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Genetic Mechanisms of Y Chromosomal Microdeletions and Male Sterility: A Review

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Abstract
Infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. The Y chromosome plays a major role in male fertility, as it contains genes responsible for testis development and the initiation and maintenance of spermatogenesis in adulthood. However, anomalies in these genes can cause male infertility. There are several ampliconic and palindromic sequences on the long arm of the Y chromosome (Yq), which makes it prone to self-recombination during spermatogenesis and thus susceptible to intra-chromosomal deletions. Y chromosome microdeletions are the second most common genetic cause of male infertility as it is present in about 5% and 10% of men suffering from oligospermia and azoospermia. The exact role of the genes affected by Y chromosome microdeletions in spermatogenesis is not fully understood. However, it is suggested that they play a critical role in germ cell development, particularly in males. Y chromosome microdeletions in infertile males typically occur within the three subregions of the long arm of the Y chromosome; azoospermia factor regions (AZF) a, b, and c. AZFa region genes support sperm cell production. AZFb region genes assist with the growth and maturity of sperm. AZFc genes do not contribute much to sperm production and hence deletions of the gene in this region, result in low sperm count. Microdeletion of AZFa genes leads to Sertoli cell-only syndrome, AZFb gene microdeletion can lead to maturation arrest and AZFc gene microdeletion can lead to hypospermatogenesis and azoospermia. This review aims to discuss in detail the effects and genetic underpinnings of Y chromosome microdeletions in male infertility.

Keywords: Y Chromosome, Microdeletion, Male Sterility, Genes, Azoospermia, Oligospermia.

Introduction

Infertility is the inability to generate a pregnancy after 12 months of regular unprotected sexual intercourse (World Health Organization, 2023). It is believed that between 8 and 12% of reproductive-aged couples globally are affected. Males are determined to be primarily responsible for 20-30% of total cases (Vander Borght & Wyns, 2018). According to the Centres for Disease Control (CDC), about 12% of sexually active people in the United States experience infertility. Since many birth cases are not reported in other countries worldwide, the number of cases may be much higher. Data suggest that male infertility has increased in some people. According to studies conducted around the world, the rise in infertility in recent years may be related to anatomical, physiological, and genetic reasons. Many environmental and acquired factors, including smoking and alcohol intake, changes in sexual behaviour and food, can affect fertility and sperm quality, and can thus result in various types of infertility making various regions have varied causes and levels of infertility. Azoospermia (lack of sperm), severe oligozoospermia (1 x 106 sperm/mL semen), moderate oligozoospermia (1-5 x 106 sperm/mL semen), or mild oligozoospermia (5-20 x 106 sperm/mL semen) describe Y chromosomal infertility. Males with Y chromosomal infertility typically do not exhibit any evident symptoms, though a physical examination may indicate testes that are considered small. Pregnancies can occur via in-vitro fertilization using intracytoplasmic sperm injection (ICSI), a procedure in which spermatozoa extracted from

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ejaculate (in males with oligozoospermia) or extracted from testicular tissues (in males with azoospermia) are injected into an egg harvested from the reproductive partner. Male children of ICSI pregnancies have the same deletion as their fathers, putting them at high risk of male infertility. Prenatal testing or preimplantation tests might be used to detect the sex of the foetus and/or the existence of Y chromosome deletion in pregnancies conceived with assisted reproductive technology (ART) and known to be at risk of male Y chromosome deletion.

An Overview of Chromosomes

Chromosome is formed from the Greek words for colour (chroma) and body (soma). Scientists gave chromosomes this moniker because they are cell structures or entities that are heavily stained by several colourful dyes used in research. Chromosomes are thread-like structures that are found within the nucleus of animal and plant cells. Each chromosome is made up of protein and one molecule of deoxyribonucleic acid (DNA). DNA, which is passed down from parents to children, contains the specific instructions that distinguish each living species (Pathak & Bordoni, 2023). The unique structure of chromosomes keeps DNA firmly wrapped around proteins called histones. Cells must divide repeatedly for organisms to grow and function properly, so old cells will be replaced with new cells. DNA must remain intact and evenly distributed throughout cells during cell division. Chromosomes play a vital role in the mechanism that guarantees DNA is appropriately replicated and distributed in the vast majority of cell divisions. Even yet, errors do happen on occasion. Changes in the number or shape of chromosomes in new cells might cause major difficulties. It is also critical that reproductive cells, such as eggs and sperm, possess the correct number of chromosomes and have the proper shape. Otherwise, the developing kids may not develop appropriately. It is essential to remember that the number and shape of chromosomes vary amongst living things. The majority of bacteria have one or two circular chromosomes. Humans, like other animals and plants, have linear chromosomes arranged in pairs within the cell's nucleus. Only reproductive cells or gametes, have two copies of each chromosome. When two reproductive cells fuse, they create a single cell that has two copies of each chromosome.

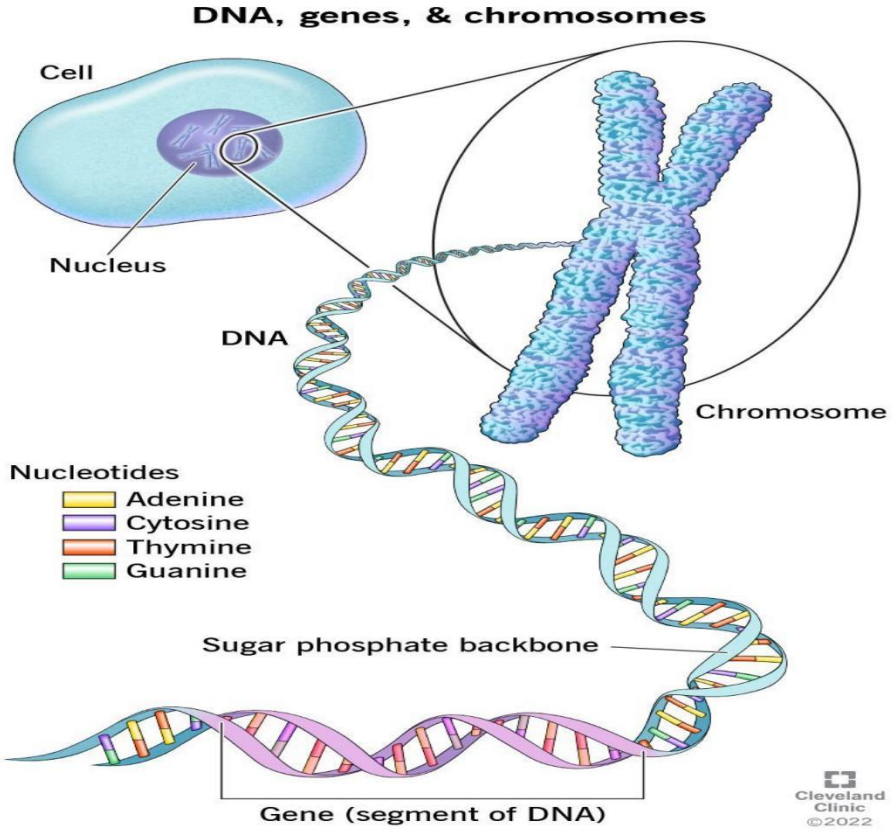

Figure 1: A diagram illustrating the structure of a chromosome and its constituents (Pathak & Bordoni, 2023)

This cell divides and its progeny subsequently divides multiple times, eventually producing a mature human with a complete set of paired chromosomes in almost all of its cells. The centromere is the restricted area of linear chromosomes; it is often not located directly in the centre of the chromosome, rather it is located close to

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the end of the chromosome in certain situations. The chromosomal arms are the areas on either side of the centromere. Centromeres help to maintain chromosomes accurately aligned throughout the laborious process of cell division. During the process of cell division, as the chromosomes are replicated to form a new cell, the centromere serves as the attachment point that holds the two identical halves of each replicated chromosome, known as sister chromatids, together. Humans have 23 pairs of chromosomes, for a total of 46 chromosomes. These are made up of one sex chromosome and 22 autosomes. Each parent gives one chromosome to each pair, resulting in a kid who receives half of his or her chromosomes from their mother and half from their father. In humans and most other complex creatures, the female parent inherits one copy of each chromosome and the male parent inherits the other. Males and females differ in a pair of chromosomes known as the sex chromosomes, males have one X and one Y chromosome and females have two X chromosomes (Pathak & Bordoni, 2023). The X chromosome resembles a large autosomal chromosome with two distinct arms: one short and one long while the Y chromosome has one long and one extremely short arm. The human X chromosome is approximately three times bigger than the human Y chromosome, having around nine hundred (900) genes, whereas the Y chromosome has approximately fifty-five (55) genes.

