Systematic Review

The Genetic Causes of Male Infertility in Iranian Population; A systematic Review

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Abstract: **Introduction:** Infertility affects an estimated 15% of couples globally and in Iran, a quarter of couples experiences primary infertility. Males are found to be individually responsible for 20-30% of infertility cases and contribute to 50% of cases totally. When assisted reproductive technologies (ARTs) are used to acquire pregnancy, a sufficient (epi) genetic diagnosis of male infertility (MI) is of main matter to consider if a genetic abnormality will be transmit-ted to offspring. Infertility centers together with Infertility research centers had been founded since 1994 in Iran and many articles from research projects have been published.

Materials and Methods: This literature investigated the possible genetic causes mechanisms underlying Iranian male infertility by extensive article searches. First, we reviewed available data from the Google Scholar, PubMed, Scopus, Web of Science, IranMedex, MEDLIB, IranDoc and Scientific Information Database were searched for articles published until 2018, using the MeSH terms for a variety of chromosome abnormalities, Y-chromosome microdeletions, gene mutations, expression and polymorphisms, Male infertility and/or Iranian, regional and international population, to provides the evidence- based and a comprehensive, up-to- date evaluation of the multifactorial factors involved in Iranian infertile men.

Results: According to the strategy adopted initially, 274 manuscripts were found. After reviewing the titles, abstracts and manuscripts entirely cited, the total of 139 articles were obtained and selected according to the eligibility criteria. The 139 studies were divided into four predetermined categories that mentioned above. Studies have good methodological validity. The sample is quite heterogeneous, given the very different design of the studies.

Conclusion: MI is a complex, multi-factorial disease and the underlying reasons frequently remain unknown. It seems that the first line of genetic diagnosis in Iranian male infertility is similar to Global One. In all investigations conducted in Iran, there are vacancies in studies such as epigenetic modification studies, RNA (lncRNA, miRNA and piRNA) abnormalities, mutation detection and polymorphism studies in other genes involved in the spermatogenesis process. At present, we have a little information for some polymorphisms (MTHFR, GST, ER, and DAZL) and mutations (mtDNA, CATSPER) which require more extensive studies. Such articles help to find a better insight into the causes of infertility in the Iranian men's community and will provide valuable visions into the development of targeted personalized treatments for patients and the ascertainment of the reasons of idiopathic infertility.

Keyword: Iranian infertile men; chromosome abnormalities; Y-chromosome microdeletions; gene mutations; expression and polymorphisms

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1. Introduction

Infertility is a usual obstacle affecting approximately 15% of a couple in the world (1) but in Iran, a quarter of couple experience primary

infertility, which is above the global average (2). Male infertility is a complex disorder that in more than half of infertile men, the cause of their infertility is idiopathic and could be acquired or congenital. In approximately 15% of men, there are genetic abnormalities that include chromosomal abnormalities and single-gene mutations. However, patients with some genetic abnormalities (such as chromosomal changes and chromosome Y deletions) produce more aneuploid sperms (1). Albeit the majority of the genetic causes of male infertility are still unclear. The cause of aneuploid sperm is a misdiagnosis of meiosis due to the modified testicular environment (3). There is a risk of genetic abnormalities transmitted through ICSI, which is even likely to occur in people with normal sperm, as they can also have genetic defects (e.g. 47, XYY men). Natural selection prevents the transmission of infertility mutations; however, fertility methods perhaps overcome this protective mechanism. The result is an increase in the genetic causes of infertility in the future and hence identification of genetic factors in the better management of infertile couples can be useful (4). This review discusses the genetic causes of Iranian male infertility known to date, and ultimately examines the polymorphism that may be associated with male infertility.

2. Method

2.1. Search strategy and databases

A complete literature review was performed to retrieve the original Farsi and English language papers about "The genetic causes of male infertility among Iranian men population", a systematic search was performed on international and Iranian databases including Web of Science, Google Scholar, PubMed, Scopus, IranMedex, MED-LIB, IranDoc and Scientific Information Database (SID). All relevant papers which contained the selected key terms (chromosome abnormalities, Y- chromosome Microdeletions, gene mutations, gene expression, polymorphism, Male infertility and/or Iranian, regional and international population) and published until May 2018, were included. Moreover, the reference lists of the extracted articles were checked to find other helpful sources.

2.2. Selection criteria

The selection of papers occurred firstly through the analysis of titles and abstracts/summaries. The analysis of the manuscripts followed the predetermined eligibility criteria for the inclusion criteria: (a) papers that had in the title at least a mixture of the terms outlined in the search strategy; (b) articles written in English or Farsi; (c) papers had been published and indexed in one of the above-mentioned databases. The excluded elements encompassed: (1) non-original studies such as Letters to the Editor, Prefaces, brief communication, Corrections/Editorials, and Monographs. (2) Papers repeated in more than one database were counted just once.

2.2. Data extraction

Each sample item was read in its entirety, and the information was recorded into a spreadsheet that included authors, year of publication, sample statement of the study and major findings. Some of the papers found focused on the theme of male infertility correlated to other causes that it is not the genetic factors. In fact, this re-view focused on male infertility as resulting from genetic causes of male infertility in Iranian population, correlated data to other elements were not analyzed. Due to het-erogeneity in the literature, a qualitative analysis was carried out. Reference lists of all included full-text manuscripts were screened for additional articles. Authors of papers were contacted to ask clarification where inadequate information was provided. According to the strategy adopted initially, 274 manuscripts were found. After reviewing the titles, abstracts and manuscripts entirely cited, the total of 139 articles were obtained and selected according to the eligibility criteria. The 139 studies were divided into four predetermined categories: "chromosomal abnormalities, Y-chromosome microdeletions, gene mutations and gene polymorphisms of male infertility in Iran". Studies have good methodological validity. The sample is quite heterogeneous, given the very different design of the studies.

3. Result

3.1. Genetic causes of male infertility:

Genetic anomalies have been recognized in men with oligozoospermia and azoospermia, overlay in review articles genetic factors involved in male infertility pre-sent as chromosomal abnormalities, gene mutations and polymorphisms, mitochondrial DNA mutations, monogenic disorders, multifactorial disorders and endocrine disorders of genetic origin (1) (Fig.1) (Table1) (3,5-22). For each category, we explain focused finding of Iranian articles and compare with regional and international articles.

