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MALE INFERTILITY- ROLE OF GENETICS AND EPIGENETICS- A NARRATIVE REVIEW

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ABSTRACT

Male infertility is a complex condition with a strong genetic and epigenetic background. This review discusses the importance of genetic and epigenetic factors in the pathophysiology of male infertility. The interplay between thousands of genes, the epigenetic control of gene expression, and environmental and lifestyle factors, which influence genetic and epigenetic variants, determines the resulting male infertility phenotype. Currently, Y-chromosome microdeletion screening, AZF gene mutation tests, SRY gene mutation tests and AR (Androgen receptor) gene mutation tests along with their procedures are reviewed and demonstrated genetic etiological correlation in the pathogenies of azoospermia and severe oligozoospermia the root cause of Male Infertility. The rate of infertility in less industrialized nations is markedly higher than in infectious diseases and is responsible for a greater proportion of infertility. According to the latest data, globally, 15 % of couples have Infertility problems of which alone 40% account for male infertility and out of about 40% causes are idiopathic. Male infertility contributes to 10 % of all cases and is caused due to genetic factors. Regardless of whether it is primary or secondary infertility, the affected couples suffer from enormous emotional and psychological trauma and it can constitute a major life crisis in a social context. Infertility can be caused due to certain biological changes in gonads and the reproductive system like azoospermia, oligospermia, asthenospermia, teratozoospermia, and hypospermatogenesis. Genetic causes of azoospermia include Y-chromosome microdeletions, and deletion or other mutations of Y-linked genes. Many Y-linked genes regulate spermatogenesis. The maximum number of the genesis is located in the AZF region of the long arm of the Y chromosome. Y chromosome microdeletion is known as the second major genetic cause of

spermatogenetic failure. This article aims to Systematic review the latest updates on the involvement of Y-chromosome microdeletion, AZF gene mutation, SRY gene mutation and AR (androgen receptor) gene mutation in the etiopathogenesis of male infertility for outcomes for our patients following Prisma guidelines.

Keywords: Azoospermia factor, AZF mutation, cytogenetic, male infertility, Y chromosome microdeletion, SRY gene mutation

Introduction- Male fertility is regulated by several genes responsible for spermatogenesis and those genes are required for DNA recombination, repair, and replication. The maintenance of genomic integrity has vital importance for germ cells[1]Using the advanced approaches of genomics, and proteomics and applying the advanced gene expression techniques as microarray would help to interpret the causative mechanisms for Infertility[2] This would not only minimize the risks associated with ART but will also provide an insight into the unexplored aspects of Infertility. Thus, not only understanding the role of fertility-related genes is needed but also a deeper insight into the functions of promoters, regulators, and micro-RNA is required[3]Although much has been explored to understand the interactive mechanisms associated with fertility, still there are lacunae in our knowledge that need to be filled so that the confirmative diagnosis can be possible in all the cases and treatment of Infertility becomes better and a non-empirical approach can be adopted in idiopathic cases. This manuscript would also help the ART clinicians, in aiding their patients to produce healthy fertile offspring through genetic workouts.
Males and females differ genetically by their respective sex chromosome composition, that is, XY is male and XX is female [4] Although both X and Y chromosomes evolved from the same ancestor pair of autosomes, the Y chromosome harbours male-specific genes, which play pivotal roles in male sex determination, germ cell differentiation, and masculinisation of various tissues.

1. Definition

Infertility can be defined as the inability to conceive after one year of unprotected intercourse. This problem affects approximately 10% to 15% of married couples globally and male infertility accounts for 50% of the cases[5].
Genetic factors contribute up to 15%–30% of cases of Male Infertility. The formation of spermatozoa occurs sequentially with mitotic, meiotic, and postmeiotic differentiation phases, each of which is controlled by an intricate genetic program. Genes control a variety of physiologic processes, such as the hypothalamus–pituitary-gonadal axis, germ cell development, and differentiation. In the era of assisted reproduction technology, it is important to understand the genetic basis of infertility to provide maximum adapted therapeutics and counselling to the couple[6]

2. Role of genetics and epigenetics in Male Infertility

Numerous candidate genes have been identified as responsible for the pathogenesis of male infertility, the consequences and their correlation along with a role in diagnosis are discussed as follows-

