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REVIEW

Genetics and male infertility

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Abstract

The goal of this review is to explain the requirement for understanding the genetic structure of infertility arising from male factor and to discuss the essentials of these genetic elements (2). The majority of the population is affected by this disorder caused by male factor infertility (1); but the etiologies are still unknown. After the primary genetic structure in infertile phenotypes is searched, an evaluation can be made. Thus the reasons causing infertility can be discovered and patients can benefit from effective therapies (1). Publications about male infertility within the recent 10 years in the Pubmed database were discussed (1). There are some approachments for describing the function of specific genes, but no adequate study is present to be useful for diagnosing and treating male infertility (1). Male fertility and fertility in offspring of males are considerably affected by the exact transition of epigenetic information (1). When the genetic factors playing a role in male infertility were analysed, significant steps will be taken for treating patients and determining the reasons of idiopathic infertility (1). Developments in technology associated with the impact of genetics may enable to specify the etiology of male infertility by determining specific infertile phenotype marks (1).

Key words: Male infertility; Chromosomal abnormality; Y chromosome microdeletion; Genetics; Azoospermia factor

Core tip: In the case of being unable to be pregnant after regular unprotected intercourse for one year (6), it is defined as infertility, affecting about 10%-15% of all the couples. Male factor is responsible for about half of cases (6). Genes playing a role in testicular differentiation and full spermatogenesis are found in human Y chromosome (6). The main goal of this study is to mention the various chromosomal abnormalities and deletions of Y chromosome, which cause infertility; for this reason (14) it is important to know the genetic mechanisms that are responsible from the infertility especially for the clinicians.

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GENETICS AND MALE INFERTILITY

Infertility is mentioned when a female is unable to be pregnant after 1 year of unprotected regular intercourse, and this problem is encountered in

10%-15% of couples[1] (4). Male infertility is seen in about 30%-55% of cases of infertility[2,3] (4). If there is no pregnancy before, it is called as primary infertility; it results in live birth or not, if there is at least one pregnancy before, it is named as secondary infertility[1]. Infertility is encountered in 10%-15% of couples in the reproductive age as a significant health problem[2,3] (16). Approximately one third of infertility cases arise from pathologies due to the male, one third due to female, and one third due to both partners. Therefore the male factor is responsible for at least 50% of infertile couples[4]. Medical treatment for infertility is requested by only 1 in 13 men of reproductive age[4] (4). According to data created using standard diagnostic protocols of the World Health Organization (WHO), the female factor has been found in 37% of infertile partners, the male factor in 8%, both factors together in 35% and the cause is unknown in 5%[5].

Male infertility

Infertility (infertility with male factor) occurs in approximately 50% of infertile couples due to causes associated with male partner being unable to product spermatozoa in adequate number to enable fertility[6]. In 40% of infertile population, qualitative and quantitative sperm production abnormalities are detected. In 60%-70% of cases, the source of reduced testicular sperm function is unclear[3]. The sources of male infertility can be classified as follows: (1) Idiopathic; (2) Mechanic urogenital obstruction (vas deferens, ductal system, *etc.*); (3) Physical trauma; (4) Infection; (5) Life style (obesity, psychological problems, age, exercise, drugs, smoking)[7]; (6) Varicocele; (7) Endocrine disorders[3,8]; (8) Malignity[9]; (9) Cryptorchidism[10-12]; and (10) Genetic causes.

Spermatogenesis changes may occur due to many reasons such as systemic diseases, cryptorchidism, endocrinological diseases, obstruction in the seminal tract, and infections. Human spermatogenesis disorders frequently (50%) occur idiopathically and because of genetic causes. Mutations in genes under hypothalamic/pituitary control of spermatogenesis are described and these mutations are responsible for some types of hypogonadotropic hypogonadism[10-12].

Azoospermia is observed in 1% of all men, 10%-15% of infertile men[4,13]. Idiopathic non-obstructive azoospermia or serious oligospermia is a private group in male infertility. Idiopathic non-obstructive azoospermic men (INOA) is one of the primary causes of unperceived infertility; these are eugonadal and have primary infertility, low testicular volume, and high FSH levels; all of these are suggestive of testicular lesion to be likely congenital[14]. If azoospermia is due to severe intrinsic testicular defect, a prominent increase is seen at serum FSH level while serum FSH level is lower than normalcy in hypogonadotropic hypogonadism.

