Am J Transl Res 2021;13(6):5767-5785
www.ajtr.org /ISSN:1943-8141/AJTR0128109

Review Article

Genetics and molecular biology of male infertility among Iranian population: an update

Majid Mojarrad[1], Ehsan Saburi[1], Alireza Golshan[2], Meysam Moghbeli[1]

[1]Department of Medical Genetics and Molecular Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; [2]Department of Urology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Received December 11, 2020; Accepted April 19, 2021; Epub June 15, 2021; Published June 30, 2021

Abstract: Infertility is one of the main social and health problems among young couples. Although a noticeable ratio of infertilities are asymptomatic, about half of the cases are observed among males. Various environmental factors such as life style, dietary patterns, and pathogens are associated with male infertility. Mutations and chromosomal abnormalities are also the most important genetic risk factors of male infertility. Similar to other populations, there is a dramatically rising trend of male infertility among Iranian. Regarding the high ratio of asymptomatic cases, it is required to clarify the molecular biology and cellular processes involved in male infertility in this population to suggest an efficient panel of diagnostic markers. In this review, we have summarized all of the cellular and molecular processes which have been reported among Iranian infertile males to clarify the molecular biology of male infertility in this population. It was observed that the stress response, cellular detoxification, and DNA repair processes were the most common aberrant cellular mechanisms among Iranian infertile males. This review paves the way of introducing a population-based diagnostic panel of genetic markers among Iranian infertile males.

Keywords: Male infertility, risk factor, genetics, molecular processes, diagnosis, Iran

Introduction

Infertility is one of the main global public health challenges [1, 2]. It is defined as the failure of pregnancy after normal unprotected intercourses. It has been estimated that there are more than 48 million infertile couples worldwide [3]. Developed countries have higher rates of infertility compared with developing countries, which can be associated with different socio-cultural factors [4, 5]. There is a rising trend of infertility rate due to delayed childbearing, smoking, alcohol consumption, and sexual behavior alterations [6]. Various factors, including anatomical, genetical, and environmental factors, are involved in infertility. Half of the infertilities are related to males, including antisperm immune response, ductal dysfunction, and spermatogenesis defect [7, 8]. Genetic factors can also affect hormonal homeostasis and spermatogenesis. There is about 20% of infertility among Iranian couples, which is mainly related to the males [9]. Male infertility is a multifactorial disorder with heterogeneous clinical manifestations, including azoospermia, spermatogenic qualitative defects, ductal dysfunction, and hypothalamic-pituitary axis aberration [10]. Semen quality change is associated with various factors, such as lifestyle and dietary habits. A case-control study has reported that the fruits and vegetables consumptions significantly reduced risk of asthenozoospermia among Iranian males, while a dietary pattern based on processed meats and sweets was significantly associated with increased risk of asthenozoospermia [11]. Vitamin D is associated with various factors such as sun exposure, skin pigmentation, geographic latitude, obesity, and air pollution [13, 14]. There was a direct association between the vitamin D levels and sperm motility [15]. Opioid narcotics can also negatively affect the sperm motility and male fertility [17]. The sperm chromatin is more compact compared with the somatic cells through histone to protamine substitution which can be affected by cigarette smoking [18]. It has been

observed that there was a significant inverse correlation between the heroin use and histone-to-protamine replacement ratios among Iranian subjects [19]. Beside the environmental factors, gene mutations and chromosomal abnormalities are also involved in male infertility among Iranian population [20]. Regarding a high ratio of asymptomatic male infertilities among Iranians, it is required to clarify the molecular biology of male infertility to pave the way of introducing an efficient molecular diagnostic panel marker. In the present review, we have summarized all of the reported genes among Iranian infertile cases based on their cell and molecular functions to clarify the molecular biology of male infertility in this population (**Table 1**; **Figure 1**).

Stress response and detoxification factors

Reactive oxygen species (ROS) have negative effects on sperm cell membrane fluidity and DNA stability, which result in male infertility [21]. Therefore, antioxidant defense systems are required for the normal spermatogenesis [22]. Omega-3, vitamin C, and vitamin E are considered as important antioxidants [23, 24]. It has been reported that there were lower levels of Omega-3 in infertile men compared with controls in a sample of Iranian subjects [25, 26]. Another study has been shown that the reduced body mass index and increased vitamin C intake significantly improved motility and normal sperm morphology among Iranian subjects [27]. Glutathione-S-transferases (GSTs) have critical roles in cell protection toward oxidative stress and detoxification of xenobiotics and ROS. CYP1A1 is also involved in oxygenation of polycyclic aromatic hydrocarbons (PAHs) generated by fossil fuels to the carcinogens. Therefore, the GSTM1, GSTT1, and CYP1A1 can be associated with male infertility through their role in regulation of oxidants and antioxidants balance in reproductive system. It has been reported that there were significant correlations between the GSTT1 null and GSTM1 null genotypes and idiopathic infertility among a group of Iranian subjects [28]. Another study has observed that there were associations between null GSTM1 and GSTT1 genotypes and elevated risk of male infertility among a sub-population of Iranian cases. A combination of GSTP1 wild-type with GSTM1 or GSTT1 null genotypes can also be associated with increased risk of infertility. Moreover, the carriers of GSTP1 (Ile/Ile) and GSTM1/GSTT1 null genotypes also had elevated risk of infertility. In contrast, GSTP1 (Ile/Val and Val/Val) genotypes were protective and significantly reduced infertility risk. Therefore, GSTM1 or GSTT1null genotypes were associated with increased risk of infertility while the non-deletion GSTT1 and GSTM1 genotypes were protective among Iranians [29].