3.2. Chromosomal Abnormalities

The prevalence of chromosomal abnormalities is higher in IM, and this has a negative relevance with sperm quality. The results of the investigations display that the prevalence of chromosomal anomalies in infertile men varies from 5 to 13%. This value is increased to 15% in men with azoospermia, most of which are related to 47, XXY patients. Anomalies in sexual chromosomes are higher than autosomal, but a broad range of structural

Table 1: The average of frequency of the most common genetic causes in infertile men population.

Name of Article	% Chromosomal abnormality	% Y chromosome microdeletion	% Congenital bilateral absence of vaso deferan
Azimi C.2012.	32.81%		
Akbari MT. 2012.	13.96%		
Monabati A. 2016.	17.3%		
Mahjoubi F. 2010.	15.30%		
Salahshourifar I. 2007.	15.5%		
Mozdarani H. 2008.	5.8%		
Shaveisi-Zadeh F. 2017.	6.5%		
Totonchi M.2012.		5.06 %	
Pouriamanesh S. 2016.		10.66%	
Masoudi R. 2016.		7.4%	
Saliminejad K. 2012.		2.13%	
Asadi F. 2017.		5.2%	
Zaimy MA. 2013.		8%	
Malekasgar AM.2008.		52%	
Omrani MD.2006.		24.2%	
Mirfakhraie R.2010.		12%	
Heidari S.2017.			1 %
Safinejad K. 2011.			9.43%
Radpour R.2008.			4%
Average of Frequency	~15%	~14%	~4%

anomalies of autosomal is also found (23). In a study of 433 infertile males, with 169 azoospermia and 264 oligospermia, it was found that there were 17.3% chromosomal problems, in which 14.3% and 3% of all cases exhibited numerical and structural abnormalities, respectively (5). In a comprehensive study to evaluate 829 infertile men, the incidence of chromosomal abnormalities is estimated to be 32.81%, of which 23.52% is 47, XXY and was the most frequent aberration (6). In another study, 1052 infertile men cases were analyzed that 15.30% had chromosomal abnormality and 22.98% of them showed structural abnormalities. 47, XXY found in 58.38% of patients and was the most frequent aberration in this study (7). Furthermore, in 2007, researchers analyzed 874 infertile men that 15.5% of patients had chromosomal abnormality, from which 13.2% showed sex chromosome abnormalities and 2.3% autosomal chromo-some abnormalities, respectively (8). When new methods such as ICSI were used, the prevalence of chromosomal abnormalities were increased. Therefore, the karyotype of blood cells is strongly recommended for men with severe oligspermia and azoospermia. Even in cas-es where spermatic parameters are within the natural range or have slight changes, cytogenetic testing is recommended because some karyotype abnormalities such as 47, XYY or some chromosomal translocations can cause infertility, while the individual is normal for se-men analysis (9). The percentage of chromosomal ab-normalities among infertile men differs in various studies. For instance, in a cytogenetic survey in a 1792 Dutch infertile men, as low as 72 cases (4%) with chromosomal abnormalities were described and 47, XXY was found in merely 12 patients (0.6%). Also, in Germany, the results of a large study on 781 infertile couples showed that, the rate of chromosomal aberrations was just 1.9% for the male subjects including sex chromosome abnormalities (0.6%). Due to the fair control and easy accessibility of cases to clinical genetics laboratories, the rates of chromosomal abnormality among European countries could be low. The results of the study on 489 azoospermia Chinese men reported that 102 (20.86%) cases had chromosomal abnormalities, among them, 86 (84.31%) cases had a sex chromosome abnormalities and 73 (14.9%) 47, XXY karyotype. In non-European countries, fewer published papers are available on cytogenetic studies of infertile men, but all representation rather high rates of chromosomal abnormalities among infertile populations. For example, among 1000 infertile men in India, about 14% had a chromosomal abnormality and in a study on 179 men with infertility in Turkey, 21 (11.49%) cases had chromosomal abnormalities, including 13 (7.2%) cases with 47, XXY syndrome (1, 7). The results of a large study on 1,052 Iranian infertile men show an increase in chromosomal aberration. Total chromosome anomalies were revealed in 161 (15.30%) infertile men. The most frequent chromosomal alteration was 47, XXY, which was seen in 94 (58.38%) men while one of them had a mosaic karyotype: mos 47, XX [54]/47, XXY [18]/46, XY [9]. In 37 (22.98%) cases, structural alterations were founded. The cases of sex reversal were 30 (18.63%) (6). In a study conducted by Monabati et al. on 433 infertile men in Iran, it was showed that there is a correlation between infertility and autosomal translocation

Table 2: The prevalence of genetic abnormalities and related phenotypes associated with Iranian infertile men.

Genetic disorder	Phenotype	Prevalence
Chromosomal anomalies:		~ 10-15 %
Klinefelter syndrome	(1)[1]	~ 9 %
Other changes in sex chromosomes	(1)	~ 0.2 %
Robertsonian translocations	(1)	~ 1 %
Reciprocal translocations	(1)	~ 1 %
Y-chromosome microdeletion (YCM)	(1)	~ 12 %
Gene mutations:		
CFTR gene (CBAVD)	(2)[2]	~ 2-5 %
Other mutations:		~ 1-1.5 %
Androgen receptor gene (AR)	(1)	-
INSL3-LGR8 gene	(3)[3]	-
Gene polymorphisms:		
CAG repeats in exon 1 gene of AR	(4)[4]	-
Haplotypes of Y chromosome	(4)	-
MTHFR gene	(4)	-
DAZL gene	(4)	-
POLG gene	(4)	-

[1] Azo-severe oligospermia

among severe-oligo / azoospermic patients. In this research, reciprocal translocation t (16; 20) (0.2%), rob (2; 21) (0.2%), rob (13;15) (0.2%) and rob (13;21) (0.2%) were identified in oligospermic males, while t (Y;19) did in one azoospermic case. The accurate mechanism by which chromosomal anomalies induces infertility is not fully realized. While reciprocal translocation covering Y and an autosomal chromosome is ordinarily associated with azoospermia, balanced reciprocal translocation covering two autosomal chromosomes is perhaps associated with decreased sperm count and maybe recurrent abortion (5).

