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Genetic Causes Of Male Infertility: Diagnostic Significance Of DAZ Gene Cluster Analysis In Azoospermia

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ABSTRACT

Male infertility is a global health concern, and genetic factors play a crucial role in its etiology. Deletions in the DAZ (Deleted in Azoospermia) gene cluster, located on the AZFc region of the Y chromosome, have been identified as a primary cause of spermatogenic failure. The DAZ gene family, comprising DAZ1, DAZ2, DAZ3, and DAZ4, encodes RNA-binding proteins that are essential for germ cell development and spermatogenesis.

Studies have shown that complete or partial deletions of the DAZ gene cluster occur in 5–13% of men with non-obstructive azoospermia or severe oligozoospermia. These deletions disrupt sperm production and lead to impaired fertility. However, advances in assisted reproductive technologies, including testicular sperm extraction (TESE) with intracytoplasmic sperm injection (ICSI), have enabled men with DAZ deletions to achieve biological parenthood.

The evaluation of male infertility now incorporates genetic screening for Y chromosome microdeletions, including the DAZ gene cluster. PCR-based assays targeting sequence-tagged sites (STSs) within the AZFc region allow precise identification of DAZ deletions. These analyses facilitate accurate diagnosis and guide clinical decisions regarding fertility treatment options.

The assessment of DAZ gene cluster integrity remains crucial in the diagnostic workup of azoospermic men. Understanding the genetic basis of spermatogenic failure through DAZ analysis enhances our ability to provide targeted management strategies. Future research on DAZ gene function and regulation may offer new therapeutic approaches for male infertility.

Keywords: *DAZ gene cluster, Azoospermia, Y chromosome microdeletions, Male infertility, Spermatogenesis, Genetic diagnosis.*

1. INTRODUCTION

Male infertility represents a significant and growing concern within the field of reproductive health, contributing to nearly half of all cases of couple infertility. Globally, it is estimated that approximately 7% of the male population is affected by infertility, which is defined clinically as the inability to achieve conception after one year of unprotected intercourse [1,2]. The multifactorial etiology of male infertility encompasses a broad spectrum of anatomical, hormonal, environmental, and genetic factors, with recent advances highlighting the critical contribution of genetic components. Current literature suggests that genetic abnormalities may account for approximately 15–30% of male infertility cases, underscoring the importance of molecular diagnostics in both clinical evaluation and therapeutic strategy development [3].

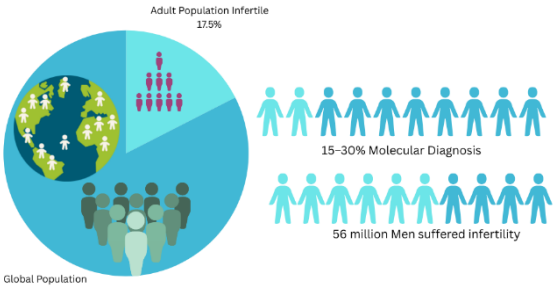


Figure 1: By 2019, global male infertility had impacted 56 million men, with around 17.5% of adults facing infertility issues. Genetic defects account for 15–30% of male infertility cases, underscoring the essential role of molecular diagnostics in clinical evaluation and the development of targeted treatments.

The landscape of genetic factors implicated in male infertility is diverse, ranging from chromosomal aberrations and Y chromosome microdeletions to monogenic mutations and epigenetic dysregulation [4,5]. Among these, Klinefelter syndrome (47,XXY), deletions in the azoospermia factor (AZF) regions of the Y chromosome, and mutations in genes such as CFTR, NR5A1, and TEX11 have been most frequently associated with impaired spermatogenesis. Additionally, advances in next-generation sequencing (NGS) technologies have facilitated the discovery of novel gene mutations and rare variants that may disrupt testicular development, meiosis, and sperm function [6]. These insights not only enhance our understanding of male reproductive genetics but also support the development of personalized treatment approaches and the integration of genetic counselling into infertility care [7].

Despite these advances, significant gaps remain in the identification and interpretation of genetic variants, particularly in idiopathic cases where no overt etiology is discernible. The complexity of gene-environment interactions, the polygenic nature of many infertility phenotypes, and limited functional characterization of newly identified genes continue to challenge researchers and clinicians alike. Moreover, variability in genetic screening practices and diagnostic criteria across clinical settings further complicates the establishment of standardized protocols for genetic testing in male infertility [8,9].

