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**The Role of Y-Chromosome Microdeletions in Azoospermia
and Oligospermia: Genetic Mechanisms, Clinical
Consequences, and Diagnostic Approaches**

Laleh Etemad-Ghazani^{1*}

Islamic Azad University, Tabriz Unit

laae77917@gmail.com

Saba adlikhatibi²

University of Tabriz

Sabaadlikhatibi@gmail.com

Abstract

Male infertility represents a major reproductive health concern, with genetic abnormalities, particularly those involving the Y chromosome, contributing substantially to severe defects in spermatogenesis. Among the established genetic causes of non-obstructive azoospermia and severe oligozoospermia, Y chromosome microdeletions are particularly important. These alterations primarily affect the Yq11 region, which contains the three major azoospermia factor (AZF) regions, namely AZFa, AZFb, and AZFc. Most Y chromosome microdeletions are thought to result from non-allelic homologous recombination between highly repetitive sequences, leading to the loss of genes and genomic elements required for normal germ-cell development and sperm production. The clinical consequences vary according to the region and extent of the deletion. Complete deletions involving AZFa or AZFb are typically associated with profound disruption of spermatogenesis and frequently result in azoospermia, whereas AZFc deletions are characterized by greater phenotypic variability, ranging from severe oligozoospermia to complete absence of spermatozoa. Partial deletions within AZFc, especially gr/gr deletions, have also been linked to impaired sperm production and an elevated susceptibility to infertility in specific populations. From a clinical perspective, molecular identification of Y chromosome microdeletions,



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particularly by sequence-tagged site (STS)-based polymerase chain reaction (PCR), is essential for establishing the genetic basis of male infertility, providing prognostic information, and guiding the selection of appropriate assisted reproductive techniques. This review examines the molecular and genetic mechanisms underlying Y chromosome microdeletions, with emphasis on the structure and characteristics of AZFa, AZFb, and AZFc deletions, their relationships with azoospermia and oligozoospermia, current diagnostic strategies, and their clinical relevance. Existing evidence and ongoing challenges in the diagnosis and clinical management of affected individuals are also addressed.

Keywords: Y chromosome microdeletion; AZF region; azoospermia; oligozoospermia; spermatogenesis.

Introduction

Male infertility is recognized as a major reproductive health concern, with abnormalities in sperm production or function contributing substantially to infertility among couples. Although a wide range of environmental, endocrine, infectious, anatomical, and lifestyle-related factors may interfere with male reproductive function, genetic abnormalities have particular relevance in patients presenting with severe defects in spermatogenesis. Among the genetic causes, chromosomal abnormalities, especially alterations involving the Y chromosome, represent important contributors to azoospermia and severe oligozoospermia (Dohle et al., 2007; Krausz et al., 2022). Beyond its fundamental function in male sex determination, the Y chromosome harbors genes and genomic elements that are critical for testicular development and the preservation of normal spermatogenesis. A considerable number of genes associated with sperm production are located within the male-specific region of the Y chromosome (MSY). The long arm of the Y chromosome (Yq) contains the azoospermia factor (AZF) regions, conventionally divided into AZFa, AZFb, and AZFc. Deletions affecting these regions can remove genes required at different stages of germ-cell development, thereby disrupting the normal progression of spermatogenesis and potentially resulting in severe impairment of sperm production (Jungwirth et al., 2012; Krausz et al., 2024). Y chromosome microdeletions (YCMs) are recognized as one of the principal molecular causes of severe male infertility. These genomic alterations predominantly involve the AZF regions and are categorized according to their genomic location and extent as AZFa, AZFb, AZFc, or combined deletions. Complete AZFc deletion represents the most frequently identified deletion pattern and is characterized by considerable phenotypic variability, with clinical manifestations extending from severe oligozoospermia to azoospermia. By comparison,



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complete deletions involving AZFa or AZFb generally produce a more profound disruption of spermatogenesis and are frequently associated with azoospermia (Guo, 2024). The structural organization of the Y chromosome contributes substantially to its susceptibility to genomic instability. The presence of extensive repetitive sequences and homologous ampliconic regions facilitates genomic rearrangements, among which non-allelic homologous recombination (NAHR) is considered a major mechanism responsible for Yq deletions. Such recombination events can result in the loss of genomic segments within the AZF regions, including genes that have essential functions in germ-cell development and spermatogenesis (Deng et al., 2022; Zhao et al., 2025). This mechanism is particularly relevant to the AZFc region, which contains a highly complex arrangement of repeated sequences and amplicons. Consequently, AZFc is susceptible not only to complete deletions but also to a variety of partial deletions and other structural rearrangements, including the well-characterized gr/gr deletion (Chianese et al., 2013). The reported prevalence of YCMs among infertile men varies considerably and is largely dependent on the severity of spermatogenic dysfunction and the clinical characteristics of the studied population. Available clinical evidence indicates that YCMs are detected more frequently in azoospermic men than in those with oligozoospermia, with the highest frequencies generally reported in individuals with severe impairment of sperm production. Current clinical recommendations recognize Yq microdeletions as important molecular causes of azoospermia and severe oligozoospermia. Their identification can therefore assist in establishing the underlying genetic etiology, estimating the probability of successful testicular sperm retrieval, and selecting an appropriate assisted reproductive strategy (Dubey et al., 2026; Neumann et al., 2024). The clinical value of YCM analysis is not limited to identifying the genetic cause of infertility. The specific type and genomic extent of a deletion may provide prognostic information regarding the residual spermatogenic capacity and the likelihood of obtaining sperm through surgical retrieval techniques, including testicular sperm extraction (TESE) and microdissection testicular sperm extraction (micro-TESE). Current evidence suggests that sperm retrieval remains feasible in a proportion of men with AZFc deletions, whereas complete AZFa and AZFb deletions are generally associated with an extremely poor likelihood of successful sperm retrieval (Applebaum & Ginsburg, 2025). Moreover, the reproductive implications of YCMs extend to the genetic counseling of affected patients. When sperm from a YCM carrier is used for intracytoplasmic sperm injection (ICSI), the underlying Y chromosome deletion can potentially be transmitted to male offspring. Consequently, molecular identification of YCMs before assisted reproductive treatment is essential for informed reproductive decision-making and appropriate genetic counseling (Krausz et al., 2026; Pashay Ahi et al., 2025). From a diagnostic standpoint, YCMs have traditionally been identified using molecular assays based on sequence-tagged sites (STS), most commonly through multiplex polymerase chain reaction (PCR). Nevertheless, advances