Heme oxygenase (HO-1) is a stress response factor activated by oxidative agents to preserve the cellular homeostasis [30, 31]. There is a highly polymorphic GT-repeat region in promoter sequence of HO-1 that is involved in transcriptional regulation. The longer GT-repeats reduce HO-1 expression and vice versa [32]. GT-repeat polymorphisms of HO-1 were assessed in Iranian infertile males, which showed that the long allele frequency was significantly more frequent in case group compared with normal subjects [33].

DJ-1 is a multifunctional factor associated with anti-oxidative defense system and mitochondrial function, which is highly expressed in sperm [34, 35]. It also regulates NRF2, one of the main transcription factors during oxidative stress and detoxification reactions [36]. DJ-1 is also associated with ROS reduction through the upregulation of SOD3 [37]. It suppresses oxidative stress-induced apoptosis [38] and induces cell growth through PI3K/AKT signaling activation [39]. It has been reported that there was a significant correlation between g.-6_+10del (rs901561484) polymorphism of DJ-1 and increased risk of infertility in a subpopulation of Iranian cases. The Del and Dup alleles of g.168_185del (rs373653682) polymorphism were also correlated with male infertility. Moreover, D-Dup and I-Del haplotype significantly increased the male infertility risk, whereas I-Ins haplotypes were protective [40].

Heat shock proteins (HSPs) are the critical stress response proteins that are involved in spermatogenesis [41]. HSPA1B and HSPA1L belong to the HSP70 protein family. There is an inverse association between the level of HSP70 expression and sperm concentration that can be related to the sperm DNA damage [42, 43]. It has been shown that there were positive associations between HSPA1L rs2227956 and HSPA1B rs1061581 polymorphisms and male infertility in a group of Iranian population, in

Table 1. Cell and molecular mechanisms associated with male infertility among Iranian cases

study (ET AL)	Year	Gene	population	Results
salehi [28]	2012	GSTM1, GSTT1, CYP1A1	150 cases 200 controls	Polymorphism was correlated with male infertility.
SAFARINEJAD [29]	2010	GSTM1, GSTT1, GSTP1	166 cases 166 controls	Polymorphism was correlated with male infertility.
SIASI [33]	2011	HO1	100 cases 100 controls	Polymorphism was correlated with male infertility.
JAHANTIGH [40]	2017	DJ1	422 cases 285 controls	Polymorphism was correlated with male infertility.
kohan [44]	2019	HSPAL, HSPA1B	308 cases 208 controls	Polymorphism was correlated with male infertility.
VATANNEJAD [46]	2019	NOX5	25 cases 28 controls	Over expression
ghani [47]	2013	NOX5	13 cases 12 controls	Over expression
safarinejad [48]	2010	eNOS	352 cases 356 controls	Polymorphism was correlated with male infertility.
SABOUHI [50]	2015	CAT	195 cases 190 controls	Polymorphism was correlated with male infertility.
safarinejad [54]	2013	AHR	176 cases 352 controls	Polymorphism was correlated with male infertility.
ghandehari [58]	2019	HIF1α, TNFα, P53	11 cases 18 controls	Over expression
jahantigh [59]	2017	XRCC5,6,7	178 cases 214 controls	Polymorphism was correlated with male infertility.
GHALKHANI [64]	2014	SPO11	113 cases 50 controls	Polymorphism was correlated with male infertility.
ghasemi [67]	2017	LIG4	191 cases 191 controls	Polymorphism was correlated with male infertility.
YOUSEFI [69]	2015	APE1	180 cases 120 controls	Polymorphism was correlated with male infertility.
safarinejad [72]	2011	MTHFR	164 cases 328 controls	Polymorphism was correlated with male infertility.
aarabi [75]	2006	SYCP3	110 cases	Lack of expression