Genetic reasons in male infertility

Genetic disorders, such as chromosomal anomalies and monogenic diseases, have been established to be responsible from 10%-15% of infertility conditions[15]. A great number of genetic reasons causing male infertility are defined in humans[16]. Genetic alterations in infertile men usually lead to reduced spermatogenesis, genital structural abnormalities, decreased testicular size, hypogonadism and sperm dysfunction[17].

Genetic anomalies can be categorized in four main groups: (1) Y chromosome microdeletions; (2) Chromosomal abnormalities; (3) Gene mutations and polymorphisms; and (4) Epigenetic disorders[18].

Y chromosome and fertility: Human Y chromosome includes the genes which are necessary for spermatogenesis and development of gonadal differentiation in favor of testis[19-21]. Although human Y chromosome incorporates nucleotides over 60 billion, it is the chromosome with the lowest number of gene in proportion to other chromosomes. Y chromosome plays a role as genetic marker of male characteristic properties and demonstrates many interesting biologic features[22]. While the proximal site of the short arm (Yp) and the long arm (Yq) of Y chromosome is euchromatic site, the distal site of Y chromosome is heterochromatin site and the length of this site is variable[23]. Male specific site forming 85% of Y chromosome carries MSY (male specific site of Y), 3 euchromatic (x-transposed, x degenerated, ampliconic), and a heterochromatic mosaic chain. To date, 156 transcription units, 78 protein-coding genes, and 27 different proteins associated with Y chromosome have been defined[22]. There are pseudoautosomal border site, PABY1 and PABY2 pseudoautosomal sites on Yp and Yq arms, respectively, and homologues on X chromosome. Sites other than these sites do not participate to meiotic recombination. Accordingly, this situation leaves 95% of Y chromosome as non-recombinant[22,24].

Human Y chromosome, so as its majority consists of repetition elements, includes a limited number of functional genes; additionally some alphoid repetitions incorporate major human short interspersed nuclear element (SINE) and a few satellite sequence family. Alphoid sequences are conglomerated near the Y chromosome centromere and can be distinguished from other chromosomes. The majority of Alu repetitions of Y chromosome show quite less similarity with genomic Alu sequence. Alu sequence is the most found repetition element in human genome[22]. As non-coding repetitive DNA is more, deletions are frequently seen in Y chromosome[7]. Some different spermatogenic differences are caused by Y chromosome microdeletions. These include hypospermatogenesis, maturation arrest, Sertoli cell only syndrome (SCOS)[23,25,26]. Infertility may also occur with autosomal genes controlling mutations or paracrine systems in protooncogenes in the infertility signal mechanism as well as Y-linked sequences[22].

Y chromosome and testis determining factor: Numerous genes have been examined during researching

factor or factors determining testis development. H-Y antigen (Histocompatibility Antigen) and ZFY (Zinc Finger Protein, Y-linked) gene are among these. Today, however, these factors are accepted not to have a role in determinating testis. The gene which is required for differentiation of bipotential gonad in favor of testis is testis determining factor (TDF) This gene is not adequate, although it is necessary for differentiation. Proteins produced by 1.1 kb-length transcripts formed by single exon of SRY defined in Yp11.3 band and having no intron have a length of 204 amino acids and include homologue sequences related to HMG-BOX. HMG (high mobility group)-BOX is a DNA-binding motif that is composed of 79-amino acids which is strongly protected. It enables acceleration or deceleration of transcription in gene and suppression or activation of the target gene by helping DNA bending. SRY gene can suppress the only active copy of SRVX in normal 46 XY men and 47 XXY men with Klinefelter syndrome; thus freed autosomal locus can carry out testis formation. SRVX is active in 46 XX females and enables differentiation of bipotential gonad in favor of ovary by suppressing autosomal genes. If SRVX is in case of two active copies, SRY will be unable to adequately decrease functions of SRVX and testis formation will be prevented. This model explains that X, Y, and autosomal genes work together in gonadal differentiation[5,19-21].