Spermatogenesis

The process by which male creatures make mature sperm cells, also known as spermatozoa, is known as spermatogenesis. The process begins at puberty and continues throughout the male organism's existence (Nishimura et al., 2017). The seminiferous tubules in the testes are where spermatogenesis occurs. Spermatogonia, diploid cells that give rise to sperm cells, divide and differentiate during the process. Spermatogonia undergo mitotic division during the process to create primary spermatocytes, which are diploid cells (Nishimura et al., 2017). Following meiosis, the primary spermatocytes divide into secondary spermatocytes, which are haploid cells. Following their initial round of meiosis, the secondary spermatocytes divide once again to create haploid spermatids. Eventually, these spermatids undergo a process known as spermiogenesis, during which they develop into mature sperm cells by differentiation (O'Donnell, 2014). The spermatids go through significant structural changes during spermiogenesis, such as the acrosome's development, the flagellum's elongation, and the shedding of extra cytoplasm. An adult sperm cell with the ability to fertilise an egg is the end product.

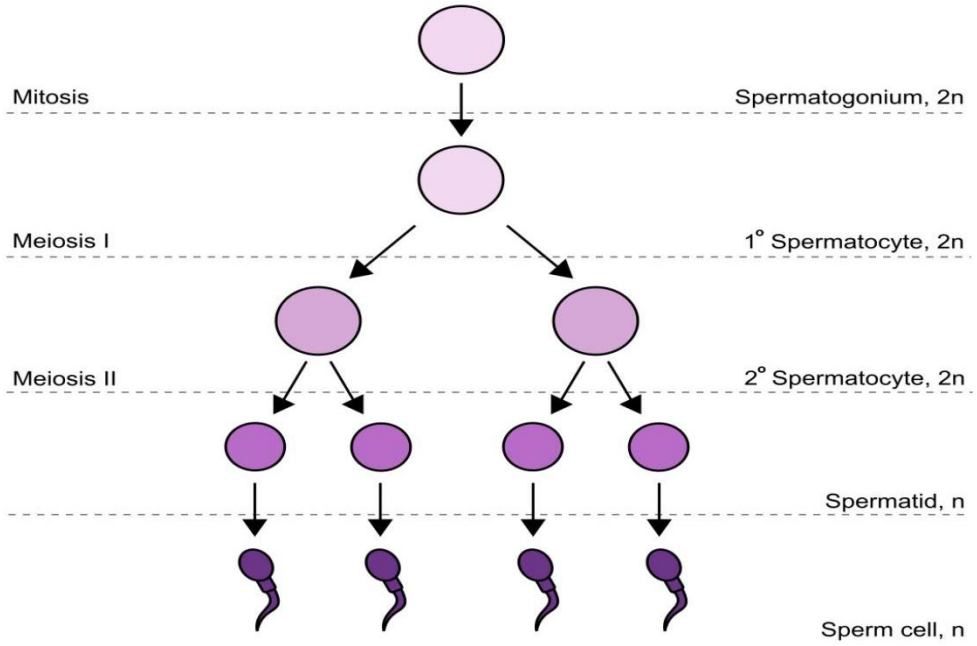

Figure 2: A schematic illustration of the process of spermatogenesis. Mitotic proliferation is the initial phase where spermatogonial cells undergo mitotic divisions to produce primary spermatocytes.

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These primary spermatocytes then undergo the first meiotic division to form secondary spermatocytes, which undergo the second meiotic division to produce haploid spermatids. Finally, spermatids undergo spermiogenesis to transform into mature spermatozoa (Nishimura et al., 2017)

Structure of the Y Chromosome

The Y chromosome is a compact chromosome, characterized by a diminutive p arm and an extended q arm. The p arm primarily consists of genes and DNA sequences essential for determining maleness, including the TDF (Testis determining region) and SRY (Sex determining region on Y). The Yp regions, though brief, possess a euchromatin composition that promotes gene abundance and frequent transcription. The Y chromosome, a sex chromosome, is relatively small compared to other chromosomes in the human genome, accounting for approximately 2% to 3% of the haploid genome. Although often considered a gene of lesser importance, the human Y chromosome plays a vital role in reproduction as its presence or absence determines the gonadal sex(S Al-Ouqaili et al., 2022). Male development is primarily facilitated by 95% of the Y chromosome, while the remaining 5% is referred to as PAR (pseudoautosomal regions), which are characterized by their transcriptional inactivity (Rabinowitz et al., 2021). The Male-specific region of Y (MSY) is a segment on the Y chromosome that plays a key role in the development of male gonads and is essential for spermatogenesis. This region contains genes responsible for these developments. It is made up of euchromatin and heterochromatin regions. The euchromatin area comprises SRY (sex-determining region Y gene),

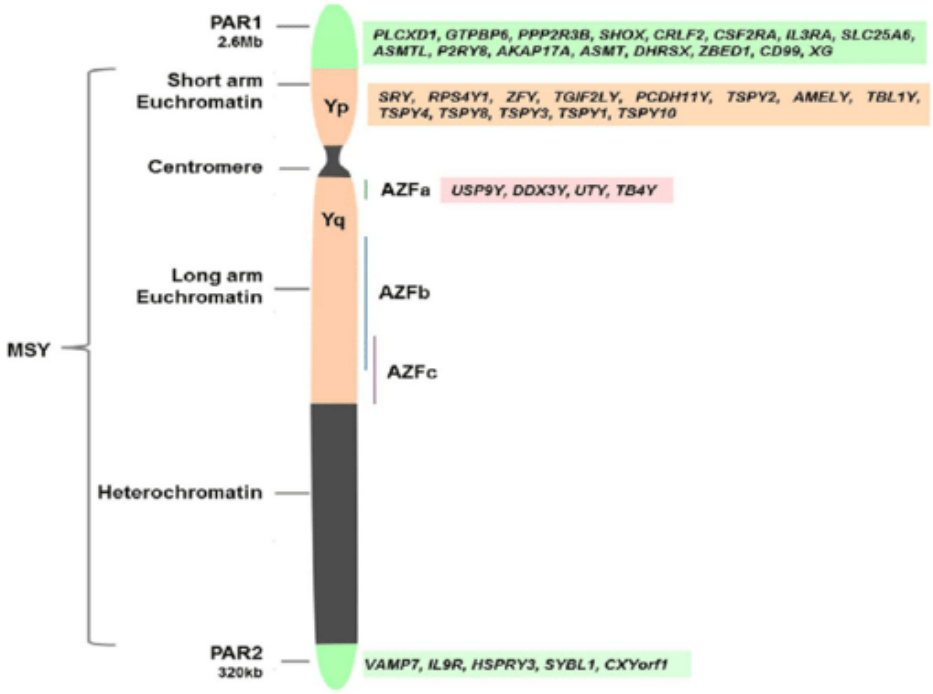

Figure 3: Diagrammatic representation of the segments of the male Y chromosome, where AZFa, AZFb, and AZFc are located on the long arm of the chromosome. (Colaco & Modi, 2018)

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TDF (Testis determining Factor), and AZF-like (Azoospermia Factor-like) genes, whereas the heterochromatin section has SINEs (short interspersed nuclear elements) sequences that are tandemly repeated throughout the MSY region. Beyond the SRY gene, the Y chromosome also contains genes which play important roles in spermatogenesis. The PAR region contains genes that are homologous to those on the X chromosome and participate in recombination during meiosis. These regions are located at the ends of both chromosomes with PAR1 being a 2.7Mb segment at the tip of the short arm and PAR2 being a smaller 0.3Mb segment at the end of the long arm. During male meiosis, the PAR regions of X and Y unite and exchange genetic information. The rest of Y, on the other hand, is preserved.

