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GENETICS AND MALE INFERTILITY

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ABSTRACT

Male are the sole cause of infertility in approximately 20% of infertile couples and are an important contributing factor in another 20-40% of couples with reproductive failure. Male infertility can result from a variety of causes. Some, like ductal obstruction and hypogonadotropic hypogonadism, can be accurately defined and effectively treated. Genetic abnormalities can cause infertility by interfering with sperm production or transport. Genetic conditions have implications that extend beyond their association with azoospermia and severe oligospermia because they may have consequences for the offspring of affected couples. In this article we have discussed various aspects of genetics and male infertility.

KEYWORDS: Hypogonadotropic hypogonadism, azoospermia, severe oligospermia.

INTRODUCTION

Infertility globally affects around 15% of couples with 15 -18 million being in added to this cohort every year in India alone[1]. The male contributes to 50% causes implying 8 to 9 million infertile males are there in India. The incidence and prevalence and of this disorders with varied etiologies (Fig 1) and diagnosis in the reproductive field is rising. In men, oligozoospermia, asthenozoospermia, teratozoospermia and azoospermia (OTA) are the main causes of infertility, and these account for 20%–25% of cases. Genetics contributes to infertility by influencing a variety of physiological processes including hormonal

homeostasis, spermatogenesis, and sperm quality. Therefore, an understanding of the genetic basis of reproductive failure is essential to appropriately manage an infertile couple.

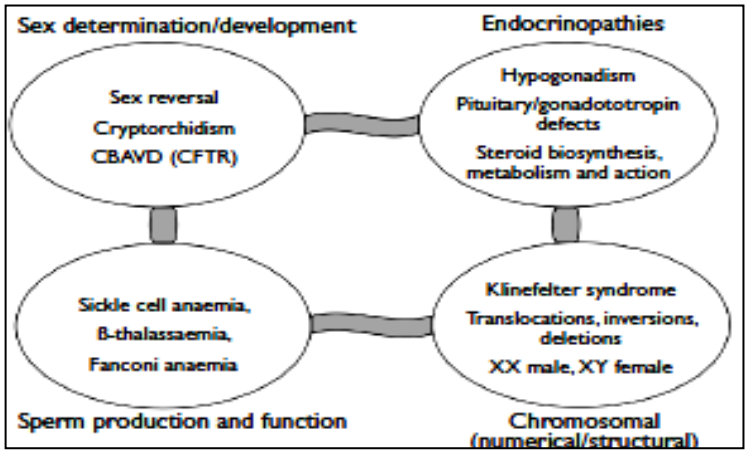

FIG 1: Aetiology of Male Infertility

Genetic or molecular causes of male infertility

Genetic abnormalities have been identified in men with OTA include numerical and structural chromosomal abnormalities.[2] Genetic factors involved in male infertility manifest as chromosomal disorders, mitochondrial DNA (mtDNA) mutations, monogenic disorders, multifactorial disorders and endocrine disorders of genetic origin.

Chromosomal Abnormalities

Chromosomal errors are a pertinent area of research to determine the role of genetics in male factor infertility. Aneuploidy is most common error resulting from chromosomal abnormalities in infertile men.[3] Men with nonobstructive azoospermia have a particularly high incidence of aneuploidy, especially in their sex chromosomes.[4,5] And occasionally they can successfully fertilize the oocyte and pass on an incorrect chromosome number to their offspring .[6] The most common chromosomal abnormality caused by aneuploidy is Klinefelter syndrome with prevalence of 5% in men with severe oligozoospermia and 10% in azoospermic men.[7] There are two forms of Klinefelter syndrome: nonmosaic, 47, XXY; and mosaic, 47, XXY/ 46, XY. Some of the nonmosaic Klinefelter syndrome patients have sperm in their ejaculate while those with mosaic disease may have residual spermatogenesis in their seminiferous tubules; but 74% of the men are azoospermic.[7] Klinefelter syndrome patients can produce offsprings with ICSI, and have risk of transferring the abnormality to offspring.[8] However, some studies have produced successful results with non-mosaic men and ICSI.[9] It is advised that preimplantation genetic diagnosis (PGD) be performed before ART to ensure that the offspring is not aneuploidy.[3]

Chromosomal translocations cause the loss of genetic material at the break points of genes, which can corrupt the genetic message are an additional source of aneuploidy.[10] Infertile males were found to be 4–10 times more likely to have autosomal translocations in in comparison with normal males.[11, 12] The most frequent structural chromosomal abnormalities in humans are Robertsonian translocations, which occur when two acrocentric chromosomes fuse, and they affect fertility in one out of 1000 men. In infertile males the prevalence of Robertsonian translocations is 0.8% which is 9 times higher than in the general population.[13]

Variety of sperm production phenotypes from normal spermatogenesis to an inability to produce spermatogonia are seen with translocations. Robertsonian translocations are more common in oligozoospermic and azoospermic men, with rates of 1.6% and 0.09%, respectively.[14 15] Carriers of Robertsonian translocations may exhibit a normal phenotype but could be infertile because of a lack of gamete production. Because of the risk of passing on the translocation to offspring, fluorescent in situ hybridization, with additional probes added for common translocations, is recommended to determine the chromosomal composition of the sperm.

