

Review

Unraveling the Role of Non-Coding Genetic Variants in Male Infertility: Insights from the Chinese Population

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Abstract

Male infertility is a growing concern worldwide, with almost half of infertility cases being male, and the trend is rising in China as a result of multifaceted genetics-environment interaction. Important breakthroughs have been made in identifying mutations in annotated protein-coding genes associated with male infertility. However, a significant part of the human genome, namely non-coding DNA, has not yet been explored. Recent breakthroughs in the realm of high-throughput genomic technologies have unveiled the indispensable role played by non-coding single-nucleotide polymorphisms (SNPs) and non-coding RNAs in the regulation of gene expression and normal spermatogenesis. This article illuminates advances in understanding the contribution of non-coding genetic variation to male infertility among the Chinese population. Key studies linking non-coding SNPs in regulatory regions of genes such as *PRM1*, *PRM2*, *KIT*, and *KITLG* with azoospermia and oligozoospermia are summarized. In addition, there is a discussion about the deregulation of several classes of ncRNAs, such as microRNAs (miRNAs), long non-coding RNAs, PIWI-interacting RNAs (piRNAs), and circular RNAs, and how these deregulations affect testicular functionality, germ cell development, and sperm quality. These unique population-specific genetic backgrounds have revealed unique patterns of association of noncoding variants with male infertility in Chinese cohorts,



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suggesting the relevance of ethnicity-focused genetic research. This review underscores the importance of non-coding genomic variation in the etiology of male infertility and emphasizes the potential of precision medicine strategies tailored to the Chinese population.

Keywords

Male infertility; non-coding SNPs; non-coding RNAs; Chinese population; spermatogenesis; genetic variation; precision medicine

1. Introduction

Male infertility is an intricate and multifactorial affliction that forms the basis for about 50 percent of infertility cases worldwide [1]. In China, the rising male infertility rate is being affected by environmental pollution, changes in lifestyles, and later marriages. While classical studies have focused on mutations of protein-coding genes, more recent studies have defined the importance of non-coding genetic variations in male reproductive health [2].

Composed of nearly 98% of non-coding sequences, non-coding DNA was denigrated as “junk DNA” until it was identified to play a critical role as gene regulators [3]. Non-coding regions comprise different elements: introns, promoters, enhancers, untranslated regions (UTR), and intergenic sequences [4]. Variation in these areas, including single-nucleotide polymorphisms (SNPs), can impede gene regulation and expression, leading to impaired spermatogenesis and infertility [5].

Among the Chinese population, several non-coding SNPs have been related to male infertility. While SNPs in the *DNMT3L* gene, known to be involved in DNA methylation during spermatogenesis, are associated with azoospermia, a study found that the rs2070565 A allele and the AAA haplotype were significantly more frequent among azoospermia patients than among fertile controls, suggesting genetic susceptibility in the population [6-8]. This association appears more pronounced in Chinese men than in studies in other Asian and Caucasian populations, where the same variant has shown weaker or non-significant effects [7].

In addition to variation in DNA sequence, non-coding RNA (ncRNA) types play a very important role in regulating gene expression in spermatogenesis [9]. Such ncRNAs include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), PIWI-interacting RNAs (piRNAs), and circular RNAs (circRNAs). miRNAs are typically involved in post-transcriptional regulation of gene expression and are involved in germ cell development and apoptosis [10]. In the testicular tissue of Chinese men with non-obstructive azoospermia (NOA), changes in expression of some of these miRNAs were noted, including this particular one, miR-34c, which is upregulated and functions in apoptosis of germ cells [11]. Long non-coding RNAs are another class of ncRNA that influence spermatogenesis through multiple mechanisms, such as chromatin remodeling and transcriptional regulation. Skewed levels of lncRNA, particularly H19, link these abnormal ratios in men to poor percentages of sperm parameters and infertility trials in Chinese population groups [12]. piRNAs work with PIWI proteins and are critical for preventing genomic instability in germ cells, and disruption of piRNA pathways has been associated with failure of spermatogenesis [13]. Polymorphisms in the *HIWI2* gene, which is involved in piRNA biogenesis, have been associated with non-obstructive azoospermia in the Chinese population. The high-throughput sequencing technologies have now