Evolution of the Y Chromosome

The Y chromosome, a critical component of the human genome, has long piqued the interest of researchers due to its particular characteristics and critical role in controlling male reproductive development. The Y chromosome has undergone significant changes during the history of evolution, including gene loss, structural rearrangements, and adaptations. Understanding the development of the Y chromosome provides vital information on male genetic history, including insights into the beginnings of mankind, sex determination, and the complicated architecture of the human genome. The Y chromosome, which determines male sex, can be traced back to a common ancestor with the X chromosome that lived around 180-300 million years ago. Interestingly, the Y chromosome was not always so different from its female counterpart. It shared many genes with the X chromosome in the beginning (Wilson et al., 2020). However, over time, the Y chromosome acquired genes necessary for male-specific functions such as sperm production and testicular development. Despite having a shared evolutionary origin, the Y chromosome has undergone extensive genetic decay and has lost 97% of its ancestral genes. In contrast, the X chromosome has maintained its gene content and order (Wilson et al., 2020). The Y chromosome is a fascinating subject of study due to its unique characteristics. One of its most notable features is its significant reduction in genes, a process known as "gene decay." This process involved the gradual accumulation of mutations and the elimination of genes that were unnecessary for the male-specific functions of the organism. Interestingly, over the course of millions of years, the human Y chromosome underwent a complex transformation. While it lost 90% of its genes that were once shared with the X chromosome, it also gained new genes through transposition and amplification (Wilson, 2021). The Y chromosome has undergone degeneration throughout evolution, resulting in a reduction in size and gene composition. This incidence is attributed to a lack of recombination with the X chromosome during meiosis, which makes it vulnerable to genetic degradation. As a result, the Y chromosome has lost a significant amount of its hereditary genes, with just a small number of genes remaining active. In addition to gene loss, the Y chromosome has experienced multiple structural changes over the course of evolution. These changes have resulted in the creation of ampliconic regions, which consist of repeated sequences that are susceptible to rearrangements and duplications. These structure variations contribute to the differentiation of the Y chromosome and may impact fertility and the ability to reproduce successfully. To summarize, the progression of the Y chromosome signifies a fascinating expedition through the past of male genetics. Notwithstanding its reduced dimensions and genetic composition, the Y chromosome still influences the growth of males and provides a significant understanding of the evolution of humanity, the history of populations, and the determination of sex. The ongoing investigation into the Y chromosome holds the potential to solve additional enigmas and illuminate the intricate relationship between genetics, gender, and the variety of human beings. The Y chromosome is a remarkable example of the evolutionary processes that shape our genetic makeup. Its evolution highlights the importance of adaptation and the constant changes that occur over time, ultimately leading to the diversity of life we see today.

Role of the Y Chromosome in Fertility

The Y chromosome is crucial for male fertility, containing several genes that contribute to the development and function of the male reproductive system, including sperm production. Its presence dictates the formation of a male foetus during early embryonic development. The Y chromosome encompasses the SRY (Sex-determining Region Y) gene, which initiates the distinction of undifferentiated gonads into testes. The testes then generate hormones, like testosterone, that stimulate the growth of male reproductive organs (Subrini & Turner, 2021). The Y chromosome also harbours genes necessary for spermatogenesis, the process of sperm The Y chromosome plays an essential role in male fertility. It contains multiple genes involved in the growth and function of the male reproductive system, as well as production. The AZF (Azoospermia Factor) regions on the Y chromosome contain genes crucial for the growth and maturation of sperm cells. These genes have roles in various aspects of spermatogenesis, including germ cell proliferation, meiosis, sperm motility, and sperm maturation. It impacts the regulation of hormones involved in male reproductive function (Subrini & Turner,

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2021). The genes on the Y chromosome are responsible for the production and control of hormones such as testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Appropriate hormone equilibrium is essential for the growth and upkeep of male reproductive organs and optimal sperm production. The Y chromosome contributes to the development of secondary sexual characteristics in males. Genes on the Y chromosome influence traits such as facial hair growth, deepening of the voice, muscle development, and body structure. The Y chromosome carries genetic information that is passed down from father to son through generations. It plays a crucial role in preserving the genetic integrity of the male lineage. Genetic mutations or microdeletions on the Y chromosome can disturb normal sperm production and lead to fertility problems. The MSY is believed to play a crucial role in spermatogenesis by performing a range of functions such as gene silencing, transcription, ubiquitination, and maintenance of microtubule networks. As a result, it's not surprising that deletions within the MSY region, specifically Y-chromosome microdeletions, are the most common genetic causes of impaired spermatogenesis. These deletions are responsible for up to 5% of severe oligospermia cases and 10% of azoospermia cases in men (Rabinowitz et al., 2021).

Overview of Male Infertility

Infertility can be a frustrating and disheartening experience for couples. It is defined as the inability to conceive a child after a year of unprotected sex. Shockingly, statistics show that around 15% of couples fall into this category. Of this percentage, approximately 35% of cases are caused by female factors, while 30% are caused by male factors. Another 20% of cases arise from a combination of both male and female factors. Surprisingly, 15% of cases remain unexplained. Understanding the root cause of infertility can help couples take the next steps towards achieving a successful pregnancy (Carson & Kallen, 2021). Male infertility is described as the lack of ability of a male to make a fertile woman pregnant, for at the very least one year of unprotected intercourse. Infertility in men can result from deficiencies in sperm formation, concentration, or transportation.

Causes of Male Infertility

1. Sperm Abnormalities: Most cases of male infertility are caused by sperm abnormalities which affects either sperm function or sperm production. These abnormalities include teratospermia, oligospermia, asthenospermia, and azoospermia which can impact fertilization negatively (Leslie et al., 2023).
2. Hormonal Imbalances: Sperm production and maturation involves hormones like testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and gonadotropin-releasing hormone (GnRH). When there is an imbalance in the levels of this hormone, sperm maturation and production can be impaired. These imbalances can be caused by several factors such as head injuries in which the hypothalamus or pituitary glands can be affected, which then can cause infertility (Leslie et al., 2023).
3. Varicocele: A varicocele is an enlargement of the veins that drain the testis. It can raise the temperature of the scrotum, impacting sperm production and quality (Leslie et al., 2023).
4. Genetic Factors: Certain genetic conditions can cause male infertility, such as Klinefelter's syndrome, Y chromosome microdeletions and genetic mutations in cystic fibrosis (Leslie et al., 2023).
5. Testicular damage: injury, disease, and some medical treatments, such as radiotherapy or chemotherapy, can cause testicular damage and reduce sperm production (Leslie et al., 2023).
6. Lifestyle factors: Bad habits such as smoking, excessive alcohol consumption, drug abuse and obesity can have adverse effects on sperm quality and fertility (Leslie et al., 2023).

Management of Male Infertility

The treatment of male infertility depends on the underlying cause and severity of the condition. Some common treatment options include:

1. Lifestyle Modifications: Encouraging healthy lifestyle habits, such as quitting smoking, reducing alcohol consumption, and maintaining a balanced diet, can improve sperm quality (Fedder et al., 2021).
2. Hormone Therapy: If hormonal imbalances are detected, hormone replacement therapy may be prescribed to restore normal levels (Fedder et al., 2021).
3. Varicocele Repair: Surgical intervention to repair varicoceles can improve sperm production and function.
4. Assisted Reproductive Techniques: For severe male infertility, assisted reproductive techniques like Intrauterine Insemination (IUI) and In-vitro fertilization (IVF) may be recommended. These methods involve manually fertilizing the egg with sperm outside the body before implanting the embryo into the woman's uterus (Fedder et al., 2021).

