Distribution And Clinical Significance of Microdeletions in The AZF Region of The Y Chromosome in Male Infertility

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ABSTRACT

This article examines various types of microdeletions in the AZF region of the Y chromosome and their impact on male infertility. Particular attention is given to the prevalence of AZF microdeletions among patients with azoospermia and oligozoospermia, as well as their clinical manifestations. Data are presented on the prevalence of AZFa, AZFb, and AZFc microdeletions and their effects on male reproductive function. The primary focus is on the pathogenesis, molecular mechanisms, and diagnosis of these abnormalities. For each type of microdeletion, clinical features, diagnostic methods, and treatment approaches using assisted reproductive technologies are described.

Keywords: AZF, microdeletion, male infertility, azoospermia, oligozoospermia, spermatogenesis, diagnosis, in vitro fertilization, ICSI, genetic analysis.

Introduction. Microdeletions of the Y chromosome, particularly in the AZF (azoospermia factor) region, represent one of the most significant genetic causes of male infertility identified in clinical practice. These defects, affecting small segments of the long arm of the Y chromosome (Yq11), are caused by the loss of one or more key genes responsible for the normal process of sperm formation [11,14]. The most commonly observed types of such deletions include DAZ (deleted in azoospermia), GOLGA2L4 (or BCRP), and USP9Y, which are located within three main subregions: AZFa, AZFb, and AZFc, respectively. Each of these regions contains unique genes whose

expression is essential for successful spermatogenesis [10,12,13].

Thus, a deletion in the AZFa region is associated with a severe disruption of the early stage of spermatogonial development, leading to the complete absence of sperm precursor cells. In such cases, total cessation of spermatogenesis occurs already at the level of primary spermatogonia—a condition known as azoospermia [9]. In the case of deletions in AZFb, a severe impairment of spermatogenesis is also observed, characterized by arrest of the process at the meiotic stage or at late spermatocyte stages; this type of deletion is usually accompanied by azoospermia or an extremely low number of spermatozoa in the ejaculate. In contrast, deletions in the AZFc region are most often associated with hypospermia (low sperm concentration) or even severe forms of azoospermia; however, there remains a certain probability of the presence of spermatozoa in the testes, which creates opportunities for the use of assisted reproductive technologies such as ICSI (intracytoplasmic sperm injection) [4,8].

The variability of clinical manifestations depends not only on the type of deletion but also on the extent of its distribution within an individual patient, as well as on genetic predisposition and additional environmental factors. Some patients with AZFc deletions may exhibit a mild form of spermatogenesis, allowing sperm retrieval through testicular sperm extraction (TESE). This makes accurate diagnosis and classification of microdeletions particularly important, as the results of the analysis directly influence the choice of treatment strategy [5].

Given the high prevalence of AZF deletions—up to 6–10% among men with azoospermia and approximately 3–5% in cases of hypospermia—genetic screening becomes an essential component of the comprehensive assessment of male fertility [7]. Analytical methods such as PCR using specific primers targeting marker sequences in each subregion (sY127, sY138, sY143, sY147) provide high sensitivity and specificity. This enables precise detection of deletions, as well as determination of their boundaries and types, allowing for prediction of therapeutic outcomes and informed counseling of patients and their partners [1].

The obtained data will not only help to refine the epidemiological profile of AZF microdeletions in the studied population but also contribute to the development of recommendations for standardizing genetic testing protocols in male infertility. In addition, information on the frequency and types of deletions will be valuable for conducting large-scale prospective studies, assessing the long-term effects of transmission of genetic abnormalities to children born through IVF/ICSI, and for establishing databases that support a personalized approach to the treatment and prevention of reproductive disorders [2,3,6]. Thus, a deep understanding of the genetic basis of male infertility is a key step toward developing effective, safe, and individualized solutions in reproductive medicine.

The Aim Of The Study was to analyze various types of AZF microdeletions and their prevalence among patients with azoospermia and other forms of male infertility. In addition, the study sought to investigate the relationship between different variants of microdeletions and their impact on male reproductive function.

Materials And Methods. The study included 69 patients diagnosed with male infertility, including those with azoospermia, who presented for consultation at a genetic clinic. Molecular genetic analysis using polymerase chain reaction (PCR) was employed to detect microdeletions in the AZF region. The following types of microdeletions were analyzed:

– AZFa (all variants)
– AZFb (all variants)
– Isolated AZFc

Each patient underwent genetic testing using specific markers corresponding to these types of microdeletions. Statistical analysis included evaluation of the distribution of microdeletion types among patients, as well as their association with clinical manifestations of infertility.