2.1. Role of Y Chromosome

Y chromosome is one of the smallest human chromosomes (60 Mb) and is highly polymorphic in length. It is male-specific and the only haploid component of the human genome. Till now 156 transcription units, 78 protein-coding genes, and 27 distinct proteins (9 on Yp and 18 on Yq) encoded by the Y chromosome have been identified[7]
The Y chromosome is divided into 7 deletion intervals. The region critical for spermatogenesis is on intervals 5 and 6. The length of euchromatic DNA sequences on the Y is about 23 Mb, including 8 Mb on the short arm and 14.5 Mb on the long arm. There are 3 classes of euchromatic sequences those transposed from the X chromosome during the process of the evolution of the Y

(X-transposed), those similar to sequence information from the X chromosome (X-degenerate), and those repeated units across the proximal short arm of the Yp and most of the Yq (amplicons). Within the X transposed segments, only 2 protein-encoding genes have been identified (TGIF2LY and PCDH11Y)[8]

The X-degenerate regions, with a combined length of 8.5 Mb, are dotted with single-copy genes or pseudogenes that are mostly expressed ubiquitously (ie, expressed in multiple organs in the body and not confined to a specific tissue). The sex-determining gene (SRY) is located in this region. The SRY gene expresses a transcription factor that switches on the genes for male sexual differentiation.[9] The genes in the AZFa (DBY and USP9Y) are located in the X-degenerate region. The most complex regions of the Y chromosome are the unique ampliconic regions in the euchromatin that are 10.5 Mb in length.[10] Amplicons are families of units composed of nucleotide sequences that are similar to each other. They are located in 7 segments that are scattered across the euchromatin on Yp and Yq. The amplicons harbour the highest density of the Y chromosome genes that are exclusively expressed in the testes and enhance sexual fitness. Genes related to the AZFb and AZFc are located in the ampliconic regions. The array of the amplicons forms 8 palindromes (P1–P8). [11] A palindrome is a DNA sequence containing different amplicons, which has a twin along the chromosome that read the same in a reverse direction. Most of the recognized genes that are deleted in infertile men are located in the palindromic regions of the Yq. [12]

Microdeletions on the long arm of the Y chromosome (Yq) is one of the most significant pathogenic defects associated with male infertility. Tiepolo and Zuffardihypothesized a correlation between Y chromosome deletions and male infertility.[12] [13]

2.2. Testing for Y microdeletions

Recent biomedical research showed that the testing for microdeletions is now widespread in IVF/ICSI units, but there is no standardised methodology and, therefore, it is difficult to make a direct comparison between reported results. Several centres have developed screening methodologies[14,15,16]. As there is no correlation between histopathology and deletion of DAZ, it is premature to rely on specific gene probes as these will fail to detect a significant proportion of men with microdeletions[17]. Also testing using peripheral blood may not be reliable. Lack of DAZ mRNA in testicular cells has been reported in a man with apparently normal DAZ gene constitution on DNA extraction from leukocytes[18,19]. These findings may be explained by unrecognized very small deletions encompassing active copies of DAZ, mosaicism, or abnormalities of DAZ transcription.

2.3. Clinical implications of Y microdeletions

There are no reports that men with microdeletions have any phenotypic abnormalities other than abnormal spermatogenesis and men with microdeletions appear to be in perfect health m every other respect[20]As there is only one Y chromosome, we may predict that Y microdeletions will be transmitted to their sons although this is likely to be rare in the normal population.[21] More information is needed from the father/son pair where the son has a very low sperm count and also about the outcome of ICSI attempts where sperm have been used from men with microdeletions. There is a need for long-term follow-up of any male children. However, although it may be desirable to obtain information about the genetic status of ICSI babies, there are ethical questions about whether young babies should be tested and, if so, whether the test results should be identifiable.

2.4.Y genes and male infertility

In 1992, we reported three men with severe damage to spermatogenesis and normal chromosome analysis, but where molecular probes revealed microdeletions on the long arm of the Y chromosome [22,23] Recent investigations have suggested stimulation to probe the long arm of the Y chromosome because of men with azoospermia and deletions of the long arm of the Y chromosome transecting interval 6 with the loss of all distal genetic material and an infertile man

with a short arm dicentric Y, there have been a large number of publications of case series and it is clear that, while microdeletions may occur in the fertile population they are more prevalent in the infertile populations. It has been reported that the microdeletion detected might be large, but there are preliminary reports of much smaller deletions within genes[24]. Microdeletions have been found in three non-overlapping regions of the Y chromosome AZF a-b-c[25]. Several genes have been described and these include RBM, DAZ, DFFRY40, DBY and CDY[26]. The abnormality most commonly reported in the literature is a microdeletion in the AZFc region encompassing the DAZ gene. However, there is no exact correlation between DAZ deletion and the presence or absence of spermatogenesis, but this may be because for the DAZ gene there is also an autosomal copy.