made it easier to find differentially expressed circRNAs in the testes of infertile men, and they have been proven to be better indicators of male infertility [14]. Although numerous reviews have summarized the genetic basis of male infertility or the roles of non-coding RNAs in spermatogenesis, most adopt a global or predominantly Western-centric perspective. To our knowledge, this is one of the first reviews that systematically integrates non-coding genetic variants (regulatory SNPs and multiple ncRNA classes) with a primary focus on the Chinese population. This focus is justified by (1) the rapid increase in male infertility prevalence in China, (2) repeated reports of ethnicity-specific association signals, haplotype structures, and ncRNA expression profiles not consistently replicated in non-Chinese cohorts, and (3) the relative under-representation of Chinese data in international review articles. By combining population-specific findings with critical evaluation of evidence strength and mechanistic interpretation, this review aims to offer insights directly relevant to genetic counseling, risk assessment, and future precision medicine strategies in the Chinese context.

The results indicate that non-coding genetic variations and ncRNAs are very important in the cause of male infertility [15]. This review not only summarizes associations but also emphasizes proposed mechanistic links between non-coding variants/ncRNAs and specific defects in spermatogenesis, sperm maturation, and functional outcomes [16].

This review aims to bring together the latest information on how noncoding DNA differences may contribute to male infertility among Chinese individuals. With the help of computers, we study the role of non-coding SNPs and various ncRNA classes, hoping to understand their functions, medical backgrounds, and potential for treatment and detection. Such knowledge is important for improving the use of precision medicine to treat male infertility [16]. Unlike most existing reviews that present global or Western-dominated syntheses, the present work uniquely centers on Chinese population-specific patterns of non-coding variation and ncRNA dysregulation, providing ethnicity-informed insights that remain significantly underrepresented in the current literature.

2. Non-Coding SNPs and Male Infertility in the Chinese Population

Because of their possible roles in regulating genes and in disease, SNPs found in regions of the genome aside from protein-coding are attracting increased attention. Researchers have found that non-coding SNPs can cause problems with sperm formation among men from China [17-20]. A remarkable example is that polymorphisms in the genes *PRM1* and *PRM2* are vital for sperm to condense their chromatin into DNA. Jiang et al. conducted a study (in 2017) by examining the impact of five SNPs, i.e., rs737008, rs2301365, rs2070923, rs1646022, and rs62180545, in 636 infertile men and 442 fertile controls from China's Han population. Although single SNPs were not strongly linked, some haplotypes, including GCTGC, TCGCA, and TCGCC, were protective for male infertility. In comparison, the presence of the TCGGA, GCTCC, and TCGGC haplotypes was associated with an increased risk of spermatogenic failure. From these studies, it appears that mixes of non-coding SNPs in *PRM1* and *PRM2* might increase the risk of male infertility [21]. Notably, while individual *PRM1* and *PRM2* SNPs have shown inconsistent or weak associations in European and Middle Eastern cohorts, haplotype-based analyses in Chinese populations have revealed more consistent risk and protective patterns, possibly reflecting population-specific haplotype architecture [20].

Another research project examined the *KIT* and *KITLG* genes, which support the *KIT/KITLG* signaling pathway and help produce sperm. In 2013, Cheng et al. identified SNPs rs3819392 in *KIT* and rs4474514 in *KITLG* by analyzing 372 patients with idiopathic azoospermia or oligospermia and

205 fertile controls. Results showed that more oligospermic patients than controls carried the G allele and GG genotype of rs3819392 in *KIT* as well as the CC genotype of rs4474514 in *KITLG* [22]. In contrast to some European studies that found no significant association between *KITLG* variants and spermatogenic failure, the Chinese cohort showed a stronger association of the rs4474514 CC genotype with oligospermia, underscoring the importance of ethnicity-specific analyses [21].

Moreover, changes in antioxidant genes are thought to contribute to male infertility. It was Yin et al. (2020) who examined seven SNPs in antioxidant genes, such as *NQO1* rs1800566 and *GSTM3* rs1571858, in 248 infertile patients and 310 healthy people who can have children. SNPs did not appear to be linked, but grouping the genes *GSTM3* rs3814309 and *NQO1* rs1800566 together suggested they are linked to improved male reproductive health. A strong link was observed between the simultaneous presence of risk variants in *GSTM3* rs1571858, *NQO1* rs1800566, and azoospermia, suggesting non-coding SNP interactions may play a role in male infertility [23]. They demonstrate that non-coding SNPs are important in how male infertility is inherited in Chinese men. Finding which SNPs and haplotypes relate to issues with sperm production in men gives us important clues about the biology of infertility and future treatment methods [24-28].