The Y Chromosome

The Y chromosome contains many of the genes that are critical for spermatogenesis and the development of male gonads and is obvious area of interest male factor infertility.

The Y chromosome is one of the smallest human chromosomes and consists of a short (Yp) and a long (Yq) arm. The Y chromosome is male-specific, 60 megabases (Mb) in size, consisting of 60 million nucleotides, but has the least number of genes compared to any other chromosome. Of the 27 Y chromosome genes identified, nine are located on the Yp and the remaining 18 on the Yq. The male specific region of the Y (MSY) was reported by Skaletsky et al as complete sequence of the 23 Mb euchromatin segment.[16] 95% of the Y chromosome is covered by MSY, which represents a mosaic of three classes of euchromatic (X-transposed, X-degenerate and ampliconic) and heterochromatic sequences. A schematic representation of the Y chromosome is provided in Fig.2.

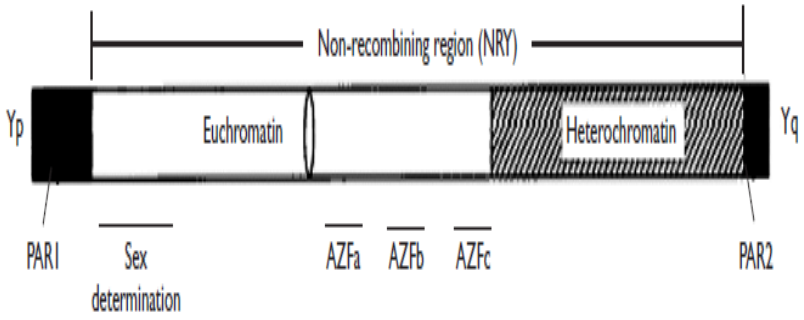

Fig 2. Diagram shows the schematic structure of the Y chromosome.[17]

The pseudoautosomal regions (PARs), which pair with the X chromosome during meiosis, are located at both ends of the Y chromosome. The region outside the PARs that does not recombine is called the non-recombining region of the Y chromosome (NRY). The Yp and the proximal part of the Yq consist of euchromatin, while the distal part of the Yq is made up of heterochromatin, and this region may vary in length to constitute about one-half to two-thirds of the Yq. Therefore, the Yq may be cytogenetically divided into an euchromatic proximal region (Yq11, subdivided into Yq11.1, 11.21, 11.22, and 11.23) and a heterochromatic distal region (Yq12), whereas the euchromatic short arm is called the Yp11.[17]

Recently, molecular methods have identified the loci involved in the production and differentiation of the sperm. The Y chromosome has been divided into seven deletion intervals. Each of these intervals is further subdivided into subintervals (A, B, C, etc.). Vollrath et al constructed a 43-interval deletion map of the human Y chromosome that contained an ordered array of sequence tagged sites (STS) which span the entire length of the Y chromosome.[18] The short arm and the centromere contain intervals 1–4, distal to proximal; the euchromatic part of the Yq is represented by intervals 5 and 6, proximal to distal; the heterochromatic region is defined as interval 7. Deletion interval 5 corresponds approximately to Yq11.21 through the middle part of Yq11.22, and deletion interval 6 corresponds to the middle part of Yq11.22–Yq11.23.

Tiepolo et al were the first to hypothesise a correlation between Y chromosome deletions and male infertility.[19] Yq microdeletions with prevalence between 10- 15% azoospermic men while it was 5% in oligospermic men, include the total Yq12 heterochromatin block and at least part of the adjacent euchromatin part of the Yq (Yq11.23), and are clustered within intervals 5 and 6 of the Y chromosome. Consequently, it was postulated that at least one

genetic Y factor essential for male germ cell development is located in the distal Yq11. It was defined as the Y borne fertile gene or Azoospermia Factor (AZF). The AZF, found on the Yq, may be the most thoroughly studied pure male sterile locus in humans. It has been suggested that the AZF resides in the distal non-fluorescent region on the Yq.

Three different AZF regions exist in Yq11

The AZF region is further subdivided into three non-overlapping hot spot regions defined as AZFa, AZFb and AZFc.[20] Furthermore, recently a fourth region, AZFd, has been proposed between AZFb and AZFc. So far at least 12 genes have been isolated from these regions. Several genes located in the AZF regions are expressed in the testes and could therefore be viewed as "AZF candidate genes". Fig. 3 depicts the three different AZF regions of the Y chromosome.