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in genomic technologies and the refinement of diagnostic criteria have highlighted the importance of appropriate marker selection, reliable characterization of deletion boundaries, and the detection of partial AZF deletions. The updated EAA/EMQN recommendations emphasize the use of standardized STS marker panels, appropriate laboratory quality-control procedures, and careful interpretation of molecular findings in conjunction with the patient's clinical and reproductive characteristics. Such an approach is particularly important when distinguishing complete from partial deletions and when assessing their potential clinical significance(Krausz et al., 2024). Considering the strong relationship between Y chromosome microdeletions, severe spermatogenic dysfunction, the probability of sperm retrieval, and reproductive outcomes following assisted reproductive techniques, a detailed understanding of these abnormalities is highly relevant to the fields of medical genetics, andrology, and reproductive medicine. Therefore, this review examines the organization and biological functions of the AZF regions, the molecular mechanisms responsible for Y chromosome microdeletions, and the phenotypic consequences associated with different deletion patterns. Particular attention is given to their relationship with azoospermia and oligozoospermia, their clinical and reproductive implications, current molecular diagnostic strategies, and the interpretation of YCM findings in the context of male infertility management(Yuen et al., 2021).

1.Structure and Genetic Organization of the Y Chromosome

The Y chromosome is the smallest human chromosome with respect to its gene content and has a central role in male sex determination and the development and maintenance of male reproductive functions. Structurally, it is composed of a short arm (Yp), a long arm (Yq), and pseudoautosomal regions (PARs) that share homology with the X chromosome. The majority of Y chromosome-specific genetic content is located within the non-recombining region of the chromosome, commonly referred to as the male-specific region of the Y chromosome (MSY) (Rozen et al., 2003; Skaletsky et al., 2003). From a genomic perspective, the MSY is broadly organized into unique sequence regions and ampliconic domains. Ampliconic regions are characterized by extensive arrays of highly homologous repetitive sequences. Although this organization is important for the preservation and expression of several genes involved in male reproduction, it also increases genomic instability and susceptibility to structural variation. In particular, the Yq11 region is vulnerable to deletions and other rearrangements mediated by non-allelic homologous recombination (NAHR), which represents a major molecular mechanism underlying the generation of Y chromosome microdeletions(Adler et al., 2006; Skaletsky et al., 2003). The Yq11 region has particular relevance to male reproductive capacity because it contains three functionally defined azoospermia factor (AZF) regions: AZFa, AZFb, and AZFc. These genomic intervals include genes that participate in multiple



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stages of germ-cell development, including germ-cell proliferation, spermatogonial differentiation, meiotic progression, and the subsequent stages of sperm formation. Accordingly, deletion of one or more AZF regions can interfere with spermatogenesis to different degrees, depending on the specific genomic segment affected and the extent of the deletion, and may ultimately result in severe spermatogenic failure or complete cessation of sperm production (Hughes et al., 2010; Jobling & Tyler-Smith, 2003). The AZFa interval includes genes such as DDX3Y (DBY) and USP9Y, which have important roles in germ-cell development and maintenance. Complete loss of the AZFa region is strongly associated with a severe impairment of spermatogenesis and is frequently accompanied by a Sertoli cell-only phenotype, in which germ cells are largely absent from the seminiferous epithelium. The AZFb region contains several genes involved in germ-cell RNA metabolism and meiotic regulation, including members of the RBMY gene family. Deletion of AZFb therefore commonly results in disruption of meiotic progression and is associated with a severe spermatogenic phenotype, frequently presenting as azoospermia (Hughes et al., 2012). Among the three AZF regions, AZFc exhibits the most complex genomic architecture and contains numerous ampliconic sequences as well as genes with established functions in spermatogenesis. Notably, this region includes multiple copies of the DAZ (Deleted in Azoospermia) gene family, which is closely associated with normal sperm production. The high degree of sequence repetition within AZFc facilitates homologous recombination events and consequently increases its susceptibility to deletions and other structural rearrangements. Complete AZFc deletion may therefore produce a heterogeneous clinical phenotype, extending from severe oligozoospermia to azoospermia. Partial AZFc deletions, including the well-characterized gr/gr deletion, may also affect spermatogenic capacity, although their clinical impact appears to vary according to genetic background, Y-chromosome haplogroup, and population-specific factors (Bellott et al., 2014; Hughes & Rozen, 2012). Taken together, the distinctive genomic architecture of the Y chromosome, particularly the abundance of repetitive and ampliconic sequences within Yq11, provides a structural basis for its susceptibility to microdeletions and other rearrangements. A detailed understanding of MSY organization and the genomic composition of the AZFa, AZFb, and AZFc regions is therefore essential for interpreting how specific deletion patterns influence spermatogenesis and for understanding their association with the clinical manifestations and reproductive outcomes observed in infertile men (de Carvalho & Santos, 2005; Jain et al., 2017).

