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Y CHROMOSOME MICRODELETION AND POSSIBLE RISK FOR REPRODUCTIVE CANCER

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ABSTRACT

Y chromosome microdeletions (YCMs) are now recognized as important genetic variables impacting the health of male reproduction. This article explores the relationship between Y chromosomal microdeletions and cancer risk in the reproductive system, namely prostate and testicular germ cell tumors (TGCTs). Y chromosomal microdeletions, specificallythe gr/gr deletion, have been established through multiple investigations as factors associated with male infertility and spermatogenic failure. Recent research indicates a potential correlation between certain YCMs and an increased susceptibility to reproductive malignancies. Despite the unclear nature of the connection between YCMs and prostate cancer,thorough investigation remains crucial. It is imperative to delve deeper into the intricate interconnections between YCMs and this prevalent male reproductive cancer, as several studiespropose associations suggesting a heightened risk of prostate cancer linked to YCMs.

Key words: *Microdeletion, Y chromosome microdeletion, Azoospermic factor, Oligospermia,Testicular germ cell tumour*

INTRODUCTION

Infertility is the inability to conceive after a year or more of regular, unprotected sex, usually resulting from reproductive difficulties in either partner [1]. Kumar and Singh suggested that approximately one out of every twelve males are expected to encounter infertility during their lifetime. Among those experiencing infertility, it is anticipated that 90% will have either azoospermia or oligospermia as the primary underlying conditions [2]. Cooper et al., found that oligospermia is characterized by a sperm count of fewer than 15 million sperm per ml of ejaculate, which indicates that it falls below the 5th percentile among fertile men [3]. Hoops et al., proposed that the condition is stratified into three severity groups: moderate, mild and severe [4]. The complete absence of sperm in the ejaculate is the distinguishing feature of azoospermia, which is classified into two types: non-obstructive and obstructive.

In the study conducted by McElreavey et al., it was elucidated that the Y chromosome, despite its relatively diminutive size, constitutes a mere 2-3% of the haploid genome [1]. Notwithstanding its limited physical presence, this chromosome plays a pivotal role in encoding genes crucial for both spermatogenesis and the determination of male sex [1]. In the 1970s Tiepolo and Zuffardi studied, men with azoospermia were found to have anomalies in their Y chromosome, notably deletions in its long arm. The discovery gave rise to the formulation of the azoospermic factor (AZF) theory [6]. This theory proposes that the factor is encoded by one or more genes exclusive to the Y chromosome. Genes in the male-specific Y chromosome, according to Krausz and Casamonti, control vital functions such as transcription, ubiquitination, gene silence and microtubule network maintenance, making them crucial for spermatogenesis. Proficient spermatogenesis is frequently linked to Y chromosomal microdeletions, which are common in this site. Further research by Krausz and Casamonti revealed that these deletions were present in roughly 5% and 10%, respectively, of severe cases of oligospermia and azoospermia [7].

Y chromosome microdeletions, or YCMs for short, are the term used to refer to the deletions connected to the AZF [8,9]. Bianchi et al., reported that deletions in the AZF are associated with testicular germ cell tumors (TGCT) and other malignancies. In these cases, AZF deficiencies may occur in both tumor and non-tumor cells and in non-tumor cells, they are recognized to precede the onset of cancer [10]. The objective of this review is to investigate the reproductive cancer risk among patients with Y chromosome microdeletions.

METHODS

This thorough analysis uses a wide range of clinical and scientific data to examine the risk of reproductive cancer linked to Y chromosome microdeletions. To find relevant studies, a thorough database search was carried out using PubMed and Google Scholar. Approximately one hundred original papers directly related to the topic were carefully chosen for inclusion out of a large pool of 17,400 review articles. The gathered information was thoroughly scrutinized in order to provide crucial information on the connection between Y chromosomal microdeletions and their risk of reproductive cancer.