NABI [83]	2018	PRM1,2	92 cases 87 controls	Polymorphism was correlated with male infertility.
JAMALI [84]	2016	PRM1	130 cases 130 controls	Polymorphism was correlated with male infertility.
DEHGHANPOUR [85]	2019	PRM1,2	30 cases 35 controls	Polymorphism was correlated with male infertility.
ELAMINEJAD [87]	2017	JMJD1A	79 cases	Under expression in spermatid maturation and sertoli cell only syndrome.
HEYDARIAN [89]	2016	CDY	29 cases	Over expression
najafipour [93]	2015	YXB2	50 cases 12 controls	Under expression
NAJAFIPOUR [94]	2016	YBX2	180 cases 96 controls	Polymorphism was correlated with male infertility.
MOGHBELINEJAD [96]	2015	PRM2, YBX2	50 cases 12 controls	Under expression
RAFATMANESH [100]	2018	H2BFWT	109 cases 123 controls	Polymorphism was correlated with male infertility.
HAJI EBRAHIM ZARGAR [101]	2015	H2BW	92 cases 60 controls	Polymorphism was correlated with male infertility.
hashemi [103]	2018	ZMYND15	63 cases	Under expression in non-obstructive azoospermia
SAFARINEJAD [106]	2010	ESR1,2	164 cases 164 controls	Polymorphism was correlated with male infertility.
SAFARINEJAD [108]	2011	SHBG	168 cases 168 controls	Polymorphism was correlated with male infertility.
khosropour [115]	2017	LEP, LEPR	150 cases 150 controls	Polymorphism was correlated with male infertility.
asadi [119]	2019	CFTR	100 cases 100 controls	Polymorphism was correlated with male infertility.
HOJATI [121]	2012	CFTR	110 cases 60 controls	Mutation analysis
HEIDARY [125]	2019	CRISP2, SEMG1	35 cases 35 controls	CRISP2 under expression and SEMG1 over expression
ROSHANKHAH [128]	2019	TIMP2, MMP9	101 cases 106 controls	Polymorphism was correlated with male infertility.
asgari [132]	2017	FAS, FASL	102 cases 110 controls	Polymorphism was correlated with male infertility.

ashrafzadeh [134]	2017	TNFR1	108 cases 119 controls	Polymorphism was correlated with male infertility.
MASHAYEKHI [136]	2012	TP53	110 cases 180 controls	Polymorphism was correlated with male infertility.
ESLAMINEJAD [140]	2019	BMP4	100 cases 126 controls	Polymorphism was correlated with male infertility.
nazarian [143]	2014	GSK3B	20 cases	Under expression
HOSSEINI [144]	2017	RABL2B	90 cases	Polymorphism was correlated with male infertility.
shahhoseini [145]	2015	SEPT12	67 cases 100 controls	Polymorphism was correlated with male infertility.
KAMALIYAN [148]	2017	HIWI2	121 cases 100 controls	Polymorphism was correlated with male infertility.
SARKARDEH [150]	2014	MOV10L1	30 cases 70 controls	Polymorphism was correlated with male infertility.
MOGHBELINEJAD [152]	2018	DICER1	385 cases 120 controls	Polymorphism was correlated with male infertility.
KHOSRONEZHAD [153]	2015	NSUN7	90 cases 30 controls	Polymorphism was correlated with male infertility.
ZAMANI-BADI [156]	2019	IL-1β	207 cases 230 controls	Polymorphism was correlated with male infertility.
ZAMANI-BADI [158]	2018	IL-1RA, IL-1α	230 cases 230 controls	Polymorphism was correlated with male infertility.
zamani-badi [159]	2018	IL-1α	230 cases 230 controls	Polymorphism was correlated with male infertility.

