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ORIGINAL RESEARCH

Association of Y Chromosome Microdeletions with Reproductive Profiles in 2010 Infertile Male Patients in China

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Objective: To analyze the incidence of different types of Y chromosome microdeletions in infertile male patients in China, and to investigate the relationship between microdeletions in different azoospermia factor (AZF) regions and sperm kinetic parameters, sperm morphological parameters, and sex hormone levels.

Methods: A total of 2010 infertile male patients who visited the Fujian Provincial Maternity and Child Health Hospital from 2022 to 2025 were selected. Their Y chromosome microdeletions (YCMD), semen routine, sperm morphology, sperm DNA fragmentation index (DFI), and sex hormone levels were detected, and the relationships between these parameters were analyzed.

Results: The incidence of Y chromosome microdeletions in patients was 8.66% (174/2010). Among the 174 patients with AZF microdeletions, the proportion of AZFc region deletions was 85.63% (149/174), AZFa region deletions accounted for 2.30% (4/174), AZFb/c region deletions accounted for 8.05% (14/174), AZFa/b/c region deletions accounted for 2.87% (5/174), and heterochromosome deletions accounted for 1.15% (2/174). There were no statistically significant differences in semen volume, testosterone (T), and prolactin (PRL) levels between patients with different types of AZF deletions and the normal group ($P>0.05$). There were statistically significant differences in sperm concentration, progressive motility (PR), non-progressive motility (NP), total sperm motility, normal sperm morphology rate, sperm DFI, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) between patients with different types of AZF deletions and the normal group ($P<0.05$).

Conclusion: AZFc deletion is the most common type of Y chromosome microdeletion in infertile male patients in China. Patients with AZFa and AZFa/b/c combined deletions often present with azoospermia. AZFc deletion is associated with abnormal sperm quality parameters and disordered hormone levels.

Keywords: Y chromosome, AZF region microdeletion, sperm quality, sex hormone

Introduction

Male infertility is an increasingly serious global health problem that affects millions of families.[1] Genetic factors are an important cause of male infertility, and YCMD play an important role in genetic factors.[2] The Azoospermia Factor (AZF) regions of the Y chromosome contain multiple genes essential for spermatogenesis, which controls the occurrence of spermatocytes, sperm meiosis, and sperm maturation.[3] The AZF region is rich in highly similar palindromic structures (P1-P8). The AZF region of the Y chromosome is artificially divided into AZFa, b, and c regions. Due to its repetitive structure, the AZF region is highly susceptible to rearrangements and microdeletions.[4,5] The occurrence of YCMD varies among males in different regions, and the impact of different types of microdeletions on sperm quality is also different.[6]

Previous studies suggest correlations between AZF microdeletions and reproductive hormones, but the evidence remains inconsistent. Some researchers believe that AZF microdeletion is associated with FSH, LH, and,[7,8] while others believe that Y chromosome deletion can lead to elevated FSH, while LH and T are not affected.[9] The aim of

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this study was to determine the incidence of AZF microdeletions in 2010 infertile men in China and to evaluate their associations with semen quality and hormone profiles. These studies can open up new theoretical basis for the diagnosis and treatment of male infertility.

Materials and Methods

Materials

This retrospective study enrolled a cohort of 2010 infertile male patients who presented at Fujian Maternal and Child Health Hospital between 2022 and 2025.These patients included those with normal semen, oligoasthenospermia and azoospermia. Among these participants, 174 were identified with YCMD through diagnostic screening. For comparative analysis, 99 fertile males with age matching and non-YCMD were selected as controls. The study protocol received ethical approval from the Institutional Review Board of Fujian Maternal and Child Health Hospital, China (Approval No.: 2023KY093). Following the ethical guidelines, all patient data were anonymized before analysis, ensuring the impossibility of individual identification. Consequently, the Ethics Committee granted a waiver for obtaining individual informed consent. The study complies with the Declaration of Helsinki.