1) Y CHROMOSOME MICRODELETION

Y chromosome microdeletions refer to minute submicroscopic deletions occurring in the proximal Yq, which result in the removal of either the entire AZF region or specific portions of it, leading to complete deletions [11, 12]. Extensive studies on deletion mapping in infertile men have identified five distinct deletion patterns on the Yq chromosome, as reported by Soars et al., in their studies [13]. These are grouped together and referred to as AZFa, AZFb, AZFd and AZFc deletions.

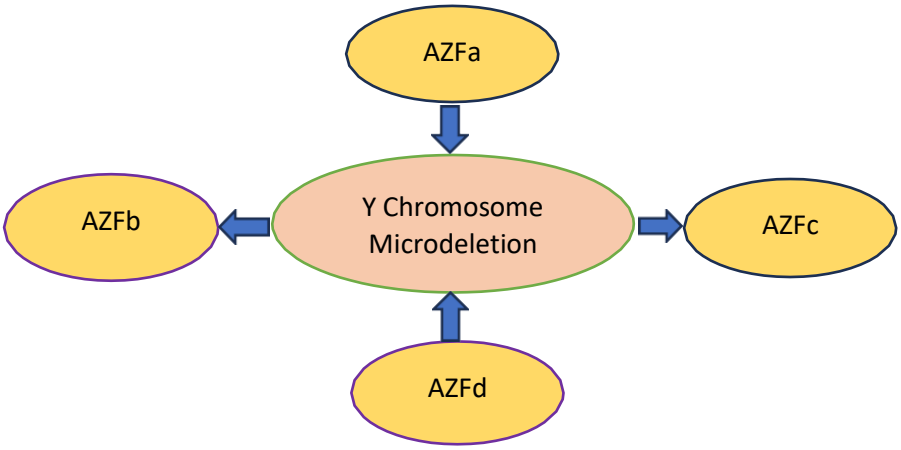

Figure 1: Y Chromosome Microdeletion

Sen et al., found the occurrence of these deletions ranks among the primary contributors to spermatogenic failure [14]. Consequently, the screening for AZF deletions explained by Simoni et al., has integrated into the standard diagnostic evaluation for infertile men [15]. Luddi et al., assessed individuals exhibiting the most significant decline in spermatogenesis. They noted that deletions within AZFb, AZFa and AZFc, which are located closest to the centromere, are linked to the greatest degree of damage. It is believed that AZFd has little clinical

significance in this situation. Besides the particular deleted locus, the deletion size plays a crucial role in prognosis, as multiple deletions have a more detrimental impact on sperm counts compared to single deletions [16]. Stahl et al., discovered that some individuals with Y chromosome microdeletions might exhibit a typical sperm in their ejaculate, whereas others may require surgical extraction of sperm from the testis [17]. In addition to deletions within the AZFc region, various types of complete deletion result in substantial impairment of spermatogenesis, leads to low or non-existent sperm retrieval rates (SRRs) as reported by Shi et al., in 2011 [18].

Table 1: Role of AZF factors

AZF region	Role of AZF region	References
AZFa	Essential for spermatogonia development, AZFa plays a crucial role in male reproductive health. Deletions in AZFa are associated with Sertoli cell-only syndrome and a complete absence of sperm (azoospermia), resulting in a severe impact on male fertility.	[19]
AZFb	A factor in sperm motility and maturation, AZFb is linked to reproductive processes. The effects of AZFb deletions on male fertility are mild since they are associated with oligozoospermia, or low sperm count, and decreased sperm motility.	[20]
AZFc	Crucial for sperm production, AZFc is integral to reproductive processes. Deletions in AZFc are associated with oligozoospermia and may have a variable impact on sperm production, potentially leading to male infertility.	[21]
	The role of AZFd is not completely understood, and ongoing research is needed for a clearer comprehension. Some studies	

AZFd	suggest its potential involvement in sperm production and maturation, emphasizing the necessity for further investigation to elucidate its specific role in male reproductive health.	[22]

1.1) AZFa Deletions

Azoospermia and Sertoli cell-only syndrome (SCOS) occur by the absence of the AZFa region [23, 24, 25, 26, 27]. SCOS may have numerous genes missing, according to Gueler et al., which could result in the demise of germ cells during development [28]. This occurs as a result of the AZFa genes being expressed in germ cells during fetal development. Wei and associates evaluated the role that loss of genetic content plays in forecasting the frequency of azoospermia resulting from AZFa deletions. For this reason, partial deletions have been connected to a variety of abnormalities, including normozoospermia and azoospermia [29]. MSY of the Y chromosome contributes to the process controlling the incidence of YCMs.