Y chromosome and azoospermia factor: Many genes on the autosomal and Y chromosome control germ cell development. Gene and gene families involving in spermatogenesis are available in the long arm of Y chromosome and have a crucial importance in germ cell development and differentiation[27,28]. In infertile men, microdeletions in the long arm of Y chromosome (Yq) can be morbific cause[3]. Y chromosome is separated into 7 deletion periods. Each of these spaces is also separated into subperiods. The hypothesis that one or one group gene on Y chromosome exists, having a place in human spermatogenesis, has been reported by Tiepolo *et al*[27] for the first time in 1976. Genes which are crucial in spermatogenesis are localized on 11.23 band in the long arm of Y chromosome. This band is at the 5th and 6th deletion interval. This site is known as azoospermic factor sites (AZF). While AZFa is on the proximal Yq11, AZFb and AZFc are on the distal Yq11. These sites do not conflict with each other. RNA-binding proteins are encoded by these AZF genes. They take part in gene expression, RNA metabolism, packaging, transport to cytoplasm, and splicing regulation[27]. In 1992, Vollrath *et al*[29] arranged a deletion map with 43 intervals of Y chromosome; these sites also contain the sites extending along Y chromosome and called "sequence tagged sites" (STS)[3,20,26,28-30]. In male infertility and spermatogenic disorder after Klinefelter syndrome, Y chromosome microdeletions are the second closest reason[21,31,32]. Therefore, genetic screening of AZF deletions must be absolutely performed in studies of male infertility. With discovery of human Y chromosome sequence, molecular mechanism of Y chromosome microdeletions has been understood to carry out as a result of homologue recombination between similar pieces in palindromic sequences. This also results in deletions or rearrangements of Y chromosome[21,33]. Some patients with idiopathic male infertility may be caused by microdeletions on the long arm of Y chromosome (11). Y chromosome microdeletions usually are not found in karyotype and responsible for loss of genes forming AZF factor[14,33]. Furthermore, microdeletions in these AZF sites are related with different testicular histology exchanging from Sertoli cell only syndrome to hypospermatogenesis as well as azoospermia[3].

Each AZF site deletion causes different phenotypic effects[8]. In the study performed by Sargent *et al*[34], AZFa site in 4 infertile men have been examined, and deletion has been detected in one only[34]. Deletions in the AZFb site have been found to be related to azoospermia, oligospermia, and normospermia. Deletions of the AZFc site have been shown to be associated with azoospermia and serious oligospermia[35]. In many cases, deletions in the AZF site have been demonstrated to lead to loss of spermatogenesis. AZFc is the site where the most deletion is found among three AZF sites; AZFb site follows that[36].

Y chromosome microdeletion has been defined in 9% of azoospermic infertile men and 11.6% of severe oligospermic men. In other words, although Y chromosome microdeletions are the closest molecular hereditary reason in infertile men, there is no deletion in 85% of azoospermic men and 90% of oligospermic men because other Y chromosome-dependent factors, for example some re-arrangements such as changes in repetition sequences in gene families with multicopy, polymorphism or mutations in Y chromosome-specific genes, and duplication, contribute to infertile phenotype[37]. That triggering AZF site deletions may be a Y chromosome haplotype. For this reason, some individuals may prone to more novo deletion. Advanced paternal age may also trigger loss of Y sequences[38].

Y chromosome deletion mechanism: In clinical and molecular studies performed since 1994, the role of Y chromosome genes and Y chromosome microdeletions in male infertility have been examined[37]. Analysis of microdeletions in patients tries to reveal the roles of gene or gene families in spermatogenesis regulation[22]. Frequently seeing *de novo* Y deletions is attributed to impetuous decrement of genetic material. Y chromosome's structural difference may be associated with elements repeated alongside chromosome to be more and these repetitions to be seen in the site (homologue site between X and Y chromosomes) where recombination is done. Furthermore, specific Y chromosome sequences increasing AZF deletion sites are available, and consequently some individuals are

able to be predisposed for *de novo* deletions more than the others. High fatherly age is also considered to increase Y chromosome gene sequence loss[39].