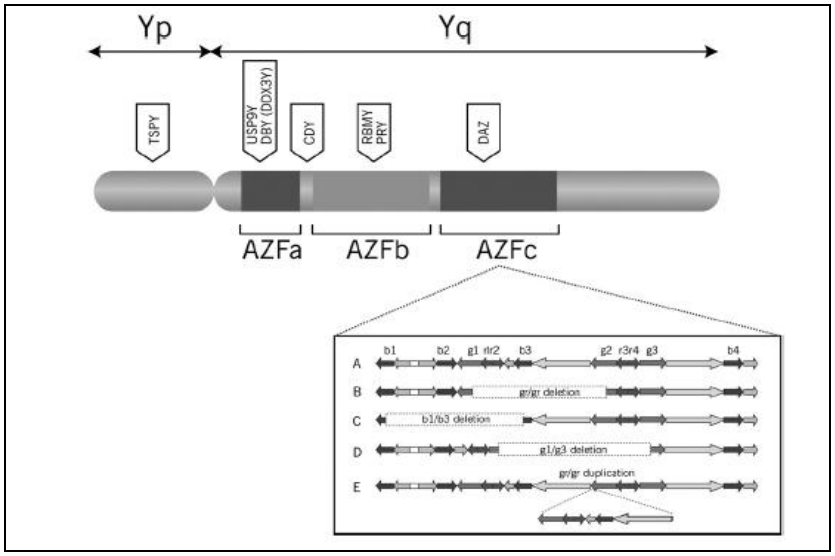

Fig 3. Image of Y chromosome displaying AZF regions and associated genes. Enlarged portion of AZFc region highlights discussed microdeletions.(A) Normal AZFc region; (B) gr/gr deletion; (C) b1/b3 deletion; (D) g1/g3 deletion; (E) gr/gr duplication.[45]

AZFa region

The AZFa is located at the proximal portion of deletion interval 5 (subinterval 5C) and it has been estimated to span 400–600 kb of DNA. The two main genes located in the AZFa region are USP9Yand DBY (also called DDX3Y).[20] Deletions in the AZFa region that remove both of these genes cause Sertoli cell–only syndrome, a condition characterized by the presence of complete Sertoli cells in the testes but a lack of spermatozoa in the ejaculate.[21] DBY, the major gene located in the AZFa region, has a probable role in infertility because it is

localized in the testis and is involved in the development of premeiotic germ cells.[21] The USP9Y gene is also involved in spermatogenesis.[22] Shortening or deletion of the USP9Y gene causes azoospermia, oligozoospermia or oligoasthenozoospermia.[22, 23] However, it seems that this gene may only be involved in the efficiency of spermatogenesis because it can be passed on to offspring. Further research studies must be performed to determine the exact roles of each of these genes in fertility to develop more targeted Y chromosome screening practices for infertile males.[23]

AZFb region

The AZFb spans from the distal portion of deletion interval 5 to the proximal end of deletion interval 6 (subinterval 5O–6B) and it spans around 1–3 Mb of DNA. The candidate gene RBMY (RNA binding motif on the Y) and six copies of the gene are located on Y chromosome.[21] RBMY1 codes for an RNA binding protein, which is a testis-specific splicing factor expressed in the nuclei of spermatogonia, spermatocytes, and round spermatids.[21,24] In AZFb region PRY genes are involved in the regulation of apoptosis.[21] In cases in which all the genes in the AZFb region except RBMY and PRY are deleted, patients present with hypospermatogenesis.[25] Removal of RBMY and PRY genes results in arrest of spermatogenesis.[26] Patients with large AZFb deletions are azoospermic microdeletions present with mild and severe oligozoospermia.

AZFc region

AZFc is located at the distal part of deletion interval 6 (subintervals 6C–6E) on the Y chromosome. Deletions are found, in 2 approximately 12% of nonobstructive azoospermia and 6% of severe oligozoospermia.[19] The AZFc region spans 3.5 Mb and contains seven gene families that are all thought to be involved in spermatogenesis. Deleted in azoospermia (DAZ) is the prime candidate gene in the AZFc region. Several genes other than DAZ have been mapped to the AZFc region, including CDY1 (chromodomain Y 1), BPY2 (basic protein Y 2), PRY (PTA-BL related Y) and TTY2 (testis transcript Y 2).