3.3. Sex chromosomal abnormalities Klinefelter syndrome (KS) and mosaics [46, XY / 47, XXY; 47, XXY]

This syndrome is the most common aneuploidy of sex chromosomes in humans, the incidence of KS is found about was 9.45% in Iran (23). About 4.5% of oligospermic men and 9% of azoospermic men have this syndrome. More than 90% of 47, XXY men are non-mosaicazoospermic. Of course, it is possible that in some of these individuals, spermatogenesis will occur. It has been considered that more than 90% of non-mosaic 47, XXY males are azoospermic (24, 25). Combination studies of ICSI and PGD on embryos in patients with Klinefelter syndrome show that the rate of formation of abnormal embryos is higher than that of healthy people, therefore, PGD or PND is strongly recommended for them (26,27).

3.4. Other sex chromosomal abnormalities

The 47, XYY karyotype is the second most common aneuploidy of the sex chromosomes. Most of the FISH-based studies on XYY male sperm indicate an increased incidence of sexual chromosomal abnormalities. However, no evidence of increased aneuploidy risk has been found in the children of these men (28). Karyotype 46, XX is commonly seen in 0.8% azoospermic men. The phenotype is similar to Klinefelter syndrome, but with natural height and intelligence. SRY gene is present in most cases (SRY + XX), but these infertile men are azoospermic be-cause of testicular atrophy (29). The next group of men is SRY-XX which has a mutation in an autosomal gene or a continuous X gene that should be the successor to SRY in the sex determination process and allow the development of the testes in the absence of SRY (1, 29). Y chromosome rearrangement in male infertile men, especially in azoospermic men, increases. The association of phenotype of infertility with AZF (Yq11.23) region rear rangements (Yq reversals and deletions) has been widely studied. The loss of Yq is not detectable by karyotype (10, 30). On the other hand, 45, X/46, XY mosaicism is an infrequent karyotype, and its outbreak is about 1.5 in 10,000 newborns. It has an effect on the hormonal bal-ance, growth, gonad development and histology. In 45, X/46, XY cases, both 45, X and 46, XY cell lines are detect-ed. Diverse distributions of both cell lines can reflect a large range of phenotypes, hence, it seems that karyotyping as a major diagnostic test can enable specialists to detect these rare cases (31).

3.5. Sex chromosomal translocations

The phenotypic or reproductive effects of X-Autosomal translocations are different based on the sex-chromosome carrier (male or female), the fracture points, and

the inactivation pattern of the chromosome. Particularly in men, can cause azoospermia although a few cases have been published with oligozoospermia (5, 7, 29).

3.6. Autosomal abnormalities

The most common autosomal abnormalities are Robertsonian translocations, Reciprocal translocations, Paracentric inversions and marker chromosomes. Similar to Klinefelter syndrome, the FISH method is very effective in identifying a disorder. Performing PGD or amniocentesis seems essential (1).

3.7. Robertsonian and Reciprocal translocations

Robertsonian occurs when two acrocentric chromosomes are connected to each other. The prevalence rate of Robertsonian translocation is 0.9% in infertile males, this rate is more than general population. Fertility problems in men with Robertsonian translocation are due to disturbances in the distribution of meiosis and, as a result, damage to spermatogenesis (1). Reciprocal translocation is detected in 0.9 of 1000 newborns and involve the exchange of chromosome parts between the two urelated chromosome segments. There is no phenotypic change in carriers. The magnitude of this disorder is higher in oligo/azoospermic patients than normal individuals. Carriers produce more unbalanced sperm that is due to disturbances in meiosis divisions (7, 32). Both of them are the most commonly observed structural chromosomal anomalies in humans. They have been found in approximately 1 % of infertile men and commonly occur in azoospermia compared to oligozoospermia (1).

3.8. Y chromosome microdeletions (YCMs)

The role of YCMs, as the second most important genetic cause of male infertility, should not be neglected. The YCMs have been examined in many countries and so far, the incidence of microdeletions in AZF locus in infertile men has not been clarified, but according to different articles, the world frequency of these microdeletions in infertile males is about 1-55% (33). In the long arm of the Y chromosome, the proximal to the distal section is AZFa, b, and c, respectively. There are at least 14 gene coding proteins in the AZF locus. Deletion of these genes happens in six classic classes, containing AZFabc, AZFbc, AZFc, AZFb, AZFa, and partial elimination of AZFc. Most of these deletions are stated in areas b and c. In 57% of YCM cases, the partial and complete removal of AZFc has been observed. A total of 25-30% of the deletions are AZFb or AZFab and 65-70% of the observed deletions are related to AZFc. These high frequency of deletions should be confirmed through more precise studies (11). Also, Krausz (2013) has been shown that a significant proportion of sperm in men with YCM are nullisomic for sex chromosomes and can be a potential risk for newborns to develop Turner syndrome (45, XO) or other malformations and in mosaic patients 45, XO / 46, XY, which have a hermaphroditic sign, a high prevalence of AZFc have been observed (33). The fourth part of the AZF re-gion reported between AZFb and c, called AZFd, and associated with mild oligospermia. A group of researchers believe that elimination of this locus can be a