Role of Y Chromosome Microdeletions in Male Infertility

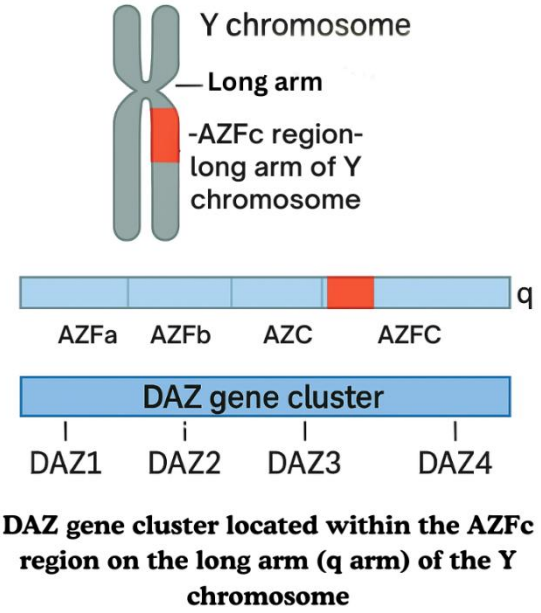
Y chromosome microdeletions in the azoospermia factor (AZF) regions represent a critical genetic cause of male infertility, affecting individuals with non-obstructive azoospermia (NOA) or severe oligozoospermia [10]. These microdeletions are well-characterized genetic defects in male infertility, and their identification is essential for genetic screening in infertile men. The AZF locus on the Y chromosomes long arm (Yq11) is subdivided into three subregions—AZFa, AZFb, and AZFc—containing genes integral to spermatogenesis regulation [11,12].

Deletions in the AZFc region are most frequent, accounting for about 60% of Y chromosome microdeletions associated with spermatogenic failure [13,14]. The AZFc region spans 3.5 Mb and contains gene families including DAZ (Deleted in Azoospermia), BPY2, CDY1, and HSFY, involved in germ cell development. The DAZ gene cluster regulates RNA metabolism in pre-meiotic germ cells. Deletion of these genes impairs sperm production, resulting in oligozoospermia or azoospermia [15,16].

AZFa and AZFb deletions are less common but cause more severe phenotypes. AZFa deletions lead to Sertoli cell-only syndrome, with complete absence of germ cells in seminiferous tubules [17]. AZFb deletions typically cause meiotic arrest, halting spermatogenesis at the primary spermatocyte stage. Combined AZFb+c or complete AZF deletions result in complete absence of spermatozoa and are generally untreatable with current assisted reproductive technologies (ARTs) [18].

Y chromosome microdeletion detection significantly impacts male infertility management. Genetic testing for AZF deletions is recommended for men with unexplained azoospermia or severe oligozoospermia before testicular sperm extraction (TESE) or in vitro fertilization (IVF) (Silber). The presence and type of AZF deletion can predict sperm retrieval success. Men with AZFc deletions may produce limited sperm and benefit from TESE with intracytoplasmic sperm injection (ICSI), while those with AZFa or AZFb deletions typically cannot recover sperm [19,20,21].

DAZ Gene Cluster Overview



DAZ gene cluster located within the AZFc region on the long arm (q arm) of the Y chromosome

Figure 2: Schematic representation of the DAZ gene cluster within the AZFc region of the Y chromosome. The diagram shows the AZFc region on the Y chromosome's long arm (q arm), a segment crucial for spermatogenesis. The AZF region includes AZFa, AZFb, AZFc, and AZC. The DAZ gene cluster in AZFc contains four nearly identical copies: DAZ1, DAZ2, DAZ3, and DAZ4. These genes encode RNA-binding proteins essential for germ cell development. Deletions in this cluster link to non-obstructive azoospermia and severe oligozoospermia.

The DAZ (Deleted in Azoospermia) gene cluster, within the azoospermia factor c (AZFc) region on the Y chromosome (Yq11.23), is crucial for human spermatogenesis (Figure-2). This region is highly complex with ampliconic sequences prone to recombination and deletion events. The DAZ gene cluster contains four nearly identical copies (DAZ1, DAZ2, DAZ3, and DAZ4) arranged in two pairs of inverted repeats, embedded within palindromic sequences that facilitate homologous recombination [22,23].