Y chromosome molecular screening indications: Y chromosome microdeletion screening helps to understand the reason for azoospermia or oligospermia in patients and to determine prognosis. Which patients need for Y chromosome molecular screening can be determined as follows: according to world literature, deletions are clinically seen in those who are azoospermic or have a spermiogram counts of 1×10^6/mL. Infrequently, deletion can be seen in infertile patients who have a sperm concentration of $1\text{-}5 \times 10^6$/mL (3). Although microdeletion is more frequent in patients selected by testicular histology, for example, in patients with Sertoli cell only syndrome (SCOS), it is unable to give certain selection criteria about which patients are a nominee for molecular analysis[23,40]. Deletion screening must be suggested for severe oligospermic or azoospermic patients being a candidate for intracytoplasmic sperm injection (ICSI) or TESE/ICSI because TESE should not be performed in patients who have (3) complete deletion in the AZFa site or in cases with complete deletion in the AZFb site or AZFb+c site. Additionally, deletions in the AZFc site can pass male offspring if an assisted reproductive method is used[29,41]. Therefore, detection of deletion has a prognostic importance and is crucial in therapeutic approach[32,42]. To date, it has been reported that only 17 male and 18 female ICSI babies were borned from fathers with Yq microdeletion; while these babies are phenotypically normal, one male baby only has been diagnosed with pulmonary atresia and left ventricular hypoplasia. Generally, molecular diagnosis indication for Y chromosome microdeletion is a crucial clinical decision varying from case to case, and it is quite important that clinicians approve this diagnosis for which patients[31]. Diagnostic evaluations of deletions are carried out by polymerase chain reaction of selected sites on Y chromosome. MSY-specific sequence tagged sites (STS) primers implify nameless genes, in other words common genes, in chromosome or genes[43]. That being important in diagnosis of Y chromosome microdeletion is which STS primers in Y chromosome will be used. The sites where STS primers used are found should not be polymorphic; they should be the sites where deletions are specifically known in men influenced by oligo/azoospermia with respect to microdeletion clinically certain[31].

Deletions found in the Y chromosome site where deletion events are less frequently seen have been reported to result in severe infertility as in AZFa. Increasing the number of STS in sites where deletions are mostly found, for example as in AZFc, will inform about the dimensions of deletion. Based on these principles, well screening of the important sites of Y chromosome can be achieved by 20-30 STS. In the study performed by Pryor *et al*[44] (1997), only one STS deletion found in oligozoospermic patients has been revealed to represent a polymorphism not leading to infertility of patient. However, it is suggested in this study that these STSs should not be excluded from STS panel while evaluating Y chromosome in an infertile patient as these deletions are also found in infertile patients[44].

Other Y chromosome genes: Another gene that takes part in spermatogenesis is CDY, the chromodomain protein Y-linked gene. It is located on Yq. It is explicited in the testis. It can be involved in enabling the exchange of histones in spermatogenesis. It also helps the proteins which adjust transcription easier accession to the postmeiotic sperm DNA. This is occurred by the acetylation of histones[34]. During evolution, functional separation from *CDY* gene's autosomal homologue and migration to the Y chromosome are considered (CDYL, located on chromosome 6) (1). Thus the gene becomes interesting to study[45] (1). The *TSPY* gene is located on the short arm of the Y chromosome; it also has transcripts on the long arm of the chromosome[46]. Protein of the gene expressed in the testis has been identified in spermatogonia[47] (1). The *TSPY* gene signals spermatogonia in order to enter meiosis, thus it may regulate the timing of spermatogenesis[48] (1). In a study about copy number diversity of the TSPY gene, it was reported that there were more copies in infertile patients[49] (1). This stands for further investigation of TSPY to specify its position in infertility (1).