3. Azoospermia

Azoospermia, defined by the absence of sperm in the ejaculate, is estimated to act up to 1% of men in the general population. Assisted reproductive technologies have revolutionized the treatment of infertility, and some azoospermic men, those with a post-meiotic defect, can conceive following the use of viable spermatozoa recovered from testicular or epididymal biopsies. Although male infertility is a multifactorial disease, it is believed that genetic factors are predominant in the aetiology of azoospermia and severe oligozoospermia[27]. Despite that assumption, substantiated by the high number of infertile knockout (KO) mice and the even higher number of genes expressed essentially in the testis, little is known about the pathophysiology of reduced sperm production, its primary causes or the genetic and epigenetic consequences for the gamete and the future concepts[28]. The identification of genetic abnormalities is therefore paramount to understand spermatogenesis, adopting the best course of action for the patient and providing adequate genetic counselling. The author tried to review the recent literature on the genetics of azoospermia and oligozoospermia, focusing on defects directly altering sperm production. New sequencing technologies are contributing to the rapid evolution of recently of infertility genetics.

Azoospermia is defined as the absence of sperm in at least two different ejaculates[29]. Contrary to most other sperm defects which can be treated by assisted reproductive technologies (ART) using in vitro fertilization, often in combination with intracytoplasmic sperm injection (ICSI), highlighting the importance of focusing on this condition. When spermatogenesis is not completely abolished, ICSI can, however, be envisaged following testicular or epididymal biopsy. As a whole, azoospermia can nevertheless be placed among the most severe cases of male infertility and scientists believe that the study and elucidation of its molecular pathophysiologies are paramount to improving patient care and treatment. The Indian ancient system of medicine i.e.Ayurveda also described various herbal formulations which are scientifically proven to provide better outcomes on Azoospermia[30] and other sperm dysfunctions[31]

The aetiology of azoospermia[32] can be broadly divided into three main categories: pre-testicular, testicular, and post-testicular. (i) Pre-testicular azoospermia can be caused by endocrine abnormalities mainly characterized by low levels of sex steroids and abnormal gonadotropin levels. These abnormalities can be congenital (e.g.Kallmann syndrome), acquired (e.g. hypothalamic or pituitary disorders) or secondary (mostly due to environmental factors such as endocrine disruptors or iatrogenic actions). (ii) Post-testicular causes include ejaculatory disorders or obstructions, which impair the transport of spermatozoa from the testis. These obstructions can be caused by a congenital bilateral absence of the vas deferens (CBAVD), or acquired following surgery (vasectomy), cancer, injury or infections. (iii) Testicular causes of azoospermia, which are discussed in most detail here, can also be congenital, acquired or idiopathic. Similar to obstructive causes of azoospermia, testicular causes include trauma, torsion, infections (e.g. mumps and orchitis), testicular tumours, iatrogenic effects, irradiation, surgery (compromising vascularization of testis), systemic diseases (cirrhosis and renal failure) or varicocele 2. Testicular causes include genetic abnormalities (Y-chromosome deletions), germ cell aplasia (Sertoli cell-only syndrome, SCOS) or spermatogenesis arrest. The typical phenotype of testicular failure results in azoospermia or severe oligozoospermia (SO) (sperm density $\leq 5 \times 10$ /ml). Surprisingly, despite the abundance of

genes known to be necessary for spermatogenesis [but identified only in animal models 3], Y-microdeletions and chromosomal abnormalities such as Klinefelter (47, XXY) have long remained the only known recurrent genetic cause of non-obstructive azoospermia (NOA) and SO[33]. Nevertheless, most testicular defects are believed to have a genetic basis. At present, however, even after a complete diagnostic work-up, the aetiology of primary testicular failure remains unknown in more than half of the cases

Genetic factors play well-recognized roles in male infertility, and genetic alterations of the Y chromosome are especially important [34]. The major genetic factors in male infertility are chromosomal abnormalities and Y chromosomal microdeletions (YCMs) [35]. YCMsoccur in approximately 10 to 15% of azoospermic patients and 5 to 10% of severe oligospermia patients and are commonly found at the azoospermia factor (AZF) locus in the q11.23 band.