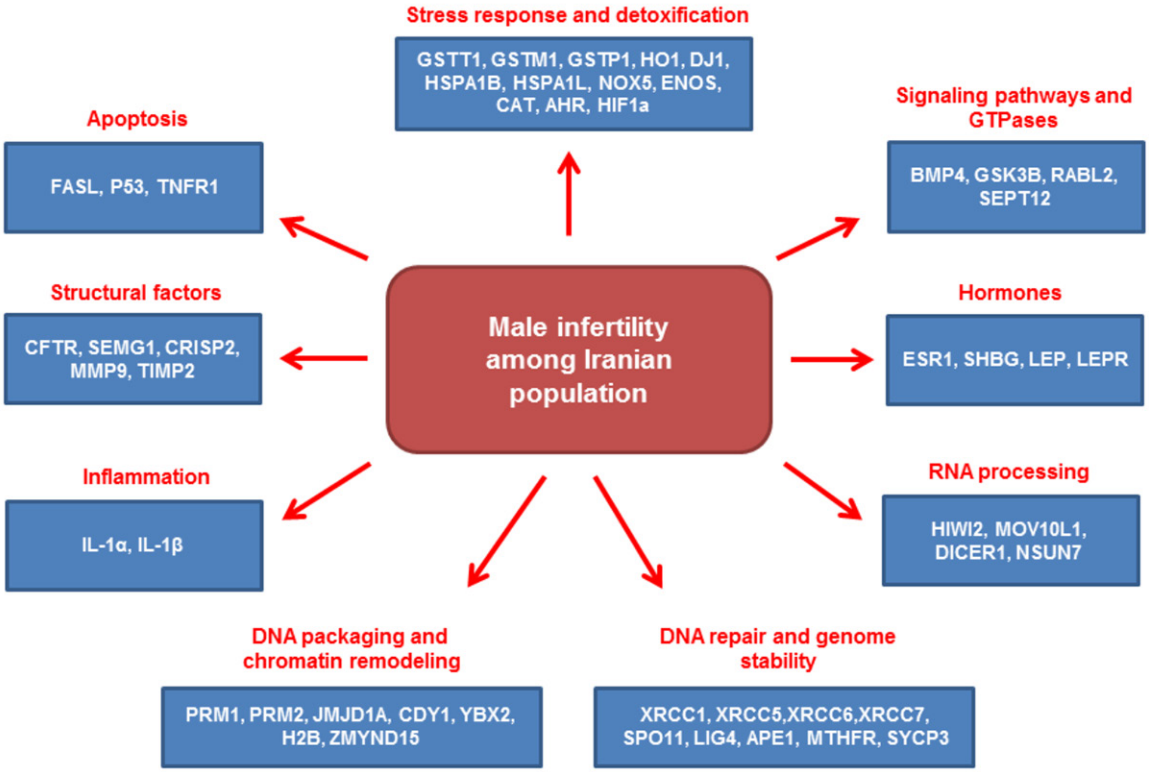

Figure 1. Cell and molecular processes involved in male infertility among Iranian population.

which the HSPA1L rs2227956 C and HSPA1B G alleles were correlated with elevated risk of male infertility. Moreover, the CG and TA (rs2227956/rs1061581) haplotype significantly changed the risk of male infertility [44].

NADPH oxidases (NOXs) are the main sources of hydrogen peroxide and superoxide anions [45]. Role of NOX5 expression was assessed in sperm motility and ROS production in samples of Iranian infertile asthenozoospermic cases. It was reported that the level of NOX5 expression was significantly increased in asthenozoospermic cases compared with controls. The asthenozoospermic cases had significantly higher apoptotic sperm cells compared with normal subjects. There was also an inverse association between the level of NOX5 expression and sperm motility. Therefore, NOX5 upregulation can induce ROS production and DNA damage in asthenozoospermic cases [46]. Another study has shown higher level of NOX5 expression in teratozoospermic semen samples compared with normal subjects among a sub-population of Iranians. There was a direct association between ROS generation and NOX5 expression in teratozoospermia [47]. Nitric oxide (NO) is a free radical and important mediator in signaling pathways, which is produced by nitric oxide synthase (NOS). It has been shown that there were significant correlations between 4a/4b, 786CC, and 894 TT polymorphisms of eNOS and idiopathic male infertility among a subpopulation of Iranian cases, in which the 786CC, 894 TT, and 4aa genotypes were significantly more frequent in azoospermic cases compared with oligoasthenoteratozoospermic subjects [48].

H_2O_2 has important negative effects on sperm motility and sperm-oocyte fusion [49]. Catalase is an important enzyme protecting the cells from oxidative damage by H_2O_2. This enzyme is mainly produced in erythrocytes and hepatocytes while there is a low level of catalase in connective tissue. It has been reported that there was a correlation between CAT C-262T polymorphism and male infertility among a subpopulation of Iranian subjects, in which there was a significantly decreased frequency of TT genotype among infertile cases compared with healthy controls. Therefore, it was concluded that the CAT-262T/T genotype reduced the risk of male infertility among Iranians [50].

Tetrachlorodebenzo-p-dioxin is a xenobiotic that reduces number and size of leydig cells [51]. The aryl hydrocarbon receptor (AhR) is a transcriptional regulator mediating the xenobiotics effects that leads to infertility [52]. The PAH also binds to AhR and induces the CYP1A1 expression that is associated with reproductive toxicity [53]. It has been observed that there were significant inverse associations between the frequencies of AhR rs2066853 GG and rs2282885 CC polymorphisms and sperm density in a sample of Iranian males. The rs2066853AA genotype and AACACAG haplotype carriers had reduced risk of infertility. Whereas, the AACACGA haplotype carriers had increased risk of infertility [54]. Hypoxia can change the level of p53 expression dependent or independent of HIF-1α. There is a low level of p53 expression in normal condition, whereas the hypoxia promotes apoptosis through HIF-1α and p53 up regulations. The level of oxidative stress was higher in asthenozoospermic cases compared with healthy group [55]. Tumor necrosis factor alpha (TNFα), as a multifunctional cytokine, is associated with cell proliferation, inflammation, sperm motility, and morphology [56, 57]. It has been reported that there was significantly increased levels of HIF-1α, TNF-α, and P53 expression among a group of Iranian infertile men with asthenozoospermia in comparison with fertile men. There were also significant negative associations between the levels of HIF-1α and p53 expression and sperm motility. Moreover, there were significant direct correlations between the levels of p53, HIF-1α, and TNF-α expression. It seems that the HIF-1α upregulation and DNA damage induce apoptosis during asthenozoospermia [58].

Generally, It has been reported that the stress response factors involved in regulation of oxidants/antioxidants balance, xenobiotic detoxification, and ROS concentration were the main factors among Iranian infertile males.

