

Genetics of male infertility and related genes within Y chromosome

Tutku Melis Aygün^{1*}

Abstract

Objective: The infertility is a reproductive health problem that affects nearly 7% of all couples in the human population. It has been estimated that nearly 50% of infertility cases are due to genetic defects. Male infertility may be contributory to 30 - 40 % of infertile couples. Male infertility focuses on genetic factors impairing spermatogenesis and structural abnormalities such as Y chromosome microdeletions. The Y chromosome microdeletions are the most frequent genetic cause of male infertility. In this review article, we will focus on the structural abnormality and related gene functions on infertility.

Key words: AZF regions, male infertility, spermatogenetic failure, Y chromosome microdeletions

Introduction

Infertility is defined as the inability to conceive an offspring after a year of regular unprotected intercourse [1]. Nearly 15% of couples are affected with infertility, in which male factor infertility accounts for approximately 50% with genetic abnormalities such as structural abnormalities [2]. Genetic factors contribute to male infertility by influencing hormonal balance, spermatogenesis, and sperm quality. Male infertility screening is carried out by using semen analysis according to the standard criteria of the World Health Organization (WHO) [3].

In structural abnormalities, microdeletions of the Y chromosome is considered to be a major cause of male infertility for azoospermic males [4]. Mostly the male infertility is a de novo event of genetic origin that originates during the normal process of spermatogenesis. Azoospermia is referred

to as the absence of spermatozoa in the ejaculate of a man. More than 4000 genes are mentioned to be involved in human spermatogenesis [5,6,7].

Recognition of Azoospermia Factor (AZF) region on the long arm of the Y chromosome (Yq) is the second most common genetic cause of spermatogenic failure [8]. Molecular screening of Y chromosome microdeletions explain some related region that determine azoospermia factors like AZFa, AZFb, AZFc region which are responsible for regulating the spermatogenesis [9,10].

In this review article, I present a brief overview of the AZFc subregion as microdeletions in this region that is a genetically risk factor for spermatogenic failure, also to understand the genetic problem of the AZFc subregion of the human Y chromosome [11,12].

Structure and organization of y chromosome

Y chromosome is the smallest chromosome that consists of 2-3% of the haploid genome and contains between 70 and 200 genes in their structure [13]. Cytogenetic observations are based on chromosome banding studies that are allowed different Y regions to be identified, the pseudoautosomal portion, PAR1 and PAR2, the euchromatic and heterochromatic regions.

Several phenotypes have been associated with the non-recombining portion of the Y chromosome [14]. For obvious reasons, most of these are male-specific and make the Y a specialised chromosome during human evolution. The most characterising features of this chromosome remain its implication in human sex determination and in male germ cell development and maintenance [15,16].

Some of the important genes, also regions (Azoospermia Factor – AZF) on the human Y-chromosome have been discovered and then characterized [17]. These genes have been covered in this review. Important features such as cytogenetic location, function, and mutational deficiencies associated with some of the male-related genes are shown below in Table 1.



Table 1. Male-Related Functional Genes (Azoospermia / Infertility)

GENE	LOCATION	LONG NAME	FUNCTION	X HOMOLOGS
USP9Y	Yq: 5C	Ubiquitin-specific Protease	Azoospermia	+
DBY	Yq: 5C	DEAD box, Y	Infertility	+
UTY	Yq: 5C	Ubiquitous TRY motif, Y	Infertility	+
TB4Y	Yq: 5D	Thymosin 4, Y isoform	Infertility	+
EIF1AY	Yq: 5Q	Translation initiation factor 1A, Y	Infertility	+
CDY	Yq: 5L, 6F	Chromodomain, Y	Infertility	-
RBMV	Yp + q	RNA-binding motif, Y	Infertility	-
PRY	Y: 4A, 6E	Putative tyrosine phosphatase protein-related Y	Infertility	
DAZ	Yq: 6F	Deleted in azoospermia	Infertility	+

Table 2. AZF Regions and Their Functions within the Y Chromosome

LOCUS	FUNCTIONS
AZF - A	Deletion of AZFa associated with lack of germ cells and Sertoli Cell Only Syndrome.
AZF - B	Deletion of AZFb associated with spermatogenesis arrest.
AZF - C	Deletion of AZFc associated with the failure of the maturation process of germ cells.