Results And Discussion. AZFa microdeletions were identified in 12 patients, accounting for 17.4% of the total study population. This subtype represents one of the most severe genetic defects associated with azoospermia and teratozoospermia, as the AZFa region contains key genes responsible for early stages of spermatogenesis. Loss of these genes almost invariably results in the complete absence of spermatozoa in the ejaculate. Among patients with AZFa microdeletions, different patterns of genetic loss were observed.

One variant is the complex AZFabc microdeletion, identified in 4 patients. This type is characterized by the simultaneous deletion of all three regions—AZFa, AZFb, and AZFc. Such extensive chromosomal disruption is associated with the most severe clinical presentation. Most of these patients exhibited complete azoospermia, and restoration of spermatogenesis, even with assisted reproductive technologies such as ICSI (intracytoplasmic sperm injection), is крайне unlikely. Genetic analysis revealed significant loss of functionally important genes, including USP9Y, DBY, XG, and RPS4Y, which play a central role in the development and maturation of spermatogonia. Testicular biopsy in these patients showed no presence of spermatozoa or precursor germ cells.

The second variant is the AZFab microdeletion, identified in 2 patients. This type involves the combined deletion of AZFa and AZFb regions. Although less common, these microdeletions also have a profound impact on fertility. Both patients had complete azoospermia; however, testicular biopsy samples revealed minimal spermatogenic elements—isolated spermatogonia in one case and scattered spermatocytes in the other. This indicates partial preservation of spermatogenic potential, although the likelihood of successful retrieval of viable sperm for in vitro fertilization remains extremely low. At the molecular level, these patients exhibited decreased expression of genes such as RBMY, DAZ, CDY1, and EIF1AY, indicating disruption of regulatory networks controlling division and differentiation of spermatogonial cells.

Another AZFa subtype was identified in 4 patients who exhibited isolated deletion of the AZFa region. This region contains several genes essential for the initiation of spermatogenesis. Although the deletion does not affect other chromosomal regions, its impact on fertility is catastrophic. All patients with this microdeletion had complete azoospermia. Testicular biopsy demonstrated a complete absence of all forms of spermatogenesis—no spermatogonia, spermatocytes, or spermatids were detected. However, in one case, primitive cellular structures resembling spermatogonial precursors were observed, although they showed no signs of active differentiation. This confirms the critical role of AZFa genes in initiating and maintaining spermatogenesis. Their absence results in a complete “shutdown” of male germ cell formation at early developmental stages. Patients with this type of microdeletion are unable to produce their own sperm and require the use of donor sperm.

These findings highlight the importance of molecular genetic analysis for accurate diagnosis of male infertility and demonstrate how the loss of key genes within the AZF region disrupts spermatogenesis at multiple levels.

Microdeletions of the AZFb region were identified in 20 out of 68 examined men with azoospermia or severe oligozoospermia, accounting for 29% of all cases. This makes AZFb one of the most frequently affected genetic regions in the context of male infertility, particularly in cases of absent sperm in the ejaculate. Among these 20 patients, two main types of deletions were identified.

One variant is the AZFbc microdeletion, which was detected in 15 men. This defect affects both the AZFb and AZFc regions, forming a combined deletion known as AZFbc. Such a form is characterized by a complete loss of gene regions responsible for normal spermatogenesis, including key genes such as DAZ, CDY1, and RBMX**.** Patients with this microdeletion demonstrate severe impairment of spermatogenesis, and the majority present with complete azoospermia. However, in isolated cases, rare spermatozoa may still be found in the testes. Due to the extensive loss of genetic material, these patients have virtually

no chance of natural conception and require assisted reproductive technologies, specifically in vitro fertilization using ICSI (intracytoplasmic sperm injection) after testicular sperm extraction (TESE) or IMSI. The AZFbc defect also carries a high risk of transmission through the paternal line, which may affect future male offspring.