DNA repair and genome stability

DNA damage is one of the main causes of male infertility and aberrant spermatogenesis [59]. Aberrant DNA repair during spermatogenesis has negative influences on sperm motility and number that results in infertility [60]. Single and double-strand breaks (DSBs) are the most common types of DNA damages that can be formed through various extra and intracellular factors, including radiation and oxidative stress [61]. The DSB can be repaired by homologous recombination or non-homologous end joining (NHEJ) mechanisms [62]. NHEJ involves several components such as XRCC5-7. The XRCC6 -61C>G, XRCC5 VNTR, and XRCC7 6721G>T polymorphisms were assessed among Iranian infertile males. The XRCC5-6 polymorphisms locate in promoter sequences, while the XRCC7 polymorphism locates inside a splicing site. It has been shown that the 2R allele of XRCC5 VNTR was protective and significantly reduced risk of male infertility. In contrast, increased risk of male infertility was observed in cases with G allele of XRCC6 -61C>G or T allele of the XRCC7 6721G>T polymorphisms [59]. SPO11 is a topoisomerase-like protein expressed in gonads of both genders to regulate DSB formation during meiotic prophase [63]. It has been observed that there was a correlation between rs28368082 polymorphism of SPO11 and azoospermia among a sample of Iranian infertile males [64]. XRCC1 is a scaffold protein that interacts with other DNA repair components such as Pol-b, APE1, and LIG3 to facilitate strand break repair [65, 66]. The LIG4 Thr9Ile and XRCC1 Arg399Gln polymorphisms were assessed among a group of Iranian infertile subjects. It has been reported that there was a significantly different frequency of LIG4 Thr9Ile genotype between infertile and normal cases. The cases with LIG4 TT genotype had significantly reduced sperm motility in comparison with the CC genotype carriers. CT genotype carriers also had a significantly lower sperm concentration compared with CC genotype carriers. Moreover, combinations of GG/CT and GA/CT genotypes significantly elevated the risk of infertility [67]. The APE1 endonuclease is involved in base excision repair that protects cells from endogenous and exogenous mutagenic agents [68]. It has been observed that there was a significant association between 656T>G APE1 polymorphism and male infertility in a sample of Iranian cases, in which the TG genotype carriers had increased risk of infertility [69].

The methylenetetrahydrofolate reductase (MTHFR) has a key function in folate metabolism through 5-methyltetrahydrofolate production, which is an important factor during spermatogenesis and DNA methylation [70]. It is also involved in formation of S-adenosylmethionine

(SAM) that is the methyl donor during DNA repair [71]. It has been observed that there was a significant correlation between MTHFR C677T polymorphism and risk of infertility among a sub-population of Iranian males, in which 677TT, 677TT þ1298AC, and 677TTþ1793GG genotypes increased the risk of male infertility. The 677 (TC or TT) allele carriers had significantly increased risk of infertility in comparison with CC carriers. Moreover, there were significantly increased and decreased serum levels of tHcy and folate in 1298C, 677T, and 1793G alleles carriers, respectively. Serum folate level was correlated with sperm density and motility [72].

Homologous recombination is a critical mechanism during chromosome segregation in meiotic prophase which is regulated by synaptonemal complex. Synaptonemal complex protein 3 (SYCP3) prepares a molecular framework for the attachment of other proteins. Therefore, It regulates sister chromatid adhesion, recombination, and synapsis [73, 74]. It has been observed that there was not any testicular SYCP3 expression in Iranian subjects with spermatogonial arrest and testicular atrophy [75]. Zinc is a cofactor of various proteins such as zinc finger proteins and DNA repair factors [76]. It is a pivotal factor during testis development and sperm function [77]. Lack of zinc impairs antioxidant reactions, which increases the sperm susceptibility to oxidative damage [78]. It has been reported that the infertile males had significantly lower seminal plasma zinc levels compared with controls among a sub-population of Iranian cases. There was a significant direct association between the zinc level and normal sperm morphology. Moreover, smokers had lower seminal plasma zinc level compared with fertile or infertile nonsmokers. Therefore, low seminal zinc level can be a risk factor of male infertility among Iranian males [79].

Generally, it was observed that there were associations between the DNA repair, chromosomal serration, and male infertility among Iranian cases. Dysfunctions of the factors involved in homologous recombination, base excision repair, NHEJ, and chromosomal segregation processes were frequently reported in this population that highlights genome stability as an important prerequisite for the normal gametogenesis and fertility in this population.

