

## **THE Y-CHROMOSOME : Genetics of Male Infertility**

**Greeshma Gopalan\*\*\*, Sadia Tabassum Khan\*\*, Ketki Sharma\*\* & Aparna Sarkar \***

*\*\*\* Tutor at Physiology Department, Rama Medical College, Hapur, Ghaziabad.;\*\*M.Sc Medical Physiology student, Amity Institute of Physiology & Allied Sciences, Amity University Uttar Pradesh, India.*

*Corresponding author: \*Associate Professor, Department of Physiology, Amity University Uttarpradesh, India.  
asarkar@amity.edu*

### **ABSTRACT:**

Y chromosome is a specific sex chromosome, responsible for male sex determination in humans, and is inherited more or less unchanged, from paternal end to the next generation male, indefinitely. Male specific Y chromosome region or MSY of the chromosome is a non-recombining region, mainly comprising of Sex Determining region of Y (SRY) of short arm; euchromatic regions of both the arms and heterochromatic region of long arm. In the embryo the initiation of testes differentiation is controlled by the SRY region which encodes the responsible testes determining factor. The functional genes are present in the euchromatic regions whereas the heterochromatic regions lack genes. Both X and Y chromosome has same genes present in their pseudoautosomal region (PAR) due to which there are two functional copies of these genes in both men and women each, which are vital for normal development. Deletion of any of the genes in this chromosome, may therefore, account for infertility in males. Furthermore, since the Y chromosome is being inherited almost unchanged, these alterations, along with the genes may also get inherited to the next progeny. The consequences of these aberrations could be reduced fertility or infertility caused due to conditions such as oligozoospermia (significant lack of sperm) or azoospermia (complete lack of sperm) and so forth.

### **INTRODUCTION:**

The human genome consists of many small chromosomes, out of which the smallest one is the Y chromosome. It is also known as the sex chromosome and represents approximately 2.5% of haploid genome. Normally each cell in a person has a couple of sex chromosomes i.e. in case of males as XY and in case of females as XX. Hence it is basically the Y chromosome that determines the sex of a person i.e. if present then as male and if not then as a female. On account of various researches done by the researchers it was known that there are numerous genes present in the Y chromosome but as the method used to study was different by each thus the number of estimated genes varies. Hence on an average it was concluded that a Y chromosome contains about 50-60 genes responsible for the protein synthesis.

There are many unique genes present only on the Y chromosome and not there in the X chromosome, and they are-

#### **# Arms of Y chromosome:-**

Yp= it is the short arm of the chromosome which has the euchromatic region

Yq= it is the long arm of the Y chromosome which has a proximal euchromatic and distal heterochromatic portion.

### **# Regions and Genes of chromosome:-**

**PAR**= it is the pseudoautosomal region which is responsible for the X chromosome pairing and recombination at the time of meiosis.

Both X and Y chromosome has same genes present in their pseudoautosomal region (PAR) due to which there are two functional copies of these genes in both men and women each, which are vital for normal development.

**SRY**= responsible for encoding the testis determining factor.

**AZF**= it is the azoospermia factor

**AZF<sub>a</sub>**= has USP9Y and DBY, i.e. ubiquitin-specific protease 9 of Y chromosome; also called as DFFRY (i.e. Drosophila fat facets related Y) and dead box on Y gene, respectively.

**AZF<sub>b</sub>**= has RBM gene i.e. RNA binding motif on Y gene family.

**AZF<sub>c</sub>**= has DAZ gene which is deleted in the azoospermia gene family.

### **PATTERN OF INHERITENCE:**

As the Y chromosome has unique characteristics, hence gets inherited from father to son in an unchanged manner. Thus, chromosomes when inherited from one generation to another mostly will contain genetic codes that are randomly mixed but it is only the Y chromosome that will be present identical or nearly identical to that of his male parent or one of his previous generation male parents. Therefore if there occurs any genetic changes in the Y chromosome it gets easily passed on to its male progeny, due to which the male progeny will also have an affected Y chromosome. Such form of inheritance is known as Y-linked inheritance. As daughters do not inherit the Y chromosome, hence they remain unaffected.

### **STRUCTURAL AND FUNCTIONAL ASPECTS OF Y CHROMOSOME:**

Different regions and genes were identified on the Y chromosome as a result of various chromosome-banding studies and they were-

#### **PAR REGION:**

It is the pseudoautosomal region which is divided into two parts i.e. PAR1 and PAR2. 5% of the entire chromosome is represented by these two regions. The terminal region of the short arm i.e. approximately 2600kb of DNA and the tip of the long arm of Y chromosome i.e. about 320kb of DNA is covered by PAR1 and PAR2 respectively. During the meiosis, PAR1 is the site where the Y chromosome pairing and genetic material exchange takes place with the X chromosome's pseudoautosomal region. Moreover the PAR genes are inherited likely as the autosomal genes are.

#### **SRY GENE:**

This is the sex determining region of the Y chromosome. It was determined in 1990 on the basis of various studies that were done on the Klinefelter's Syndrome and Turners Syndrome. It is located closely

to the pseudoautosomal boundary of the Y chromosome and encodes a 204 amino acid containing protein. This gene is responsible for the development and differentiation of the testis along with various testicular pathways.