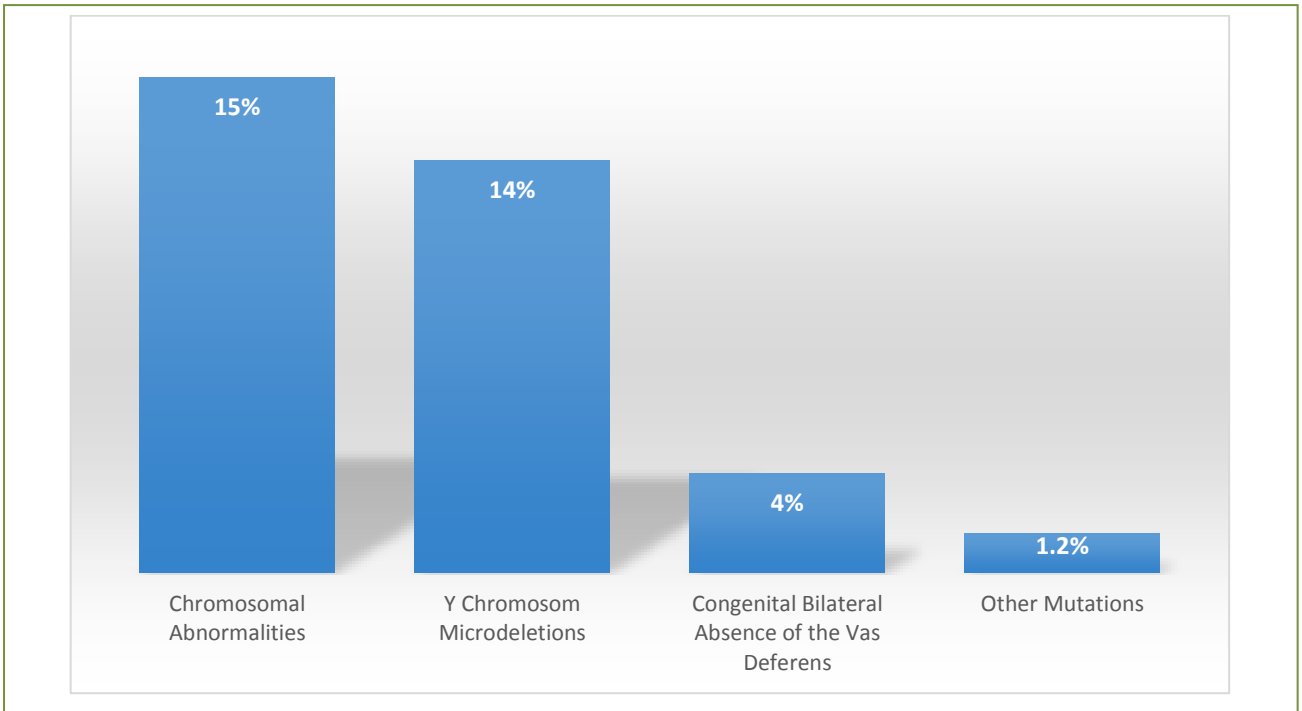

Figure 1. The chart shows the frequency of the most common genetic causes in infertile men population.

polymorphism. The STS markers of the AZFd region are in fact located within the AZFc region and are eliminated in some types of AZFc partial deletions. There is now a general belief that AZFd is not present and the initial report in this area is probably a technical error, therefore AZFd is not considered in a clinical setting (12). Based on comparison investigations done among infertile male's population in Italy, France and Denmark, it has been assumed that under study populations and the geographical location are two impressive factors in the frequency of microdeletions. These factors can alter the frequency, more or less of worldwide statistical standards (33). Limited studies have been conducted in the Middle East, and the frequency of YCMs in Saudi Arabia, Turkey, and Kuwait has been reported to be 3.2; .3.3 and 2.6, respectively. Previous studies carried out in Iran, the Y micro-deletion frequency has shown variable ranges from 5 to 52% which is within the range that has been reported worldwide. There are wide variations in the reported frequency of microdeletions in Iranian populations and this discrepancy maybe rooted in the patient's selection criteria, genetic background and ethnicity. Furthermore, lack of consistency in protocols applied to detect micro-deletions and methodological errors may lead to variation in the results in some of the studies done in Iran as mentioned by Masoudi et al (13). The meta-analysis study of, Omrani et al. in 2016 showed that the frequency of such microdeletions was 12.1% (95% CI, 6.5-22.6). Also, they mentioned, the frequency of Y-chromosome microdeletions was higher in Gilan 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 and the more information collected from these ethnicities (34). Masoudi et al. in 2016 demonstrated that their data were consistent with the report by Saliminejad et al. in 2012, which showed a frequency of 2.13% of complete micro-deletions in the Y chromosome (13, 14). In a large study, by Asadi et al. 1885 infertile men with azoospermia/severe oligospermia were examined for YCMs (27). Their results were in agreement with similar studies as Totonchi et al. and Zaimy et al. similar to the world researchers which have mostly reported a frequency of less than 10% (~5.4%) for YCMs (11, 16). Some of the Iranian investigations had methodological errors and some applied many STS markers while there are stand-ardized STS markers endorsed by the EAA and EMQN which can find 95% of all reported AZF microdeletions (33). Although, despite the EAA and EMQN recommendation, the result of Nowroozi et al., study, that comprised of fathers who had at least a son with ICSI due to severe oligospermia or azoospermia (60 fathers was evaluated along with their 70 sons) have been shown that YCMS is not prevalent in fathers with successful ICSI and it is not urgent to be analyzed before ICSI (35,36).

3.9. Gene Mutations

Many autosomal, X-linked and mitochondrial genes are also being investigated for possible roles in Iranian male infertility. Many genes are required for sexual, testicular evolution and normal spermatogenesis, although only a small number of them are clinically important (4). These genes are the CFTR gene where the mutation is associated with CF and CBAVD, the androgen receptor gene, where the mutation is associated with androgen-susceptibility syndrome and spermatogenic disorder, the INSL3-LGR8 gene that mutations cause abnormalities and an impairment of testicular dysfunction and mutations in the KALIG-1 gene that cause Kallmann syndrome (1).