DNA packaging and chromatin remodeling

Chromatin remodeling is an epigenetic process involved in genome condensation and stability, spermatogenesis, and fertility [80]. Protamine (PRM) and transition proteins (TNP1 and TNP2) are nuclear proteins involved in chromatin remodeling and DNA condensation [81]. Protamines have pivotal roles in sperm biology through regulation of chromatin condensation, maternal genome protection, and imprinting pattern [81]. Protamines are the most abundant nucleoproteins in mature sperm. They promote higher levels of DNA condensation in sperm during spermiogenesis, which preserve the parental genomic integrity during transportation in reproductive tracts [82]. It has been observed that there were associations between the PRM1 (139C>A) and PRM2 (373C>A, 298G>C) polymorphisms and asthenozoospermia in a sample of Iranian subjects [83]. There were also significant correlations between -190CA and -190AA genotypes of PRM1 and increased oligozoospermia susceptibility in a sample of Iranian cases [84]. Another study showed that there was a significant correlation between PRM1 c.230A>C polymorphism and male infertility in a sample of Iranian cases, in which the teratozoospermic cases had increased frequency of CA genotype. Moreover, the PRM2 G398C and A473C polymorphisms were also correlated with sperm apoptosis and morphology [85].

JMJD1A is a histone demethylase expressed in sperms and activates the TNP and PRM genes through demethylation of H3 lysine 9 in promoter sequences [86]. It has been reported that there was significant JMJD1A downregulation in sertoli cell only syndrome (SCOS) and SMA compared with OA cases in a sub-population of Iranian cases [87]. Sperm DNA packaging involves histone-protamine substitution during spermatogenesis, which is facilitated by CDY1 as a histone acetyltransferase [88]. It has been reported that there was significant CDY1 upregulation in a sample of Iranian cases with successful sperm retrieval compared with failed retrieval subjects [89]. PRM has limited transcription only in round spermatids and remained translationally silent in elongated spermatids [90].

Y box binding protein 2 (YBX2) is a DNA/RNA-binding protein which functions as the tran-

scriptional regulator of protamine expression [91]. The JHDM2A is also an H3K9 demethylase associated with regulation of TP1 and protamine [92]. It has been shown that there was a significant YBX2 downregulation in a sample of Iranian azoospermic men compared with normal subjects [93]. It has been reported that there was significantly higher frequency of TT genotype in YBX2 rs222859 polymorphism among a sub-population of Iranian azoospermic males in comparison with control group. Azoospermic cases also had significant YBX2 downregulation in blood and testis tissues compared with control cases [94]. The PRM1/PRM2 ratio is associated with sperm counts, motility, and morphology [90, 95]. There was significantly increased testicular PRM1/PRM2 mRNA ratio in a sample of Iranian azoospermic cases compared with normal subjects. There was also significant PRM2 downregulation in azoospermic cases. Moreover, a significantly lower expression of YBX2 was observed in azoospermic males compared with controls, which was also directly associated with PRM expression [96].

Histones are the main factors in chromatin condensation and DNA packaging, which have a fundamental role during spermatogenesis [97, 98]. The H2B.W is a testis specific histone expressed during spermatogenesis [99]. It has been observed that there were significant correlations between c.-9C>T and c.368A>G polymorphisms of H2BFWT and azoospermia and oligozoospermia respectively in a group of Iranian subjects [100]. The -9C>T and 368A>G polymorphisms of H2B.W were also assessed in a sample of Iranian azoospermic and oligozoospermic subjects. There was a significantly increased frequency of -9T at the -9C>T locus in maturation arrest compared with SCOS cases. Moreover, the maturation arrest cases had significantly higher frequency of TA haplotype compared with SCOS subjects, which suggested the haplotype TA as inhibitor of spermatids maturation during spermatogenesis [101]. ZMYND15 is associated with histone deacetylases to suppress transcription of TNP1, SPEM1, and CATPSER3 which are involved in spermatogenesis [102]. It has been reported that there was significant downregulation of ZMYND15 in testicular samples of non-obstructive azoospermia in comparison with obstructive azoospermia among a sub-population of Iranian cases [103].

DNA packaging and condensation are pivotal cellular processes to maintain the genome stability in sperm cells. Genetic alterations of the Protamines and their specific transcription factors have been frequently reported among Iranian infertile males.

Hormones

Androgens have critical roles during the normal spermatogenesis. Estrogen reduces testosterone levels through reducing the gonadotropin secretion [104]. It can also stimulate the oxidative DNA damage that is associated with male reproduction [105]. It has been shown that the ER-PvuII CC and XbaI AG genotypes of ESR1 were significantly correlated with decreased infertility rates in comparison with PvuII TT and XbaI AA genotypes among a group of Iranian infertile males. Moreover, infertility rate was significantly higher in cases with RsaI GA and AluI AG genotypes of ESR2 in comparison with RsaI GG and AluI AA carriers [106]. SHBG is involved in plasma transportation of testosterone and estradiol [107]. The Asp327Asn and (TAAAA)n polymorphisms of SHBG were assessed among a sub-population of Iranian infertile males. It was observed that the infertile cases had longer (TAAAA)n repeat alleles compared with normal subjects. The cases with long alleles had lower SHBG levels than shorter alleles carriers. Moreover, there was a correlation between Asn allele and increased plasma SHBG levels and decreased infertility rate. The long alleles (L/L) with Asp/Asp genotype was more frequent among infertile cases compared with short alleles (S/S) and Asn/Asn genotype. The plasma SHBG was significantly correlated with sperm count and motility. Therefore, the (TAAAA)9 repeat and Asp alleles of SHBG can be correlated with reduced serum SHBG levels and increased infertility rate among Iranians [108].