AZFa and AZFb regions are needed to initiate spermatogenesis but that without the AZFc region, spermatogenesis will not be completely normal. Complete deletions of the AZFc region may occur in two different ways: either as a result of a previous deletion within the AZFc or spontaneously from a normal AZFc region.[3] A deletion of the AZFc region may also predispose men to Y chromosome loss, leading to sexual reversal. Several studies have found this deletion to be a premutation for 45,X0 and for the mosaic phenotype

45,X/46,XY.[27,28,29] Intrachromosomal recombinations at the AZFc region may lead to many smaller subdeletions that produce a wide array of phenotypes, ranging from normospermic to azoospermic, due to many factors, including the interaction of the environment and the genetic background.[2] These can be attributed to their genomes that have evolved over generations to cope with environmental pressures specific to their region.[30] Conflicting results in studies of the partial deletions of the AZFc region may that relate to the genetic makeup of the haplogroups studied.[2] gr/gr deletions

Table 1: Genes with their location on Y chromosome and effect on spermatogenesis.[45]

Gene	Location	Reason for investigation
USP9Y	AZFa	Involved in efficiency of spermatogenesis; deletion or shortening may cause azoospermia,oligozoospermia, or oligoasthenozoospermia
DBY	AZFa	Involved in premeiotic germ cell development
RBMY	AZFb	RNA binding protein/testis-specific splicing factor; reduced expression in azoospermic men
PRY	AZFb	Regulation of apoptosis
DAZ	AZFc	Regulation of translation, meiosis, and germ cell population; codes for RNA binding proteins;reduced expression in azoospermic men; partial deletions related to oligozoospermia
CDY	Yq	Involved in histone replacement
TSPY	Yp	Regulates timing of spermatogenesis; greater copy number in infertile patients

The classical AZFc deletion, which removes 3.5 Mb between the b2/b4 amplicons, is the most common type of deletion. The three most frequent subdeletions on the AZFc region of the Y chromosome are gr/gr, b1/b3, and g1/g3 (b2/b3).[31] Several studies have identified the deletion as a risk factor for the loss of spermatogenesis, while others failed to find a correlation

The DAZ gene has four copies are thought to serve a variety of roles throughout the spermatogenic process from regulation of translation, code for germ cell–specific RNA binding proteins , involvement in the control of meiosis to maintenance of the primordial germ cell population.[32,33] Deletions of the DAZ genes can cause varied spectrum from oligozoospermia to azoospermia.[34] The azoospermic and severely oligozoospermic men be tested for microdeletions both for accurate diagnosis and genetic counselling before performing ART.[35,36] Mitra et al. demonstrated the utility of this strategy by developing a targeted multiplex PCR using STS specific to the Indian population. This type of procedure could be used as an initial screen for Y chromosome microdeletions before employing more

expensive and technically challenging testing methods.[37] However, to be effective, specific STS would need to be defined for different ethnic populations

AZFd region

The AZFd region is found between AZFb and AZFc. STS markers like SY133, SY145, SY153, and SY152 are used for screening the AZFd region. No candidate gene has been identified till now. However, detection of the deletion of the DYS237 locus of the AZFd region has frequently been identified by Muslumanoglu et al, who indicated the possible importance of the genes located in this region in spermatogenesis.[37] Although many variations in deletion length have been reported, the most frequently noted deletion extends from the STS marker, SY153, in AZFd to the junction of the euchromatic and heterochromatic regions. Patients with microdeletions restricted to AZFd may present with mild oligozoospermia or even a normal sperm count associated with abnormal sperm morphology.

Other Genes on the Y chromosome

Another gene involved in spermatogenesis and located on Yq is CDY, the cromodomain protein Y-linked gene. It is expressed exclusively in the testis and is involved in facilitating the replacement of histones in spermatogenesis and also grants the proteins that regulate transcription easier access to the postmeiotic sperm DNA through the acetylation of histones.[25]

The TSPY gene is located on the short arm of the Y chromosome, Yp, and it also has copies on the long arm of the chromosome,[38] and expressed in the testis. Its protein has been identified in spermatogonia and may regulate the timing of spermatogenesis by signaling spermatogonia to enter meiosis. Variation in TSPY gene in studies of infertile patient warrants further investigation of TSPY to characterize its role in infertility.[39]

CONCLUSION

Deletions and/or mutations of one or more of the myriad of genes required for spermatogenesis most likely cause infertility in male. In past couple of decades introduction of molecular techniques has provided great insight into the genetics of infertility. There has been progress in the identification of candidate genes with suspected involvement in male factor infertility but clinically relevant applications of these discoveries have not been discovered. Yet, our understanding of the genetic regulation of spermatogenesis remains

limited. In particular, we are still unable to establish the precise genotype–phenotype correlation between specific Y chromosome deletions and the various testicular histology patterns seen in infertile Men. Novel Technologies currently being developed, which provide promising leads for more effective methods to diagnose and treat infertility.

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