SIGNIFICANCE OF AZF GENE ANALYSIS IN THE EVALUATION OF MALE INFERTILITY

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Infertility is defined as the inability of a sexually active couple to achieve pregnancy after 12 months of regular unprotected intercourse. It represents a significant global medical and social concern, affecting approximately 8–15% of couples of reproductive age worldwide. According to the World Health Organization (WHO), between 48 and 180 million couples currently experience infertility. Epidemiological data indicate considerable regional variation, with the highest prevalence observed in Southeast Asia and sub-Saharan Africa, and rates reaching up to 30% in certain regions of Central and Eastern Europe and Central and Southern Asia. Male factors contribute to nearly 50% of infertility cases, either as a primary or contributing cause. Genetic abnormalities play a substantial role in male infertility, accounting for approximately 10–15% of cases. Among these, microdeletions of the long arm of the Y chromosome (Yq), particularly within the azoospermia factor (AZF) locus, represent one of the most significant molecular etiologies of spermatogenic failure. The AZF region is subdivided into AZFa, AZFb, and AZFc subregions, each containing genes essential for normal spermatogenesis. Microdeletions affecting these regions are identified in 5–20% of infertile men worldwide and are especially prevalent among patients with azoospermia and severe oligozoospermia. Complete deletions of AZFa and AZFb are strongly associated with severe spermatogenic impairment, whereas the clinical significance of AZFc deletions remains under active investigation.

Y-chromosome microdeletions are typically de novo mutations, although their frequency varies across populations, underscoring the importance of population-specific genetic studies. Structural rearrangements in the ampliconic regions of the Y chromosome, often mediated by non-allelic homologous recombination, further contribute to genomic instability and impaired sperm production. Following Tiepolo and Zuffardi's initial identification of Y-chromosome deletions associated with azoospermia in 1976, molecular screening for Y-chromosome microdeletions has become an essential component of the diagnostic workup for men presenting with sperm concentrations below 5 million/mL or with azoospermia. The Y chromosome contains numerous genes crucial for testicular development, sex determination, and regulation of spermatogenesis. Although over one hundred genes and pseudogenes have been identified, the precise functional contribution of many remains incompletely characterized. After Klinefelter syndrome, complete AZF deletions represent the second most common genetic cause of spermatogenic failure.

Advances in molecular diagnostics have enabled reliable detection of AZF microdeletions through polymerase chain reaction (PCR)-based techniques, including real-time PCR, multiplex PCR, multiplex ligation-dependent probe amplification (MLPA), and

quantitative fluorescent PCR. Screening for complete AZFa and AZFb deletions is now considered mandatory in men with azoospermia and severe oligozoospermia.

Contemporary clinical guidelines, including those updated by the WHO in 2020, emphasize standardized semen analysis, histological evaluation of testicular biopsy when indicated, and molecular genetic testing as integral components of male infertility assessment. In this context, the identification of major deletions and microdeletions within the extended AZF region holds considerable clinical value. It informs diagnosis, therapeutic decision-making, and prognostic evaluation, while also contributing to genetic counseling and population-based research.

Comprehensive classification of idiopathic male infertility based on underlying genetic mechanisms remains a central objective in reproductive medicine, facilitating improved patient management and advancing understanding of male reproductive pathophysiology.

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