1.2) AZFb Deletions

The genes located within the AZFb locus are believed to play a crucial role in facilitating the accurate progression of sperm development, guiding the process from meiosis to spermiogenesis by promoting the growth and maturation of sperm [29]. Navarro-Costa et al., showed that individuals with deletions in the AZFb region commonly display a testicular phenotype marked by maturation arrest. This means that a significant number of tubules lack post-meiotic germ cells, in spermatocyte stage [30]. A significant association was noted by Kleiman et al., between the degree of the AZFb deletion and the histological characteristics of testicular tissue. Partial deletions of AZFb/b + c often exhibit hypospermatogenesis, while complete deletions of more severe symptoms are seen in AZFb and AZFb+c. This implied that rather than causing a severe phenotype, AZFb deletions impede spermatogenesis. The character of maturation arrest associated with AZFb deletions is probably the result of a blend of genetic disruption and structural abnormalities in the chromosome [27, 31].

Jungwirth et al., acknowledged that in cases of AZFb deletion, there is very little chance of collecting mature sperm cells through ejaculation or testicular sperm extraction [32]. Nevertheless, there are reports by Liu et al., and others the effective sperm extraction from

testes of people with AZFb deletions [33, 34, 35, 36]. These discrepancies can represent variances in the degree of deletion in various cases. As per the report by Kleiman et al., it is noteworthy to emphasize that guys with complete AZFb deletions have a much-reduced chance of having sperm cells than males with partial AZFb deletions [27].

1.3) AZFc deletions

The phenotype observed in individuals with AZFc deletions displays considerable variability, encompassing complete azoospermia to mild oligozoospermia [37]. Guys with AZFc deletions typically have elongating spermatids in their testes, while infertile guys with AZFc deletions can retrieve significant amounts of sperm, as reported by Simoni et al., [15, 25]. Abid et al., evaluated that the majority of people with AZFc deletion, spermatogenesis is finalized but occurs on a diminished scale, leading to oligozoospermia [26]. Sen et al., concluded the drastic reductions in sperm count are associated with complete AZFc deletions, with most males displaying severe oligozoospermia [38, 14]. In the study of Krausz et al., suggested that in certain instances, individuals may even manifest azoospermia [38, 24]. Saut et al., conducted a study on males with AZFc deletions, revealing rare instances where these individuals, despite the genetic anomaly, have naturally fathered multiple children. Nevertheless, all sons born to these males have been determined to be infertile [39, 40, 41]. Fu et al., analyzed the evidence that sperm count steadily decreases in a subgroup of males with AZFc microdeletions, despite the fact that AZFc deletions are generally less detrimental in and of themselves. According to the assessment of Simoni et al., these people may develop azoospermia or potentially advance from oligozoospermia to its severe form [42, 43, 44]. This suggests that spermatogenesis is temporarily hampered by AZFc deletions, which lowers the amount and quality of sperm. Consequently, men with AZFc deletions may still have sperm in their ejaculate, but to circumvent the need for invasive procedures like testicular sperm aspiration (TESA) for sperm retrieval later in life, it is recommended to offer their semen for cryopreservation.

