keywords**: Azoospermia, Microdeletions, Oligoazoospermia, STR markers, Y-chromosome.
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## Introduction

Infertility affects about 10%-15% of couples around the world (1). Male factor infertility is believed to be responsible for almost 50% of these cases (2). Genetic factors can be blamed for only 10% of cases of infertility in men (3). Male infertility is actually a multifactorial condition in which a variety of other factors including hormonal imbalance, erectile dysfunction, infections, antisperm antibodies, exposure to chemicals and radiation, testicular cancer, and varicocele may be involved (4). Nevertheless, infertility causes are unknown in 12%-41% of men (5).

As one of the most common causes of male infertility, chromosomal abnormalities, particularly sex chromosome anomalies, have been noticed in one out of every five men with azoospermia (6).

Meanwhile, one or several chromosomal abnormalities, especially autosomal aberrations (including Robertsonian and balanced translocations) and pericentric and paracentric inversions, have been documented in about 8% of men with severe oligozoospermia (7). Azoospermia factor (AZF) microdeletion on the Y chromosome is another major genetic factor involved in male infertility (8-9). Since karyotype tests fail to detect the mentioned microdeletions in about 10%-15% of infertile men with azoospermia or severe oligozoospermia (10), a combination of a karyotype test and screening for Y chromosome microdeletions is necessary to confirm the presence of such microdeletions. Moreover, while the association between large deletions on the Y chromosome and male infertility

has been well established, rare cases of such deletions have been identified. A previous study estimated the frequency of microdeletions on the Y chromosome among infertile and azoospermic men to be 5-10% and 6-16%, respectively (11). As the frequency of Y chromosome microdeletions in infertile men apparently depends on geographical factors and the number of evaluated sequence-tagged site (STS) markers, a meta-analysis was conducted to compare and combine the results of previous research on Y chromosome microdeletions in Iranian infertile men.

## Methods

***Literature search:*** In an attempt to retrieve the original English and Farsi language articles about the frequency of Y chromosome microdeletions among Iranian infertile men with azoospermia or severe oligozoospermia, a systematic search was performed on international and Iranian databases including PubMed, Scopus, Web of Science, Google Scholar, IranMedex (iranmedex.com), MEDLIB (medlib.ir), IranDoc (irandoc.ac.ir), and Scientific Information Database (sid.ir). All relevant articles which contained the selected key terms (Y chromosome microdeletion and/or Iran) and published until December 1, 2014 were included. The reference lists of the extracted manuscripts were also checked to find other helpful articles.

***Inclusion and exclusion criteria:*** Studies were included just if they had been published and indexed in one of the above-mentioned databases, used at least six STS markers in their screening procedures, and recruited azoospermic and/or oligozoospermic patients without a trace of chromosomal abnormalities or obstructive tracts problems.

***Data extraction:*** After selecting the relevant articles, the researchers extracted the first author's name, and the geographical location and publication year of the study, the mean age of the participants, and the number of positive cases of infertility.

***Statistical analysis:*** The random effects model was applied to ensure the selection of more conservative estimates. Moreover, odd ratios (ORs) of individual studies were presented as forest plots. Cochran's Q test and $I^2$ were used to assess statistical heterogeneity. The p-values less than 0.05 suggested statistically significant heterogeneity in Cochran's Q tests. In order to measure publication bias, funnel plots of precision and standard error against log (OR) were developed, *i.e.* asymmetrical funnel plots indicated publication bias. Begg and Mazumdar's rank correlation and Egger's regression intercept were also carried out to evaluate publication bias. The Comprehensive Meta-Analysis 2.2 was used in all analyses (12).

## Results

Following the above-mentioned procedure (Figure 1), 942 papers were extracted at the initial phase of their work. Of these, 13 articles were finally retrieved and analyzed (Table 1). Y chromosome microdeletions were detected in roughly 12.1% (95% CI, 6.5-21.5) of Iranian infertile men with azoospermia and severe oligozoospermia (Figure 2). Forest plot analysis indicated the heterogeneity of the frequency of Y chromosome microdeletions in azoospermic and oligozoospermic men.

Meanwhile, as shown in figure 3, there was enough evidence indicating the presence of publication bias (p=0.01734 for Begg and Mazumdar's rank correlation analysis; p=0.00161 for Egger's regression intercept). Also, the frequency of Y-chromosome microdeletions was related to ethnic and territorial differences (Table 2).