The DAZ genes evolved from the autosomal DAZL gene on chromosome 3, which transposed to the Y chromosome during primate evolution. Each DAZ gene copy contains 16 to 19 exons with two main domains: an RNA recognition motif (RRM) for binding target RNAs and a DAZ repeat domain for protein-protein interactions in germ cell development [24]. The high sequence identity among DAZ copies challenges gene-specific analysis and contributes to regional instability [24].

DAZ gene products are germ cell-specific RNA-binding proteins essential for spermatogenesis, expressed mainly in spermatogonia and early spermatocytes. They regulate post-transcriptional mRNAs needed for germ cell development [24]. While all DAZ copies are transcribed, they show differential expression levels, indicating that the collective dosage and configuration of the gene cluster are vital for normal testicular function.

Deletions in the DAZ gene cluster commonly cause non-obstructive azoospermia and severe oligozoospermia, typically resulting from non-allelic homologous recombination between ampliconic sequences. Genetic screening for AZFc deletions has become standard in male infertility diagnosis [25]. The phenotypic outcomes vary between partial and complete DAZ deletions, suggesting the influence of modifying factors and necessitating individualized genetic counselling.

Function of DAZ Genes in Germ Cell Development and Spermatogenesis

The Deleted in Azoospermia (DAZ) gene family comprises a group of RNA-binding proteins that are pivotal in the regulation of germ cell development and spermatogenesis [24]. This family includes three primary members: BOULE (BOLL), DAZL (DAZ-like), and DAZ. While BOULE and DAZL are located on autosomes and are conserved across various species, DAZ is situated on the Y chromosome and is specific to higher primates [26].

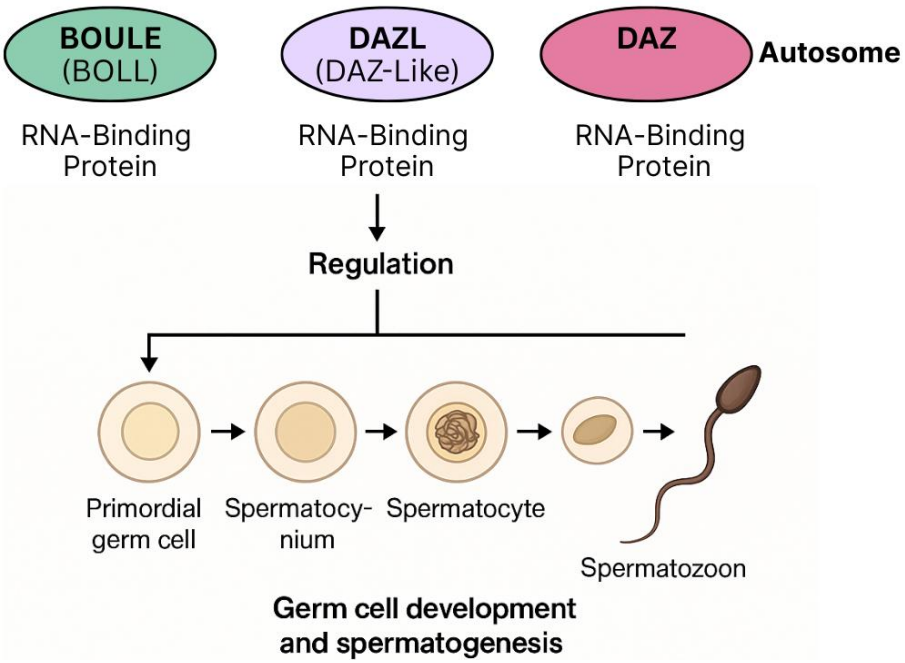


Figure 3: This schematic shows how BOULE (BOLL), DAZL (DAZ-like), and DAZ—evolutionarily related RNA-binding proteins—regulate germ cell development. BOULE and DAZL are autosomal genes, while DAZ is Y-linked in higher primates. These proteins regulate mRNAs essential for germ cell progression. The lower panel shows their influence across male germ cell stages from primordial cells to mature spermatozoa.

DAZ family proteins contain a conserved RNA recognition motif (RRM) and DAZ repeats - 24-amino-acid sequences that facilitate protein-protein interactions. These features allow DAZ proteins to bind target mRNAs and interact with other RNA-binding proteins, influencing post-transcriptional gene regulation during germ cell development [27].