Y Chromosome micro-deletion (YCM)

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Y chromosome microdeletion, also known as Y chromosomal deletion or Y chromosome deletion, refers to the partial or complete loss of genetic material on the Y chromosome. The Y chromosome is one of the two sex chromosomes in humans, with males having one X chromosome and one Y chromosome (XY), while females have two X chromosomes (XX). The Y chromosome is a crucial piece of genetic information responsible for the proper growth of testicles and the production of sperm. However, a particular segment of the Y-chromosome, known as Yq, is prone to self-recombination during sperm production, making it more vulnerable to deletions. While the occurrence of these deletions is estimated to be 1 in 4000in the general population, infertile men appear to be at a significantly higher risk (Witherspoon et al., 2021). In simpler terms, the Y-chromosome is like the key to the locker that holds the secret to healthy testicles and sperm production. Unfortunately, a part of this key, known as Yq, is prone to breakage during the process of sperm production. This makes it more likely for men who have trouble conceiving to have missing pieces of this key. While this issue is relatively rare in the general population, it appears to be more common in men with fertility problems. Male infertility can be caused by genetic factors, with Y-chromosomal deletions being the second most commonly diagnosed cause after Klinefelter syndrome. These deletions can cause instability in the Y chromosome, leading to an increased risk of further deletions. This can be seen as a form of "genomic instability," which can have significant consequences for male fertility (Colaco & Modi, 2018). As a result, screening for these deletions is now routine in males with azoospermia and severe oligospermia. The Azoospermia factor (AZF) refers to a group of proteins or genes encoded by the azf region on the human male Y chromosome. Deficiencies in this region are linked to an inability to produce sperm. The AZF region can be split into three subregions: AZFa (also referred to as AZF1), AZFb (also called AZF2), and AZFc. Microdeletions in the AZF region are a significant factor in male infertility, causing complete absence of sperm in the ejaculate (azoospermia) and severely low sperm count (less than 5 million spermatozoa in the ejaculate) in males (Witherspoon et al., 2021). The MSY comprises a variety of heterochromatic sequences and three distinct types of euchromatic sequences: X-transposed, X-degenerate, and ampliconic. The ampliconic sequences are particularly notable for their distinctiveness. They display exceptional uniformity, with nearly identical sequence identity and include many gene regions that are specific to the testes (Xia et al.,2019). The MSY, or male-specific region of the Y Chromosome, encompasses a significant 95% of the chromosome that does not undergo recombination or crossover with the X chromosome during meiosis. This region has remained unchanged in primate and eutherian genomes for countless years, consisting partly of amplicon sequences that are predominantly expressed in the testis. Approximately a fourth of the MSY euchromatin in humans is composed of these amplicon regions, which are organized into eight extensive palindromic sequences that are practically indistinguishable. The amplicon sequences frequently undergo gene conversion, a non-reciprocal transfer, which has effectively prevented their genetic deterioration. However, these large amplicon regions are susceptible to homologous recombination, which may lead to deletions within the MSY regions (Rabinowitz et al., 2021). The Y chromosome in humans is inherited exclusively from the father to the son and is not shielded against the build-up of replication mistakes, in contrast to other chromosomes that are corrected by combining genetic information from both parents. This could mean that natural selection is the primary mechanism for repairing the Y chromosome. As daughters do not receive a Y chromosome from their fathers, they will not encounter any fertility or health issues themselves. On the other hand, the sons will inherit the anomaly and, as a result, may also experience similar fertility problems as their fathers.

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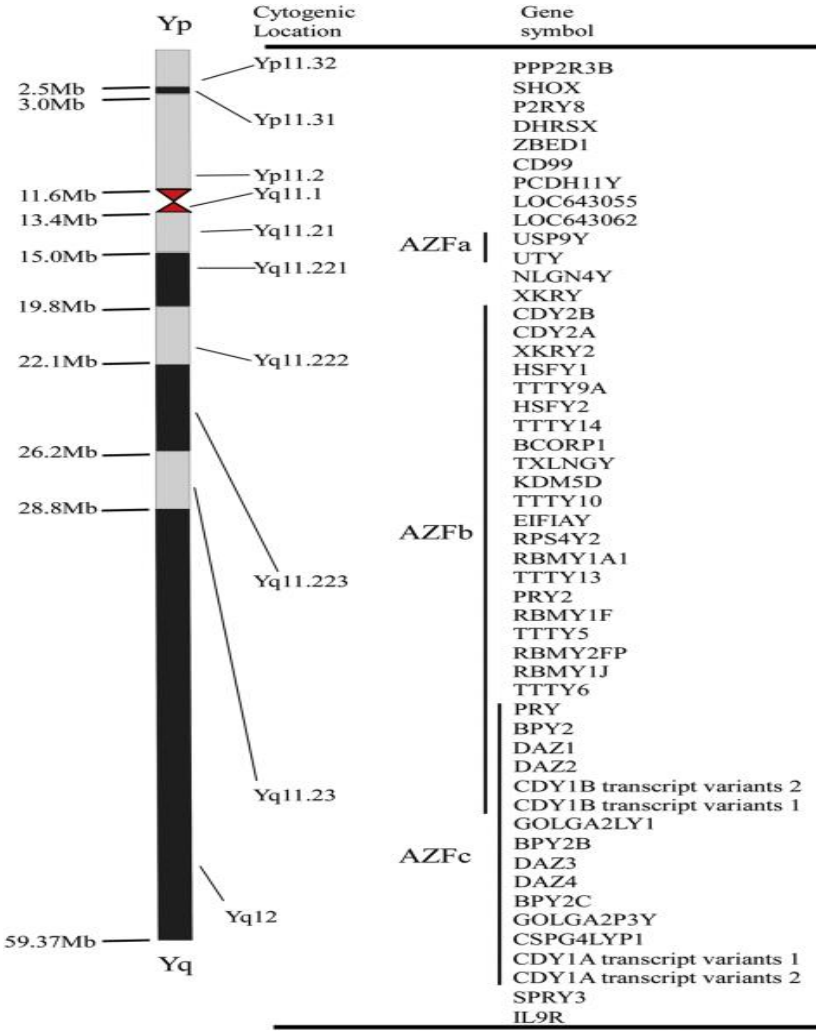

Figure 4: Schematic diagram highlighting the specific genes involved in the deletion of the AZFa, AZFb, and AZFc segments of the Y chromosome (Lan et al., 2023)

AZF 1: AZFa Deletions

The AZFa sub-region occupies a position in the vicinity of the elongated arm of the Y chromosome Yq. AZFa region deletions make up a percentage ranging from 0.5% to 4% of all Yq-microdeletions. Complete deletions of the AZFa region lead to azoospermia and Sertoli cell-only syndrome (SCOS). When these deletions are present, the chances of finding spermatozoa during surgical testicular exploration for intracytoplasmic sperm injection (ICSI) are non-existent. Consequently, offering testicular sperm extraction (TESE) or micro-TESE is not recommended (Witherspoon et al., 2021). This extensive region spans over 1 Mb and includes four distinct genes. Among them is the ubiquitin-specific peptidase 9 Y (USP9Y) chromosome gene, formerly known as DFFRY or the Drosophila fat facets related Y gene. Additionally, it contains the DEAD-box RNA helicases, Box 3, Y-linked (DDX3Y or DBY); the widely transcribed tetratricopeptide repeat containing, Y-linked (UTY); and the thymosin beta 4 Y-linked (TB4Y) gene (Alksere et al., 2019). Spermatogenesis, the process of sperm production, involves the participation of two specific genes, namely DBY and USP9Y. The key gene in the AZFa region, DDX3Y, is mainly active in the testes and plays a role in the development of germ cells before meiosis. Reduced expression of DDX3Y is linked to prenatal germ cell depletion resulting in infertility. In addition, the USP9Y gene contributes to the spermatogenesis process (S Al-Ouqaili et al., 2022). Azoospermia, oligozoospermia, and oligoasthenozoospermia occur due to the reduction or absence of the USP9Y gene. When the AZFa region is completely deleted, along with both of these genes, it typically results in Sertoli cell-only syndrome (SCOS). This condition is marked by the presence of Sertoli cells in the testes but the absence of spermatozoa leading to azoospermia. However, partial deletions of the AZFa region have been found to result in a range of phenotypes, from azoospermia to normozoospermia (S Al-Ouqaili et al., 2022). Partially deleted AZFa genes may not influence spermatogenesis, and sperm production may be significantly impaired only if