Chromosomes in fertility and chromosomal abnormalities

Condensed chromosomes involve in gamete formation, also in premeiotic divisions, meiosis, fertilization, and all consecutive mitotic divisions. So, chromosomal errors can also be a ground of investigation to identify the role of genetics in male factor infertility[50]. Chromosomal abnormalities are accountable from nearly 5% of male infertility. The prevalence rises to 15% azoospermic cases[51]. Chromosomal abnormalities found in infertile men are classified as numerical abnormalities (gonosomal aneuploidy) and structural abnormalities[7,10]. While sex chromosomal abnormalities are more frequently encountered in azoospermic patients, autosomal abnormalities are mostly seen in oligospermic patients. The frequency of reciprocal translocation, Robertsonian translocation and inversion is increased in infertile men compared to newborn population[52].

Numerical chromosome abnormalities: The most common reason of chromosomal abnormalities in infertile men is aneuploidy, or alterations in chromosome number[50]. The rate of aneuploidy in men with nonobstructive azoospermia is exclusively high[53] (1),

especially in their sexuality chromosomes. Despite different quantity of genetic material from normal sperms in aneuploid sperm, these sperms can prosperously fertilize the oocyte (1). Ultimately, their offspring gain an incorrect chromosome number[54] (1). Classical trisomies (trisomy 21) and sex chromosome trisomies (XXY or XYY) are within numeral abnormalities that can be mosaic or non-mosaic. Another kind of numeric abnormalities is aneuploidy seen in sperm[7,10]. The most seen numerical chromosome abnormalities are emphasized below.

Klinefelter syndrome: Klinefelter syndrome is the most prevalent chromosomal abnormality induced by aneuploidy. It is present in 5% of men with severe oligozoospermia and in 10% of azoospermia[55]. The syndrome usually gives rise to the arrest of spermatogenesis at the primary spermatocyte stage, but rarely later stages of sperm growth are detected[3]. Klinefelter syndrome has two types (1): nonmosaic, 47, XXY; and mosaic, 47, XXY/46, XY. Although formerly believed to be infertile, it has been predicted that 25% of nonmosaic Klinefelter syndrome cases have sperm in their ejaculate[2]. Patients with Klinefelter syndrome may become pregnant using ICSI, but there is a risk for producing offspring with chromosomal abnormalities[10,11] (1). This syndrome is characterized by the presence of one or more X chromosome. Extra X chromosome can come paternally or maternally. In 67% of studies, both X chromosomes have been reported to come maternally. Maternal and paternal ages are high. Even if extra X chromosome originates either maternally or paternally, clinic of patients does not change[5]. Extra X chromosome occurs with nondisjunction in the paternal meiosis Ⅰ by a possibility over 50%, in the maternal meiosis Ⅰ or Ⅱ by a possibility of 40%; the rest ensues postzygotically[8]. A male prototype with Klinefelter syndrome is usually characterized by a long height, narrow shoulder, wide hip, rare body hiring, gynecomastia, small penis, androgen failure, azoospermia, and decreased verbal intelligence. A little part of them is diagnosed before puberty[55]. Variably spermatogenic disorders are present in these patients, but men are generally sterile unless karyotype is not mosaic. Even in non-mosaic cases, germ cells which function and have 46 XY karyotype have been encountered; this is because patients are gonadal mosaic. Therefore, reproductive men with Klinefelter syndrome are predisposed to have an aneuploidic child[8]. Men with Klinefelter syndrome are under more risk in terms of breast cancer and osteoporosis. Therefore, diagnosing the syndrome is not important only for reproductive health, but also for long term general health of patient[56]. In treatment of patients with Klinefelter syndrome, androgen replacement must be done for cases where especially puberty is delayed or not seen and for patients whose testosterone levels are under normalcy according their ages[5].

47, XYY syndrome: It is seen by 0.1%-0.4% in newborns. They have no other phenotypic characteristic except their typical long height. They have aggressive and antisocial characteristic by 1%-2%. Even if spermatogenic evaluation varies between normalcy and azoospermia, they are generally fertile. The results varying from various maturation arrest forms to complete germinal aplasia are obtained from testicular biopsies of those who are infertile. Though LH and testosterone levels are normal in a bulk of patients, FSH level is detected as normal or high similar with germ cell injury[5]. Through Y chromosome non-disjunction in the paternal meiosis Ⅱ, 47 XYY syndrome is considered to occur. This syndrome causes hormonal imbalance, affecting human chorionic gonadotropin function. Fertility may occur as a result of gonadal mosaicism. Marker chromosome carriers are under high infertility risk due to meiotic arrest and instability[7].