DAZ proteins are expressed in germ cells and are essential for spermatogenesis stages. They transport and activate specific mRNAs critical for germ cell differentiation. DAZL binds to 3' untranslated regions (UTRs) of target mRNAs and interacts with poly(A)-binding proteins (PABPs) to enhance translation efficiency of mRNAs necessary for germ cell development [28].

DAZ and DAZL proteins regulate mRNA stability and localization in germ cells through ribonucleoprotein (RNP) complexes, crucial for proper gene expression during spermatogenesis. Deletions or mutations in DAZ genes have been linked to impaired spermatogenesis and male infertility, highlighting their importance in reproductive biology.

Table 1. Functions of DAZ Genes in Germ Cell Development and Spermatogenesis

Function	Description	Key References
RNA Binding	DAZ proteins contain RNA Recognition Motifs (RRMs) enabling selective binding to target mRNAs.	[29, 30]
mRNA Stabilization	Stabilize germ cell-specific mRNAs critical for spermatogenesis.	[29]
Translation Activation	Promote translation of mRNAs by interacting with poly(A)-binding proteins.	[31,32]
Germ Cell Differentiation	Involved in progression from spermatogonia to spermatocytes.	[26]
RNP Complex Formation	Participate in ribonucleoprotein (RNP) granules for mRNA regulation in germ cells.	[33]
Stage-Specific Expression	Expressed primarily in pre-meiotic and early meiotic germ cells.	[34]

Functional Redundancy	Share functions with DAZL and BOULE, compensating in certain developmental stages.	[35]

Impact of DAZ Deletions on Spermatogenesis

Deletions within the Deleted in Azoospermia (DAZ) gene cluster in the AZFc region of the Y chromosome have been studied for their association with spermatogenic failure. Complete or partial deletions of the DAZ gene cluster occur in 5–13% of men with non-obstructive azoospermia or severe oligozoospermia. These deletions are de novo events and common genetic causes of male infertility [36, 37].

The DAZ gene cluster consists of four nearly identical copies: DAZ1, DAZ2, DAZ3, and DAZ4. These genes encode RNA-binding proteins essential for germ cell development and spermatogenesis [22, 23]. Their loss disrupts sperm production, causing varying degrees of spermatogenic impairment. Deletions of all four DAZ genes result in more severe phenotypes, while partial deletions may lead to hypospermatogenesis or maturation arrest.

DAZ gene deletions do not always prevent sperm production, as some men with complete deletions have rare spermatozoa in their testicular tissue. Testicular sperm extraction (TESE) with intracytoplasmic sperm injection (ICSI) has enabled these individuals to achieve biological parenthood, though success rates are lower than in individuals without deletions [38, 39].

Given the Y-linked inheritance pattern, there is a risk of transmitting these deletions to male offspring, potentially continuing the cycle of infertility. Genetic counselling is recommended for those considering assisted reproduction to discuss potential risks for future generations.

Table 2. Impact of DAZ Gene Deletions on Spermatogenesis

Type of DAZ Deletion	Affected Gene Copies	Phenotypic Manifestation	Sperm Retrieval Potential	Clinical Implications
Complete AZFc Deletion	DAZ1–DAZ4	Sertoli cell-only syndrome; azoospermia	Low–Rare	Common in non-obstructive azoospermia; poor prognosis
Partial DAZ Deletion (gr/gr)	Typically, DAZ1/DAZ2	Oligozoospermia to azoospermia	Moderate	Variable phenotype; may affect sperm concentration
b2/b3 Deletion	Varies	Often subclinical; mild oligozoospermia	High	Less clinically significant; may be a benign variant
Heterogeneous Deletions	Mosaic loss of DAZ copies	Mixed testicular histology; hypospermatogenesis	Variable	May permit assisted reproduction (e.g., TESE-ICSI)
No DAZ Deletion	Intact DAZ1–DAZ4	Normal to mild fertility impairment	High	Indicates alternate etiology for infertility

AZFc = Azoospermia Factor c; TESE = Testicular Sperm Extraction; ICSI = Intracytoplasmic Sperm Injection

Phenotypic Variability Associated with DAZ Gene Cluster Deletions

Deletions within the Deleted in Azoospermia (DAZ) gene cluster in the AZFc region of the Y chromosome are a genetic cause of male infertility. The extent of spermatogenic impairment from these deletions shows phenotypic variability, correlating with the deletion size and location within the DAZ cluster [25].