### **AZF GENE:**

This is the gene on Yq11 that encodes the azoospermia factor which has been suggested to be the controller of spermatogenesis. AZF gene is further divided into three non-overlapping sub regions i.e. –

- i. **AZF<sub>a</sub>:** present within the deletion interval 5 at the proximal end of Yq with an estimated extension of about 1-3 Mb. This region encodes different genes like DBY, UTY, TB4Y, DFFRY genes, out of which the first three genes are responsible for the housekeeping functions whereas the DFFRY has been proposed to have a vital role in the process of gametogenesis. The DFFRY gene encodes the protein which is responsible to carry out the process by which the proteins are tagged for its degradation fate.
- ii. **AZF<sub>b</sub>:** present between the deletion interval 5 and the proximal end of deletion interval 6 with the molecular extension of 1-3 Mb. This region encodes five genes namely RBM, CDY, XKRY, eIF-1A and SMCY. The specific nuclear proteins that contain the RNA binding motif are encoded by the RBM gene. The CDY and XKRY genes are specifically expressed in the adult testis.
- iii. **AZF<sub>c</sub>:** present distal to Yq11 i.e. in the proximity heterochromatic region with the molecular extension of about 500kb. This region mainly contains several copies of DAZ gene which encodes the testis-specific RNA binding protein. Other genes found in this region are PRY, BPY2 and copies of CDY and RBM genes.

The 95% of the chromosome is made by the so called Non-Recombining Y (NRY) region which includes the euchromatic and heterochromatic regions of the chromosome.

### **EUCHROMATIC REGION:**

It is located distally to PAR1 region consisting paracentromeric region of the short and long arm along with the centromere.

### **HETEROCHROMATIC REGION:**

It is located distal Yq corresponding to Yq12 comprising of two repetitive sequences families, DYZ1 and DYZ2. Even though this region is considered genetically inert but it also contains some genes that are responsible for important biological functions.

### **DELETION/ MUTATION OF GENES AND LINKED ABNORMALITIES:**

It was hypothesized by Tiepolo and Zuffardi in 1976 that there is a correlation between the Y chromosome deletions and male infertility as 13% azoospermic men and about 1-7% severely oligospermic men showed micro deletion in Yq arm of the Y chromosome.

#### **I. SRY DELETION AND IT'S CLINICAL IMPLICATIONS:**

In humans SRY is the gene which is responsible for the determination of male sex as they initiates the differentiation and proliferation of the primordial gonads that lie along the urogenital ridges to become the male cells (sertoli and leydig cells) leading to the formation of testes by activating the male-specific transcription factors. Thus despite the presence of Y chromosome, the deletion of this gene results in no testes formation leading to an infertile male.

In the absence of SRY gene, the testis development can no longer be initiated and when such a Y chromosome which lacks SRY gene is inherited from father to son leads to the Swyer Syndrome in the progeny which is characterized by a male karyotype (XY) and a female phenotype. It has been suggested that there are some other factors also that affect the function of the SRY gene. Therefore female phenotype can still develop even in the presence of SRY gene because of the defect in such contributing factors.

## **II. AZF DELETION AND IT'S CLINICAL IMPLICATIONS:**

### **i. AZFa region:**

It spans around 400-600 kb of DNA that encodes two genes namely USP9Y and DBY. Deletion of this region is characterized by the sertoli cell only syndrome type I.

### **ii. AZFb region:**

It has the RBMY gene which encodes testis specific RNA binding protein responsible for the mRNA processing, transport and splicing. As the AZFb gene is expressed in the primary spermatocytes, thus its deletion leads to meiosis and maturation arrest followed by the accumulation of these primary spermatocytes.

### **iii. AZFc region:**

In men with idiopathic oligozoospermia, deletion of this region is most commonly seen as this region encodes the genes that are responsible for spermatogenesis. One of which is DAZ gene which has its four copies present. Deletion of each member of DAZ has varied effects as deletion in DAZ2, DAZ3, and DAZ4 are found in both fertile and infertile men but the DAZ1 deletion is restricted only to infertile men. Hence the deletion of AZFc region leads to different phenotypes that range from hypo-spermatogenesis to maturation arrest followed by azoospermia.

Sometimes infertile men shows partial deletions in AZFb and AZFc loci resulting in subfertility rather than infertility.

AZF deletions is related to the spermatogenic failure. In such cases there is a decline in sperm count over time leading to azoospermia. In such cases ART is the best technique used but the chances of iatrogenic transmission of Yq microdeletion to the offsprings are present.

## **CONCLUSIONS:**

The Y chromosome is always seen in the haploid state with its unique features and genes that are responsible for sex determination and male fertility. Hence it can be used as a powerful tool for the study of human evolutionary pathway as the non-recombining region of the Y chromosome persists the record of the mutations that have occurred throughout the evolution as it is passed on to the progeny without recombination at meiosis. Thus male infertility is most likely due to the deletion or mutation of the genes responsible for spermatogenesis as well as other biological significance.

## **FUTURE ASPECTS:**

As it can be concluded that a male's ability of being fertile is controlled by a number of genes present in the Y chromosome which are the core controllers of various reproductive functioning like spermatogenesis, DNA recombination and replication, etc. As these genes forms the genetic basis of fertility thus their maintenance is mandatory which otherwise could lead to infertility. To keep a check on

these genes various advanced gene expression techniques like PCR screening are used which helps in knowing the causative mechanism for infertility followed by which we can also reduce the risk associated with ART. But some deletions that cause male infertility might occur in regions other than the one in which these studied controller genes are encoded. Such cases could be answered by the study of autosomal genes that could affect spermatogenesis.

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