

# Microdeletion of Y-chromosome and Their High Impact on Male Infertility

## INTRODUCTION

Male infertility is a multifactorial genetic disorder. WHO defined infertility as an inability to conceive naturally after at least 1-year of unprotected intercourse. It is expected that 15% of couples worldwide who seeks children have infertility while male factor alone contributes about 50% in childless couples. In more than half of infertile male are unknown idiopathic causes. Semen analysis shows abnormal conditions such as azoospermia, oligozoospermia, teratozoospermia, asthenozoospermia, necrospermia, and pyospermia.<sup>[1-6]</sup> The prevalence of primary and secondary infertility varies between 29% and 71%, but about 30% of cases of reduced infertility are still unknown. The Y-chromosomes play a significant role in maintaining fertility in human. Hence, it is essential to understand the molecular structure of Y-chromosome and their regions associated with infertility. Y-Chromosome is one of the smallest chromosomes. It consists of euchromatic, heterochromatic regions, and covered 95% by male-specific region. There are 60 million nucleotides including 156 transcription units, 78 protein-coding genes, and 27 distinct proteins as shown in Figure 1.

Both ends of the Y-chromosome contains pseudo autosomal regions (PARs) join up with the X-chromosome during crossing over (meiosis). The region outside PARs does not play a significant role in linkage and known as the nonrecombining region of the Y-chromosome. However, molecular deletion studies of Y-chromosomes (Yq11.21, Yq11.22, and Yq11.23) are based on sequence tagged sites have identified the loci responsible for the production and differentiation of sperm. A large number of factors are

known to interfere with spermatogenesis. Undoubtedly, among the genetic factors associated deletion of azoospermic factor (AZF) are known to play a crucial role in regulating infertility. Y-chromosomal imbalance contributes about 14% of azoospermic and 5% of oligozoospermia and plays a significant role in infertility with abnormal seminograms.<sup>[7]</sup> The expected phenotype ranges from oligozoospermia to azoospermia, and have a variable impact because of the same karyotype within the same family has been reported earlier.<sup>[8]</sup> In most of the cases, the distal region of Y-chromosome is translocated to the short arm of an acrocentric chromosome and can be visualized by fluorescence *in situ* hybridization This seems to be relevant for diagnosing of microdeletion of Y-chromosome in karyotypes of 47, XXY or mosaic 46, XY/47, XXY cases with clinical features characterized by testicular hypotrophy, azoospermia and increased FSH levels. The deletion frequency varies in azoospermic cases due to different regions (AZFa, AZFb, and AZFc) with various karyotypes. The incidence (0.5–1.0%) of Robertsonian translocations varies between two acrocentric chromosomes (i.e., chromosomes 13, 14, 15, 21, and 22), resulting either in a single abnormal chromosome or dicentric chromosome, leading to reported cases of male infertility.<sup>[8-10]</sup> In this review, the authors have initially selected relevant articles from the last five years using PubMed or Google Search as the primary tool during the preparation of this article. The author’s contributions on the deletion of AZF regions and the impact on male infertility in Indian population was also incorporated.

*De novo* microdeletion of Y-chromosome occurs due to recombination events between repetitive DNA sequences during meiosis in infertility.<sup>[11-13]</sup> The euchromatic region

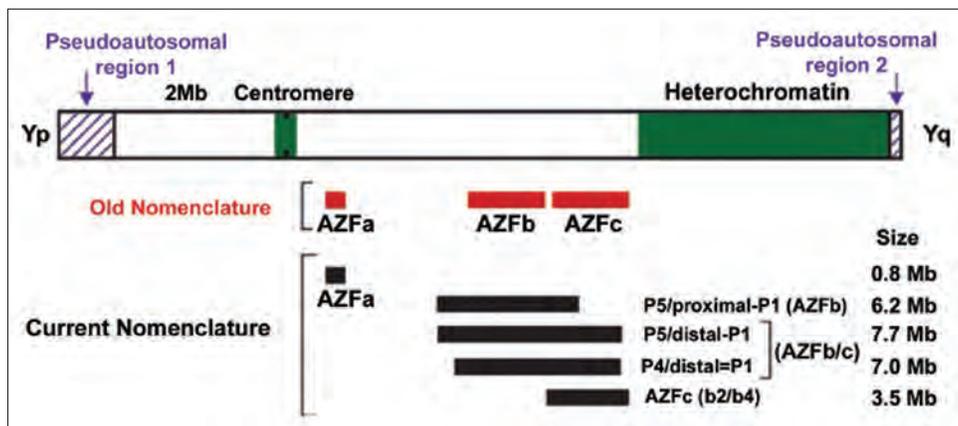


Figure 1: Schematic representation of DNA of Y-chromosome regions linked with male infertility in human

of Yq11 locus regulate spermatogenesis, and AZF has been further divided into four nonoverlapping coding regions with varying sizes (1.0–3.0Mb) designated as AZFa, AZFb, AZFc, and AZFd.<sup>[14,15]</sup> Although a definite genotype-phenotype correlation has not been clear during microdeletions of Y-chromosome. The larger deletions or multiple AZFa regions are usually linked to Sertoli cell-only syndrome. The AZFb or AZFc regions are restricted to moderate oligozoospermia, whereas AZFd region is linked to mild oligozoospermia or even normal sperm counts with abnormal sperm morphological features suggesting the lack of correlation exist between genotype-phenotype.<sup>[16-18]</sup>