Detailed molecular analyses further subdivide the AZF locus into three (possibly four) subregions: AZFa, AZFb and AZFc[36], along with a fourth possible AZFd region [37]. Microdeletions in these regions result in different degrees of spermatogenetic failure; however, AZF gene function and the exact genotype-phenotype relationship of microdeletions and infertility in the AZF locus have not been fully explored. Sequence-tagged site polymerase chain reaction (STS-PCR) is recognized as the gold-standard method for laboratory AZF microdeletion diagnosis [38], however, multi-analyte suspension array (MASA) technology also provides a rapid, sensitive and high-throughput method for detecting Y chromosome microdeletions [39].

The rapid development of assisted reproductive technologies (ART) such as in-vitro fertilization, intracytoplasmic sperm injection (ICSI) and testicular sperm extraction (TESE) make reproduction possible for millions of infertile couples; however, these techniques elevate the risk of transmitting genetic defects, including the vertical transmission of AZF microdeletions and the related infertility problems to their sons [40]. Thus, routine screening for AZF microdeletions before undergoing ART treatment is a critical diagnostic test. In this review, we will systematically update the progress that has been made in AZF region identification, describe novel approaches for AZF microdeletion screening and summarize the current understanding of associated gene functions, AZF microdeletion types and AZF microdeletion phenotypes.

4. mRNA and Infertility

RNA profiling of fertile and infertile men has shown dynamic cellular variation and thus has proved to be a biomarker for male infertility. Round spermatids contain numerous varieties of transcripts that are produced either throughout early spermatogenesis or during spermiogenesis from the haploid genome coding for sperm-specific proteins. The transcripts are stored in the spermatid cytoplasm before the related proteins are expressed.[40] In mid-spermiogenesis, chromatin remodelling leads to the transcriptional inactivation of the genome.[41] Thus the highly condensed sperm nucleus is transcriptionally inert and contains diverse RNA populations, mRNA, antisense, and miRNAs that have been transcribed before inactivation.[42] The presence of transcripts in human spermatozoa has been established using reverse transcription-polymerase chain reaction (PCR) and real-time PCR.

5. Role of AZF Gene

Spermatogenesis is an essential reproductive process that is regulated by many Y chromosome-specific genes. Most of these genes are located in a specific region known as the azoospermia factor region (AZF) in the long arm of the human Y chromosome. AZF microdeletions are recognized as the most frequent structural chromosomal abnormalities and are the major cause of male infertility. Assisted reproductive techniques (ART) such as intra-cytoplasmic sperm injection (ICSI) and testicular sperm extraction (TESE) can overcome natural fertilization barriers and help a proportion of infertile couples produce children; however, these techniques increase the transmission risk of genetic defects. AZF microdeletions and their associated phenotypes in infertile males have been extensively studied, and different AZF microdeletion types have been identified by sequence-tagged site polymerase chain reaction (STS-PCR), suspension array technology (SAT) and

arraycomparative genomic hybridization (aCGH); however, each of these approaches has limitations that need to be overcome. Even though the transmission of AZF microdeletions has been reported worldwide, arguments correlating ART and the incidence of AZF microdeletions and explaining the occurrence of de novo deletions and expansion have not been resolved. Usingthe newest findings in the field, this review presents a systematic update concerning progress in understanding the functions of AZF regions and their associated genes, AZF microdeletions and their phenotypes and novel approaches for screening AZF microdeletions. Moreover, the transmission characteristics of AZF microdeletions and the future direction of research in the field will be specifically discussed. Deletions or translocation of the sex-determining gene, SRY, from the Y chromosome causes disorders of sex development (previously termed as an intersex condition) with dysgenic gonads. Failure of gonadal development results not only in infertility but also in increased risks of germ cell tumour (GCT), such as gonadoblastoma and various types of testicular GCT. [42][43]

5.1. The AZFa region

The AZFa spans around 400-600 kb of DNA and is located in the proximal portion of deletion interval 5. AZFa region harbours 2 protein-encoding genes, namely, USP9Y and DBY (recently termed DDX3Y). Deletions of AZFa loci are characterized by Sertoli-cell-only syndrome, type I.[44]