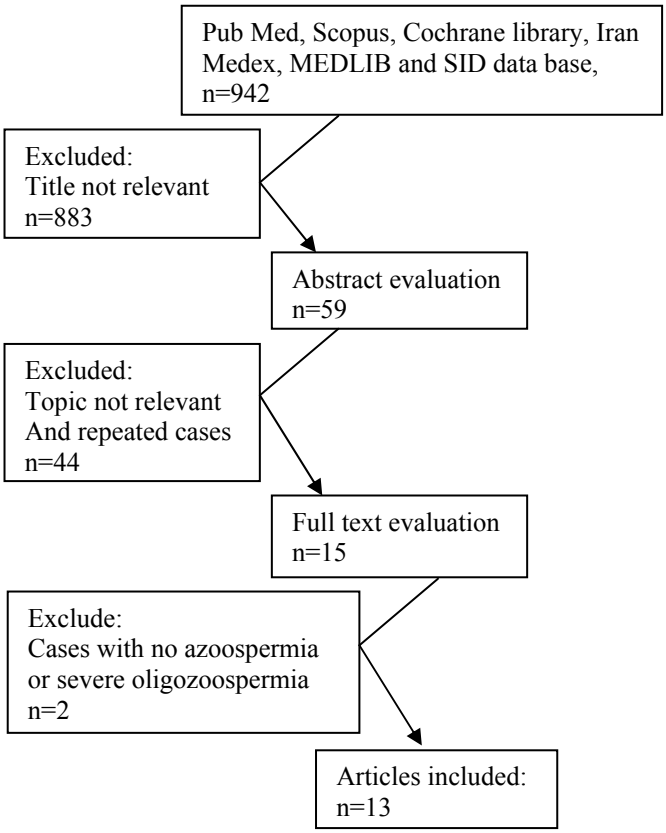


**Figure 1.** Summary of the literature search and study selection. Studies dealing only with Y chromosome microdeletions among Iranian infertile men with azoospermia and severe oligozoospermia

**Table 1.** Included studies after full-text evaluation

| Author name | Number of cases | Positive cases | Year of publication | Year of project | City | Province | Average age | Azoo-spermia | Olio-spermia |
|---|---|---|---|---|---|---|---|---|---|
| **Zamia (3)** | 50 | 4 | 2013 | 2012 | Yazd | Yazd | -- | 16 | 34 |
| **Mirfakhraie (11)** | 100 | 12 | 2010 | 2008-2009 | Tehran | Tehran | 32.41±6.43 | 100 | -- |
| **Saliminejad (13)** | 115 | 2 | 2012 | 2009-2010 | Tehran | Tehran | 40.05 | 94 | 21 |
| **Malekasgar (14)** | 50 | 26 | 2008 | -- | Rasht | Gilan | -- | 31 | 19 |
| **Konar (15)** | 84 | 12 | 2013 | -- | Ahvaz | khozestan | 32 | 36 | 48 |
| **Torfeh (16)** | 100 | 4 | 2012 | 2008-2009 | Kashan and Tabriz | Esfahan and East Azarbyjan | -- | 40 | 60 |
| **Omrani (17)** | 99 | 24 | 2006 | 2001-2003 | Urmia | West Azarbaijan | -- | 60 | 39 |
| **Sheikhha (18)** | 25 | 5 | 2013 | 2011 | Yazd | Yazd | -- | 25 | -- |
| **Asbagh (19)** | 40 | 2 | 2003 | -- | Tehran | Tehran | 34.4 | 37 | 3 |
| **Akbarzadeh (20)** | 94 | 48 | 2013 | -- | Tabriz | East Azarbaijan | 39.5 | 94 | 0 |
| **Etemadi (21)** | 56 | 1 | 2013 | 2008-2009 | Hamedan | Hamedan | -- | 25 | 31 |
| **Kalantar (22)** | 90 | 8 | -- | -- | Yazd | Yazd | -- | -- | -- |
| **Keshvari (23)** | 47 | 4 | 2011 | 2008-9 | Mashhad | Khorasan Razavi | 27/5±5/8 | 27 | 20 |

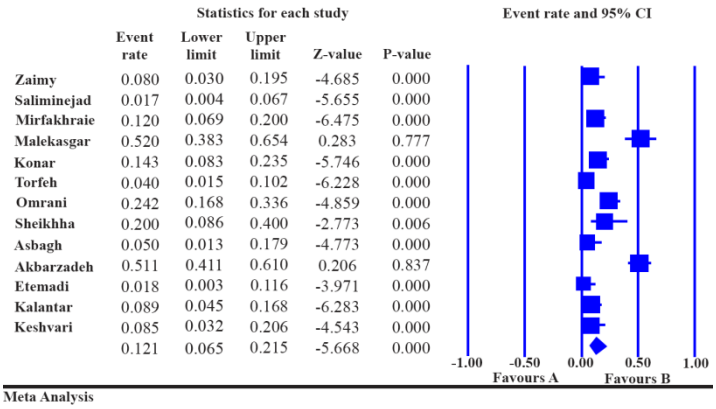


**Figure 2.** Forest plot of the meta-analysis on Y chromosome microdeletions among Iranian infertile men with azoospermia and severe oligozoospermia