2. AZF Regions and Y Chromosome Microdeletions

The azoospermia factor (AZF) regions are located within the male-specific portion of the long arm of the Y chromosome, mainly in the Yq11 region, and represent critical genomic domains required for normal spermatogenesis. According to their genomic position and



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the extent of the deleted segment, Y chromosome microdeletions are conventionally classified as AZFa, AZFb, and AZFc deletions, with additional categories including combined AZFbc and AZFabc deletions. Loss of these regions can remove genes and genomic elements involved in germ-cell proliferation, differentiation, meiotic progression, and sperm development. Consequently, the clinical phenotype may vary considerably, ranging from severe oligozoospermia to complete azoospermia (Krausz & Casamonti, 2017; Krausz et al., 2024).

2.1. AZFa Deletion

The AZFa region occupies the proximal segment of Yq11 and contains genes such as USP9Y and DDX3Y (DBY), which have important functions in germ-cell maintenance and development and contribute to normal spermatogenic activity. Complete deletion of AZFa is considered one of the most severe forms of Y chromosome-related spermatogenic failure. Affected individuals frequently exhibit a Sertoli cell-only syndrome (SCOS) phenotype, characterized by a marked depletion or complete absence of germ cells within the seminiferous tubules. Accordingly, complete AZFa deletion is strongly associated with azoospermia, and the probability of obtaining sperm through surgical retrieval is considered extremely low (Feng et al., 2025; Yan & Wang, 2025).

2.2. AZFb Deletion

The AZFb region is positioned in the central portion of Yq11 and encompasses several genes with essential roles in germ-cell development, RNA metabolism, and meiotic regulation. Among these are members of the RBMY gene family, which are particularly relevant to RNA processing and the progression of germ cells through meiosis. Complete AZFb deletion generally results in profound disruption of spermatogenesis and is frequently associated with meiotic arrest and azoospermia. Larger deletions extending across both AZFb and AZFc, commonly referred to as AZFbc deletions, generally involve the loss of a greater number of spermatogenesis-related sequences and are consequently associated with a particularly severe reproductive phenotype (Feng et al., 2025; Wang et al., 2025).

2.3. AZFc Deletion

AZFc represents the most distal of the three classical AZF regions and has the most complex genomic architecture. This region is characterized by a high density of ampliconic and repetitive sequences and contains several genes that contribute to germ-cell development and sperm production, most notably members of the DAZ (Deleted in Azoospermia) gene family. Because of its repetitive structure, AZFc is particularly prone to intrachromosomal homologous recombination, which can generate both complete and



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partial deletions(Krausz et al., 2026; Repping et al., 2002). Complete AZFc deletion is regarded as the most frequently observed classical Y chromosome microdeletion pattern. In contrast to complete AZFa or AZFb deletions, however, AZFc loss is associated with considerable clinical heterogeneity. While some carriers have complete azoospermia, others retain residual spermatogenic activity and may present with severe oligozoospermia. The variability in clinical expression may reflect differences in the precise genomic extent of the deletion, the amount of remaining functional genetic material, and individual or population-specific genetic background(Ferlin et al., 2007; Halder et al., 2017; Rozen et al., 2012).

2.4. Partial AZFc Deletions

Structural alterations of AZFc are not limited to complete deletion of the entire region. Partial AZFc deletions are also clinically relevant, with the gr/gr deletion being the most extensively investigated example. This rearrangement results in the loss of a subset of AZFc ampliconic units and can reduce the copy number of genes involved in spermatogenesis. Importantly, the phenotypic consequences of gr/gr deletion are not uniform across populations. Its impact appears to be influenced by the underlying Y chromosome haplogroup and other population-specific genetic factors. In certain populations, gr/gr deletion has been associated with decreased sperm production and an increased susceptibility to impaired fertility; nevertheless, its presence should not be interpreted as an independent or definitive diagnosis of infertility(Hamed, 2022; Jackson, 2007; Pashay Ahi et al., 2025).

2.5. Combined AZF Deletions

Y chromosome microdeletions may occasionally extend beyond a single AZF region and involve two or, in severe cases, all three classical AZF domains. Combined deletions such as AZFbc and AZFabc result in the loss of a larger number of genes and genomic sequences required for spermatogenesis. Compared with isolated AZFc deletions, these extensive rearrangements generally produce a more severe spermatogenic phenotype. In particular, when the deleted segment includes AZFa or AZFb, the degree of spermatogenic failure is usually profound and the likelihood of successful sperm retrieval is extremely limited(Moro, 2001; Ruiz, 2017).

2.6. Association Between Deletion Type and Spermatogenic Phenotype

The clinical severity associated with Y chromosome microdeletions is closely related to both the genomic location and the extent of the deleted region. In general, complete AZFa and AZFb deletions are associated with the most severe forms of spermatogenic failure, whereas AZFc deletions demonstrate substantially greater phenotypic heterogeneity.



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This genotype–phenotype relationship is also evident in the outcomes of sperm retrieval procedures. Available evidence indicates that, among men with complete AZF deletions, the possibility of recovering sperm is largely restricted to individuals carrying complete AZFc deletions, while complete AZFa and AZFb deletions are associated with a markedly unfavorable prognosis for sperm retrieval (Chen et al., 2025; Zhu et al., 2025). Taken together, the AZFa, AZFb, and AZFc regions form a clinically relevant genetic–phenotypic continuum in which the specific location, size, and structural nature of a deletion influence the degree of spermatogenic impairment. Therefore, identifying a patient simply as a carrier of a “Y chromosome microdeletion” does not provide sufficient information for clinical interpretation. Accurate characterization of the affected AZF region, together with discrimination between complete and partial deletions, is essential for estimating the expected spermatogenic phenotype, evaluating the likelihood of sperm retrieval, providing appropriate genetic counseling, and selecting suitable assisted reproductive strategies (Babaei et al., 2022; Bansal et al., 2016).