5.2. The AZFb region

The AZFb spans around 1–3 Mb of DNA and is located on the distal portion of deletion interval 5 to the proximal end of deletion interval 6 (subinterval 5O–6B). Protein-encoding genes in AZFb region are EIF1AY, RPS4Y2, and SMCY that are located in X-degenerate euchromatin, and HSFY, XKRY, PRY, and RBMY that are in the ampliconic region.[44]

5.3. The AZFc region

AZFc spans 3.5 Mb of euchromatin and is located at the distal part of deletion interval 6 (subinterval 6C-6E) on the Y chromosome. Deletions of the AZFc region are most common in men with idiopathic oligozoospermia or azoospermia. The AZFc region contains 8 gene families that are involved in spermatogenesis—BPY2, CDY, DAZ, CSPG4LY, GOLGAZLY, TTY3.1, TTY4.1, and TTY7[45]

5.4. Prevalence of AZF microdeletion transmission

AZF microdeletions are inherited through the paternal germline or occur as de novo events. It has been reported by many studies that more than 80% of AZF microdeletions are of de novo origin [45]. Most deletions occur during the pre-fertilization stage, while some deletions are post-fertilization events. If a sperm with YCMs fertilizes an egg, it will transmit the YCMs to the male child. On the other hand, if the deletion occurs as a post-fertilization event, it may cause mosaicism characterized by normal Y chromosomes in leukocytes and Y chromosomes with the post-fertilization deletion in sperm or testicular DNA [46]. Since infertility is the major phenotype of men with AZF microdeletions, the natural transmission of AZF microdeletions has rarely been reported. Dai et al. reported that YCMs in 7 of 10 infertile men were naturally transmitted from father to son. Samli et al. Also observed the natural transmission of an AZFb microdeletion from a father to each of his three sons [47]. In contrast, vertical transmission of AZF microdeletions from father to son through ICSI has been widely reported. Old researches described the sons produced by a population of 32 couples with infertile fathers who received reproductive assistance via ICSI and also found that the incidence of microdeletions in the ICSI population was about 9.4%, which was close to the incidence of AZF microdeletions in infertile men. ART has been associated with elevated incidences of sexual chromosomal aberrations, de novo chromosomal abnormalities and sperm aneuploidy. Thus, one of the major concerns regarding ART is whether ART cause AZF microdeletions. A new study by Liu et al. compared the YCM occurrence in 19 candidate genes

from 199 fathers and their 228 sons (Chinese, Han ethnicity) that were conceived by IVF (85 sons), ICSI (73 sons) or natural conception (70 sons). They observed that the YCM incidences of the fathers for IVF, ICSI and naturally conceived sons was 10.7%, 3.2% and 8.2%, respectively [48]. They identified one de novo YCM among the 70 naturally conceived offspring but none among the 158 ART conceived offspring. There were no statistically significant differences in incidence among the three groups or of de novo YCMs between the naturally conceived and ART conceived sons. Therefore, they finally concluded that ART does not significantly increase the risk of YCM in male offspring. However, this conclusion remains controversial; the correlation between the incidence of AZF microdeletions and ART needs to be verified in a large, ethnically and geographically diverse cohort of infertile men and their offspring.

5.5. Expansion of AZF microdeletions in the offspring

A significant amount of research in recent years has focused on investigating the genetic changes in offspring conceived by ICSI. Some studies have reported that ICSI can only vertically transmit YCMs without the expansion of de novo occurrence of YCMs. Rolf et al. reported a case of what was probably an identical, partial deletion of the distal part of the AZFb region over three generations [49].

A study by Minor et al. also identified an identical and partial AZFc gr/gr deletion that was vertically transmitted over three generations via fathers receiving reproductive assistance through ICSI. However, a growing number of studies have reported that YCM can be transmitted vertically from father to son via ICSI and that ICSI can contribute to YCM expansions as well as de novo YCM. Dai et al. examined the expansion of AZF deletions in 10 father-son pairs and found expansion microdeletions (S1/F1, S2/F2, S6/F6, S7/F7, S8/F8, S9/F9 and S10/F10) in seven father-son pairs and de novo microdeletions (S3/F3, S4/F4 and S5/F5) in the three remaining father-son pairs [50]. Samli et al. reported an unusual family in which an azoospermic patient (proband) and three brothers inherited a Yq microdeletion from their father through spontaneous pregnancy. The brothers and their father all carried a Yq microdeletion in the AZFbsubregion involving the RBM1 loci. Additionally, an uncle carried a different deletion in the AZFc region (sY1539). The proband and one of his brothers shared an identical deletion with their father, plus additional de novo deletions in the AZFa and AZFbsubregions.