Complete deletions of all four DAZ gene copies (DAZ1–DAZ4) typically cause severe spermatogenic failure and non-obstructive azoospermia. Partial deletions affecting subsets of DAZ genes can lead to phenotypes from severe oligozoospermia to normozoospermia [40]. Deletions of DAZ1 and DAZ2 cause more severe spermatogenic defects compared to DAZ3 and DAZ4 deletions, indicating varying functional significance among DAZ copies [41].

The phenotypic outcomes are influenced by genetic factors and environmental conditions. Y chromosome haplogroups may modulate DAZ deletion impacts on spermatogenesis [42]. Lifestyle factors like environmental toxins and smoking can worsen the effects of DAZ deletions [43, 55].

Non-allelic homologous recombination events between repetitive sequences cause various deletion patterns with distinct outcomes. The gr/gr deletions, removing half of the AZFc region, are associated with moderate spermatogenic failure risk, while b2/b4 deletions cause more severe phenotypes [41]. DAZ deletions do not always result in infertility, as some men with partial deletions maintain sufficient spermatogenic function. Genetic counselling should consider the deletion type, risk factors, and potential residual spermatogenic activity.

4. Diagnostic Approaches

Molecular Techniques

The detection of microdeletions within the AZFc region, particularly affecting the DAZ gene cluster, is crucial in genetic evaluation of male infertility. PCR assays targeting sequence-tagged sites (STSs) have become the standard method for identifying deletions. Multiplex PCR enables simultaneous amplification of multiple STSs, allowing efficient screening of AZF regions. This technique is widely used due to its sensitivity, specificity, and cost-effectiveness [38].

The European Academy of Andrology (EAA) and European Molecular Genetics Quality Network (EMQN) have established guidelines recommending specific STS markers for detecting AZF deletions. For the AZFc region, markers sY254 and sY255 are commonly used. Absence of amplification indicates a deletion in the corresponding region [39]. Internal controls like the SRY gene ensure PCR process integrity and confirm Y-chromosomal material presence.

Advanced techniques like real-time quantitative PCR and array comparative genomic hybridization (aCGH) enable detailed analysis. These methods allow quantification of gene copy numbers and detection of partial deletions or duplications within the AZFc region, providing comprehensive genetic assessment [44].

Table 3: Molecular Techniques for Detecting AZFc Region Microdeletions

Technique	Description	Advantages	Limitations
PCR-based STS analysis	Uses sequence-tagged sites (STS) specific to AZF subregions (e.g., sY254, sY255)	Widely available; cost-effective; rapid	May miss partial deletions; limited resolution
Multiplex PCR	Amplifies multiple STS markers in a single reaction	Efficient; suitable for initial screening	Cannot determine copy number changes
Real-time quantitative PCR (qPCR)	Quantifies DAZ gene copy number	High sensitivity; quantitative data	Requires standardization; more expensive
Array CGH (Comparative Genomic Hybridization)	Detects copy number variations across the genome including Y chromosome	Genome-wide analysis; high resolution	Costly; requires specialized equipment
Next-generation sequencing (NGS)	Sequencing of Y chromosome or targeted exome panels	High accuracy; detects rare and novel deletions	Interpretation of results may be complex
MLPA (Multiplex Ligation-dependent Probe Amplification)	Detects deletions and duplications in DAZ gene copies	Quantitative; distinguishes between DAZ1–DAZ4	Technically demanding; availability limited in some settings

Clinical Guidelines

Genetic screening for Y chromosome microdeletions, including the DAZ gene cluster, is recommended for men with unexplained non-obstructive azoospermia or severe oligozoospermia. The EAA and EMQN guidelines indicate this screening should be part of the diagnostic workup, as it identifies genetic causes of infertility and informs clinical decisions [43].

The identification of Y chromosome microdeletions has key implications for patient management. Men with AZFc deletions may have residual spermatogenesis and could benefit from assisted reproductive techniques like testicular sperm extraction (TESE) with intracytoplasmic sperm injection (ICSI). These deletions can be transmitted to male offspring, requiring genetic counselling to discuss potential risks and implications [38].