Leptin (LEP) is an adipose related hormone mainly produced by adipocytes and enterocytes of small intestine, which is involved in energy balance, fat storage, immune response, and reproduction [109, 110]. It functions via leptin receptors (LEPR) that belong to the IL-6R family [111]. LEP has pivotal roles in reproduction through the regulation of hypothalamic-pituitary-gonadal axis, testis volume, sperm counts, and motility [112-114]. The LEP -2548G/A and LEPR Gln223Arg polymorphisms

were assessed in a sample of Iranian infertile subjects. It has been observed that the AG genotype of LEP-2548G/A polymorphism was protective and significantly reduced the risk of male infertility. AG and GG genotype carriers had significantly higher sperm counts compared with infertile cases with AA genotype. Moreover, the LEPR RR genotype carriers had significantly increased ratio of motile sperms compared with other genotypes [115]. Severe hypothyroidism has a negative effect on reproduction [116]. It has been shown that there was an inverse correlation between hypothyroidism and erectile function and sperm count and motility among Iranian cases [117].

Ion channels, structural, and extracellular proteins

The CFTR is an epithelial chloride channel associated with chronic obstructive pulmonary disease and male infertility [118]. It has been shown that there were associations between CFTR mutations, IVS8-Tn polymorphisms, and congenital bilateral absence of the vas deferens (CBAVD) in a group of Iranian infertile men [119]. CBAVD is one of the common cystic fibrosis (CF) features that results in male infertility. The CFTR is mainly expressed in post meiotic spermatids, in which intracellular water reduction results in decrease in cytoplasm volume. Capacitation is a critical step during sperm maturation that is associated with elevation of intracellular pH and membrane hyperpolarization. Therefore, CFTR has a key role in sperm capacitation and fertility via Cl^- and $HCO3^-$ transportation [120]. The M469I mutation in CFTR was assessed in a sample of Iranian males with azoospermia, in which the M469I was only present among infertile cases [121].

CRISP2 is a specific protein observed in acrosome and sperm tail involving in several processes such as sperm-egg fusion and regulation of flagellar motility [122, 123]. SEMG1 is a structural protein in semen coagulum associated with sperm capacitation through semen coagulation and sperm immobilization [124]. It has been reported that there were significant under and over expressions of CRISP2 and SEMG1 respectively in a sample of Iranian infertile cases in comparison with the controls [125]. Matrix metalloproteinases (MMPs) and tissue inhibitor matrix metalloproteinases (TIMPs) are critical factors for the regulation of testicular extracellular matrix and tissue remodeling [126, 127]. MMP9-1562C/T (rs39-18242) and TIMP2-418G/C (rs8179090) polymorphisms locate in promoter sequences and binding sites of AP-1 and SP-1 transcription factors, respectively. It has been reported that there was a significantly different frequency of TIMP2-418G/C between a sample of Iranian infertile cases and controls. The CC, GC and CC + GC genotype carriers of TIMP2-418G/C had elevated risk of infertility in comparison with cases with GG genotype. Moreover, the MMP9-1562T and TIMP2-418C alleles significantly increased risk of infertility among Iranian subjects [128].

Apoptosis

Apoptosis is the key process in cell elimination which is involved in male fertility [129]. FAS belongs to the TNFR family and plays an important role in apoptosis pathway through binding with FASL [130]. FADD binds with FAS to form the Death Inducing Signaling Complex (DISC) following the FAS activation. Subsequently, FADD activates the pro-caspase 8 or 10 to induce apoptosis [131]. It has been reported that there was a significantly different frequency of FASL-844C/T polymorphism between a sub-population of Iranian azoospermic cases and controls. Cases with FASL-844TT and CT genotypes had higher risk of azoospermia compared with CC genotype carriers [132].

TNF-α is an apoptotic cytokine belong to the TNF family that is produced by testicular germ cells and macrophages. It affects the target cells via two types of receptors, including TNFR1 and TNFR2 that are expressed by Sertoli and Leydig cells. TNFR1 induces the caspase-dependent apoptosis through a cytoplasmic death domain [133]. The association between TNFR1 36A/G polymorphism and sperm abnormalities was assessed among a sub-population of Iranian subjects which showed significantly increased frequency of G allele and GG genotype in azoospermic infertile males. G allele upregulated the TNFR1 and stimulated the function of TNF-α that leads to increased azoospermia susceptibility. TNF-α upregulation was associated with sperm DNA chromatin abnormalities, impaired motility and reduced testosterone levels [134]. The p53 has pivotal roles in various cellular processes, such as genome stability, cell cycle arrest, and apopto-

sis [135]. It has been reported that there was increased frequency of Arg allele of p53 R72P polymorphism among a group of Iranian males with idiopathic infertility compared with controls. There was significantly different frequencies of the Arg/Arg and Arg/Pro + Pro/Pro genotypes between infertile cases and controls [136].