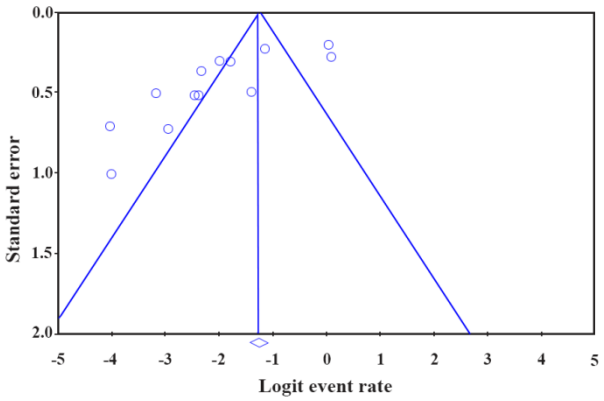


**Figure 3.** Funnel plot of the meta-analysis on Y chromosome microdeletions among Iranian infertile men with azoospermia and severe oligozoospermia

**Table 2.** Frequency of Y-chromosome microdeletion in AZF regains

| Author name | Number of cases | Positive cases | AZFc | AZFb | AZFd | AZFa | AZF regions near the SRY gene | SRY |
|---|---|---|---|---|---|---|---|---|
| **Zaimy (3)** | 50 | 4 | 3.2 | 0.8 | -- | -- | -- | -- |
| **Mirfakhraie (11)** | 100 | 12 | 3.36 | 5.33 | 2.66 | 0.66 | -- | -- |
| **Saliminejad (13)** | 115 | 2 | 1.333 | 0.666 | -- | -- | -- | -- |
| **Malekasgar (14)** | 50 | 26 | 18 | 2 | -- | 6 | -- | -- |
| **Konar (15)** | 84 | 12 | 0.92 | 2.78 | -- | 8.28 | -- | -- |
| **Torfeh (16)** | 100 | 4 | 1 | 2.5 | -- | 0.5 | -- | -- |
| **Omrani (17)** | 99 | 24 | 15.483 | 5.419 | -- | 0 | 3.069 | -- |
| **Sheikhha (18)** | 25 | 5 | 2.058 | 1.176 | -- | 1.764 | -- | -- |
| **Asbagh (19)** | 40 | 2 | 2 | -- | -- | -- | -- | -- |
| **Akbarzadeh (20)** | 94 | 48 | 25.565 | 18.26 | 2.782 | -- | -- | 1.391 |
| **Etemadi (21)** | 56 | 1 | 0.25 | 0.5 | 0.25 | -- | -- | -- |
| **kalantar (22)** | 90 | 8 | 3.733 | 1.6 | -- | 2.666 | -- | -- |
| **Keshvari (23)** | 47 | 4 | 2.285 | 1.142 | -- | 0.571 | -- | -- |

AZF: Azoospermia Factor, SRY: Sex Determining Region Y

## Discussion

Normal spermatogenesis depends on various factors including interactions between somatic cells and sex chromosome genes. While Klinefelter's syndrome is the most important genetic condition associated with male infertility, the role of Y chromosome microdeletions, as the second most important genetic cause of male infertility, should not be neglected. Furthermore, microdeletions in the AZF locus of the long arm of Y chromosome have been identified as the most frequent genetic factor leading to spermatogenic failure. Previous studies, carried out in Iran, have reported that Yq microdeletion frequency varies from 1% to 55% in infertile men. However, in most studies performed in other countries, this ratio is under 15% (24). This discrepancy maybe rooted in ethnicity differences or technical failure in some of the studies done in Iran as mentioned by Salimnejad et al. (26, 27). In fact, ethnicity can be a determinant of the type and frequency of Y-chromosome microdeletions among infertile men of different populations (25). Results of the present study showed that Y chromosome microdeletions existed in 152 out of 950 Iranian infertile men with azoospermia or severe oligozoospermia, and therefore the frequency of such microdeletions was 12.1% (95% CI, 6.5-22.6) in Iran and that is comparable to the frequencies reported in many of the valid published data.

Based on the obtained data, at least 12% of infertile men who volunteer for *in vitro* fertilization (IVF) need to undergo specific screening for Y-chromosome microdeletions. Therefore, health policy makers and insurance companies should cover the expenses of not only routine infertility care and IVF procedures, but also such additional screening programs. Moreover, health authorities need to bear in mind that using sperm of patients with oligozoospermia can be associated with the possible risk of transferring Y-chromosome microdeletions, in about 12 percent of the infertile men, to the next generation.

The frequency of Y-chromosome microdeletions was higher in Guilan and Azerbaijan provinces. The higher incidence of microdeletions among these two ethnic groups might have been simply caused by the greater number of studies performed in the mentioned provinces and the higher level of information collected from these ethnicities. Nevertheless, since other unidentified factors might have also been involved, further studies are required to clarify other causes of Y-chromosome microdeletions, happening at such high rates or maybe other unidentified factors have also been involved that need to be evaluated.

## Conclusion

Because of the presence of Y-chromosome microdeletion in at least 12% of Iranian infertile men, it is necessary all the IVF centers, implement this Y-chromosome microdeletion screening tests in the work-up of male infertility.

## Conflict of Interest

Authors declare no conflict of interest.

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