Although Liu et al. claimed that ART is not associated with the expansion or occurrence of de novo microdeletions, a significant number of studies have demonstrated that AZF microdeletions are capable of transmitting themselves and expanding over the generations through natural pregnancy or ART [48,49,50].

6. Role of SRY Gene

Testis-determining factor (TDF), also known as sex-determining region Y (SRY) protein, is a DNA-binding protein (also known as gene-regulatory protein/transcription factor) encoded by the SRY gene that is responsible for the initiation of male sex determination in therian mammals (placental mammals and marsupials) SRY is an intronless sex-determining gene on the Y chromosome. Mutations in this gene lead to a range of disorders of sex development (DSD) with varying effects on an individual's phenotype and genotype[51].

TDF is a member of the SOX (SRY-like box) gene family of DNA-binding proteins. When complex with the SF-1 protein, TDF acts as a transcription factor that causes up-regulation of other transcription factors, most importantly SOX9 Its expression causes the development of primary sex cords, which later develop into seminiferous tubules. These cords form in the central part of the yet-undifferentiated gonad, turning it into a testis.[52]. The now-induced Leydig cells of the testis then start secreting testosterone, while the Sertoli cells produce anti-Müllerian hormone.SRY gene effects normally take place 6–8 weeks after fetus formation which inhibits the female anatomical structural growth in males. It also works towards developing the dominant male characteristics.[53] [54]

6.1. Regulation

SRY gene has little in common with sex determination genes of other model organisms, therefore, mice are the main model research organisms that can be utilized for its study. Understanding its regulation is further complicated because even between mammalian species, there is little protein sequence conservation. The only conserved group between mice and other mammals is the High-mobility group (HMG) box region that is responsible for DNA binding. Mutations in this region result in sex reversal, where the opposite sex is produced.[55]57]

Additionally, other sex-determining systems that rely on SRY/TDF beyond XY are the processes that come after SRY is present or absent in the development of an embryo. In a normal system, if SRY is present for XY, the TDF will activate the medulla to develop gonads into testes. Testosterone will then be produced and initiate the development of other male sexual characteristics. Comparably, if SRY is not present for XX, there will be a lack of the TDF based on no Y chromosome. The lack of TDF will allow the cortex of embryonic gonads to develop into ovaries, which will then produce estrogen, and lead to the development of other female sexual characteristics.

6.2. Role in other diseases

SRY has been shown to interact with the androgen receptor and individuals with XY karyotype and a functional SRY gene can have an outwardly female phenotype due to an underlying androgen insensitivity syndrome (AIS). Individuals with AIS are unable to respond to androgens properly due to a defect in their androgen receptor gene, and affected individuals can have complete or partial AIS. SRY has also been linked to the fact that males are more likely than females to develop dopamine-related diseases such as schizophrenia and Parkinson's disease. SRY encodes a protein that controls the concentration of dopamine, the neurotransmitter that carries signals from the brain that control movement and coordination. [58][59].

7. AR (androgen receptor) Gene

It has been demonstrated that mutations and polymorphisms of the androgen receptor (AR) gene and its expressed protein are significantly associated with depressed spermatogenesis and `idiopathic' male infertility.

7.1. Molecular biology of the AR

Development of the male phenotype and the initiation of spermatogenesis leading to the production of the male gametes are intricately dependent on the cellular events that respond to androgens. The two most important physiological androgens are testosterone and 5a-dihydrotestosterone (DHT). The actions of androgens are mediated by AR. Despite the existence of two different forms of androgens, only one AR has been identified and cloned (Trapman et al., 1988). Testosterone is crucial for the survival of the Wolfian duct and its subsequent development and differentiation into the epididymis, ductus deferens and seminal vesicles. DHT, a metabolite of testosterone, is involved in the development of the penis and scrotum. At puberty, androgens drive the initiation of spermatogenesis and the growth of accessory sex organs, including the prostate. All these androgen-dependent developmental processes culminate in successful spermatogenesis; thus, perturbation to any of these steps can result in spermatogenic failure[60].