3. Molecular and Genetic Mechanisms Underlying Y Chromosome Microdeletions

Y chromosome microdeletions arise primarily from genomic instability within the male-specific region of the Y chromosome. The distinctive organization of this chromosome, particularly the abundance of repetitive sequences, ampliconic units, and large palindromic structures in Yq11, creates a genomic context that is particularly prone to structural rearrangements. Such events can eliminate genes or other genomic elements required for normal germ-cell development and spermatogenesis, ultimately compromising sperm production to varying degrees (Krausz et al., 2024; Puri et al., 2002).

3.1. Role of Ampliconic and Repetitive Sequences

The Yq11 region, and especially the AZFc interval, is characterized by a highly complex arrangement of homologous ampliconic sequences. These regions contain repeated genomic units that occur in multiple copies across the Y chromosome and contribute to its distinctive structural organization. However, the extensive sequence similarity among these copies can also increase the probability of incorrect alignment during DNA replication, repair, or recombination. Such misalignment may facilitate aberrant recombination events and consequently contribute to the development of Y chromosome structural variants (Repping et al., 2002; Rozen et al., 2003).

3.2. Non-Allelic Homologous Recombination

Non-allelic homologous recombination (NAHR) is considered one of the principal molecular mechanisms responsible for the generation of Yq microdeletions. During this process, highly homologous sequences located at different genomic positions can be



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incorrectly aligned and undergo recombination. When the homologous sequences are arranged in the appropriate orientation, recombination between them results in the excision and loss of the intervening DNA segment. NAHR is particularly relevant to classical AZF deletions and has a prominent role in the generation of structural abnormalities involving the AZFc region (Guo, 2024; Krausz et al., 2024; Kuroda-Kawaguchi et al., 2001).

3.3. Palindromes and Intrachromosomal Rearrangements

Large palindromic sequences represent another distinctive feature of the Y chromosome and contain highly homologous arms that can interact through intrachromosomal recombination. Misalignment between these homologous regions may result in structural alterations, including deletions and inversions. A well-established example involves recombination between the P5 and P1 palindromic structures, which can generate extensive deletions encompassing portions of the AZFb and AZFc regions. Such large-scale rearrangements are generally associated with severe disruption of spermatogenesis (Deng et al., 2022; Ioannou & Tempest, 2025).

3.4. Gene Conversion and Its Role in Genomic Stability

Gene conversion also contributes to the evolutionary dynamics and structural organization of the Y chromosome. In this non-reciprocal process, genetic information is transferred from one homologous or paralogous sequence to another, thereby increasing or maintaining sequence similarity between duplicated regions. Although this mechanism may help preserve functional similarity among ampliconic copies, elevated sequence homology can simultaneously increase the susceptibility of these regions to subsequent non-allelic recombination. Molecular studies have also identified evidence of gene conversion activity in recombination-prone regions of the AZF locus, including regions within AZFa (Foresta et al., 2000; Sun et al., 1999).

3.5. Complete and Partial AZF Deletions

Y chromosome microdeletions can be broadly distinguished into complete deletions of an AZF region and partial deletions affecting only specific genomic components. Complete AZFa, AZFb, or AZFc deletions generally remove multiple genes or gene copies involved in spermatogenesis and therefore tend to produce severe reproductive phenotypes. In contrast, partial deletions may affect a limited number of ampliconic units or specific copies of spermatogenesis-associated genes. Because a considerable proportion of the remaining genomic content is preserved, their phenotypic consequences are often more heterogeneous (Elliott et al., 1997; Kamp et al., 2001).

3.6. Mechanisms Underlying Partial AZFc Deletions

The complex repetitive architecture of AZFc permits recombination between distinct ampliconic sequences and can give rise to recurrent partial deletions, including the well-characterized gr/gr deletion. This rearrangement removes a subset of AZFc ampliconic material and consequently alters the copy number of several genes implicated in spermatogenesis. Nevertheless, the biological and clinical consequences of gr/gr deletion are not consistent among all carriers. Its effect appears to depend on factors such as Y chromosome haplogroup, individual genetic background, and population-specific genomic characteristics. Thus, gr/gr deletion is generally considered a susceptibility or risk factor for impaired spermatogenesis rather than an independent determinant of male infertility (Foresta et al., 2001; Vogt et al., 2017).

3.7. Loss of Spermatogenic Gene Dosage

A key molecular consequence of Y chromosome microdeletions is the reduction or complete loss of dosage of genes required for normal spermatogenesis. Several Y-linked genes, including DAZ, RBMY, DDX3Y, and USP9Y, contribute to distinct biological processes involved in germ-cell development, RNA metabolism, meiotic progression, and spermatid differentiation. Deletion-associated reductions in gene copy number or functional gene loss can disturb the coordinated molecular pathways necessary for germ-cell maturation. Depending on the affected genes and the extent of the deletion, this disruption may manifest as reduced sperm production, severe oligozoospermia, or complete failure of spermatogenesis (Rozen et al., 2003; Skaletsky et al., 2003).

3.8. Relationship Between Deletion Mechanisms and Clinical Phenotype

The clinical phenotype associated with a Y chromosome microdeletion is largely determined by the genomic position, size, and gene content of the deleted segment. Complete AZFa and AZFb deletions generally result in profound impairment of spermatogenesis because they eliminate genomic regions containing genes that are critical for germ-cell development and meiotic progression. In contrast, AZFc deletions can produce a considerably broader range of phenotypes, reflecting differences in residual gene content and individual genetic background. These genotype–phenotype relationships demonstrate why detection of a Y chromosome microdeletion alone is not sufficient for clinical assessment and why accurate characterization of the affected region and deletion boundaries is essential for estimating spermatogenic potential (Gunes & Esteves, 2021; Liu et al., 2026; Skov, 2017). Overall, the molecular basis of Y chromosome microdeletions reflects the interaction of several genomic mechanisms, including the repetitive and ampliconic architecture of the Y chromosome, NAHR, intrachromosomal recombination, gene conversion, and alterations in the dosage of



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genes required for spermatogenesis. Together, these mechanisms explain both the high susceptibility of specific Yq11 regions to structural rearrangement and the marked variation in clinical phenotype observed among men carrying different types of AZF deletions. Understanding these processes is therefore fundamental to linking the molecular characteristics of each deletion with the severity of spermatogenic dysfunction and its associated reproductive consequences (Repping et al., 2003; Signore et al., 2019).