Functional genes on three azf regions

The azoospermia factor (AZF) region on the Y chromosome consists of genes required for spermatogenesis. The AZFa harbours some single-copy genes which are involved in spermatogenesis that have X-homologs [18,19]. The overlapping AZFb and AZFc regions are jointly termed as AZF2. In the AZFb region, the eukaryotic translation initiation factor EIF1AY and RBMY genes have been mapped in man. EIF1A protein is involved in stabilizing the binding of the initiator methionine-bearing-tRNA to 40S ribosomal subunits.

The AZFc region harbours five genes: DAZ, BPY2, PRY. The candidate gene of AZFc is known as deleted in azoospermia gene, which is studied with interest because it is involved in germ cell development and most frequently deleted genes leading to azoospermia [20]. Also, AZF regions and their functions are shown in summarize, in Table 2.

Azf-a locus its genes and functions

The AZFa encodes only single-copy genes. It is constituted by single-copy, ubiquitously expressed genes with X homologs that escape inactivation. genes have been mapped to AZFa.

*USP9Y: USP9Y is a single copy gene that is located in the AZFa region. USP9Y enzyme belongs to the peptidase C19 family and has a role in sperm cell production and development in mammals.

Besides, its role in spermatogenesis, studies have discovered that a nine-residue peptide derived from USP9Y represents a minor histocompatibility antigen involved in graft rejection.

*DBY: AZFa microdeletion is a result of non-homologous end joining (NHEJ) between two nearly identical repeats. The general view is the deletion of one gene is, this. DBY plays a key role in the spermatogenic process which is essential for cell cycle progression from G1 to S phase.

*UTY: In human, the six mRNA transcripts of UTY gene translate into the enzyme histone demethylase UTY that contains tetra-trico-peptide repeats and are thought to be involved in protein-protein interactions. The UTY protein being a minor histocompatibility antigen could induce rejection of male stem cell grafts. Suppression of recombination between the homologous genes UTY and X-chromosomal UTX, results in a point mutation in mRNA transcripts of these genes, whereas the reading frames. UTY has essential for prostate differentiation and that disruption of this network predisposes males to prostate cancer.

*TB4Y: TB4Y is expressed in various tissues that encodes a novel human leukocyte antigen HLA-A*3303-restricted, minor histocompatibility antigen and is a key activator of natural killer cell cytotoxicity. The involvement of TB4Y in testicular functions is unknown.

Azf-b locus its genes and functions

AZFb microdeletions cause spermatogenesis arrest at the spermatocyte stage, loss of mature sperm and milder azoospermia. The AZFb region has a complex structure that prone to NHEJ. The AZFb microdeletions remove multiple copies of testis-specific CDY, RBMY and PRY genes [21].

*CDY: This gene aids in regulation of gene expression and encodes a histone acetyltransferase. Deletion of this gene associated with azoospermia and severe oligozoospermia.

*RBMV: It is one of the most important genes of the AZFb region within the Y chromosome. Deletion of this gene leads to a decrease in sperm count in semen. RBMY must have diverse functional roles during different stages of spermatogenesis. Indeed analysis of the human testicular RBMY bound transcriptome have led to identification of 20 target genes some of which are testis-specific and have diverse cellular functions and is proposed to regulate alternative splicing during the spermatogenesis.

*PRY: It is a testis-specific gene that encodes a protein similar to protein tyrosine phosphatase. When PRY levels are increased in sperm which can lead the abnormal semen parameters, suggesting a link between its expression and defective spermatogenesis.

Azf-c locus its genes and functions

AZFa and AZFb regions are essential in initiating spermatogenesis, the AZFc region is essential to complete the process of spermatogenesis [22,23]. The AZFc is the most commonly deleted region of the AZF locus in infertile men. There are no single-copy sequences in the AZFc. The AZFc region includes 12 genes and transcription units, each present in a variable number of copies making a total of 32 copies. Amongst the various transcriptional units, only active copies of four protein-coding gene families map to the AZFc interval. These include the PRY2, BPY2, DAZ and CDY1 [24,25].