3.10. CFTR gene mutation

Cystic fibrosis (CF) is the most common inherited disorder in Caucasian populations and a large part of adult males with CF (99%) has CBAVD. CBAVD is also encountered in 1- 2% of infertile males without CF (20). Nearly 70% of men with CBAVD and no clinical evidence of CF have a known defect of CFTR gene. Nearly 10% of infertile men with OA are congenital and caused by CF gene mutations. There are just a few publications that describe the distribution and frequency of CFTR gene mutations in Iran (37, 38). In the 53 Iranian infertile men with CBAVD obstructive azoospermia, Safinejad et al. evaluated five common CFTR mutations (ΔF508, G542X, R117H, W1282X, and N1303K). The common CFTR mutations were detected in 9/53(17%) cases (21). In an extensive research of CBAVD in Iran, among 120 cases of men with CBAVD, Radpour et al. identified 19 different mutations in Iranian CBAVD patients especially two mutations, IVS8-5T and F508del, were recognized to be more com-mon in Iranian CBAVD patients. Also, they recommended, screening for the IVS8-5T and F508del together led to the identification more than one-third of alleles (22). Totally, distribution of CFTR mutations in the Iranian population appreciably varies from those published in the neighbouring countries like Turkey, Pakistan, and Arabian countries. The Iranian patients were from 44 cities located in different geographic areas, the distribution and frequency of the most common CFTR mutations differ among these ethnic groups and geographic areas (38). Another study in infertile Indian males with non-obstructive azoospermia and spermatogenic failure showed that ΔF508 mutation was presented in 3.6% of patients with non-obstructive azoospermia (39). Because over 1,300 different mutations have been recognized in this gene, this type of limited analysis is only informative if a mutation is discovered. A negative test result just indicates that the CBAVD patient does not have the most common mutations causing

Table 3: List of the gene mutations in Iranian infertile men.

Gene Name	Number of patients	Mutation and deletion	Reference
DNAH1	10	c.8626-1G > A	Amiri-Yekta A., 2016.
DAZ	154	gr/gr deletions and b2/b3 were not significantly different.	Alimardanian L., 2016.
SEPT12	100	No mutation	Hosseinifar H, 2014.
NR5A1	90	missense mutations (p.P97T)	Zare-Abdollahi D., 2015.
FABP9	100	No mutation	Jamshidi J., 2014.
AR	-	1510C→A trans version in exon 1	Mirfakhraie R., 2011.
mtDNA	60	4977 and 7599 bp deletions	Talebi E., 2017.
mtDNA	256	4,977-bp deletion	Bahrehmand Namaghi I., 2017
mtDNA	60	4977-bp deletion	Gashti NG., 2014
CATSPER1/2		c.539-540insT and c.948-949insATGGC	Kahrizi k., 2010. Kahrizi k., 2009.
ESR β	96	(IVS 8–4G>A) near the 5' splicing region of intron 8	Omrani MD., 2005.
MTHFR promoter hyper methylation	55	No differences	Khazamipour N., 2009.
STRC and CATSPER2		contiguous gene deletions (15q15.3)	Kahrizi k., 2007.
USP26	166	370-371insACA, 1423C > T and 494 T > C	Asadpor U., 2013.
sperm DNA damage with protamine deficiency	30	Positive correlation (P < 0.01)	Nili H.A., 2009.

CF. Direct sequence analysis of the entire gene is commercially available but very ex-pensive. Since infertility in many patients can be treated nowadays by ART, if couple are carrier of CFTR mutations, the risk of having children with CF will be in-creased (4).

3.11. INSL3-LGR8 gene mutations

The pseudo insulin agent (INSL3), also recognized as the quasi-relaxin factor (RLF), is a member of the pseudo-relaxin hormone family produced by Leydig cells. The prevalence of these mutations is reported to be 4-5% in men with cryptorchidism and ex-cryptorchidism. Data have stated that mutations in LGR8/GREAT or INSL3 gene occur in nearly 5 % of men with cryptorchidism. Although, there is disagreement proof to trust that these pathologies could possibly be caused by mutations in other genes too. It seems that this hormone has endocrine and paracrine functions in the adult population and its deficiency can be considered as an important sign for hypogonadism (1).

3.12. Gene mutation of the Androgen Receptor

Androgens and their active receptor (AR) are necessary for the development and preservation of male phenotypes and spermatogenesis. AR is coded by a gene that is located on X chromosome and has 8 exons. Mutations in this gene cause a variety of disorders commonly referred to as androgenic insensitivity syndrome (AIS). Patients with a mild mood syndrome (MAIS) show infertility alone or with other symptoms. Although more than 700 mutations and polymorphisms have been reported in the AR gene, only 5% of these mutations lead to the MAIS phenotype in which infertility may be the only symptom (40). In 2011 Mirfakhraei and et al. for the first time, presented p. Pro504Thr substitution, according to previous reports on AR gene alterations, 8 mutations have been determined in patients with azoospermia and 4 of these mutations are located in exon 1, until then (41).

3.13. The Kallmann (KAL-1) gene mutations

The most commonly reported X-linked infertility is the Kallmann syndrome. This syndrome is due to the mutation in the KAL-1 gene (Xp22.3). Of course, today, many other genes have been identified on other autosomal chromosomes. In 2015, Ahmadzadeh et al. studied on 8 males and detected 5 male patients with hemizygous mutation (42). The main symptoms of a hypogonadotropic disease are hypogonadism and anosmia. Treatment with gonadotropins can lead to normal pregnancies, even in cases of low sperm concentration or Azoospermia. Therefore, it is advisable to carry out a precise genetic consultation before engaging in ARTs and to estimate the risk of transmission by identifying the gene (1).

3.14. The mitochondrial DNA (mtDNA)

Recent information has represented that mtDNA multiple deletions or point mutations, mtDNA single nucleotide polymorphisms (SNPs) and mtDNA haplogroups can considerably impression sperm quality and are associated with asthenozoospermia or oligoasthenozoospermia (43,44). Among the mitochondrial deletions detected, the deletion of 4977 bp was the most common

and numerous one (45).

3.15. Other Mutations

An unexpectedly high number of genes with a testis-specific or enriched expression pattern have been recognized. Nonetheless, to date merely a few genes have been screened in Iranian population and none of them become manifest related to male infertility. In table 3, 15 published articles in Iran have been summarized to show their finding in studied mutations on male fertility (46-57).

3.16. Gene Polymorphisms

In the last decade, a great number of researches focused on the recognition of gene variants affecting spermatogenesis in human. Several studies have been carried out in this regard, which has not necessarily been accompanied by similar outcomes, often due to the following factors: types of polymorphism and methods, the size and composition of the population studied, ethnic and geographic differences, multi-functional and heterogeneous phenotypes of male infertility. Various polymorphisms have been surveyed in several genes to specify their association with infertility in men, but many of them have not been repeatable, and hence no accurate results are available, except for some of these polymorphisms (1, 58).