1.4) Partial AZFc deletions

Due to the repeating sequences and parallax, the AZFc area is particularly prone to deletions. Repping et al., found several transcriptional unit copies inside AZFc and the full deletion of 12 genes in the b2/b4 area. Partial deletions involving b1/b3 (1.6 Mb), gr/gr (1.6 Mb), and b2/b3 (1.8 Mb) were also detected in the AZFc locus, and they were related to b2/b4

[45]. Repping et al., assert that despite this, all three variations are consistently labeled as gr/gr throughout the analysis and are not categorized into any other group [45]. Three distinct gr/gr deletion types arise from homologous recombination operations at the g1/g2, r1/r3 and r2/r4 amplicons inside the P1 and P2 palindromes found in the AZFc region. However, they do reduce the overall number of copies within those gene families [46]. In the study by Fernandes et al., it is found that loss occurs in four DAZ gene copies, one CDY1 gene copy, one BPY2 gene copy and one gr/gr deletion. Moreover, the elimination extends to one of the three BPY2 copies and two DAZ genes [47].

- **b2/b3 deletion**

Originating from an inversion, the b2/b3 deletion, which is larger at 1.6 Mb in comparison to the 1.8 Mb gr/gr deletion, came into existence. According to Bansal et al., the connection between partial deletions of b2/b3 and spermatogenic failure remains unclear [48]. In 2016, Bansal et al., analyzed 11,684 Y chromosomes from fertile, normozoospermic males and 17,784 Y chromosomes from infertile men. The results suggested a slight yet statistically significant association between the b2/b3 deletion. Asians shows the highest prevalence in b2/b3 deletion at around 3%, while Europeans have the lowest prevalence, approximately 0.5%. There is no appreciable difference in its incidence in either case between males who are fertile and those who are not. Unexpectedly, there is no observed correlation between b2/b3 deletions and male infertility in Australian men. The prevalence of b2/b3 deletions differs significantly between normozoospermic-fertile and infertile men of African origin (1.17 vs. 0.25), in contrast to gr/gr deletions, which do not indicate a significant connection with male infertility in African males, as shown by Rozen et al. [49].

- **b1/b3 deletion**

After investigating the b1/b3 deletion, Rozen et al., found that it is not the same as the gr/gr or b2/b3 deletions [49]. More specifically, its influence results in the loss of six RBMY1 copies and two PRY copies from a particular region of AZFb. Approximately one in every 994 men have the b1/b3 deletion, according to a 20,000 Y chromosome examination. This deletion, which has an odds ratio of 2.5, dramatically increases the likelihood of spermatogenetic failure despite its very modest frequency. Nonetheless, the majority of populations do not realize the connection between this loss and male infertility because it occurs so frequently [49].

ii) Prevalence of Y chromosome microdeletions

Y-chromosomal microdeletions, also known as YCMs, have been detected in up to 2% of men in the general population who were not specifically chosen based on any particular characteristics, as reported by the Practice Committee of the American Society for Reproductive Medicine (ASRM) [50]. The European Academy of Andrology reports that approximately 1 in 4,000 males, constituting 0.025%, are affected by Y-chromosomal microdeletions (YCMs). nevertheless, in guys who are not expressly picked or selected, their prevalence is far lower [51]. Genetic screening studies have enhanced their comprehension, revealing that Y-chromosomal microdeletions (YCMs) are exceedingly uncommon among men categorized as normospermic those with a sperm concentration exceeding 20 million/mL of ejaculate.

Krausz et al., imply that Y-chromosomal microdeletions (YCMs) are rare within normospermic men whose sperm quantity is more than 20 million per milliliter of ejaculate based on genetic screening data. In a 2001 study that included 392 normospermic men, the screening revealed no Yq deletions [51]. Moreover, an AZF microdeletion was found in 5% of people who were categorized as severely oligospermic (having fewer than one million sperm per milliliter of ejaculate), according to a recent meta-analysis conducted by Kohn et al., which included over 10,000 men in North America [52]. The frequency of these deletions, however, was fewer than 1% in guys whose sperm count exceeded 20 million in their ejaculate or normospermic concentrations [52].