Methods

Y Chromosome Microdeletion Analysis

Peripheral blood samples were collected from participants, and genomic DNA was isolated using a commercial DNA extraction kit (Shenzhen Yaneng Biotechnology Co., Ltd). Multiplex PCR amplification was performed using a standardized protocol (Shenzhen Yaneng Biotechnology Co., Ltd)., targeting 15 specific loci (AZFa: sY82, sY84, sY86, sY88, sY1064, sY1065. AZFb: sY105, sY121, sY127, sY134. AZFc: sY254, sY255. AZFb/c: sY153, sY1192 and sY160.) with ZFX/Y and SRY serving as dual internal controls. These sites were consistent with those recommended in the EAA/EMQN guide.[4,10] Amplification products were subsequently resolved and analyzed through agarose gel electrophoresis (Agarose concentration:2%; Electrophoresis voltage: 6V/cm).

Semen Parameter Assessment

After abstinence of 2–7 days, semen samples were collected and incubated at 37°C for 30 minutes before analysis. Semen parameters, including concentration, motility, and movement patterns, were evaluated using a computer-assisted sperm analysis system (Beiang Pharmaceutical Technology Co., Ltd., Shanghai, China) in accordance with the fifth edition of the WHO Laboratory Manual for the Examination and Processing of Human Semen.[11]

Sperm Morphological Evaluation

Sperm morphology was assessed using Papanicolaou staining (Anke Biotechnology Co., Ltd., Anhui, China) following the manufacturer's protocol. Morphological characteristics were examined under 1000x magnification, with classification performed according to the fifth edition of the WHO guidelines.[11]

Sperm DNA Fragmentation Analysis

Sperm chromatin integrity was evaluated using the Sperm Chromatin Dispersion (SCD) test (Anke Biotechnology Co., Ltd., Anhui, China). A minimum of 500 spermatozoa were examined under 400x magnification, and the DNA fragmentation index (DFI) was calculated based on established the fifth edition of the WHO criteria.[11] The normal range of sperm DFI was defined according to relevant literature.[12]

Hormonal Profile Assessment

Six milliliters of peripheral blood were collected for hormonal analysis. Serum concentrations of LH, FSH, PRL, and T were quantified using chemiluminescent microparticle immunoassay (American Standard Biotechnology Co., Ltd., Jiangsu, China).

Statistical Analysis

All statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), and between-group comparisons were performed using independent samples *t*-tests. Categorical data were presented as percentages (%), and group differences were assessed using continuity-corrected chi-square tests. A two-tailed p-value < 0.05 was considered statistically significant for all analyses.

Results

Analysis of Y Chromosome Microdeletions

In a cohort of 2010 male infertility patients, YCMD were identified in 174 cases, yielding an incidence rate of 8.66% (174/2010). The AZFa region exhibited deletions in 2.30% (4/174) of cases, with prevalent deletion sites including sY84, sY86, sY1064, and sY1065. No isolated deletions in the AZFb region were observed. The AZFc region demonstrated deletions in 85.63% (149/174) of cases, with common deletion sites being sY254, sY255, sY153, and sY1192. Combined deletions of the AZFb/c region were present in 8.05% (14/174) of cases, while combined deletions of the AZFa/b/c region were observed in 2.87% (5/174) of cases. Heterochromosomal deletions were identified in 1.15% (2/174) of cases (Figure 1).

General Characteristics of AZF Deficient Patients

No statistically significant differences were observed between the AZF deficient groups and the normal control group in terms of age, body mass index (BMI), primary infertility rate, varicocele prevalence, abstinence duration, semen volume, or semen PH ($P > 0.05$) (Table 1).

Sperm Quality Analysis in AZFc Deletion

All groups except for the AZFc deletion group exhibited azoospermia. The AZFc deletion group demonstrated a significantly reduced sperm concentration compared to the normal control group, with patients presenting varying degrees of oligospermia or azoospermia. Progressive motility (PR), non-progressive motility (NP), and total sperm motility were also significantly lower in the AZFc deletion group compared to the control group. Additionally, the normal sperm morphology rate was lower, and the sperm DNA fragmentation rate was higher in the AZFc deletion group than in the control group (Table 2 and Figure 2).

Hormonal Profile Comparison Among AZF Deletion Groups

Analysis of FSH, LH, PRL, and T levels in patients with different AZF microdeletions revealed no statistically significant differences in T and PRL levels among the groups ($P > 0.05$). However, FSH and LH levels were significantly elevated in the AZF microdeletion groups compared to the normal control group ($P < 0.05$) (Table 3).