Most association studies included in this section enrolled between 200 and 700 individuals (cases + controls), which is generally underpowered to robustly detect variants with small-to-moderate effect sizes (OR 1.2-1.8). Moreover, the majority of reported associations have not been independently replicated in large-scale Chinese or multi-ethnic cohorts, limiting confidence in their generalizability. While global reviews often emphasize coding-region mutations, the stronger and more consistent haplotype-level signals observed in Chinese cohorts underscore the particular relevance of non-coding regulatory variation in this population [23, 24].

2.1 Mechanisms of Non-Coding SNPs in Male Infertility

2.1.1 Disruption of Transcriptional Regulation

SNPs that are not in genes may modify where transcription factors bind, and this can influence genes required for spermatogenesis. Reduced expression of *SOX9* in the enhancer caused by SNP rs10842262 affects the function of Sertoli cells and spermatogenesis [29], while differences in the FSHB promoter (rs10835638) resulting from polymorphisms lower FSH levels and cause problems with germ cell development [30].

2.1.2 Alteration of miRNA Binding Sites

Disruption of miRNA-mRNA interactions by SNPs in 3' UTRs of genes may cause genes to become abnormally expressed. One instance is a SNP (rs17070145) in the 3' UTR of *KITLG*, which leads to a drop in miR-221 binding, boosts *KITLG* expression, and negatively affects early spermatogonia development [22].

2.1.3 Splicing and Post-Transcriptional Modifications

Intronic SNPs can disrupt the usual splice sites, leading to incorrect isoforms. Apart from that, a specific SNP (rs3129878) in *NR5A1* (SF-1) disrupts splicing, reducing the expression of steroidogenic enzymes and testosterone production [31, 32]. The intronic SNP (rs2307111) within *CATSPER1* causes sperm motility problems by disrupting the function of the sperm calcium channel [33-35].

Collectively, these non-coding SNPs appear to impair spermatogenesis through altered gene dosage, disrupted miRNA regulation, or incorrect splicing, ultimately leading to reduced germ cell numbers, meiotic failure, defective chromatin packaging, or impaired sperm motility [34]. Table 1 shows some of the non-coding SNPs associated with male Infertility.

Table 1 Key non-coding SNPs Associated with Male Infertility.

Gene/Region	SNP ID	Effect	Reference
SOX9 enhancer	rs10842262	Reduced Sertoli cell function	[36]
FSHB promoter	rs10835638	Low FSH, impaired spermatogenesis	[30]
KITLG 3' UTR	rs17070145	Disrupted miR-221 binding, germ cell defects	[22]
TEX11 3' UTR	rs6525433	Altered miR-34a regulation, meiotic arrest	[37]
NR5A1 intron	rs3129878	Aberrant splicing, low testosterone	[31, 32]
CATSPER1 intron	rs2307111	Defective calcium channels, poor sperm motility	[33]

3. MicroRNAs (miRNAs) in Spermatogenesis

MicroRNAs are tiny non-coding RNAs (22 nucleotides long) that regulate the expression of other genes by binding to target mRNA's 3' end after transcription, thereby either destroying them or stopping their translation [36]. For spermatogenesis to happen, stem cell division and differentiation inside a man's testes result in the production of mature spermatozoa. Current studies show that miRNAs regulate several stages of spermatogenesis, such as cell development, meiosis, and spermiogenesis [37]. Most miRNA expression studies in human testes are based on small cohorts (n < 50 per group) obtained from testicular biopsies, limiting generalizability. Furthermore, functional follow-up experiments that link specific miRNAs to causal spermatogenic defects are still scarce [36].

3.1 Role of miRNAs in Different Stages of Spermatogenesis

3.1.1 Spermatogonial Stem Cell Maintenance and Proliferation

To maintain spermatogenesis, Spermatogonial stem cells (SSCs) divide to maintain their numbers, while some of their progeny differentiate into other cell types. This is regulated in part by miR-21, miR-34c, and miR-221/222 that control important pathways such as TGF- β , PI3K/Akt, and Wnt [38, 39]. MiR-21 promotes SSC division by targeting PTEN, thereby activating the PI3K/Akt pathway, as reported by [40].