3.17. Haplotypes of Y chromosome

In Masoudi et al. study, b2/b3 frequency equated to 1.25% and gr/gr 5% in a case group and a control group of fertile males, 4% gr/gr microdeletions was detected while there were no b2/b3 microdeletions (13). In another study, thirty oligozoospermia were examined for AZFc deletions. Six fertile men had partial deletions (five gr/gr and one b2/b3) with a higher level of FSH, LH in their group ($p < 0.05$) and in five patient's partial deletions in AZFc region (four had gr/gr and one had b2/b3 deletions) had been identified. The role of b2/b3 deletions in male sterility is still unclear because of its low frequency. It appears that the role of DAZ3/4 deletion in male sterility is limited to the b2/b3 sub deletion. Hence; more researches should be done for discovered the role of gr/gr deletion and b2/b3 sub deletion in the context of Y haplogroups (59). Overall, no definitive conclusions have been reached on the role of haplogroups in male infertility or its deletions (60, 61).

3.18. Polymorphism in the Methylenetetrahydro-folate reductase (MTHFR) gene

MTHFR functions as a significant regulatory enzyme in folate metabolism. Genetic association study defined a significant association of MTHFR-222Val/Val genotype with oligozoospermia and azoospermia. Meta-analysis for allelic, showed a significant association between the Ala222Val polymorphism and the risk of male infertility ($P < 0.001$). The investigations showed significant association of MTHFR-Ala222Val with a risk of male infertility, especially in Asian population (62).

Some studies have shown that there is a relationship between the C677T polymorphism and infertility in men, but there is no definitive conclusion that this is due to the heterogeneity of the selective population and racial differences. In fact, studies in Germany, India, and the United Kingdom showed homozygote (TT), heterozygous (CT), and azo-oligospermic studies, while studies in the Dutch population did not show such an association and the results of studies in Italy were also contradictory (63-66).

3.19. Polymorphism in the DAZL gene

This gene is an autosomal homologous DAZ gene continuous to Y, no mutations have been reported in this gene, except for two SNPs in exon 2 (A260G) and exon 3 (A386G). There is no significant association between DAZL A386G and male infertility in Iranian population (67). However, in meta-analysis, within Asian population, a significant association between DAZL A386G and male infertility has been found (68).

3.20. The polymorphisms of the exon 1 of the androgen receptor gene

The androgen receptor 2 has a polymorphic site in exon 1, due to the difference in the number of repetitions of CAG and GGC that produces polyglutamine and polyglycine strands of different lengths in the N region of the AR terminal protein terminal (69). A number of recent stud-ies have examined the association between CAG repeat length and infertility in men. The basis of these studies was that a loud repeat of CAG would reduce the AR transcription activity (70, 71). In a study of 307 Iranian men, 104 infertile men with NOA and 203 fertile controls, a significant correlation between CAG repeat length and risk of non-obstructive was showed (72). In studies on patients in Singapore, Australia, North America, and Japan, there was a correlation between the length of repeated CAG and male infertility, while there was no such relationship in European populations. Regarding the distribution of GGC repeat lengths among infertile men, no difference was found in the natural population (73-75). An examination of these two repetitions simultaneously suggests that some haplotypes may affect AR activity and can predispose a person to infertility (69).

3.21. Polymorphism in a polymerase gamma (POLG) gene

Mutation in the POLG gene perhaps present a mutation in the mtDNA during replication, which finally could influence the motility of the spermatozoa. POLG gene included a changeable number of CAG repeats, of which 10 copies of CAG repeats were assumed as a common allele.

Table 4: List of the gene polymorphisms in Iranian infertile men.

Gene name	Cases/Controls	Association	Reference
GST	166 / 166	Yes	Safarinejad. R., 2010.
TNFR1 36	108 / 119	Yes	Ashrafzadeh HR., 2017.
interleukin 1β	207 / 230	Yes	Zamani-Badi T., 2017.
FAS and FASL	102 / 110	Yes	Asgari R1., 2017.
AHR	135 / 130	No	Aftabi Y., 2017.
XRCC5, XRCC6 and XRCC7	178 / 214	Yes	Jahantigh D., 2017.
H2BFWT	109 / 123	Yes	Rafatmanesh A, 2017.
HIWI2	121 / 100	Yes	Kamaliyan Z., 2017.
INSR, SLC6A14, TAS2R38, and OR2W3	96 / 100	Yes (for INSR and SLC6A14)	Siasi E, 2016.
YBX2	180 / 96	Yes	Najafipour R, 2016.
FSHR	212 / 200	Yes	Gharesi-Fard , 2015.
SEPT12	67 / 100	Yes	Shahhoseini M,2015.
MTHFR	242 / 255	Yes	Nikzad H, 2015.
H2B.W	92 / 60	No	Haji Ebrahim Zargar ,2015.
PD-1 gene, G/A	61 / 84	Yes	Zamani MR, 2015.
USP26	72 / 60	Yes	Asadpor U., 2013
POLG CAG repeat	40 / 30	No	Heidari MM, 2011.
GST	95 / 26	No	Lakpour N, 2013.
PRM1, PRM2 and TNP2	96 / 100	No	Siasi E, 2012.
Tp53	110 / 180	Yes	Mashayekhi F. 2012.
GST and CYP	150 / 200	Yes and No	Salehi Z, 2012.
ER-α and ER-β	164 / 164	Yes	Safarinejad MR, 2010.
protamine1 and protamine 2	273 / 35	No	Salamian, 2008.
ER-β	120 / 204	Yes	Omrani MD, 2006.
SPO11	100 / 100	No	Karimian M., 2015.
FSH-R	172 / 172	No	Safarinejad M.,2010.
SPATA16	130 / 110	No	Roozbahani G.,j.mgene.2017.
TAF7L gene	100 / 105	No	Heidari , 2017.
CPEB1	70 / 70	Yes	Yadollahy,A., 2017.
DAZ T > C	110 / 200	No	Hadiyan S.P., 2015.
Catalase	195 / 190	Yes	Sabouhi S., 2014.
MMP-2	200 / 200	Yes	Mohagheghi A. 2015.
KISS1R	50 / 50	Yes	Poursharif A., 2017.
HSPA1L	143 / 199	Yes	Kohan L., 2016.
GST	75 / 134	Yes	Naghavi A., 2013.
mir-34 b/c	244 / 105	Yes	Majidi H., 2017.
DAZL	100 / 100	Yes	Nejati M., 2016.
CHDH	50 / 50	Yes	Ebrahimi M.,2014
MOV10L1	30 / 70	Yes	Sarkardeh H., 2014.
RABL2B	60 / 30	Yes	Hosseini SH., 2017.
DEFB126	35 / 40	Yes	Rostami Chayjan M, 2014.
CGA	224 +196	Yes	Jamalvandi M., 2018.
DICER1	385 / 120	Yes	Moghbelinejad, S., 2018.
PHGPX	128 / 36	No	Lakpour N, 2006.