Discussion

Microdeletions in the AZF region of the Y chromosome represent a significant etiological factor in azoospermia and oligoasthenospermia, with a prevalence ranging from 5.7% to 21.0% among male infertility populations.[13] Among these deletions, AZFc microdeletion constitutes the predominant type across diverse geographical regions, accounting for over 80% of cases in certain areas.[13,14] The underlying mechanism involves amplicon-mediated non-allelic homologous recombination of MSY sequences, which directly contributes to AZF microdeletions.[15] The study collected 2010 male patients with infertility and combined analysis of their semen quality and hormone levels which provides valuable insights into the clinical diagnosis and treatment management of male infertility.

Our investigation revealed that the prevalence of YCMD among male infertility patients in Fujian Province, China, was 8.66%, aligning with previously reported data.[13] The result is also similar to the study of Y chromosome deletion rates in other regions of China.[16] Different types of patients have different rates of YCMD occurrence, so it is necessary to study different populations. Specifically, AZFc region deletions accounted for 85.63% (149/174) of cases, while the remaining cases comprised isolated AZFa region deletions, combined AZFb/c region deletions, and

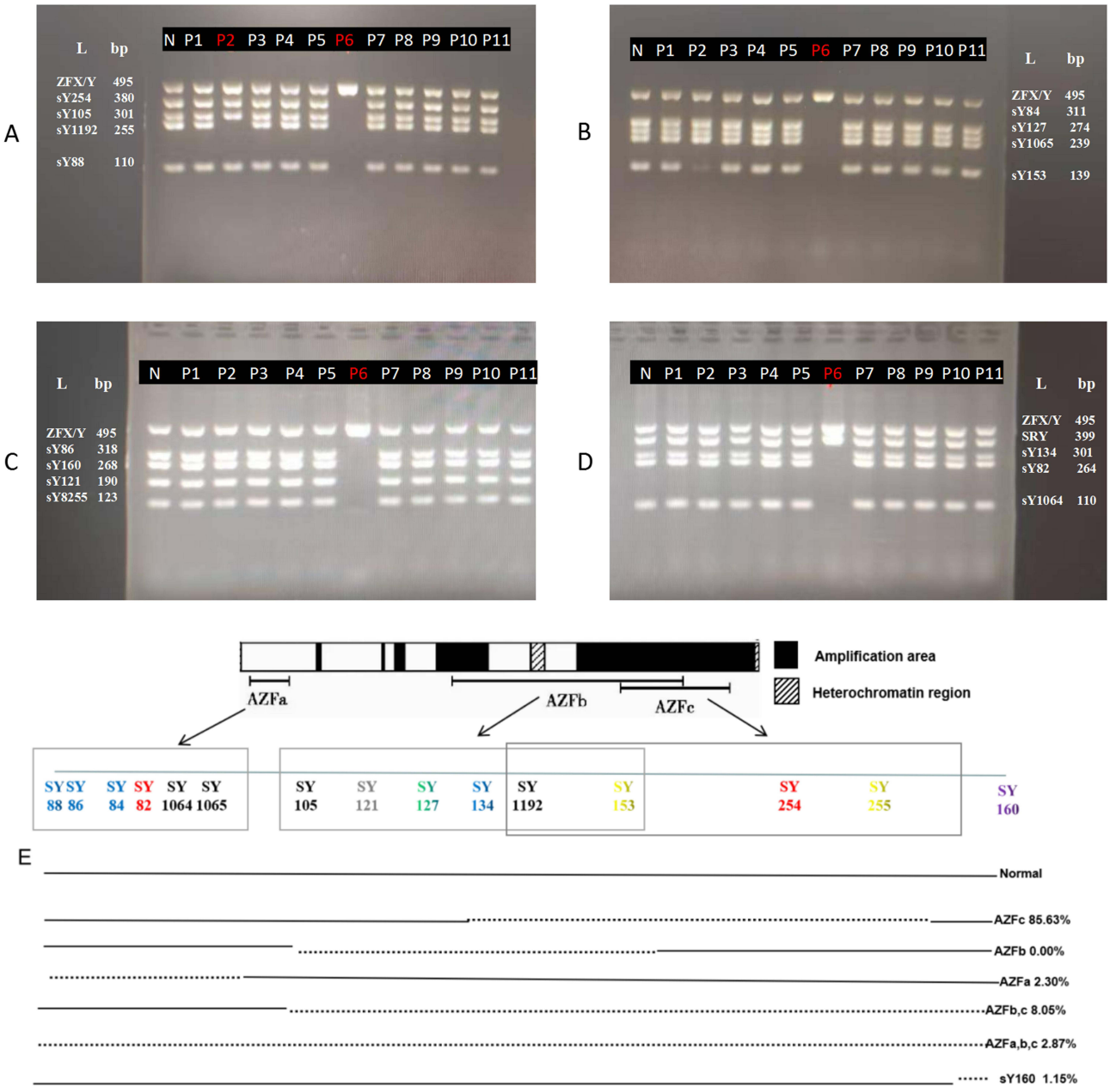

Figure 1 Y chromosome deletion status.

Notes: (**A**–**D**) Electrophoresis of microdeletion of different types of Y chromosome. Each sample was separated in four gel by electrophoresis, each gel contained five pairs of primers, and the last tube contained SRY gene. "N" denotes the normal control; "p2" indicates the deletion of the sY1192 locus; "p6" represents the complete deletion of the AZFa/b/c fragments, and the remaining "p" samples correspond to an intact Y chromosome. (**E**) The locus and deletion ratio of different AZF region deletion types of the Y chromosome. Deletion of the "sY160" locus indicates a complete deletion of the terminal end of the Y chromosome long arm.