4. Association of Y Chromosome Microdeletions with Spermatogenic Impairment

Y chromosome microdeletions (YCMs) represent an important genetic cause of severe impairment of spermatogenesis in infertile men and are most frequently identified in patients presenting with azoospermia or severe oligozoospermia. Deletion of critical genomic sequences within the AZF regions can reduce or eliminate the expression of Y-linked genes required for germ-cell proliferation, differentiation, maturation, and meiotic progression. Disruption of these molecular pathways may consequently result in partial or complete arrest of spermatogenesis. The severity of the resulting phenotype is closely related to the specific AZF region affected, the size of the deleted segment, and the nature of the genomic rearrangement, resulting in a distinct but not absolute genotype–phenotype relationship among AZF subregions (Krausz et al., 2024; Yuen et al., 2021).

4.1. AZFa Microdeletion and Severe Spermatogenic Failure

Complete deletion of the AZFa region is strongly associated with profound impairment of spermatogenesis and represents one of the most severe Y chromosome deletion phenotypes. The loss of genes such as DDX3Y and USP9Y, which contribute to early germ-cell development and the maintenance of normal spermatogenic function, is frequently associated with a Sertoli cell-only syndrome (SCOS) pattern and non-obstructive azoospermia. In these patients, germ cells are severely depleted or absent within the seminiferous epithelium. Accordingly, the probability of finding spermatozoa either in the ejaculate or through surgical testicular sperm retrieval is extremely low, and the reproductive prognosis for sperm retrieval is generally considered unfavorable (Colaco & Modi, 2024; Jiao et al., 2024).

4.2. AZFb Microdeletion and Germ Cell Maturation Arrest

The AZFb region contains several genes involved in RNA processing, RNA binding, meiotic regulation, and germ-cell differentiation, including members of the RBMY gene family. Complete deletion of AZFb can interfere with the normal progression of germ cells through meiosis and may lead to spermatogenic maturation arrest. When the deletion extends from AZFb into AZFc, the loss of additional spermatogenesis-associated



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sequences generally results in a more severe phenotype, most commonly manifested as persistent azoospermia. Histological investigations have further demonstrated that AZFb-associated deletions may be accompanied by substantial depletion of germ cells and disruption of the normal sequence of spermatogenic development(Krausz et al., 2014).

4.3. AZFc Microdeletion and Phenotypic Variability

In comparison with AZFa and AZFb deletions, AZFc microdeletions display considerably greater clinical and histological heterogeneity. Men carrying a complete AZFc deletion may present with severe oligozoospermia, cryptozoospermia, or azoospermia, indicating that spermatogenic activity may be preserved to different degrees. The presence of multiple copies of the DAZ gene family, together with the complex ampliconic organization of AZFc, may contribute to variation in the residual spermatogenic capacity among affected individuals. Therefore, detection of an AZFc deletion does not necessarily imply a complete and irreversible loss of sperm production(Foresta et al., 2001; Reijo et al., 1996). Testicular histopathology in AZFc deletion carriers is similarly variable. Reported patterns include Sertoli cell-only syndrome, maturation arrest, and hypospermatogenesis, while focal areas of preserved spermatogenesis may remain in some patients. This residual spermatogenic activity has important clinical implications because it provides a potential biological basis for successful sperm retrieval, particularly through testicular sperm extraction techniques such as microdissection testicular sperm extraction (micro-TESE)(Moro, 2001; Vogt, 2004).

4.4. Relationship Between Deletion Extent and Azoospermia or Oligozoospermia

The severity of spermatogenic dysfunction generally increases as the deleted segment becomes larger and encompasses a greater number of AZF regions. Extensive deletions involving AZFb+c or AZFa+b+c therefore tend to be associated with profound disruption or complete arrest of spermatogenesis and are frequently manifested as azoospermia. In contrast, more restricted deletions, particularly those limited to AZFc, may preserve a certain degree of sperm production and consequently result in oligozoospermia or, in some cases, residual focal spermatogenesis despite an absence of spermatozoa in the ejaculate. Nevertheless, the relationship between deletion genotype and clinical phenotype is not entirely linear. Y chromosome haplogroup, individual genetic background, population-specific genomic characteristics, and potentially environmental influences may contribute to differences in phenotypic expression among carriers(Huang et al., 2022; Li et al., 2022; Xia et al., 2025).

4.5. Clinical Consequences of Spermatogenic Impairment

The clinical relevance of YCMs extends beyond establishing the molecular etiology of male infertility. Precise characterization of the deleted AZF region can provide valuable prognostic information regarding residual spermatogenic activity and the probability of successful sperm retrieval, thereby influencing reproductive management. Men with complete AZFa or AZFb deletions generally have an extremely low probability of successful sperm retrieval and are therefore associated with a poor prognosis for surgical sperm recovery. In contrast, individuals with AZFc deletions may retain focal spermatogenesis even in the presence of azoospermia and can therefore be considered potential candidates for testicular sperm retrieval using TESE or micro-TESE, followed by intracytoplasmic sperm injection (ICSI) when viable sperm are obtained. Evidence from systematic investigations supports the feasibility of sperm retrieval in a proportion of azoospermic men with AZFc deletion, although reported retrieval rates differ substantially across studies because of variations in patient selection, surgical techniques, and clinical protocols (Lee et al., 2023; Nakagawa et al., 2023). Overall, Y chromosome microdeletions are associated with a broad spectrum of spermatogenic phenotypes, extending from impaired sperm production to complete and persistent spermatogenic arrest. The genomic location and extent of the deletion are among the principal determinants of disease severity. Complete AZFa and AZFb deletions generally produce profound spermatogenic failure with a highly unfavorable prognosis for sperm retrieval, whereas AZFc deletions demonstrate substantially greater phenotypic variability and may preserve residual spermatogenic activity. These differences emphasize the importance of accurate molecular characterization of the deleted region and its boundaries for diagnosis, prognostic assessment, genetic counseling, and individualized reproductive management in men with severe spermatogenic disorders (Chen et al., 2023; Peng et al., 2022).