iii) Male Infertility and Copy Number Variation

Copy Number Variation (CNV) is the term used to describe a DNA segment with a copy number variation of more than one kb that differs from a reference genome [48, 53]. Lu et al., revealed that variations in copy numbers (CNVs) influence phenotypes through diverse mechanisms, including modulation of gene dosage, the presence of formation of fusion genes, an interrupting gene, unmasking of recessive coding regions, mutations, functional Single Nucleotide Polymorphisms (SNPs), and position effects [54]. Sen et al., came to the conclusion that because the array of microdeletions inside the AZF region which change the copy numbers of Y chromosome, they might be regarded as extremely significant CNVs [55]. Noordam et al., assessed how the AZFc region's inherent instability can result in several rearrangements that alter the total number of copies among the gene families contained therein [56]. Gene CNVs within AZF are caused by full or partial deletions of AZF have adverse effects on

spermatogenesis [57, 58, 59]. Lee et al., have investigated copy number variants (CNVs) over the entire Y chromosome in addition to the AZF sites in the context of male infertility [60, 61, 62]. Large duplications in the TBL1Y and AMELY genes, partial deletions from the TSPY cluster, variations in the quantity of RBMY genes, and duplications of two intersecting segments are among them.

iv) Y Chromosome Microdeletion; Risk Factors

a) Recurrent Pregnancy Loss

Studies by Dewan et al., and Karaer et al., on the link between Y chromosomal microdeletions (YCMs) and recurrent pregnancy loss (RPL) have shown conflicting results [63, 64]. Bellver et al., reported that the frequency of YCMs in men whose partners have had RPL has been the subject of multiple research projects, yet the results have been inconsistent [65, 66]. Five of the nine relevant publications state that there is no chance of a relationship between YCMs and RPL [67, 68, 69, 70]. Since the patient selection criteria and procedures used in two of the four studies that suggested this relationship violated the guidelines set by the European Molecular Genetics Quality Network and the European Academy of Andrology, they have come under criticism [71].

b) Health Abnormalities

Two sections of the Y chromosome are known as PARs, and the roles of the majority of PAR genes are still unknown. The results of a study by Thomas and colleagues indicated that whilst differences in height are connected to duplications of the SHOX gene, short stature is linked to haploinsufficiency of the SHOX gene [72]. Jorgez et al., aimed to determine whether genetic abnormalities in the pseudoautosomal regions (PARs) are present in people with Y-chromosomal microdeletions (YCM) [73]. They proposed that YCM-causing factors could be associated with genetic abnormalities other than those seen in the AZF areas, namely those involving PARs. Males lacking PAR CNVs were on the lower end of the height distribution, whereas males with YCM and PAR CNVs were significantly shorter than the third percentile or had dramatically varied statures (<25th percentile, >95th percentile), according to the study. Interestingly, all of the individuals with unusual karyotypes and AZFbc deletions also had abnormal PAR values [73]. Concurrently, researchers Castro et al., discovered in a different study that the only individuals having copy number variants (CNVs) within the PARs were those who had terminal AZFbc deletions [74]. Katagiri et al., reported that no PAR CNVs were found in patients with interstitial deletions of AZFa, AZFb, AZFc or AZFbc. The

psychosocial, motor or intellectual development of children does not seem to be adversely affected by AZF deletions of Yq [75]. Mateu et al., noted that the patients with YCM, chromosomally aberrant embryos were seen; a notable proportion of these embryos had monosomy X [76]. Kim et al., and others have proposed a link between YCM and 45X/46XY due to the mitotic instability observed in YCM [77, 78, 79, 80, 81, 82, 83]. Nevertheless, data available from Kihaile et al., and others indicated that embryos from men with YCM do not exhibit an elevated risk of adverse traits [84, 85, 86, 87, 88, 89]. It would be advantageous for future research to explore whether the nature and extent of YCM, along with other potentially influencing factors, play a role in shaping the association, providing a more comprehensive understanding of the relationship between health abnormalities and YCM [90, 91, 92].