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there are abnormalities in the DDX3Y gene, which is one of the AZFa genes. A study showed that in partial AZFa deletion, involving part of the USP9Y gene was not harmful as it was transmitted from father to son (Alksere et al., 2019). Complete AZFa deletions are caused by recombination between HERV15 class proviruses, which might be the causes of Sertoli cell only (SCO) syndrome (Alksere et al., 2019)
Major Genes involved in AZFa deletion include:

The DDX3Y gene:
DEAD-box Y RNA helicase DBY (DDX3Y) gene located in the (AZFa) region on the human Y chromosome. Individuals with deletions of DBY may exhibit both Sertoli cell-only syndrome and severe hypo-spermatogenesis. DBY has a similar structure on the small section of the X chromosome known as DBX (DDX3X) (Colaco & Modi, 2018). The DBY gene is predominantly found in the tissues of the testis, and the translation of this gene is only in the male germ line. DBY protein has been predominantly found in spermatogonia in the testis tissue. Deletion of the DBY gene is the most probable reason for the intense testicular pathology seen in males with AZFa deletions. The DDX3Y gene, which is found on the Y chromosome, encodes an ATP-dependent DEAD-box RNA helicase that is expressed primarily in germ cells and is thought to act throughout the G1-S phase of the cell cycle (Kleiman et al., 2012). Helicases are enzymes that untangle and restructure RNA and DNA structures, which are required for a variety of biological functions such as transcription, translation, and RNA splicing. The gene is activated early in germ cell development and stays highly expressed throughout the maturation of sperm. It is essential for active control of RNA metabolism, which is required for the generation of sperm-specific proteins and the proper formation of spermatozoa. SSC (spermatogonial stem cell) self-renewal and differentiation have been connected to DDX3Y. According to research, DDX3Y is involved in limiting SSC growth and maintaining its uncommitted state. DDX3Y deficiency may result in a reduced reservoir of SSCs, thereby affecting sperm production and reproductive capabilities.

1. The USP9Y gene:
Ubiquitin-specific peptidase 9, Y-linked (fat facets-like, Drosophila), also recognized as USP9Y is an enzyme that is encoded by the USP9Y gene in humans. It is necessary for the generation of sperm. USP9Y spans 170 kilobases of DNA, has at least 46 exons, and occupies just a small section of the AZFa region. USP9Y encodes a large protein of the C19 cysteine peptidase family that removes ubiquitin and increases the stability of proteins targeted for destruction by the proteasome (Colaco & Modi, 2018). USP9Y and its X-homologue, USP9X, are X-inactivated and found in both adult and embryonic tissues. USP9Y regulates protein breakdown by inhibiting proteasome degradation of proteins via the elimination of ubiquitin from protein-ubiquitin pairs and also supports the stability of de-ubiquitinated target proteins, thereby having a significant impact on male germ cell formation Kleiman et al., 2012However, there was a study showing that complete deletion of the USP9Y gene does not result in issues with sperm production, nor does it prevent the ability to naturally conceive children (Alksere et al., 2019).

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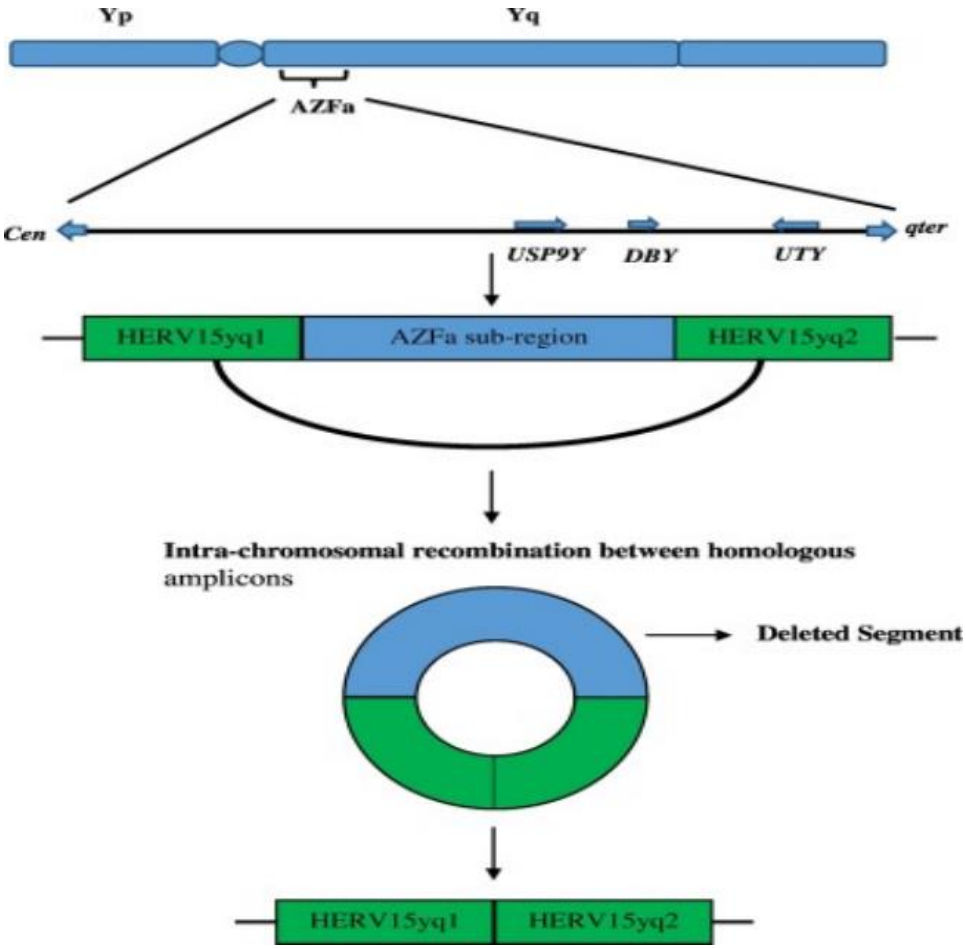

Figure 5: Illustrative representation of the complete deletion of the AZFa region of the Y chromosome (Nailwal & Chauhan, 2017)

AZF 2: AZFb Deletions

AZFb microdeletion is a condition that affects the fertility of males by causing the removal of genetic material, in the AZFb region of the Y chromosome. The presence of AZFb microdeletion is strongly linked to issues, in the production of sperm resulting in either an absence of sperm (azoospermia) or a severe reduction, in sperm count (severe oligospermia). The AZFb locus is at the centre of Yq11 and spans 3.2 Mb and 1.5 Mb overlapping with AZFc. The AZFb region contains 14 multi-copy sequence units called amplicons (Colaco & Modi, 2018). AZFb and AZFc are overlapped and have caused different deletion patterns; P5/proximal P1 which leads to complete AZFb, and two AZFbc deletion patterns: P5/distal P1 and P4/distal P1. 7.7Mb and 42 copies are lost from AZFbc deletions or 7.0 Mb and 38 copies removed, respectively, and occur at a frequency of 1–3% of Yq-microdeletions. AZFbc deletions, like AZFb deletions, cause SCOS and azoospermia; hence, TESE is typically not suggested since the odds of discovering spermatozoa are limited (Witherspoon et al., 2021). The AZFb region contains several genes like, the EIFA1Y (Eukaryotic translation initiation factor 1A), HSFY (Heat Shock Transcription Factor, Y-linked), PRY also known as PTPN13 Like Y-Linked (Tyrosine-protein phosphatase non-receptor type 13), RBMY1 (RNA-binding motif protein, Y-linked, family 1), RPS4Y (Ribosomal protein S4, Y-linked), KDM5D (Lysine-Specific Demethylase 5D protein) (Vogt et al., 2021). The functions of most genes are unknown.