Another type of microdeletion is the pure AZFb deletion**,** identified in 5 patients. In this case, only the AZFb region is affected, without involvement of AZFc. Although this variant is less common than AZFbc, it also has serious clinical consequences. Genes located in AZFb, such as USP9Y, DBY, and TSPY, play a critical role in meiosis, spermatid formation, and maturation. Patients with this microdeletion also suffer from azoospermia or extremely low sperm concentration. Interestingly, in some cases of AZFb deletion, rare spermatozoa were detected in testicular biopsies, which opens the possibility for successful ICSI using TESE. However, the success rate of such procedures may be lower compared to other types of deletions due to a high level of apoptosis in germ cells. It should also be noted that these patients retain partial functional capacity for early stages of spermatogenesis, suggesting that AZFb may be involved in regulating the proliferation of germ cell precursors rather than their final maturation. Therefore, diagnostic evaluation should include not only the detection of the deletion but also assessment of testicular tissue status at the histological level and expression of markers such as VASA and PLZF.

The isolated AZFc microdeletion was the most common type identified in this study and was detected in 37 out of 69 patients, accounting for 53.6% of all cases. AZFc deletions are characterized by the loss of genes located in the distal region of the Y chromosome, including DAZ1–4, CDY1, BPY2, and other elements that play a key role in spermatogenesis. Most men with this deletion present with oligozoospermia or complete azoospermia; however, normal external male sexual development is usually preserved. Interestingly, the severity of fertility impairment may vary even among carriers of the same deletion: some patients show only mild reductions in sperm concentration, while others are completely infertile. The high frequency of AZFc deletions in this cohort highlights its significant role in male infertility pathology, particularly in the context of age-related changes in testicular function. Furthermore, these data suggest that deficiency of DAZ and CDY1 proteins—whose expression depends on the integrity of this region—is a major cause of impaired spermatogonial division and subsequent spermatocyte differentiation. Given the high prevalence of this type of microdeletion, mandatory molecular genetic testing is recommended for diagnosing the causes of non-obstructive infertility, especially when planning assisted reproduction using ICSI **(**(intracytoplasmic injection of a single spermatozoon)