- **Azoospermia factor (AZF) genes and cancer**

The RNA-binding motif protein, Y-linked (RBMY), isoforms that are often eliminated in azoospermic patients are repetitive and are encoded by genes located in the AZF area. Dreumont et al., implicated that RBMY selectively binds to RNA stem-loops that include a C[A/U] CAA pentaloop as a cap, possibly assisting in the alternative splicing of various transcripts pertaining to genes specific to the testis [93, 94]. Meiotic failure due the loss of RBMY [95]. In 36% of instances of male liver hepatocellular carcinoma (HCC), anomalies in RBMY expression were found by Tseui et al., these aberrations were not seen in normal liver tissues [96, 97]. Overexpression of RBMY caused tumorigenicity in mouse fibroblast 3T3 cells [94]. While RBMY knockdown reduced transformation and anti-apoptotic efficiency in the liver cancer cell line HepG2 [97]. Additionally, in the animal model of diethylnitrosamine-induced hepatocarcinogenesis, transgenic mice expressing liver-specific RBMY showed an accelerated onset of hepatic neoplastic alterations [97]. The data from the study of Nathanson et al., imply that abnormal RBMY gene expression may have a pivotal role in the formation of hepatocellular carcinoma (HCC), despite the lack of a defined mechanism. Microdeletion within the AZFc region contains multiple copies of the DAZ, CDY1 and BPY2 genes. The presence of these AZF gene deletions increases the risk of seminoma [98, 99].

- **Testicular cancer**

It has long been believed that the Y chromosome may be the source of gonadal malignancies because it is associated with individuals who have gonadal dysgenesis. According to Modi et al., people with whole or partial Y chromosomes, even in a small number of cells, are more likely to develop gonadal malignancies, especially gonadoblastoma [100,

101, 102, 103]. Moreover, Nathanson et al., have been proposed that Yq microdeletions and/or its CNVs may pose a risk for testicular cancer development [98]. Although these are small-scale observational studies, the outcomes of extensive case control studies are still to be obtained. Beyond infertility, it is becoming more and more clear that understanding Yq microdeletions could help forecast the occurrence of malignancies in men.

Nathanson et al., identified a connection between testicular germ cell tumors (TGCT) and the gr/gr deletion [98]. Their study found the gr/gr deletion in 2.9% of TGCT cases, 3.0% of cases with a family history, and 1.3% of males without TGCT. The deletion increased TGCT risk twofold (aOR 2.1) and threefold in those with a family history (aOR 3.2). It was also linked to a higher risk of seminoma (aOR 3.0) but not significantly to nonseminoma TGCT (aOR 1.5). These results suggest that the rare gr/gr allele is a low-penetrance risk factor for TGCT.[98].

- **Prostate cancer**

The process of alternative splicing [104], which produces many transcripts from a single gene, is not well understood in terms of how it affects the genes in Y chromosome [105]. Nonetheless, a protein with a JmjC domain is encoded by the KDM5D gene, specifically related to lysine (K), at the AZFb of the Y chromosome. Remarkably, two new splice variants of KDM5D measuring 2650 bp and 2400 bp in length were found in the human prostate cancer cell line DU-145 [105]. Prostate cancer cell proliferation was enhanced and cell-mediated death was decreased when these splice variants were silenced. The fact that these variants affect RNA processing, protein synthesis, apoptosis, cell cycle regulation and cell proliferation emphasizes how significant they are. The KDM5D splice variants that have been found offer interesting targets for the creation of chemotherapeutics that are specific to tumors [106].

CONCLUSION

Microdeletions, a type of genetic aberration, defined as chromosomal deletions that span many genes and are not detectable using traditional cytogenetic methods. Men with severe oligozoospermia and azoospermia have been found to have a greater prevalence of microdeletions. Highlighting the significance of thorough genetic evaluations in determining individual vulnerability is the complex association between YCMs and reproductive malignancies. Understanding the particular YCMs implicated in each case could improve personalized risk assessment, early identification and intervention techniques. In order to enable focused therapy strategies and knowledgeable clinical management, future research initiatives should seek to elucidate the molecular pathways connecting YCMs to reproductive

malignancies. In conclusion, the current study highlights the dynamic landscape of genetic factors impacting male reproductive health. It advocates for continued research to unravel the intricate roles of Y-chromosomal microdeletions (YCMs) concerning the susceptibility to reproductive cancers. These discoveries have the potential to reshape our understanding of male reproductive health, paving the way for more personalized treatments and preventive measures.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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