Mixed gonadal dysgenesis: Phenotypically, mixed gonadal dysgenetic patients can be male, female, or ambiguous genitalia. Sex is identified according to the appearance of sexual organs at birth. There is normal karyotype in approximately 33% of these patients. This situation is suggestive of that there are disorders also apart from sex chromosome aneuploidy. There is normal Leydig cell population if a unilateral testis is in scrotum; however, no germ cells are present in seminiferous tubules. If testis is intraabdominal, there is a tendency to malignancies belonging to male and female[16].

Structural chromosome abnormalities: Inversions (paracentric or pericentric), balanced translocations (Robertsonian/reciprocal, autosomal/gonosomal) and Y chromosome deletions are among structural abnormalities that cause male infertility[7,10].

Robertsonian and reciprocal translocations: Chromosomal translocations are also a type of aneuploidy[18]. Genetic material at the break points of genes can be lost because of translocations (1). Autosomal translocations are 4-10 times more frequent in infertile males when compared with normal males. In infertile males, the prevalence of Robertsonian translocations is only 0.8%, but in general population it is nearly 9 times lower than in the infertile males[45].

Robertsonian translocations are generally seen in 1.6% and 0.09% of oligozoospermic and azoospermic men, respectively[45]. Those who carry Robertsonian translocations can have a normal phenotype but they could be infertile due to an absence of gamete production (2) (1). Fluorescent *in situ* hybridization, with probes added for prevalent translocations, is proposed to detect the chromosomal composition of the sperm[57]. As patients with translocation between Y chromosome and autosomal chromosomes transmit azoospermia into their male children,

they can also cause male gamete deformities or idiopathic sterility[58]. Reciprocal translocations can cause diminished fertility, spontaneous abortions, and birth defects according to the site of translocation. Inter-chromosome translocations can cause meiotic mistake and cell death. Severe spermatogenic arrest and azoospermia can be seen in men with reciprocal X-autosomal translocation[8]. Reciprocal Y-autosomal translocations cause abnormal spermatogenesis because of abnormal sex chromosome matching. The most common reciprocal translocation in infertile men is the translocation between 13q and 14q [t(13q14q)]. Meiotic studies were performed in infertile men carrying t(13q14q) and t(14q21q) and these studies showed that rearranged autosomes can lead to infertility during spermatogenesis in meiosis. Nucleolar organizer regions (NOR) are found on the short heterochromatic arms of acrocentric chromosomes. These regions are needed in RNA synthesis. Therefore, Robertsonian translocations which lost their NORs cause cell disturbance, germ cell death, and decrease in fertility[7]. Translocations seen in infertile men are mostly reciprocal and such translocations are seen mostly in oligospermic men (1.7%) more frequent than azoospermic men (0.6%)[59].

Autosomal inversions: The site of polymorphic chromosomal alternatives in infertile men should be specified. The relationship between a great number of normal variant and undermined spermatogenesis is not certain yet. The incidence of polymorphic chromosomal variants in infertile men spread over a quite wide area (3.46%-35.7%). The most frequently occurring heterochromatic version is the pericentric inversion of chromosome with number 9 by a frequency of 1%-1.65% in normal population and 1.17%-5% in infertile men [inv(9)(p11q13)][59]. These inversions are related to azoospermia and severe oligoastenoteratospermia. Accordingly, translocations and inversions transmit into child at a higher rate than normalcy as hereditary in pregnancies *via* ICSI or IVF[16]. Y chromosome heterochromatin region corresponds to the distal Yq12. This region is genetically inactive and its length varies in normal population[60]. Raised length of the heterochromatin region of the long arm of Y chromosome has been declared by 7.14% and 1.4% in infertile men in normal population, respectively. Polymorphisms of Y chromosome are considered to be one of the reasons affecting spermatogenesis[61,62].