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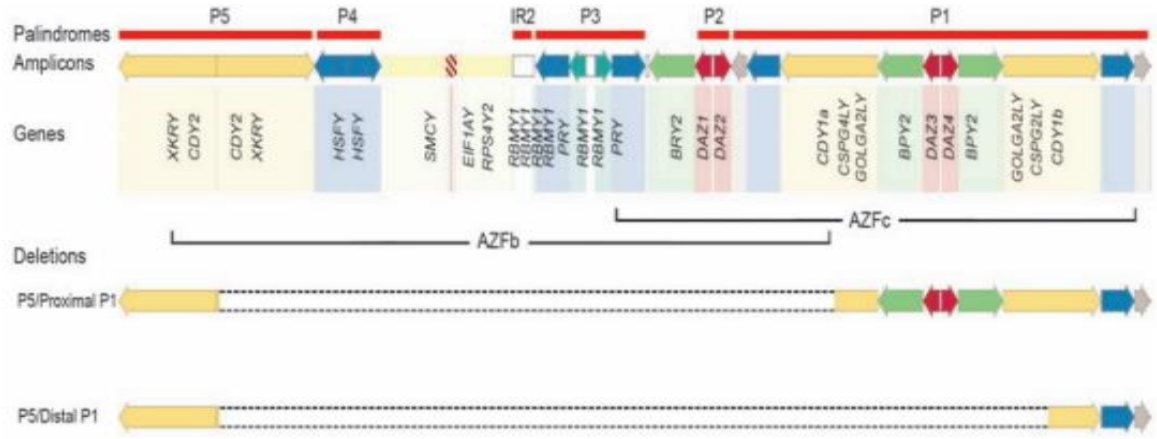

Figure 6: Complete AZFb deletion with all the genes involved (Sadeghi-Nejad & Farrokhi, 2006)

Major genes involved in AZFb deletion include:

The EIFA1Y gene:

The EIFA1Y gene is involved in the development of sperm cells in males, a process known as spermatogenesis. This gene is only found in males and is only found on the Y chromosome. Its principal purpose is to produce a protein known as eukaryotic translation initiation factor 1A (EIF1A), which is essential for starting protein synthesis via initiating translation. The EIFA1Y gene is actively transcribed in the testes during the process of spermatogenesis in a specific type of cell called spermatogonia. The expression of the EIFA1Y gene is carefully controlled to ensure the timing and coordination of spermatogenic functions. The EIFA1Y gene is responsible, for generating the eIF1A protein, which plays a role in the initiation of translation. Its primary function is to facilitate the attachment of ribosomes to messenger RNA (mRNA) molecules. This attachment enables ribosomes to initiate the process of translating instructions contained in mRNA into proteins. This mechanism is essential for the production of proteins and for the development and maturation of sperm cells. EIF-1A proteins promote the dissociation of ribosomes into subunits and help stabilise the binding of the 43S complex to the end of capped RNA during protein biosynthesis (Colaco & Modi, 2018). A defective eIF1A protein could result in faulty translation initiation, impacting the production of the necessary proteins needed for sperm formation. The testis and ovary were reported to have the highest levels of EIF1AY protein expression. Similar to DDX3Y, EIF1AY plays a role in regulating the efficiency of ribosomal translation initiation. However, single deletions of the EIF1AY gene associated with male infertility have not yet been identified (Vogt et al., 2017).

The HSFY gene:

The gene HSFY has two coding variants in the AZFb region, known as HSFY1 and HSFY2. Despite similarities with the DNA-binding domain of heat shock transcription factors (HSF), HSFY does not bind to heat shock elements and no specific promoters targeted by HSFY have been identified during sperm cell development. HSFY is exclusively expressed in the testes and the principal cells of the epididymis. It is localised in the nuclei of germ cells, especially in round spermatids. Reduced levels of HSFY protein in the testes of men with maturation arrest suggest that this gene is involved in regulating spermatogenesis. Its function remains unknown but in humans, it is thought to play a role in spermatogenesis. HSFY gene expression was found to be important for the formation of male germ cells following meiosis. According to research, the absence of HSFY gene expression may contribute to the substantial testicular abnormalities associated with meiotic arrest in the testis tubules of infertile males with AZFb deletion. HSFY protein is found in many germ cells, including spermatogonia, zygotic spermatocytes and elongated spermatids as well as in Sertoli cells. In some families in southern France with hypospermatogenesis, complete deletion of HSFY (2 gene copies) has been observed to be inherited across several generations. As a result, they are unlikely to be the cause of the primary AZFb pathology (meiotic arrest) (Vogt et al., 2017).

The PTPN13 is Like a Y-linked gene.

PRY is a gene that is specific to the testis and encodes a protein that is comparable to protein tyrosine phosphatase, non-receptor type 13. These proteins are essential regulatory elements in signal transduction pathways and cell cycle regulation and play a crucial role in the management of cell growth, multiplication, specialization, alteration, and synaptic adaptability. There are two nearly identical copies of the gene PRY1 and PRY2. The PRY genes are believed to play a role in the control of programmed cell death associated with the

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elimination of abnormal sperm. The loss of both PRY1 and PRY2 genes has been linked to meiotic arrest (Colaco & Modi, 2018). According to research, removing all of the genes in the AZFb region except RBMY and PRY reduces sperm production. However, removing both RBMY and PRY entirely stops sperm production. This shows that these two genes are important in fertility. This protein expression was found in spermatids and spermatozoa therefore, this protein phosphatase is believed to play a role in the apoptotic elimination of non-functional spermatozoa. However, since the PRY protein is not present in premeiotic germ cells, its involvement in the testicular pathology associated with AZFb deletion (meiotic arrest) remains uncertain. Detecting single deletions of the PRY gene is challenging due to the high sequence similarity between the two functional gene copies which are located in the P3 palindrome of AZFb (Vogt et al., 2017).

The RBMY1 gene:

The RBMY gene is of considerable importance in the AZFb region, with approximately six copies distributed across the Y chromosome. Proteins from the RBM gene family are characterised by an N- N-terminal RNA recognition motif (RRM) that facilitates their interaction with target RNA molecules. In contrast to other RBM genes, RBMY1A1 features a C-terminal protein interaction repeat domain rich in serine, arginine, glycine and tyrosine (SRGY). This domain likely serves as a regulatory region for modulating the function of RBMY1A1 (Colaco & Modi, 2018). RBMY1-encoded proteins are expressed only in male germ cells and probably mainly in premeiotic germ cells (Vogt et al., 2017). RBMY1 encodes an RNA-binding protein present in the nuclei of spermatogonia, spermatocytes, and round spermatids that are exclusive to the testes. Protein expression is reduced in the testes of males with AZFb deletions.

The RPS4Y gene:

The RPS4Y gene, also known as Ribosomal Protein S4 on the Y chromosome. The RPS4Y gene encodes the ribosomal protein small subunit 4, a protein that plays a function in mRNA binding and is found at the interface of the small ribosomal subunit's 40S and 60S subunits. The RPS4Y1 is present in the testicles and prostate and is expressed at higher levels during the production of sperm. It encodes for a ribosomal protein subunit that is structurally conserved and necessary for the binding of mRNA to the ribosome. During spermatogenesis, ribosomal protein S4 is selectively produced and may be critical for germ cell growth (Lopes et al., 2010). Additionally, it has a function in the regulation of the spermatogenic process after transcription. This shows that the RPS4Y protein is important in the complex processes of sperm production and maturation. RPS4Y2 is a gene that is mostly expressed in germ cell-containing testis tissue and the prostate. During primate evolution, the gene developed by duplication from RPS4Y1, which was found on the short Y arm. Infertile males did not have single RPS4Y2 gene deletions, so it is unknown whether or not the protein is essential for human male germ cell development (Vogt et al., 2017).

