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 dele-
tions have been identified. A previous study esti-
mated 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 microdele-
tions in infertile men apparently depends on geo-
ographical factors and the number of evaluated se-
quence-tagged site (STS) markers, a meta-analysis
was conducted to compare and combine the re-
sults of previous research on Y chromosome mi-
crodeletions 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 chro-
mosome microdeletion and/or Iran) and published
until December 1, 2014 were included. The refer-
ce lists of the extracted manuscripts were also
checked to find other helpful articles.

Inclusion and exclusion criteria: Studies were in-
cluded just if they had been published and index-
ed in one of the above-mentioned databases, used
at least six STS markers in their screening proce-
dures, and recruited azoospermic and/or oligozo-
spermic patients without a trace of chromosomal
abnormalities or obstructive tracts problems.

Data extraction: After selecting the relevant arti-
cles, the researchers extracted the first author’s
name, and the geographical location and publica-
tion year of the study, the mean age of the partici-
pants, and the number of positive cases of infertil-
ity.

Statistical analysis: The random effects model was
applied to ensure the selection of more conserva-
tive estimates. Moreover, odd ratios (ORs) of in-
dividual studies were presented as forest plots.
Cochran’s Q test and I² were used to assess statis-
tical 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. asymmet-
rical funnel plots indicated publication bias. Begg
and Mazumdar’s rank correlation and Egger’s re-
gression intercept were also carried out to evalu-
ate publication bias. The Comprehensive Meta-
Analysis 2.2 was used in all analyses (12).

Results

Following the above-mentioned procedure (Fig-
ure 1), 942 papers were extracted at the initial
phase of their work. Of these, 13 articles were
finally retrieved and analyzed (Table 1). Y chro-
mosome 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 het-
erogeneity of the frequency of Y chromosome mi-
crodeletions in azoospermic and oligozoospermic
men.

Meanwhile, as shown in figure 3, there was
enough evidence indicating the presence of pub-
lication 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 oligozoosper-
mia

| Pub Med, Scopus, Cochrane library, Iran Medex, MEDLIB and SID data base, n=942 |
| Excluded: Title not relevant n=883 |
| Abstract evaluation n=59 |
| Excluded: Topic not relevant And repeated cases n=44 |
| Full text evaluation n=15 |
| Exclude: Cases with no azoospermia or severe oligozoospermia n=2 |
| Articles included: n=13 |
Table 1. Included studies after full-text evaluation