Figure 2. Schematic representation of the Y chromosome, AZF regions, major microdeletion patterns and their association with spermatogenic failure

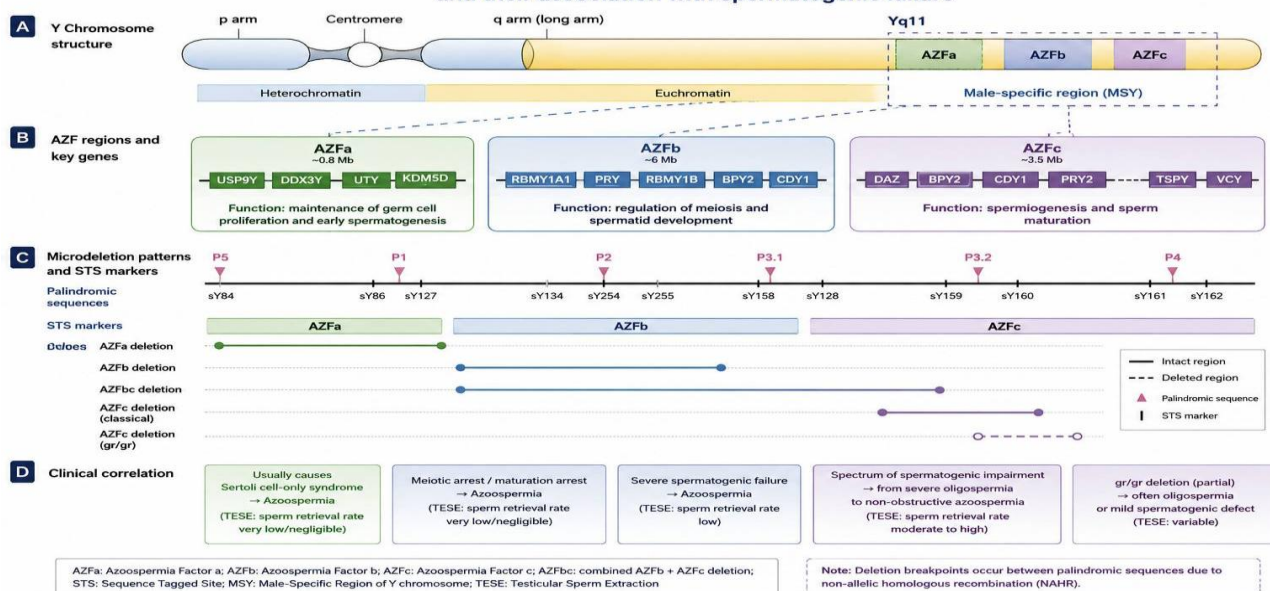


Figure 1. Schematic overview of the Y chromosome, AZF regions, major microdeletion patterns, and their relationship with spermatogenic impairment.

The schematic illustrates the overall organization of the Y chromosome and the distribution of the three major azoospermia factor (AZF) regions, namely AZFa, AZFb, and AZFc, within the long arm (Yq11). Major genes and gene families involved in germ-cell development and spermatogenesis are indicated according to their approximate genomic locations. The figure also depicts the principal patterns of Y chromosome microdeletions, including complete AZFa, AZFb, AZFbc, and AZFc deletions, as well as partial AZFc rearrangements such as the gr/gr deletion. Representative sequence-tagged site (STS) markers and relevant palindromic structures are included to illustrate the genomic architecture underlying these rearrangements. Most classical Y chromosome microdeletions arise through non-allelic homologous recombination (NAHR) between highly homologous repetitive sequences and ampliconic regions. The resulting clinical phenotype is largely determined by the location and genomic extent of the deletion. Complete AZFa and AZFb deletions are typically associated with profound spermatogenic failure and azoospermia, whereas complete AZFc deletion exhibits greater phenotypic variability, ranging from severe oligozoospermia to azoospermia. Partial AZFc deletions, particularly gr/gr rearrangements, may be associated with reduced sperm production and impaired spermatogenesis; however, their clinical significance varies according to Y chromosome haplogroup and population-specific genetic background.

5. Clinical Consequences of Y Chromosome Microdeletions

Y chromosome microdeletions (YCMs) are among the well-established genetic causes of azoospermia and severe oligozoospermia. Their clinical manifestations are largely determined by the specific AZF region involved and the genomic extent of the deletion. Complete loss of AZFa is most commonly associated with a Sertoli cell-only phenotype and severe disruption of spermatogenesis, whereas AZFb deletions are typically characterized by impaired germ-cell maturation, spermatogenic arrest, and azoospermia. AZFc deletions, in contrast, show a broader clinical spectrum, with affected individuals presenting with phenotypes ranging from severe oligozoospermia to complete azoospermia (Archana et al., 2023; Han & Liu, 2023; Krausz et al., 2024). Accurate identification of the deletion subtype is particularly important when planning treatment, as it provides valuable information regarding the likelihood of successful sperm retrieval. Complete AZFa and AZFb deletions are generally associated with an extremely poor probability of recovering sperm. Conversely, some men with AZFc deletions may retain limited or focal areas of spermatogenic activity despite azoospermia. In such cases, spermatozoa may be successfully recovered using testicular sperm extraction (TESE) or