combined AZFa/b/c region deletions. Clinical manifestations varied according to deletion type: patients with AZFc deletions presented with either azoospermia or mild oligospermia, whereas those with AZFa deletions or combined deletions uniformly exhibited azoospermia. The absence of AZFa leads to the occurrence of Sertoli cell-only syndrome (SCOS).[17] The absence of AZFb disrupts the development of spermatogenic cells and eventually leads to azoospermia.[18]

The study findings indicate that patient age, BMI, semen volume, abstinence duration, and semen pH-value showed no correlation with AZF microdeletions. Sperm quality analysis revealed that patients with various types of AZF deletions exhibited low sperm concentration or azoospermia. AZFc deletion primarily manifests as

Table 1 General Information of Patients with AZF Deficiency

Parameter	AZFc Deficiency	Other Deficiency	Normal Control	F/X^2	*P*
Number	149	25	99	–	–
Age (year)	33.41±5.42	32.28±4.92	33.42±5.06	0.53	0.58
BMI (weight/ height^2)	20.73±3.43	22.210±2.85	20.355±3.28	1.30	0.48
Primary infertility (%)	49.00% (73/149)	52.00% (13/25)	48.48% (48/99)	0.10	0.95
Varicocele (%)	13.42% (20/149)	16.00% (4/25)	16.16% (16/99)	0.39	0.82
Abstinence time (day)	3.67±1.59	3.96±1.24	3.85±1.38	0.35	0.70
Semen volume (mL)	3.67±1.59	3.13±1.29	3.57±1.58	1.26	0.28
Semen pH	7.41±0.28	7.46±0.13	7.43±0.05	0.58	0.56

Table 2 Analysis of Sperm Quality in AZFc Deficiency

Parameter	AZFc Deficiency	Normal Control	t	*P*
Number	149	99	–	–
Sperm concentration (10^6/mL)	24.75±36.64	92.12±55.91	2.04	0.01
Sperm PR (%)	12.30±16.63	47.79±18.44	6.48	0.00
Sperm NP (%)	1.82±3.77	6.04±5.90	1.84	0.01
Total sperm motility (%)	14.12±18.46	53.83±19.68	5.15	0.00
Normal sperm morphology (%)	2.61±2.38	7.49±3.95	8.30	0.00
Head abnormalities (%)	96.82±3.09	90.30±6.06	3.45	0.00
Midpiece abnormalities (%)	22.88±6.20	18.36±7.16	2.98	0.00
Sperm tail malformation (%)	12.53±3.49	8.49±5.16	2.09	0.01
DFI (%)	15.71±8.42	8.65±4.46	1.74	0.03