The KDM5D gene:

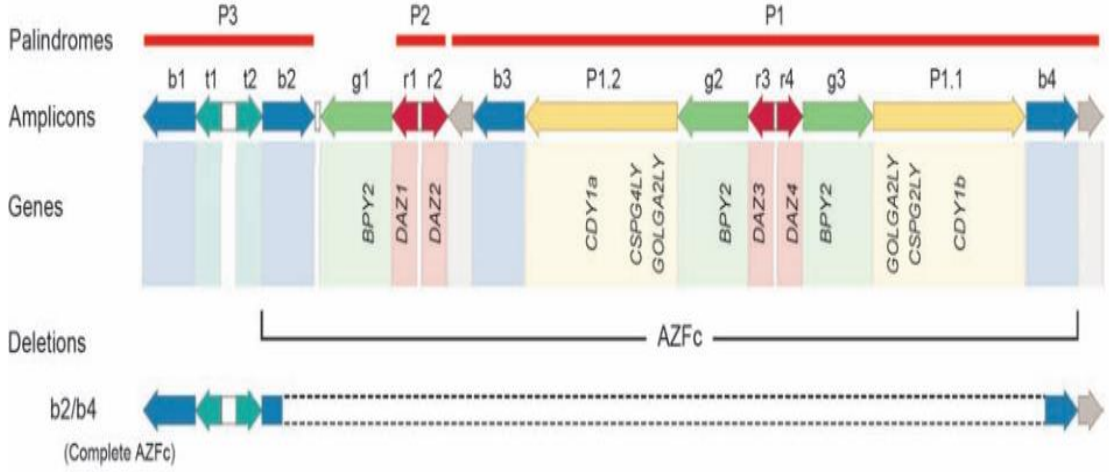
It is believed that KDM5D plays a vital function in the compaction of chromosomes during meiosis by removing methyl groups from di- and tri-methylated H3K4 (Histone H3 lysine K4), thus explaining the halt in development observed at the spermatocyte stage associated with deletions of AZFb. During spermatogenesis, the KDM5D enzyme is also known to form a protein complex with the MutS protein homologue 5 (MSH5) DNA repair factor, which may be seen on compacted DNA during the leptotene/zygotene stage, this suggests KDM5D's role in male germ cell chromatin reorganisation. MutS protein is involved in DNA mismatch repair or meiotic recombination processes (Colaco & Modi, 2018).

AZFc Deletions

Azoospermic factor c (AZFc) deletions are the most frequently observed deletions and can lead to spermatogenic failure in some men with non-obstructive azoospermia or oligospermia (Nickkholgh et al., 2015). AZFc deletions make up to 80% of Y chromosome microdeletion. This deletion occurs when there is a non-allelic homologous recombination repeats between b2, which is in palindromic region 3 and b4, which is in palindromic region 1. It deletes 3.5 Mb with 21 gene copies and transcription units. Complete AZFa deletions have been associated with a wide range of clinical and histological abnormalities, including azoospermia, residual spermatogenesis, and oligozoospermia. There is a 50% possibility of spermatozoa retrieval with TESE (Testicular Sperm Extraction) in cases of full or complete AZFc deletions leading to azoospermia. The success rate varies by approach and can vary from 9% to 80% using micro-TESE (Witherspoon et al., 2021).

The AZFc region on the human Y chromosome has been revealed to have functional importance in the process of spermatogenesis. Complete deletion of the AZFc region is a common cause of male infertility, while the effects of partial deletions (gr/gr and b2/b3 deletions) on spermatogenesis are debatable (Yu et al., 2015). The

AZFc gene is composed of numerous distinct families of long repeats (amplicons), making it susceptible to non-allelic homologous recombination across amplicons, which results in the reappearance of various deletions in the gene. The AZFc region contains five gene families, namely deleted in azoospermia (DAZ), chromodomain Y- linked 1 (CDY1), basic charge linked Y, 2 (BPY2), Golgi family autoantigen Golgi A2 like Y (GOLGA2LY) and chondroitin sulfate proteoglycan 4 like Y (CSPG4LY) (Rabinowitz et al., 2021). These genes are all expressed exclusively or predominantly in the testis and are therefore thought to play a role in spermatogenesis. AZFc deletions in humans usually result in either oligozoospermia or azoospermia (Witherspoon et al., 2021). In most men with azoospermia and AZFc deletions, mature sperm can be found in their testes upon testicular sperm extraction (TESE). Sperm from men with AZFc deletions are capable of fertilization and when used for ICSI (intracytoplasmic sperm injection), they produce viable embryos and pregnancy at rates similar to those achieved with sperm from men without AZFc deletions. In some cases, AZFc deletions have even been passed to offspring through natural conception. A 2015 in-vitro study that compared spermatogonia from men with and without AZFc deletions found that the spermatogonia from AZFc-deleted men behaved similarly to those from controls during culture, displaying comparable characteristics to non-deleted spermatogonia (Nickkholgh et al., 2015). In summary, this research could help in the treatment of AZFc deletion, the spermatogonial stem cells (SSCs) could be extracted from them and be developed in vitro and then transferred back into the testes to



increase sperm count thereby, making them fertile. Two types of partial AZFc deletions have been identified. One partial deletion is the gr/gr deletion, which is caused by homologous recombination between two g or two r amplicons. The other partial deletion is the b2/b3 deletion (also known as the g1/g3 deletion or u3-gr/gr deletion).

Figure 7: Complete AZFc deletion including the involved genes (Sadeghi-Nejad & Farrokhi, 2007)

On the other hand, total or complete AZFc deletion (known as the b2/b4 deletion), has always been recognized as a leading cause of azoospermia or oligozoospermia with very few deviations. It has been known that partial AZFc deletions can increase the risk of complete AZFc deletion, but it is still a topic of research. Genes involved in AZFc deletion include DAZ (Deleted in Azoospermia), BPY2 (Basic Protein on Y 2), CDY (Chromodomain Protein Y), EIF1AY (Eukaryotic Translation Initiation Factor 1A, Y-linked), GOLGA2LY (Golgin A2, Y-linked), PRY2 (PRYSPRY domain-containing 2).

The DAZ gene:

The DAZ gene is situated on the human Y chromosome, precisely in the AZFc area. It is part of the DAZ gene clan, which comprises DAZ1, DAZ2, DAZ3, and DAZ4. The DAZ gene clan encodes a set of RNA-binding proteins that are mainly expressed in the testes, specifically in the germ cells participating in spermatogenesis. The manifestation of DAZ genes is closely controlled, with particular chronological and spatial patterns during sperm production. DAZ genes are significantly expressed in the subsequent phases of sperm production, specifically in lengthening spermatozoa, where they have an essential function in post-transcriptional regulation. The primary function of the DAZ gene family is to aid in the proliferation and survival of germ cells during the early spermatogenesis phase. DAZ protein is an RNA-binding protein that binds to particular mRNAs and controls the translation, stability and transport of these mRNAs within the germ cells (Colaco & Modi, 2018). Post-transcriptional regulation plays a critical role in the synthesis of proteins necessary for the proper

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maturation and function of sperm. Ribonucleoprotein (RNP) complexes are formed by DAZ proteins and play a key role in the translation and metabolism of mRNA. RNP complexes are critical for synthesizing proteins that are involved in various stages of spermiogenesis, including the remodelling of chromatin, the formation of acrosomes, and motility. DAZ gene copy deletions, when combined with changes in other proteins, have an effect on spermatogenesis, which is a prevalent cause of infertility in males. DAZ is found in spermatogonia, early and late-stage spermatocytes, and postmeiotic germ cells up to mature sperm cells. (Lan et al., 2023).

The PRY2 gene:

Deletion of the PRY2 gene can cause complete meiotic arrest (Tahmasbpour et al., 2014). Studies show that deleting all of the genes in the AZFb region except RBMY and PRY results in hypospermatogenesis, whereas deleting both RBMY and PRY results in complete spermatogenesis. This shows that these two genes are the most important in fertility (Colaco & Modi, 2018). In a study, with males that had PRY2 gene deletion, there were no sperm cells found when they performed testis biopsies (Stouffs et al., 2001).

The BPY2 gene:

The BPY2 gene is primarily expressed in the testis and its protein product plays a crucial role in the formation of male germ cells. On the Y chromosome, there are three nearly identical copies of this gene- BPY2A, BPY2B, and BPY2C. Two of these copies are located at the edges of the gr/gr deletion, adjacent to the DAZ gene clusters (Colaco & Modi, 2018). BPY2 is present in the nuclei of spermatocytes, round spermatids, and spermatogonia. The BPY2 gene encodes a small positively charged protein that is believed to contribute to cytoskeletal regulation during spermatogenesis. Due to their small size and high charge, BPY proteins are thought to interact with DNA like chromatin-associated proteins such as histones and high mobility group proteins, which are involved in regulating processes such as transcription and replication. The BPY2 gene is in the non-recombinant portion of the Y chromosome and is expressed exclusively in the testes. The encoded protein interacts with the ubiquitin protein ligase E3A and may have a role in male germ cell development and male infertility (Lan et al., 2023).