Signaling pathways and GTPases

Bone morphogenetic proteins (BMPs) belong to TGFβ protein superfamily and are involved in testis formation, spermatogenesis and fertility [137]. Deregulation of BMP signaling can also increase the apoptosis ratio of spermatogenic cells [138]. BMP4 promotes proliferation of Sertoli cells and is associated with regulation of critical factors during spermatogenesis [139]. It has been shown that there was a correlation between BMP4 rs17563 polymorphism and male infertility in a sub-population of Iranians, in which the C/C genotype carriers had higher risk of idiopathic male infertility in comparison with the T/T genotype. Moreover, the infertile cases had significantly lower serum BMP4 levels compared with control cases [140].

WNT is a developmental signaling pathway that regulates cell proliferation, differentiation, and polarity [141, 142]. The β-catenin enters into the nucleus and induces the expression of WNT target genes in canonical pathway. In the absence of WNT ligands, cytoplasmic β-catenin is degraded by proteasome following the phosphorylation by APC-Axin-GSK3-β complex [142]. It has been reported that there was a significant GSK3-β downregulation among a group of Iranian non-obstructive azoospermic subjects compared with controls [143].

RABL2 is a GTPase that belongs to the Ras superfamily, which involved in transportation of proteins into the growing sperm tail. It has been reported that there was a significantly higher frequency of 50776482 delC variant among a sub-population of Iranian infertile men [144]. SEPT12 is a guanine-nucleotide binding protein belonging to the cytoskeletal GTPases that is involved in spermatogenesis. Septins have pivotal roles in cytokinesis and membrane dynamics. It has been observed that there was significantly different frequencies of SEPT12 (G5508A) polymorphism between the infertile Iranian patients and normal cases [145].

RNA processing

The PIWI-interacting RNA (piRNA) is an important non-coding RNA during spermatogenesis, which is associated with transposon inhibition via degradation and DNA methylation [146, 147]. PIWI proteins, as the members of Argonaute family, have key roles during piRNA formation and function. It has been shown that there was a correlation between the rs508485 (T>C) polymorphism of HIWI2 and increased risk of azoospermia among a sub-population of Iranian men [148]. The MOV10L1 is a germ cell-specific RNA helicase in males associated with piRNA biosynthesis [149]. MOV10L1 alterations were studied in a sub-population of Iranian infertile men that showed nonsense and intronic polymorphisms. Several haplotypes were correlated with decreased or increased risk of azoospermia. There was an association between the haplotype (AGACCCAG) and elevated risk of infertility [150].

MicroRNAs are a class of non-coding RNAs that are initially transcribed by RNA polymerase II to the primary microRNA [151]. Then, it is cleaved by DROSHA nuclease during the maturation process to form the mature miRNA. It has been shown that there was a correlation between CC genotype of rs1057035 polymorphism in DICER1 and azoospermia in a sample of Iranian cases. Moreover, DICER1 downregulation was also observed in blood samples of azoospermic males [152]. Normal sperm flagella and motility are important factors involved in male fertility. NSUN7 belongs to the methyltransferases superfamily that has critical functions in sperm motility and mitochondrial rRNA processing. It has been observed that the asthenospermic cases had significantly higher frequency of A-11337-deletion in NSUN7 compared with controls and oligospermic subjects in a sample of Iranian males. This mutation was significantly associated with poor sperm motility [153].

Inflammation

Cytokines are growth factors associated with germ cell proliferation, differentiation and normal testis function [154]. IL-1 plays an important role in preservation of the immune environment in testis [155]. It has been reported that there was an association between IL-1b C3953T polymorphism and male infertility in a group of Iranian subjects, in which the TT geno-

type and T allele were correlated with male infertility [156]. IL-1RA is normally expressed by gonad macrophages that regulates the activity of IL-1α and IL-1β [155, 157]. The IL-1RA VNTR and IL-1α 4845G>T polymorphisms were assessed among Iranian infertile males which showed that there were significant correlations between these polymorphisms and male infertility. The frequencies of the GT genotype, TT genotype and T allele were significantly correlated with idiopathic male infertility, oligozoospermia, and asthenozoospermia. The VNTR 4R/5R carriers had a high risk of oligozoospermia [158]. Another study has shown that there was a significant correlation between CC genotype of IL-1α C376A polymorphism and male infertility in a sub-population of Iranian subjects. The AC genotype and C allele were also correlated with asthenozoospermia and oligozoospermia, respectively [159].

Conclusions

In this review, we have summarized all of the genes which have been reported among Iranian infertile males to clarify the cell and molecular processes involved in male infertility in this population. It was observed that the stress response and detoxification are the most common aberrant cellular mechanisms among Iranian infertile men. This review also paves the way of introducing an efficient molecular panel of diagnostic markers for the early detection of male infertility among Iranians.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Meysam Moghbeli, Department of Medical Genetics and Molecular Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. E-mail: moghbelim@mums.ac.ir

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