In a study, 40 Varicocele patients and 30 control had been analyzed for POLG polymorphism by Heidari et al. The results were negative for finding association (76) but contrary to this research, in different countries multiple studies have shown an association between several polymorphisms, mutations or deletions in the mitochondrial genome and sperm dysfunction (77,78).

3.22. Polymorphism in Estrogen Receptor (ER) gene

Polymorphisms of the ER genes have been signified in male infertility, however, comprehensive evidence are lacking. The most common polymorphisms are XbaI and PvuII of the ESR- α gene and, RsaI and AluI polymorphisms of the ESR- β gene (79). While the accurate role of estrogen receptors in male fertility situation is accepted, finding suggests that particular polymorphisms of the ER-α and ER-β genes which admit, a lower sex hormone binding globulin and therefore a stronger unbound estrogen effect, maybe unfavourably influence spermatogenesis (80,81).

3.23. FSHR gene polymorphism

Different Single Nucleotide Polymorphisms (SNPs) have been presented within FSH receptor (FSHR) gene that

Table 4: List of gene expression in Iranian infertile men.

Gene Name	Cases	Significant	Reference
TSGA10	84	Yes	Aarabi M, 2006.
Clusterin	42	Yes	Mardi Mamaghani A., 2018.
hTSH2B	15	Yes	Faghihi Zohani, F., 2013.
TGIFLX/Y	110	Yes	Arabi M., 2008.
H2BFWT	16	Yes	Faghihi Zohani, F., 2014.

may affect the receptor function. While some meta-analyses have been reported that FSHR SNPs at positions A919G and A2039G did not play any roles in susceptibility to spermatogenetic dysfunctions, sperm abnormalities, and azoospermia, in contrast to these studies, sever-al investigations presented a relationship between FSHR polymorphisms and azoospermia or infertility (82). Gharesi-Fard et al. demonstrated that the presence of A allele at position 919 within FSHR gene might affect the receptor function and the FSH level. Both OA and NOA patients with the AA genotype at position 919 from FSHR had higher FSH plasma levels contrasted to those with AG or GG genotypes. In addition, the level of FSH was elevated in the OA patients with the AA genotype at FSHR A919G position (83).

3.24. MicroRNA

miRNAs are small, internal, single-stranded RNA molecules that control gene expression and have been rolled in different disease. It has been evidenced that some miRNAs expression is tissue-specific and disease-specific, giving the potential for recognizing miRNAs as a diagnostic tool. About 60-75% of male infertility cases are idiopathic and their molecular mechanisms cause are unclear. Semen analysis and diagnostic tests are not precise in this cases (84, 85). Newly, it has been explanted that microRNA like mir-100 and let-7b, microRNA-196, microRNA-99a were predicted to target ERα gene. The results of these investigations demonstrate that miRNA can have a significant role in spermatogenesis and per-haps have a diagnostic and prognostic value in men infertility (86, 87). On the other hand, polymorphisms in different noncoding genes such as HIWI genes contribute to spermatogenesis defects and can be assumed as risk factors for male infertility (88-90).

3.25. Other polymorphisms

Bearing in mind, the high predicted number of genes involved in male gametogenesis, so mutations or polymorphisms in spermatogenesis genes can cause most idiopathic forms of spermatogenic disorders. Although, in spite of exhaustive survey of new genetic factors, no clinically related gene mutations or polymorphisms (except those related to the Y-chromosome) have so far been known. In table 4, 44 published articles in Iran have been summarized to show their finding in studied polymorphisms and their genotypes on male fertility (56, 91-124).

3.26. Gene Expression

Disturbances in the expression of any effective gene in spermatogenic pathway is one of causes of male infertili-ty (125). Recent investigations have revealed the pres-ence of about 3000 different kinds of mRNAs in ejaculat-ed spermatozoa. Albeit, the correlation of transcriptome profile with male infertility remains ambiguous (126). Table 5, published articles in Iran have been summarized to show their finding in studied gene mutations on male fertility (127-131). As it is found, there is plenty of room for further studies.

4. Discussion

According to the above, it can be summarized as the main causes of infertility known in Iranian men are frequently related to chromosome abnormalities. Klinefelter syndrome and specific translocations are well-established reasons of male infertility. Also two significant gene defect, definitively associated with spermatogenic failure, are the point mutations in the CFTR and AR genes. On the other hand, one of the most notable pathogenetic defects associated with Iranian male infertility is YCMD. De novo deletions of Yq are mostly happening chromosomal ab-normalities in infertile men and are believed to arise from recombination events between long stretches of highly repetitive DNA sequences during meiosis or early pre-implantation development (10, 38,132). To the best of our knowledge, this is the largest and most comprehensive literature review performed so far for the evaluation of the genetic causes of male infertility in Iranian population. In 2017, a similar article was published by Mozdarani et al., which in detail refers to subjects such as protamine deficiency or sperm DNA damage. In general, the present paper considers a new perspective on the factors affecting male infertility in Iran (133). Despite the fact that a lot of genetic causes of Iranian male infertility are detected with chromosome typing, YCMD and CFTR mutation analysis, a large part remains unknown. Therefore, it seems that in such cases, the analysis of mutations and polymorphisms in the genes involved in the spermatogenesis process will be very important. In all investigations conducted in Iran, there are vacancies in studies such as epigenetic modification studies, RNA (lncRNA, miRNA and piRNA) abnormalities, mutation detection and polymorphism