The CDY gene:

The CDY gene is found on the human Y chromosome near the AZFc region, which contains spermatogenesis-related genes. CDY1 and CDY2 genes are duplicated in the CDY gene family. CDY genes code for chromodomain proteins that are involved in chromatin remodelling and epigenetic control during spermatogenesis. The deletion or low expression of CDY genes is associated with male azoospermia; however, the specific molecular mechanism involved is unknown. (Xia et al., 2019). The CDY1 gene encodes a protein with an N-terminal chromatin-binding domain that assists in gene expression control, and chromatin remodelling, and encodes a histone acetyltransferase. This protein is concentrated in the round spermatid nucleus, where histone hyperacetylation occurs, causing histones to be replaced by sperm-specific DNA-packing proteins (Colaco & Modi, 2018). Chromatin remodelling is critical during spermatogenesis for controlling gene expression and maintaining appropriate DNA packing within developing sperm cells. Chromatin remodelling is critical during spermatogenesis for controlling gene expression and maintaining appropriate DNA packing within developing sperm cells. The CDY genes were likewise found to be expressed solely in testis tissue, and the protein was mostly found in spermatids. CDY proteins are histone acetyltransferases that prefer histone H4 and are found in the nuclei of mature spermatids. This shows that they contribute functionally to the unique histone hyperacetylation process in late spermatids, resulting in a more open chromatin structure necessary to promote spermatogenic histone replacement by transition proteins and protamines (Vogt et al., 2017). In summary, the CDY gene plays a crucial role in chromatin remodelling and sperm development therefore, dysregulation or disruptions in CDY genes can result in abnormal chromatin organization, affecting sperm quality and motility.

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Selected Studies on Y Chromosome Micro-deletion

S/N	Reference	Model	Key Point
1	Alksere et al., 2019	Human	In this study, men with partial AZFa deletions involving the USP9Y gene were used and they found out that the partial deletion of this gene does not affect fertility. They also proved the inheritance of this partial deletion from father to son.
2	Kleiman et al., 2012	Human	This study involved identical twins with complete AZFa deletions. One had undergone right testis orchiopexy at 6 years of age and TESE at 32 years of age but in another facility and he reported that no spermatids were detected to undergo an IVF/ICSI procedure. On the other twin, a TESE was conducted and sperm retrieval was nil.
3	Kleiman et al., 2011	Human	This study involved men with complete and partial AZFb and AZFb-c deletions and the likelihood of finding sperm cells in men with complete versus partial AZFb and AZFb-c deletions was significantly lower.
4	Zhang et al., 2007	Human	In this study, it was observed in the pedigrees that 14.3% of the complete AZFc deletions were derived from the gr/gr deletion, indicating the possibility of a two-step process leading to complete deletions of AZFc. It remains unclear whether partially deleted AZFc is more susceptible to complete deletion compared to non-deleted AZFc.
5	Beyaz et al., 2017	Human	Turkish men may not experience a noteworthy impact on their fertility, sperm counts, and outcomes of assisted reproductive technology (ART) due to partial deletions in the AZFc region.
6	Yuen et al., 2021	Human	The following case report details the presence of sperm in the ejaculate of a man who had a complete AZFa deletion, partial AZFb and AZFc deletions.
7	Stouffs et al., 2017	Human	Two patients were found to have a deletion of the AZFb region through basic diagnostic tests. Surprisingly, both patients still exhibited some level of sperm production. Upon further investigation, it was found that the first patient, a 35-year-old male, had been trying to conceive with his partner for over two years. After undergoing basic diagnostic tests, it was discovered that he had a deletion of the AZFb region. Despite this, he was still able to produce small amounts of sperm, which were able to fertilize his partner's egg through in vitro fertilization. The second patient, a 28-year-old male, also underwent basic diagnostic tests which revealed a deletion of the AZFb region. Despite this, he was still producing small amounts of sperm, which were discovered during a routine semen analysis. While he was not actively trying to conceive, this unexpected discovery opened up the possibility for future fertility treatments should he decide to have children.
8	Nickkholgh et al., 2015	Human	This study observed that AZFc deletions do not have any significant effect on spermatogonia in culture. Interestingly, AZFc-deleted spermatogonia have been found to progress fully to spermatozoa in vivo. This discovery suggests that increasing the number of spermatogonia in culture could potentially be a direct treatment option for men with AZFc deletions.
9	Romo-Yáñez et al., 2022	Human	The presence of partial gr/gr microdeletions has been found to have a significant correlation with infertility in the Mexican population. The study conducted in Mexico revealed that these microdeletions were more prevalent in infertile men compared to fertile men, indicating a strong association between the two.
10	Hopps et al., 2003	Human	The complete deletion of the AZFa or AZFb regions of the Y chromosome is associated with an extremely unfavourable prognosis for the retrieval of viable

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			sperm. In contrast, the majority of men with AZFc deletion have sperm present within their semen or testes that can be utilized for in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI).
11	Rolf et al., 2002	Human	It has been observed that a patient who had inherited a partial deletion in the AZFb region from his father was able to transmit the same deletion to his son in a spontaneous manner. Additionally, it was found that the father of an infertile patient who had a mutation in the AZFb region had an identical deletion in the same region. These findings provide evidence that the AZFb deletion can indeed be transmitted.
12	Ferlin et al., 2005	Human	Partial deletions of the AZFc region that only remove DAZ1/DAZ2 are linked to issues with sperm production, while deletions of DAZ3/DAZ4 may have minimal or no impact on fertility. This information suggests that, in addition to complete AZFc deletions, certain partial deletions pose a risk for male infertility, although they may affect spermatogenesis differently. The retrieval of sperm from the testicles is extremely difficult for patients with non-obstructive azoospermia (NOA) who have deletions in the AZFa or AZFb genes, which makes natural conception or intra-cytoplasmic sperm injection (ICSI) impossible. Therefore, invasive testicular sperm retrieval is not recommended in such cases, and instead, donor-assisted reproduction or adoption is advised.
13	Giachini et al., 2008	Human	The findings of this research indicate that the gr/gr deletion poses a risk for reduced sperm production in Caucasian individuals, particularly those of Italian descent.
14	Luddi et al., 2009	Human	In this study, they have conducted a detailed analysis of a deletion in AZFa that leads to the absence of USP9Y in a normothermic man and his father and brother. They demonstrate that USP9Y, which was previously considered a potential infertility gene, does not play a critical role in male reproduction, as evidenced by the normal fertility of the individuals with this large deletion. Therefore, it may not be necessary to include USP9Y in the screening of the Y chromosome for microdeletions in infertile or subfertile men, based on these results.
15	Dicke et al., 2023	Human	This study presents compelling evidence that DDX3Y is the primary gene responsible for spermatogenic failure in males with complete AZFa deletions. Furthermore, three individuals carrying this variant underwent TESE and exhibited a testicular phenotype consistent with Sertoli-cell-only syndrome (SCO). This phenotype is also commonly observed in individuals with complete AZFa deletions. Therefore, this genotype-phenotype correlation strongly suggests that the absence or impaired function of the DDX3Y protein is the underlying cause of SCO, azoospermia, and male infertility. This conclusion holds regardless of whether the mechanism involves an AZFa deletion or a point variant leading to loss of function.

Conclusion

Male infertility is a complex issue with various contributing factors. Spermatogenesis, the major determinant in male fertility, is largely influenced by genes found on the male Y chromosome. The long arm of the Y chromosome (Yq) contains sequences that are prone to self-recombination during spermatogenesis, which can lead to deletions within the chromosome. Deletions of genes within the male-specific region of the Y-chromosome, known as Y-chromosome microdeletions (YCMs), have been implicated in male sterility resulting in conditions such as oligospermia and azoospermia. While the exact functions of these genes are not yet fully understood, screening for AZF deletions can aid in identifying the cause of male infertility and guide appropriate genetic counselling and management. Recognizing this, men must undergo diagnostic testing to address potential future issues. Assisted reproductive techniques such as intracytoplasmic sperm injection (ICSI) or microscopic testicular sperm extraction (mTESE) can assist infertile men in achieving reproduction.

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