<table>
<thead>
<tr>
<th>Author name</th>
<th>Number of cases</th>
<th>Positive cases</th>
<th>Year of publication</th>
<th>Year of project</th>
<th>City</th>
<th>Province</th>
<th>Average age</th>
<th>Azoo-</th>
<th>Oli-</th>
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<tr>
<td>Zamia (3)</td>
<td>50</td>
<td>4</td>
<td>2013</td>
<td>2012</td>
<td>Yazd</td>
<td>Yazd</td>
<td>--</td>
<td>16</td>
<td>34</td>
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<tr>
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<td>100</td>
<td>12</td>
<td>2010</td>
<td>2008-2009</td>
<td>Tehran</td>
<td>Tehran</td>
<td>32.4±6.43</td>
<td>100</td>
<td>--</td>
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<td>2</td>
<td>2012</td>
<td>2009-2010</td>
<td>Tehran</td>
<td>Tehran</td>
<td>40.05</td>
<td>94</td>
<td>21</td>
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<td>50</td>
<td>26</td>
<td>2008</td>
<td>--</td>
<td>Rasht</td>
<td>Gilan</td>
<td>--</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Konar (15)</td>
<td>84</td>
<td>12</td>
<td>2013</td>
<td>--</td>
<td>Ahvaz</td>
<td>khouzestan</td>
<td>32</td>
<td>36</td>
<td>48</td>
</tr>
<tr>
<td>Torfeh (16)</td>
<td>100</td>
<td>4</td>
<td>2012</td>
<td>2008-2009</td>
<td>Kashan and Tabriz</td>
<td>Esfahan and East Azarbaijan</td>
<td>--</td>
<td>40</td>
<td>60</td>
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<tr>
<td>Omrani (17)</td>
<td>99</td>
<td>24</td>
<td>2006</td>
<td>2001-2003</td>
<td>Urmia</td>
<td>West Azarbaijan</td>
<td>--</td>
<td>60</td>
<td>39</td>
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<td>Sheikha (18)</td>
<td>25</td>
<td>5</td>
<td>2013</td>
<td>2011</td>
<td>Yazd</td>
<td>Yazd</td>
<td>--</td>
<td>25</td>
<td>--</td>
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<tr>
<td>Asbagh (19)</td>
<td>40</td>
<td>2</td>
<td>2003</td>
<td>--</td>
<td>Tehran</td>
<td>Tehran</td>
<td>34.4</td>
<td>37</td>
<td>3</td>
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<td>Akbarzadeh (20)</td>
<td>94</td>
<td>48</td>
<td>2013</td>
<td>--</td>
<td>Tabriz</td>
<td>East Azarbaijan</td>
<td>39.5</td>
<td>94</td>
<td>0</td>
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<td>Etemadi (21)</td>
<td>56</td>
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<td>2013</td>
<td>2008-2009</td>
<td>Hamedan</td>
<td>Hamedan</td>
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<td>25</td>
<td>31</td>
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<tr>
<td>Kalantar (22)</td>
<td>90</td>
<td>8</td>
<td>--</td>
<td>--</td>
<td>Yazd</td>
<td>Yazd</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Keshvari (23)</td>
<td>47</td>
<td>4</td>
<td>2011</td>
<td>2008-9</td>
<td>Mashhad</td>
<td>Khorasan Razavi</td>
<td>27.5±5.5/8</td>
<td>27</td>
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</tr>
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</table>

Table 2. Frequency of Y-chromosome microdeletion in AZF regions

<table>
<thead>
<tr>
<th>Author name</th>
<th>Number of cases</th>
<th>Positive cases</th>
<th>AZFc</th>
<th>AZFb</th>
<th>AZFd</th>
<th>AZFa</th>
<th>AZF regions near the SRY gene</th>
<th>SRY</th>
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<td>0.8</td>
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<tr>
<td>Mirfakhraie (11)</td>
<td>100</td>
<td>12</td>
<td>3.36</td>
<td>5.33</td>
<td>2.66</td>
<td>0.66</td>
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<td>--</td>
</tr>
<tr>
<td>Saliminejad (13)</td>
<td>115</td>
<td>2</td>
<td>1.333</td>
<td>0.666</td>
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<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Malekasgar (14)</td>
<td>50</td>
<td>26</td>
<td>18</td>
<td>2</td>
<td>--</td>
<td>6</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Konar (15)</td>
<td>84</td>
<td>12</td>
<td>0.92</td>
<td>2.78</td>
<td>--</td>
<td>8.28</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Torfeh (16)</td>
<td>100</td>
<td>4</td>
<td>1</td>
<td>2.5</td>
<td>--</td>
<td>0.5</td>
<td>--</td>
<td>--</td>
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<tr>
<td>Omrani (17)</td>
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<td>24</td>
<td>15.483</td>
<td>5.419</td>
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<td>0</td>
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<td>Sheikha (18)</td>
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<td>5</td>
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<td>1.142</td>
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<td>0.571</td>
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<td>Asbagh (19)</td>
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<td>2</td>
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<td>94</td>
<td>48</td>
<td>25.565</td>
<td>18.26</td>
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<td>Etemadi (21)</td>
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<td>Kalantar (22)</td>
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<td>1.6</td>
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<td>2.666</td>
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<td>4</td>
<td>2.285</td>
<td>1.142</td>
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<td>0.571</td>
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</table>

AZF: Azoospermia Factor, SRY: Sex Determining Region Y

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
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.

References