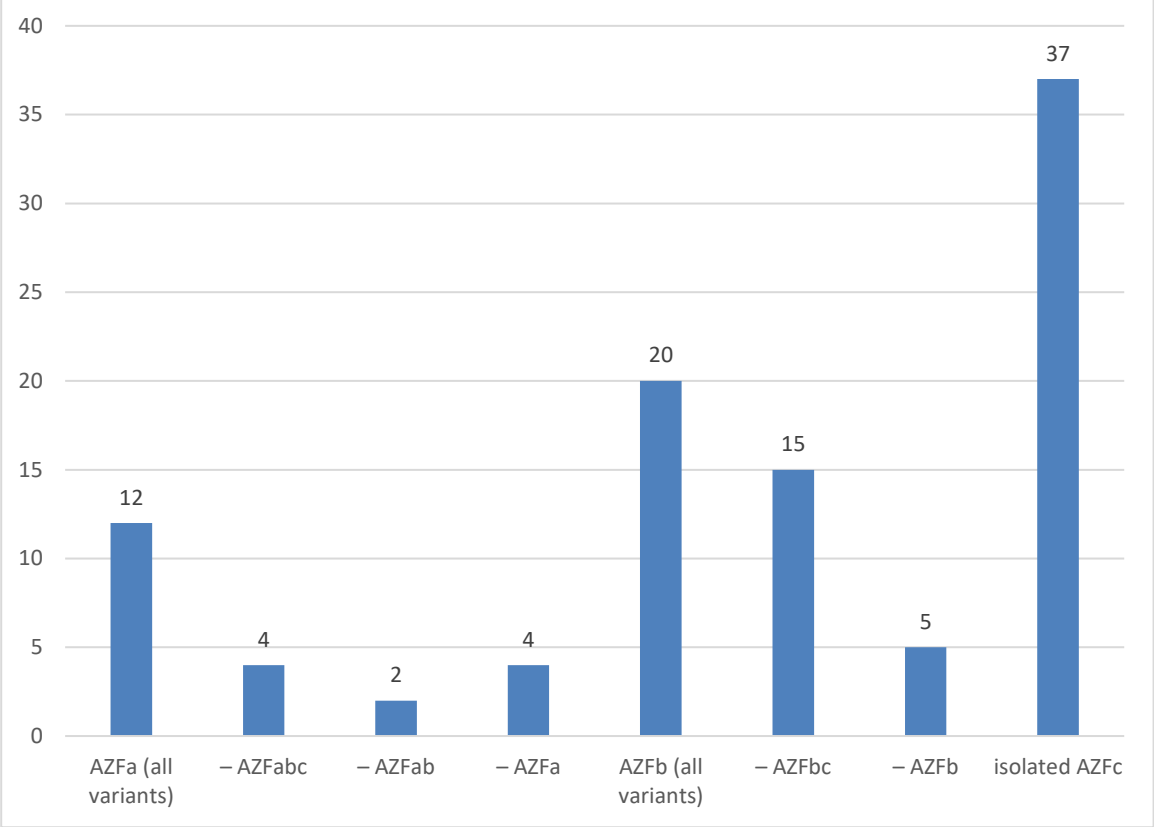

Figure. Distribution of AZF microdeletion types among the examined patients.

Thus, the results of the study show that among all types of AZF microdeletions, the most frequently observed is the isolated AZFc microdeletion, which was detected in more than half of the examined patients. In contrast, AZFa and AZFb types occur less frequently, which confirms data from the international literature regarding the lower prevalence of these variants.

Discussion of results.

The detection of an isolated AZFc microdeletion in more than half of patients with azoospermia indicates an extremely high prevalence of this genetic defect in the group of men suffering from a complete absence of spermatozoa in the ejaculate. These findings not only confirm the dominant role of AZFc deletions as one of the main molecular causes of male infertility, but also raise the question of the need for systematic assessment of this anomaly during the primary evaluation of men with impaired spermatogenesis. Despite the relatively low frequency of microdeletions in the AZFa and AZFb regions—accounting for less than 10% of all cases—their presence is always associated with a significant reduction in reproductive capacity: AZFa defects are often linked to absolute azoospermia and the absence of seminiferous tubules (Sertoli-cell-only syndrome), whereas AZFb microdeletions lead to disruption of the later stages of spermatogenesis, resulting in dysfunction of spermatogonial cells. Therefore, even though these deletion types are relatively rare, they require mandatory molecular genetic screening, as they are crucial for predicting treatment outcomes and selecting assisted reproductive technology strategies.

The obtained results are fully consistent with data from international long-term studies, including large meta-analyses conducted in Europe, Asia, and North America, where isolated AZFc microdeletion has been identified as the most common genetic cause of azoospermia and oligozoospermia. It has been established that the frequency of this anomaly in infertile male populations ranges from 6% to 15%, making it one of the most significant modifying factors affecting fertility. It is particularly important that such microdeletions are transmitted along the male line and may be detected even at the

parental level of the patient, which opens opportunities for prenatal and family counseling. Accordingly, the expanded use of modern molecular diagnostic methods—such as FISH testing, qPCR, and next-generation sequencing—allows not only precise determination of the cause of infertility, but also minimization of misinterpretation of the clinical picture by differentiating between "primary" and "secondary" infertility associated with genetic alterations.

In addition, the detection of AZFc microdeletion has direct implications for reproductive planning. In the presence of this anomaly, the probability of successful sperm retrieval from testicular tissue (TESE) remains significant—approximately 40–60%—making ICSI (intracytoplasmic sperm injection) a viable option. However, it is important to recognize that retrieved spermatozoa may carry genetic damage, which increases the risk of transmitting the defect to offspring. Therefore, preimplantation genetic testing of future children is recommended, especially when using the father's own genetic material. Moreover, inclusion of AZF region analysis in the standard diagnostic protocol for men with impaired spermatogenesis can significantly improve diagnostic efficiency, reduce the time required to determine the cause of infertility, and ensure a personalized therapeutic approach. Overall, comprehensive genetic evaluation should be considered not as an additional procedure, but as an essential component of diagnosis that ensures the reliability of conclusions and the quality of reproductive medicine.

Conclusions.

1. AZF microdeletions are one of the main causes of male infertility, especially in cases of azoospermia.
2. The most common is the isolated AZFc microdeletion, which was identified in more than half of infertile patients.
3. AZFa and AZFb microdeletions occur less frequently, but they also play an important role in impaired reproductive function.
4. Molecular genetic studies aimed at detecting microdeletions in the AZF region of the Y chromosome are an important tool in the diagnosis and treatment of male infertility.
5. The obtained results emphasize the need for the widespread use of genetic testing in clinical practice to improve the quality of diagnosis and treatment planning for infertile men.

Thus, the results of this study allow for a more precise determination of the causes of male infertility, which in turn will help improve treatment methods and increase the effectiveness of assisted reproductive technologies.

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