Notes: No sperm was detected in 25 patients with microdeletion other than AZFc, and P<0.05 indicated that the results were statistically significant.

oligospermia with significantly reduced sperm concentration compared to normal controls, while other AZF deletion types present as azoospermia. AZFa region deletion correlates with SCOS and azoospermia, accompanied by testicular shrinkage, clinically presenting as azoospermia. AZFb region deletion causes spermatogenic cells to remain at the primary spermatocyte stage, preventing sperm production. The AZFc deletion group showed higher rates of sperm morphology abnormalities compared to normal controls, with increased malformations in the head, midpiece, and tail regions. These results demonstrate that AZF deletions predispose sperm to greater deformities, particularly in head, midpiece, and tail areas. Additionally, sperm DNA integrity was significantly worse in the AZFc deletion group, with higher rates of DNA fragmentation. These findings align with previous studies.[19–21]

Existing evidence suggests that AZF microdeletions may disrupt the testicular microenvironment.[22] Structural and functional abnormalities in FSH and LH receptors on Sertoli and Leydig cells can impair signal transduction pathways, thereby compromising spermatogenesis. Additionally, AZF microdeletions have been implicated in reduced spermatogenic capacity and dysfunction within the seminiferous tubules. This spermatogenic impairment can disrupt the negative feedback regulation of the hypothalamic-pituitary-gonadal (HPG) axis, leading to compensatory elevations in FSH levels.[8] The results showed that patients with AZF deficiency had higher FSH levels than the control group and higher DFI levels than the normal group. This is because elevated FSH affects the apoptosis of spermatogenic cells, which eventually leads to sperm DNA breakage.[23] Consistent with this, our study observed elevated FSH and LH concentrations in patients with AZF microdeletions. These findings have two key clinical implications: first, they provide a basis for assessing the severity of spermatogenic dysfunction in affected individuals through reproductive hormone profiling; second, they elucidate the pathological link between