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microdissection testicular sperm extraction (micro-TESE) and subsequently utilized for intracytoplasmic sperm injection (ICSI) when viable sperm are obtained (Çift et al., 2024; Punjani et al., 2020; Zhang et al., 2013). An additional clinical consideration is the potential transmission of YCMs through assisted reproductive technologies (ART). Because the Y chromosome is transmitted from a father to his male offspring, the use of sperm from a man carrying a Y chromosome microdeletion can result in transmission of the same deletion to a son. Therefore, molecular detection of YCMs has implications beyond the diagnosis of the underlying cause of infertility. Identification of the specific deletion is relevant to prognostic evaluation, selection of appropriate sperm-retrieval and ART strategies, and comprehensive genetic counseling before treatment (Colaco & Modi, 2024; Yuen et al., 2021).

6. Genetic Counseling and Transmission of Y Chromosome Microdeletions

The identification of Y chromosome microdeletions (YCMs) in infertile men has important implications for genetic counseling and the selection of appropriate infertility treatment strategies. Since the Y chromosome is transmitted directly from father to son, men carrying YCMs who undergo assisted reproductive technologies (ART) using their own sperm, particularly intracytoplasmic sperm injection (ICSI), may transmit the underlying deletion to their male offspring. Thus, molecular diagnosis of YCMs provides clinically relevant information not only about the etiology of infertility but also about potential reproductive risks (Krausz & Abrardo, 2025; Krausz et al., 2024). The reproductive implications of YCMs vary according to the specific type and genomic extent of the deletion. Complete AZFa and AZFb deletions are generally associated with severe spermatogenic failure and an extremely low likelihood of successful sperm retrieval, which often limits the feasibility of using autologous sperm for ART. In contrast, some men carrying AZFc deletions may retain residual spermatogenic activity and have a reasonable possibility of sperm retrieval, making ART a potential treatment option. Accordingly, couples should receive detailed counseling before treatment regarding the molecular characteristics of the deletion, the expected probability of sperm retrieval, available reproductive options, and the possibility of transmitting the deletion to a male child (Deng et al., 2022; Krausz & Casamonti, 2017). It is also important to recognize that the clinical expression of a YCM in a male offspring may not necessarily reproduce the exact infertility phenotype observed in the father. Variations in the extent of the inherited deletion, individual genetic background, Y chromosome haplogroup, and other biological factors may contribute to differences in spermatogenic function and reproductive phenotype. Therefore, pre-ART genetic counseling should be considered an integral part of the clinical management of men with YCMs. Treatment decisions should ultimately be individualized on the basis of the patient's specific genetic findings, expected reproductive prognosis, and personal reproductive goals (Witherspoon et al., 2021).



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7. Molecular Diagnosis of Y Chromosome Microdeletions

Molecular detection of Y chromosome microdeletions (YCMs), particularly those affecting the AZF regions, plays a central role in the genetic evaluation of men with azoospermia and severe oligozoospermia. Identification of AZFa, AZFb, AZFbc, and AZFc deletions can help establish the underlying genetic cause of impaired spermatogenesis, provide prognostic information regarding the potential for sperm retrieval, and support the selection of appropriate assisted reproductive strategies (Krausz et al., 2024). The conventional diagnostic method is multiplex polymerase chain reaction (PCR) using sequence-tagged site (STS) markers, which allows several regions of the Y chromosome to be examined simultaneously. Failure to amplify a specific STS marker may suggest the presence of a deletion; however, appropriate internal amplification controls are essential to distinguish a true deletion from technical PCR failure. When a deletion is suspected, additional STS markers can be analyzed to confirm the finding and more precisely determine the genomic boundaries and extent of the affected region (Krausz et al., 2014). From a clinical perspective, complete AZFa and AZFb/AZFbc deletions are generally associated with severe disruption of spermatogenesis and a very low likelihood of successful sperm retrieval. In contrast, AZFc deletions demonstrate substantial phenotypic variability, and residual spermatogenic activity may be maintained in some affected individuals. Partial AZF alterations, particularly gr/gr deletions, should likewise be interpreted cautiously, as their clinical significance can vary according to Y chromosome haplogroup and population-specific genetic background and they are more appropriately regarded as susceptibility factors rather than uniformly pathogenic variants (Simoni et al., 2004). Although advanced genomic technologies have expanded the potential approaches for detecting Y chromosome structural abnormalities, multiplex PCR remains the principal diagnostic technique for routine YCM analysis because it is rapid, relatively inexpensive, technically accessible, and supported by extensive clinical experience. Reliable diagnosis further depends on standardized laboratory protocols, appropriate positive and negative controls, rigorous quality assurance, and careful interpretation of molecular findings alongside the patient's clinical, hormonal, and reproductive characteristics (Krausz et al., 2014).