5. Clinical Implications

Assisted Reproductive Technologies (ART)

Men with DAZ gene deletions, particularly in the AZFc region of the Y chromosome, often experience severe spermatogenic failure, causing non-obstructive azoospermia or severe oligozoospermia. Assisted reproductive technologies (ART) have provided ways for these individuals to achieve biological parenthood. Testicular sperm extraction (TESE), especially microdissection TESE (micro-TESE), has been used to retrieve sperm from testicular tissue. Studies show variable success rates with micro-TESE in men with AZFc deletions, with sperm retrieval rates from 9% to 80%, depending on technique and patient criteria [45, 46, 47,48]. Once sperm are retrieved, intracytoplasmic sperm injection (ICSI) facilitates fertilization. However, men with AZFc deletions may have lower fertilization rates and poorer embryo quality compared to men without deletions [49].

Genetic Counselling

DAZ gene deletions have significant implications for genetic counselling. As these deletions are on the Y chromosome, there is risk of transmission to male offspring through ART. Studies have documented Y chromosome microdeletions, including those in AZFc region, being transmitted from father to son via ICSI [39]. This transmission perpetuates infertility, highlighting the need for genetic counselling. Counselling should address potential genetic defect transmission, discuss implications for offspring's fertility, and explore options like preimplantation genetic diagnosis (PGD) or donor sperm use.

Future Perspectives

Research Directions

The Deleted in Azoospermia (DAZ) gene cluster is crucial for spermatogenesis, yet mechanisms of its deletions' impact on germ cell development remain unclear. Research should focus on elucidating molecular pathways disrupted by DAZ deletions, particularly their effects on RNA-binding and translation in germ cells. Single-cell RNA sequencing and proteomics could reveal stage-specific expression of DAZ proteins during spermatogenesis. Gene therapy approaches to restore DAZ function show promise. CRISPR/Cas9 editing and viral vectors could correct DAZ deletions, though challenges in delivery, expression regulation, and ethics need addressing before clinical use [50, 51, 52].

Personalized Medicine

Genomic technologies in clinical practice enable personalized medicine for male infertility management. Next-generation sequencing (NGS) enables screening for genetic anomalies, including DAZ deletions, allowing accurate diagnosis and risk assessment [43]. Genetic profiles enable individualized treatment plans and optimize outcomes. Personalized medicine influences reproductive counselling, where genetic information guides discussions on assisted reproduction and transmission risks. As genetic knowledge expands, our ability to tailor interventions will improve [53].

2. DISCUSSION

The DAZ gene cluster on the Y chromosome plays a critical role in spermatogenesis through germ cell development and RNA regulation. This review examines its prevalence, structure, function, and association with male infertility.

Deletions in the DAZ gene cluster account for 5–13% of non-obstructive azoospermia and severe oligozoospermia cases. The severity of spermatogenic defects correlates with deletion extent; complete deletions cause Sertoli cell-only syndrome, while partial deletions allow varying sperm production. Men with DAZ deletions can produce spermatozoa suitable for assisted reproduction [52, 54].

DAZ genes encode RNA-binding proteins essential for post-transcriptional regulation in male germ cells, affecting mRNA stabilization and translation [29]. Functional redundancy among DAZ family members complicates determining individual gene contributions. Next-generation sequencing and Y chromosome microarray technologies have improved DAZ deletion detection, enabling precise diagnosis and treatment planning. Challenges remain in interpreting partial deletions without genotype-phenotype correlation data [55].

Genetic counseling is crucial for men with DAZ deletions, as male offspring inherit the deletion through assisted reproduction [53]. While gene therapy potential exists, applications remain limited by technical constraints.

3. CONCLUSION

The DAZ gene cluster in the AZFc region of the Y chromosome is essential for human spermatogenesis through its RNA-binding protein function. Deletions in this region commonly cause non-obstructive azoospermia and severe oligozoospermia, contributing significantly to idiopathic male infertility. Recent molecular genetics advances have improved deletion detection and understanding of germ cell development.

While progress has been made, DAZ gene function and deletion effects remain partially unclear. Clinical outcome variability among men with similar deletions necessitates research into modifier genes and environmental factors. High-throughput

genomic technologies, including next-generation sequencing and single-cell transcriptomics, offer promising ways to understand spermatogenic failure associated with DAZ deletions.

Clinical management must include genetic counselling and reproductive option consideration. As personalized medicine advances, using individual genetic profiles to guide diagnosis, prognosis, and treatment will become central to male infertility care.

Acknowledgement:

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