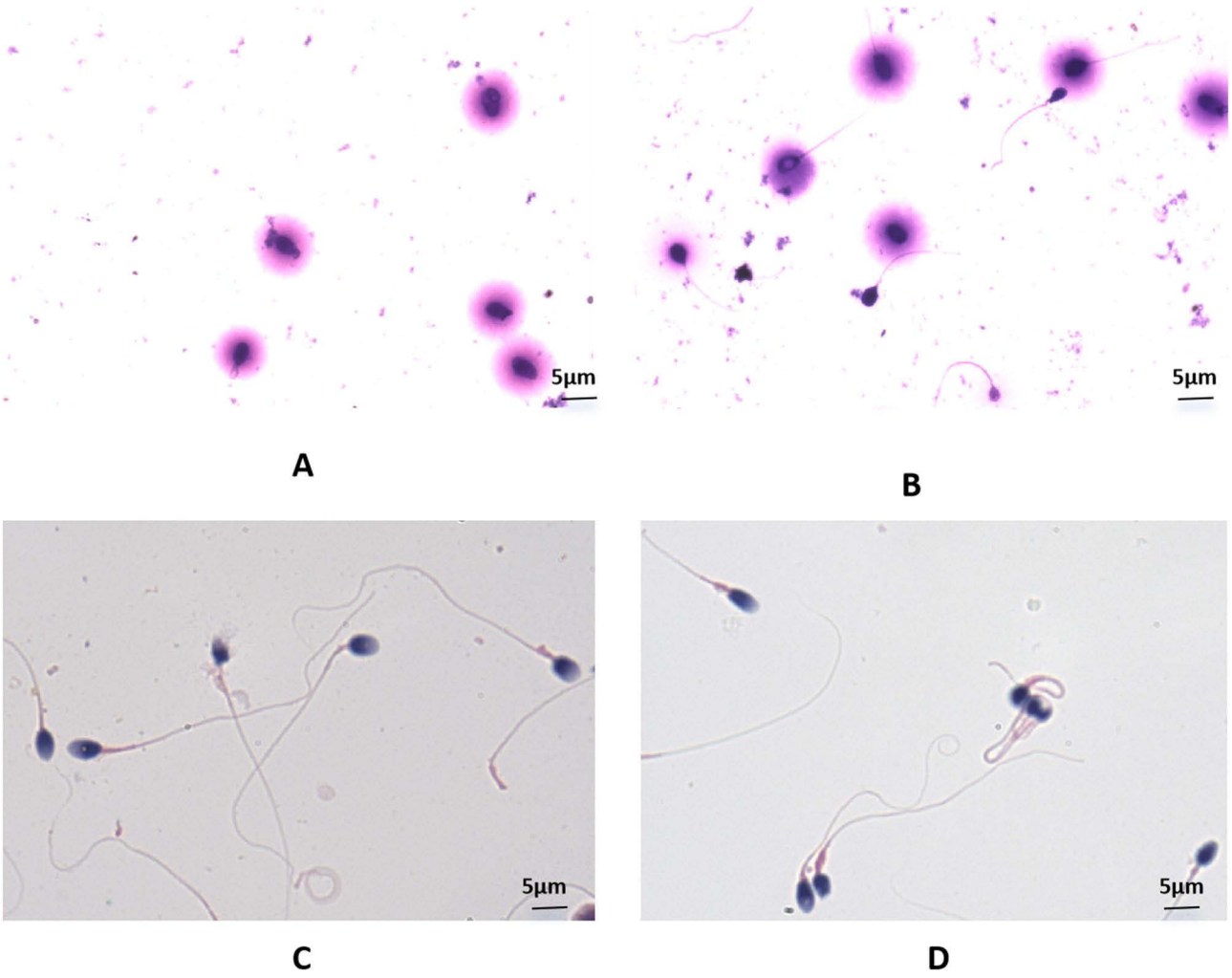

Figure 2 Schematic diagram of different sperm quality.
Notes: (**A**) Sperm with low DNA fragmentation rate. (**B**) Sperm with high DNA fragmentation rate. (**C**) Normal sperm morphology. (**D**) Abnormal sperm morphology. (**A** and **B**) was assessed by chromatin diffusion staining method and the size of the halo after staining represents the integrity of sperm DNA.The little dots in the image are the dye residue or bacteria and the big violet dots are the sperm head outlines formed after the sperm head is lysed. (**C** and **D**) was assessed by via the Papanicolaou stain. The images show that all (**C**) sperm have standard oval heads, whereas most (**D**) sperm are irregular or have small acrosomes.

HPG axis dysregulation and infertility phenotypes. This not only offers an objective framework for male fertility evaluation but also establishes a molecular-level explanation for endocrine-related infertility.

There are several limitations to our study. Firstly, it is a retrospective study and may suffer from selection bias. Secondly, the study of AZFa and AZFb in this study requires a larger sample size to support it.

Table 3 Comparison of AZF Deficiency and Hormone Levels Between Groups

Parameter	AZFc Deficiency	Other Deficiency	Normal Control	F	*P*
Number	149	25	99	–	–
FSH (IU/L)	11.35±1.14*	19.82±11.53**	4.85±3.55	8.59	0.00
LH (IU/L)	4.99±0.46*	9.77±6.61**	3.51±2.58	9.74	0.00
T (ng/dL)	4.12±0.19	3.65±2.24	4.06±2.05	1.07	0.45
PRL (ng/mL)	11.62±1.84	11.25±3.46	8.50±3.69	3.05	0.27

Notes: P<0.05 indicates that the difference between groups is statistically significant, *indicates that the group is statistically significant compared with the control group, **indicates that the group is statistically significant compared with the other two groups.

Conclusions

The incidence of YCMD in infertile men in Fujian Province of China is 8.66% and the AZFc deletion is the most common type. Patients with AZFa and AZFa/b/c combined deletions often present with azoospermia. AZFc deletion is associated with abnormal sperm quality parameters and disordered hormone levels. Next we will combine multi-center research to improve diagnosis and treatment of male infertility in the region and globally.

Data Sharing Statement

The datasets of current study are available from the corresponding author (Gangxin Chen) on reasonable request.

Ethics Approval and Consent to Participate

The study protocol received ethical approval from the Institutional Review Board of Fujian Maternal and Child Health Hospital, China (Approval No.: 2023KY093).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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