## ROLE OF MICRODELETION OF AZOOSPERMIC FACTOR IN INFERTILITY

### Azoospermic factor a region

The short arm of Y-chromosome contains AZFa region having four single copies of genes USP9Y, DBY, UTY, and TB4Y. The USP9Y encode protein ubiquitin hydrolase playing an important role in preventing degradation and removal of conjugated ubiquitin proteins. The DBY gene encodes RNA helicase which regulates the transformational event of mRNA in spermatogonia and pachytene spermatocytes during spermatogenesis.<sup>[19]</sup> However, it is still unknown whether all genes belonging to AZF region have been defined to be associated with changes in phenotype, that is, hypospermatogenesis indicates that this gene (USP9Y) is probably not essential for the initiation and completion of spermatogenesis, rather it enhances the quality and efficiency of the process.<sup>[20-22]</sup>

### Azoospermic factor b region

The AZFb region contains at least one functional RNA binding motif (RBM) located in the distal portion of Yq structure and includes active copies of two gene family with multiple copies. RBMY, a testis-specific splicing factor is homologous to RBMX gene. Both the X and Y derivative protein are highly expressed in differentiating cells and promote mitotic activity in spermatogonia.<sup>[20-22]</sup> Typically, AZFb region is partially overlapped with AZFc region (DAZ). AZFb also encodes the phosphatase which is involved in the apoptotic event in defective spermatozoa.<sup>[23]</sup> Another region of AZFb encodes RBMY protein expressed in the nuclei of spermatocytes and also in round spermatids during spermatogenesis.<sup>[24]</sup>

### Azoospermic factor c region

The deletion of AZFc is more relevant because of high frequency (3%) in infertile population and contains repeated sequences.<sup>[25]</sup> AZFc region includes two copies DAZ1 and DAZ2 and is involved in encoding testis-specific RNA binding proteins which interact with the DAZAP1 and regulate the

transportation of mRNA in late spermatids and spermatozoa during spermatogenesis. The expression of DAZ has also been found in multiple cell compartments at various points during germ cell proliferation and development.<sup>[26-29]</sup> Similarly, the genes of CDY family ubiquitously are expressed as basic nuclear proteins in spermatids and exhibit histone acetyltransferase activity with four alternative spliced transcripts encoding three different proteins.<sup>[30]</sup>

## SIGNIFICANCE AZOOSPERMIC FACTOR MUTATION

In general, it is believed that men with severe infertility should be screened for microdeletions of Y-chromosomes as a part of preclinical investigations because of deletions itself significantly predicts diagnostic, prognostic, and preventive values. Many epigenetic factors including repetitive sequences of the Y-chromosome help in the interpretation functions during spermatogenesis.<sup>[31]</sup> In azoospermic cases, the presence of a complete and the absence of AZFa or AZFb regions have a negative prognostic value for testicular sperm retrieval.<sup>[32-36]</sup>

## THE RELEVANCE OF GENETIC COUNSELING FOR INFERTILE COUPLES

Genetic counseling is a specified area that needs development. It is critical to educate the couples about “risks factor” as they pursue assisted reproductive techniques (ART). There are three common diagnoses which have a genetic risk for testing such as obstructive azoospermia, nonobstructive azoospermia, and oligozoospermia. These procedures are quite relevant because ICSI-derived male children seem to be more prone to inherit microdeletion. Similarly, in the case of oligozoospermia, sperm concentration decreases during cryopreservation, and hence, the need to inform the patients who failed to take a decision about such investigations.

## CONCLUSIONS AND OUTLOOK PERSPECTIVES

In fact, microdeletions of Y-chromosome represent an important cause of male infertility, and genetic screening becomes an essential tool to those having a sperm concentration  $<5 \times 10^6/\text{ml}$ . Due to the advancement of technology, we can help to solve infertility problem by ART. However, a variable frequency of genotype-phenotype correlation has been observed in the cases of deletion of AZFa, AZFb, and AZFc regions of Y-chromosome but epigenetic factors cannot be entirely ignored. There is a need for further research on genetic screening for

mutational spectra in homologous chromosomes to search for a new candidate gene(s) linked to infertility. The deletion studies will help in the accumulation of data for better diagnostic methods and expansion of genetics knowledge in the reproductive biology of male infertility. In spite of tremendous efforts in the field of molecular biology, the noninvasive technique should be evolved to answer unresolved issues such as the definition of the function of AZF genes with variable frequency of specific deletions in the human population.

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**Ajit Kumar Saxena, Ramanuj Kumar Gupta**

*Department of Pathology/Laboratory Medicine, Cytogenetic and Molecular Genetics Laboratory, All India Institute of Medical Sciences, Patna, Bihar, India*

#### Address for correspondence:

Dr. Ajit Kumar Saxena,  
Department of Pathology/Laboratory Medicine,  
All India Institute of Medical Sciences, Patna - 801 507, Bihar, India.  
E-mail: draksaxena1@rediffmail.com

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