studies in other genes involved in the spermatogenesis process. At present, we have a little information for some polymorphisms (MTHFR, GST, ER, and DAZL) and mutations (mtDNA, CATSPER) which require more extensive studies. It was maybe an unavoidable conclusion that gaps in the literature would be identified. Although, what was surprising was the substantial nature of the gaps where efficiently little or sometimes no survey had been carried out. Although, vice versa, a number of subjects were recognized with clear and significant opportunities for the way for-ward. Newly, further tests, such as chromatin fragmentation and ROS determination, have been suggested for research goals. In light of transcriptome and proteome pro-filing analyses, investigators powerfully advocate for new markers of male fertility or infertility that could include sperm and seminal plasma proteins or complex population of RNAs that are maintained in mature sperm (1,25,134). Due to the metacentric studies conducted by Iranian researchers from 2005 to 2018 and considering the results of this review, it seems that the first line of genetic diagnosis in Iranian male infertility is similar to Global One. That means, Karyotype and YCMD testing should be carried out on all males with severe oligozoo-spermia or non-obstructive azoospermia prior to any therapeutic procedure, and appropriate CFTR mutation analysis should be offered to all males with CBAVD or CF or his wife. Here are a few points to keep in mind, there are wide variations in the reported frequency of micro-deletions in Iranian populations and this discrepancy maybe rooted in the patient's selection criteria, genetic background, ethnicity, lack of consistency in protocols applied to detect microdeletions and methodological errors, that all of them may lead to variation in the results in some of the studies done in Iran (4,6,33). For example, in a study have been reported a high frequency of AZFb microdeletion (66.67%) versus AZFc (41.67%) and researchers suggested that AZFd could be negative for sY254 and sY255 markers, while positive for either of sY145 or sY153 STSs. Their study along with several others also conflicts with this idea that the absence of sY254 and sY255 indicates complete deletion of AZFc region. Also, it seems that at least sY153 is polymorphic and exists in multiple copies and should not be used in the study of Y chromosome microdeletions (20,135,136). On the other hand, the results of the research by Ghoraeian et al. highlighted an interesting point in the YCMD, based on their achievement; a presence of DAZ (Deleted in Azoospermia) gene in somatic cells might not be suggestive of its presence in germ cell lineage. In addition, some severe oligozoospermic men could be mosaic for the YCM in leukocytes but normal in the germ cell lineage. PCR based DAZ analysis does not display a status of DAZ gene in individual cells. There has been trying to display DAZ gene by the use of PRINS in lymphocytes either as interphase or metaphase cells or FISH on sperms or metaphase lymphocytes (137,138). It may be necessary to re-examine the YCM screening standards in accordance with the needs of the Iranian infertile men's community and with the purpose of conducting ongoing studies, Iran-specific STR panel has been designed (47). On the other hand, so far, many different studies have been conducted in various ethnic groups of Iran to inves-tigate CF and CBAVD mutations but there is a little infor-mation about the spectrum of CFTR mutations in the gen-eral Iranian population and no consensus on the mini-mum number of mutations that should be tested and un-fortunately at present, the design of a diagnostic panel is not possible at the national level. Therefore, it is essential that with the advent of fertility assisted reproductive techniques such as ICSI, with the purpose of conducting studies, the national panel CF and CBAVD have been identified and applied. Totally, the goal of designing a panel of common mutations in each country is to help improve the health system and reduce costs. A number of topics were identified for future investigations in the genetic screening of the infertile male. For example, what are the long-term health results of children born from infertile men, can cost-effective tools for genetic screening in men (karyotype, YCMs, and CF-mutation analysis) in low-income settings be developed (4, 22). There is a necessity for large Iranian population-based studies to specify the outbreak of genetic causes of male infertility in the general population. Systematic review and meta-analysis are required to search the effect of other gene mutations and polymorphisms on infertility. Ideally, large population-based cohort studies managed in a several geographical regions must be performed with constant definitions of male infertility in Iranian population and comparable clinical research designs. In addition, the development of techniques such as Next Generation Sequencing(NGS) to test for genetic anomalies or undesirable polymorphisms before performing ART is important (1,4,139). Finally, the shortage information in this area reflects the overall scarcity of high quality long-term national funding to support reproductive medicine, and especially male in-fertility. It remains a pivotal block to further development and a pivotal subject.

5. Conclusion:

We stated key points for research focus that demand examination and analysis in Iran. Overall, based on studies and findings of this review, the genetic diagnosis of infertility in Iranian men is similar to the rest of the world. One high preference area for a survey in idiopathic cases is to gain a better perception of the polymorphisms and

mutation analysis in the genes responsible for the process of spermatogenesis. There is an instant necessity to realize these cellular and molecular genetic mechanisms in order to formulate proper diagnostic tests, develop a rational therapy for male infertility. The results of this study demonstrated that genetic abnormalities happen frequently in Iranian infertile men, which underline the significance of molecular and cytogenetic surveys and the relation of its findings in the patient's management in the fertility clinics.

6. 6. Recommendations:

6.1. It may be necessary to re-examine the YCM screening standards in accordance with the needs of the Iranian infertile men's community and with the purpose of conducting ongoing studies, Iran-specific STR panel has been designed.
6.2. There is a little information about the spectrum of CFTR mutations in the general Iranian population and no consensus on the minimum number of mutations that should be tested and unfortunately at present, the design of a diagnostic panel is not possible at the national level.
6.3. There is a necessity for large Iranian population-based studies to specify the prevalence of genetic causes of male infertility in the general population.
Systematic review and meta-analysis are required to investigate the effect of other gene mutations and polymorphisms on infertility.

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All authors declare that there is no conflict of interest in this study.

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