*PRY2: The expression of PRY in germ cells is heterogeneous, with the protein being detected only in a few sperm and spermatids. Furthermore, PRY levels are increased in ejaculated sperm obtained from males with abnormal semen parameters, suggesting a link between its expression and defective spermatogenesis [26]. The PRY genes are thought to be involved in the regulation of apoptosis implicated in the removal of abnormal sperm. Deletions that include the PRY1 and PRY2 genes have also been reported to cause meiotic arrest.

*BPY2: It is expressed specifically in testis and its protein product is involved in male germ cell development. Three nearly identical copies of this gene exist on Y chromosome BPY2A, BPY2B and BPY2C. BPY2 is localized in the nuclei of spermatocytes, round spermatids and spermatogonia. The BPY2 gene encodes for a small positively charged protein which is thought to be involved in cytoskeletal regulation in spermatogenesis [27]. Due to its small size and high charge, it is thought that BPY proteins may functionally interact with DNA in a manner that resembles chromatin-associated proteins such as histones and high mobility group proteins which are known to play a role in the regulation of processes such as transcription, replication, recombination and DNA repair.

*DAZ: This is the first candidate gene to be isolated from the AZFc locus and was originally identified as a frequently deleted gene on the Y chromosome of infertile males. AZFc region contained palindromic duplications of DAZ as two clusters of four genes, DAZ1,2,3,4. The four DAZ copies are expressed in spermatogonia, encoding an RNA-binding protein important for spermatogenesis and these genes are expressed in all stages of germ cell development. Using human embryonic stem cells, it is shown that DAZ family genes function in germ cell formation. Therefore, all DAZ family genes are regarded as critical for germ cell development.

*CDY1: The human Y chromosome has two identical copies (CDY1A and CDY1B) of this gene within the AZFc region. This gene aids in regulation of gene expression, chromatin remodelling and encodes a histone acetyltransferase. This protein has been reported to

concentrate in the round spermatid nucleus, where histone hyperacetylation occurs and causes the replacement of histones by the sperm-specific DNA packaging proteins.

A genetic disorder related to y chromosome abnormality

*Azoospermia

The reproductive disorder of male known as azoospermia is characterized by the absence of sperm in ejaculate affecting approximately 20% of male fertility situations, in general. A variety of causes responsible for azoospermia which is due to abnormal chromosomes or structural abnormality. Disease-like varicocele is associated with the AZFa region of the Y chromosome. EIF1A protein results in azoospermia when deleted. Some studies have been investigated that deletion of DAZ1/DAZ2 but not DAZ3/DAZ4 is associated with spermatogenic failure [28,29].

Male infertility and y chromosome microdeletion

Deletion of genetic material in the region of Y-chromosome (AZF) results in male infertility. Some studies have been reported that the natural transmission of deletions which involves the USP9Y gene suggests that the absence of the USP9Y gene product does not have sperm-fertilizing ability. Thus, it is not critical for spermiogenesis. Deletion in DAZ1/DAZ2 gene copies, which is difficult to detect due to multicopy and will result in spermatogenic failure [30].

Missing genes within the Y chromosome result in microdeletions. Y chromosome microdeletions are recently diagnosed by isolated DNA from peripheral blood (leukocytes) and then, mixing it with some of about hundreds of known genetic markers for sequence-tagged sites (STS) on the Y chromosome, then using PCR amplification -also FISH techniques (if it's possible)- and gel electrophoresis to test whether the DNA sequence corresponding to the selected markers is present in the DNA.

Conclusion

The advantages of next-generation sequencing and some of the new perspectives have enabled researchers to identify a number of novel genes. The Y chromosomal genes have been explored to associated with several male fertility-specific traits in human.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author's Contributions: TMA; Research the literature, Collection of the Data, Preparation of review. TMA; Revision of the article.

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