8. Clinical Implications and the Role of YCMs in Infertility Treatment

Y chromosome microdeletions (YCMs) have substantial clinical relevance in the evaluation and management of male infertility, particularly because the specific type and extent of an AZF deletion can influence the severity of spermatogenic failure and the choice of an appropriate treatment strategy. The affected genomic region may determine whether spermatozoa are detectable in the ejaculate, the probability of recovering sperm from testicular tissue, and the potential outcomes of assisted reproductive technologies



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(ART). In general, complete AZFa and AZFb deletions are associated with an extremely poor likelihood of successful sperm retrieval, whereas AZFc deletions may preserve residual spermatogenic activity and therefore provide a comparatively greater opportunity for sperm recovery (Colaco & Modi, 2024; Jiao et al., 2024). In men carrying AZFc deletions, spermatozoa may occasionally be detected in the ejaculate or recovered directly from testicular tissue using techniques such as testicular sperm extraction (TESE) or microdissection testicular sperm extraction (micro-TESE). When viable sperm are obtained, intracytoplasmic sperm injection (ICSI) can provide an opportunity for biological fatherhood. Nevertheless, some studies have reported less favorable outcomes of certain ART procedures among men with YCMs, including differences in fertilization, clinical pregnancy, and live-birth rates. These findings highlight the importance of comprehensive genetic and reproductive assessment before initiating ART (Krausz et al., 2024). Another major consideration is the potential transmission of a Y chromosome deletion to male offspring when sperm from a YCM carrier are used for ART. Because the Y chromosome is transmitted from father to son, an inherited deletion may subsequently affect the reproductive potential of the male offspring. Consequently, pre-ART genetic counseling should be regarded as an essential component of patient management. Couples should receive clear information regarding the specific deletion, its reproductive implications, the potential risk of transmission, and the available reproductive options (Yuen et al., 2021). Overall, molecular identification of the specific YCM subtype provides information that extends beyond establishing the genetic etiology of infertility. Characterization of the affected AZF region can assist in prognostic assessment, selection of an appropriate sperm-retrieval approach, and planning of ART. For optimal clinical decision-making, molecular findings should be evaluated together with the patient's clinical presentation, semen characteristics, hormonal profile, and overall reproductive status, allowing treatment to be tailored to the individual patient's circumstances (Xia et al., 2025; Zhou et al., 2021).

9. Challenges and Future Perspectives

Despite considerable progress in the detection and characterization of Y chromosome microdeletions (YCMs), several challenges continue to limit the accurate diagnosis and clinical interpretation of these genomic abnormalities. Differences in genetic background among populations, variation in laboratory protocols, and the complex interpretation of partial deletions—particularly gr/gr deletions—can influence diagnostic consistency and complicate the establishment of clear genotype–phenotype relationships in male infertility (Krausz et al., 2024). The rapid development of genomic technologies, including next-generation sequencing (NGS) and whole-genome sequencing (WGS), offers new opportunities for the detailed characterization of structural variants and complex Y chromosome deletions. These approaches may provide higher resolution than



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conventional marker-based assays and could facilitate the identification of genomic alterations that are difficult to characterize using standard PCR methods. Nevertheless, the extensive repetitive sequences and complex structural organization of the Y chromosome remain major obstacles to accurate sequence alignment, variant detection, and interpretation. Accordingly, combining established STS-based PCR approaches with advanced sequencing technologies may provide a complementary strategy that improves both diagnostic reliability and genomic resolution (Krausz et al., 2018). Future research is expected to increasingly integrate Y chromosome genetic information with clinical characteristics, semen parameters, and multi-omics datasets. Such integrative approaches may provide deeper insight into the molecular mechanisms contributing to spermatogenic failure and improve the prediction of sperm-retrieval success and other reproductive outcomes. In parallel, harmonization of diagnostic protocols, establishment of robust quality-control standards, and development of population-specific genomic databases could improve the clinical interpretation of YCMs and reduce uncertainty surrounding population-dependent genetic effects (Kuroda-Kawaguchi et al., 2001). Overall, continued advances in genomic analysis, together with appropriate genetic counseling and individualized clinical management, are likely to strengthen the diagnostic and prognostic value of YCM testing. The integration of molecular findings with patient-specific clinical and reproductive characteristics may ultimately support more precise treatment selection and personalized fertility management for men carrying Y chromosome microdeletions (Repping et al., 2002; Zhang et al., 2017).

Conclusion

Y chromosome microdeletions (YCMs), particularly those involving the azoospermia factor (AZF) regions, represent some of the most significant genetic abnormalities associated with severe spermatogenic failure and male infertility. The clinical severity of these defects is largely determined by the location and extent of the deleted genomic segment. Complete AZFa and AZFb deletions are generally associated with profound impairment of spermatogenesis and an extremely unfavorable reproductive prognosis, whereas men with AZFc deletions may retain variable degrees of residual sperm production. Molecular diagnosis based on multiplex polymerase chain reaction (PCR) and sequence-tagged site (STS) markers remains a fundamental component of the genetic evaluation of infertile men. Accurate identification and characterization of YCMs can help establish the underlying etiology of infertility, provide prognostic information regarding the possibility of sperm retrieval, and support the selection of appropriate reproductive treatment strategies. Adherence to standardized diagnostic protocols and careful interpretation of molecular findings, as emphasized by the EAA/EMQN recommendations, are essential for achieving reliable and clinically meaningful results. From a clinical perspective, detection of YCMs before initiating assisted reproductive

technologies (ART) is particularly important. In selected men, especially those with AZFc deletions, viable spermatozoa may be present in the ejaculate or recovered from testicular tissue using techniques such as testicular sperm extraction (TESE) or microdissection testicular sperm extraction (micro-TESE). When viable sperm are obtained, intracytoplasmic sperm injection (ICSI) may provide an opportunity for biological fatherhood. However, because Y chromosome deletions can be transmitted from an affected father to his male offspring, pre-ART genetic counseling is essential to ensure that couples understand the potential reproductive and genetic implications. Overall, optimal management of men with YCMs requires an integrated approach combining molecular diagnosis, clinical and reproductive assessment, genetic counseling, and appropriate selection of assisted reproductive techniques. Continued advances in genomic technologies, together with multi-omics investigations and further standardization of diagnostic procedures, may improve the characterization of Y chromosome structural abnormalities and clarify their relationships with spermatogenic and reproductive phenotypes. Such developments could ultimately strengthen prognostic assessment and contribute to more individualized and evidence-based fertility management for men carrying Y chromosome microdeletions.

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