46, XX male syndrome: It is encountered in 20000 live births. Generally, phenotypic appearance, sexual and psychosocial identities are in favor of male; however, semen analyses indicate azoospermia. Even if most cases are sporadic, autosomal recessive inheritance has been also reported. In 10% cases, phenotypically ambiguous genital and hypospadias can be encountered. In 33% of cases, gynecomastia and tubular hyalinization in testis biopsy, tubular fibrosis and pseudoadenomatous conglomeration in Leydig cells are detected. While FSH is found high as secondary to spermatogenesis disorder, testosterone level is low or at the bottom level of normalcy. Despite XX genotype as a result of translocation of *SRY* gene between Xp and Yp tips during paternal meiosis, primitive gonad differentiates in favor of testis. Translocation of the distal Yp tip carrying *SRY* gene to any autosome can also cause a similar phenotype. Another alternative is, with a mutation in *SRVX* gene, removal of inhibition of this gene on another gene with autosomal localization. In conclusion, *AZF* gene is lack in patients and azoospermia is in question[5].

Gene mutations and polymorphisms

As patients with obstructive azoospermia may carry cystic fibrosis mutation, in patients with severe oligospermia or non-obstructive azoospermia, microdeletion may be present in the long arm of Y chromosome[63]. It is known that specific gene mutations affect testicular formation, internal and external genitalia development, and spermatogenesis negatively. Syndromes affecting genitourinary tract may also affect ductal function and/or ejaculation. A great number of genetic reasons causing male infertility are defined in humans[45].

X-linked genes: There are numerous X-linked genes represented in the testis and it is considered that they take role in gametogenesis (1). The androgen receptor (*AR*) gene is localised on Xq (the long arm of the X chromosome)[48,64]. In meiosis, its act is the conversion of spermatocytes, so it can round spermatids during spermatogenesis[65]. In a current study, it has been detected that while mutations are present in *AR* gene of approximately 2% of infertile men, the controls had none[45] (1). The *AR* gene mutations can also cause (1) androgen insensitivity syndrome. The *AR* gene has also two polymorphisms. These polymorphisms are important in the studies for their part in male factor infertility. The CAG and GGC polymorphisms are established on exon 1. They code for polyglutamine and polyglycine stretches, respectively[51]. The CAG polymorphism has been investigated more extensively than the GGC polymorphism. It has been determined that longer lengths of the CAG polymorphisms are related with diminished transcriptional activity of the AR gene in infertile men, so this means that longer polyglutamine tracts are concerned with male factor infertility[51]. In some studies, it has been observed that shorter CAG polymorphisms can be in relationship with higher quality sperm and altered levels of spermatogenesis[66]. Both of these polymorphisms may be affected by ethnical impacts, because studies in Europe couldn't find a relationship between the CAG polymorphism and infertility, but studies in men from Asia, Singapore and Australia detected a relationship between infertility and these polymorphisms[67,68].

USP26 is another gene that is found on the long arm of the X chromosome. It is expressed in the

early stages of spermatogenesis[69]. It takes part in histone disposal during spermatogenesis and also the corruption and rebuilding of proteins[45]. It has been found that there is an intercourse between the gene and infertility[70].

The *TAF7L* gene has also been studied to find if it is a probable participant to infertility in men. The *TAF7L* gene is expressed in the testis and related with the autosomal *TAF7* gene which is a transcription factor[45]. As transcription factor regulators control the spatial and temporal aspects, they are important in spermatogenesis[71] (1). Kallmann syndrome (KS), another genetic disorder, is inherited as both X-linked and autosomal that can also lead to infertility in males. It is also called as idiopathic hypogonadotropic hypogonadism and is combined with anosmia or hyposmia. A defect in the migration of the GnRH neurons causes this disorder[72] (1). It is characterized with low levels of sex steroids and low to normal levels of FSH and LH[73].

Epigenetic errors

There are some epigenetic regulatory mechanisms that are necessary for normal embryogenesis. These are: (1) functional role of centrosome; (2) DNA methylation; (3) histone modifications; (4) chromatin remodeling; and (5) RNA transcripts and telomere length.