The AR is encoded by a single-copy gene in the X-chromosome. The AR gene consists of eight exons, and encodes an intracellular transcription factor that belongs to the steroid/nuclear receptor superfamily; members of which include receptors to estrogen, progesterone, adrenal hormones, thyroid hormones, retinoid acid and vitamin D. Consistent with other steroid receptors, the ARÐ when activated by androgens translocates to the nucleus and binds to specific chromosomal DNA sequences (androgen response elements) in the regulatory regions (promoters/enhancers) of AR-regulated genes. The binding of the androgen±AR complex activates or represses, the expression of androgen-regulated proteins. Furthermore, the androgen±AR complex operates in conjunction with co-regulatory proteins. The liganded AR forms pre-initiation complexes composed of a variety of

coactivator proteins on promoters, thereby turning on gene transcription and protein synthesis. The AR contains four main functional domains: the amino-terminal transactivation domain (TAD); the centrally positioned DNA-binding domain (DBD); the hinge region; and the carboxyl-terminal ligand-binding domain (LBD)[61]. Within the TAD are two segments consisting of repeats of the amino acids, glutamine (encoded by CAG) and glycine (encoded by GGN). These repeat tracts are polymorphic, in that their size varies among individuals in a normal population. While each domain has specific functions, intramolecular interactions between domains and intermolecular interactions with coactivator proteins have also become major themes in understanding the structure/function properties of AR and are critical for understanding the molecular basis of male infertility caused by AR malfunction. AR mutations that severely impair the amount, structure or function of the AR cause the well-known complete AIS (testicular feminizing syndrome), evidenced by the complete feminization of 46 XY individuals at birth. Mutations that do not completely disrupt AR function cause partial AIS (PAIS) in which various degrees of ambiguous genitalia occur, including partial labial-scrotal fusion, hypospadias, bid scrotum and gynecomastia. Most interestingly, subtle mutations that result in minimal AR dysfunction lead to minimal AIS where depressed spermatogenesis occurs without any abnormalities in secondary male sexual characteristics[62]

8. Male infertility and minimal androgen insensitivity syndrome (AIS)

Defects in sperm production are found in the male partner in up to 30% of all subfertilecouples[63] However, it should be appreciated that the genetic background in the expression of AR dysfunction and that not all patients with minimal AIS are necessarily infertile. Mmutations in the transactivation domain of AR. This is a paradox, as it would be expected that mutations in the TAD, which constitutes more than half of the receptor and harbours the strongest activation function domain, would be more commonly detected in AIS. One reason for this anomaly is that genetic examination of the TAD is difficult due to its large size and the presence of CG repeat tracts which are resistant to amplification by the polymerase chain reaction. In a large cohort study involving 180 males with variable impairment of spermatogenesis, genetic screening of the AR revealed the presence of a (CCG-TCG) in the TAD of two patients, resulting in the substitution of serine for proline at position 390[64]. Both patients had a decreased sperm count and a high percentage of abnormal sperm, but the in-vitro functional assessment of this AR mutation showed no gross alterations of transcriptional activity compared with wild-type AR. Despite the limited correlation between in-vitro and in-vivo function, a critical role for Pro390 in maintaining the functional integrity of AR is suggested by the observation that a Pro390Asp AR mutation is associated with complete AIS[65]. A 20% reduction in AR transactivation capacity was also observed for a glycine-to-arginine substitution at position 214 in the AR TAD region of an infertile male [66]. However, this mutation may not be critical for AR function since the same mutation was also observed in a fertile control.

9.**Conclusion -** Infertility is a prevalent condition that affects over 70 million people globally. Current diagnostic tools are not able to explore 100% confirmative causes and hence 40% remain cause is idiopathic. Therefore, the development of novel diagnostic panels is essential to change the current landscape concerning prevention, diagnosis and management. Understanding the underlying genetic mechanisms related to the pathophysiology of male infertility, and the impact of environmental exposures and lifestyle factors on gene expression might aid clinicians in developing individualized treatment strategies. A variety of lifestyle choices and genetic issues have been implicated in the condition. While poor overall health contributes to infertility, it has also been demonstrated that infertility is associated with an increased risk of a variety of malignancies. Hence this manuscript reviewed and examined Y-chromosome microdeletion, AZF gene mutation, SRY gene mutation and AR (androgen receptor) gene mutation and its procedures in the pathogenies of Male Infertility. current efforts examining the molecular and genetic factors responsible for spermatogenesis and fertilization, we may be better able to understand genetic etiologies of male factor infertility and thus improve outcomes for our patients.

10. Conflict of interest – No

11.References –

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