The best example of the sperm epigenetic contribution to the embryo is methylation. Because if paternal methylation is abnormal, the human embryos cannot develop. DNA methylation, also called as "imprinting", is important in the choice of which genes, from parental or maternal genomes will be expressed in the embryo[50].

In epigenetics, there are some clinical methods such as direct methods (*i.e.,* single-cell gel electrophoresis) or indirect methods (*i.e.,* sperm chromatin integrity assays). All of these methods are used to detect the quality of sperm DNA. But, existing data haven't verified any correlation between DNA unity and pregnancy outcomes in ART and natural conception. So, no evidence is present for functional role of DNA integrity testing as a previsor of fertility[74] (1).

Genotype/phenotype correlation: As there is no deletion in the majority of normospermic men, Y microdeletions have been reported to be specific for spermatogenic disorder[37]. Although fertility is concordant with Y deletions, it reveals the fact that proper fertilization can carry out even in the less number of sperm, depending on fertility status of female partner. Therefore, considering Y deletions as the reason for oligo/azoospermia rather than infertility will be more appropriate. Deletion of the entire AZFa region results in complete SCOS and azoospermia. Deletion of isolated genes in the AZFa region such as USP9Y or DBY is associated with a variable testicular phenotype. Such deletions have been defined sporadically only to date. AZFb and AZFb+c complete deletions (P5/proximal P1, P5/distal P1, P4/distal P1) are descriptive of spermatogenic arrest or SCOS resulted in azoospermia. In patients with AZFa region complete deletion, no any sperm has been encountered in the procedure of testicular sperm extraction (TESE). As in AZFa deletion complete deletion, the diagnosis of AZFb or AZFb+c complete deletions is incompatible with correction of the number of sperm, and ICSI should not be suggested for these patients[31]. AZFc region deletions are in relationship with a variable clinic and histological phenotype[31,41,75]. Generally, AZFc deletions are appropriate with residual spermatogenesis. AZFc deletions can be available in azoospermic or vigorous oligospermic men and rarely transmit into male offspring. The possibility to obtain sperm with TESE is high in men with azoospermia and AZFc deletion; so they can have a child with ICSI. Male children of these patients will be those with AZFc deletion[31]. Phenotypes related to deletions are variable, and generally there is no connection between clinic phenotype and localization of deletion[11].

Treatment in male infertility

Intracytoplasmic sperm injection: ICSI has been propounded by Palermo *et al*[76] for the first time in 1992 and achieved a new breakthrough in treatment of serious infertility with male factor. But the ICSI pregnancy rates obtained from IVF centers around the world is lower (30%-50%)[76,77]. With definition of ICSI, although there is oligospermia or azoospermia, men with Y chromosome microdeletion have a possibility to have a child, using spermatozoa obtained surgically or from ejaculate. When diagnosed with Y chromosome microdeletion, couples should be informed about reproductive methods. The majority (79%) of infertile partners with Y chromosome microdeletion choose ICSI in terms of fertility problem. But, when ICSI is used, if child becomes a male, he will likely experience the same microdeletion and fertility problems[11,26,38]. While the success rate in infertile couples treated with ICSI is 76%, this ratio is 15% in those who receive standard IVF therapy, for example intrauterine insemination[78]. Due to the development of assisted reproductive techniques (ART), clinicians are in need of understanding how genetics is crucial in male factor infertility cases (1) because new technologies, such as ICSI, permit the men with suboptimal sperm quality to cope with natural selection mechanisms and produce a viable zygote[51]. As ART, such as *in vitro* fertilization (IVF) and ICSI, includes relatively new procedures, the frequency of the inheritance of mutations *via* these procedures and their impact on future generations are not yet exactly comprehended[57] (1) As a result, it is esential to identify the underlying genetic structure of male infertility to develop appropriate screens for abnormal phenotypes and to discover more effective

solutions for infertile couples' problems[54] (1).

CONCLUSION

Numerous genes are responsible for male fertility, including spermatogenesis and sperm function. Because men who have undigested infertility can hold genetic abnormalities that may accommodate their reproductive potential, further researches are needed to determine such cases (2).

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