3.1.2 Meiotic Progression

During meiosis, miRNAs are involved in holding chromosomes together and promoting recombination between chromosomes. The miR-17-92 cluster and miR-34b/c genes are required for proper meiosis by turning off E2F3 and CDK6, which oversee cell cycle transitions [39]. Additionally, members of the miR-449 family play a role in NOTCH1 signaling, ensuring proper meiotic divisions [41].

3.1.3 Spermiogenesis (Sperm Maturation)

Spermiogenesis changes round spermatids into spermatozoa, and miR-469 and miR-883a-3p play a role in this by affecting genes that structure the sperm. MiR-202 is expressed at higher levels in the testes and helps regulate the SOX5 transcription factor, which plays a key role in sperm head development [42].

While several miRNAs show consistent dysregulation patterns in non-obstructive azoospermia, most expression studies are based on small testicular biopsy cohorts ($n < 50$ per group) and lack large-scale validation in seminal plasma or peripheral blood, which would be more clinically applicable [37].

3.1.4 Dysregulation of miRNAs and Male Infertility

Problems with miRNA that disrupt the body's balance can cause male infertility. For instance, miR-34c being decreased is linked to problems with sperm production and a reduction in sperm movement [37]. Elevated miR-155 can damage the blood-testis barrier by targeting *Cldn11*, whereas a problem with miR-19b disrupts Sertoli cell function and promotes germ cell apoptosis. While miR-34c dysregulation is widely reported in male infertility globally, the direction of change (up- vs. downregulation) and the affected testicular compartment appear to differ between Chinese and Western cohorts, possibly due to differences in disease subtype distribution or environmental modifiers [40].

3.1.5 Potential Uses of miRNAs as Therapies

Because miRNAs can indicate signs of male infertility and interact with important biological processes, they are being considered for use as markers in detection and therapy. In the same way, miR-21 mimics might help SSCs multiply, and miR-34c inhibitors may improve sperm quality. miRNAs are important for regulating gene expression in spermatogenesis across different growth stages. Knowing how they function can give us insights into what causes male fertility problems and how they can be treated [39]. miRNA mimics or inhibitors (e.g., miR-21 mimics to promote SSC proliferation, or miR-34c inhibitors to reduce germ cell apoptosis) have shown promise in preclinical models and may represent interesting avenues for future therapeutic exploration, although no such approaches have yet reached clinical testing in male infertility.

4. Link between Long Non-Coding RNAs (lncRNAs) and Infertility

Long non-coding RNAs (lncRNAs) are over 200 nucleotides long and take part in important genetic activities such as gene regulation, molding chromatin, and post-transcriptional modification [43]. Evidence is arising that long non-coding RNAs are involved in making sperm, regulating sperm functions, and developing the testes, and abnormalities in their levels can result in male infertility [44]. It is estimated that lncRNA abnormalities play a major role in 7% of infertile cases in men that have no clear cause [45]. These population-distinct ncRNA expression signatures represent an important but under-explored dimension compared with most existing global reviews of ncRNAs in spermatogenesis. lncRNA studies in male infertility remain mostly descriptive, typically based on small RNA-seq datasets and lacking systematic functional validation in relevant cell types or animal models [43].

4.1 Functions of lncRNAs in Reproduction

In cells known as spermatogonial stem cells, lncRNAs guide both replication and change. Tug1 is an important example of miRNAs, and H19 is a typical lncRNA. Their main actions include promoting SSC growth and sustaining their stemness by influencing Lin28 expression and IGF2 signaling, respectively [46]. Invertebrates need Tsx and Mrhl lncRNAs: Tsx helps in MSCI and keeping prophase condensed, whereas Mrhl ensures proper chromosome and germ cell differentiation [47]. Spga-lncRNAs are abundant in fully mature sperm, and when they no longer work properly, they may cause problems with sperm motility [44]. NEAT1 (Nuclear Enriched Abundant Transcript 1) controls how chromatin is condensed during the process of spermiogenesis, according to [48-50].

Table 2 lists the lncRNAs that are found to be dysregulated in samples of male infertility.

Table 2 Dysregulated lncRNAs in Male Infertility.

lncRNA	Function	Associated Infertility Phenotype	Reference
Tug1	SSC proliferation	Oligozoospermia	[51-53]
H19	Stemness maintenance	Non-obstructive azoospermia	[54, 55]
Tsx	Meiotic sex chromosome silencing	Meiotic arrest	[56]
Mrhl	Wnt signaling regulation	Sperm count reduction	[57, 58]
NEAT1	Chromatin compaction	Teratozoospermia	[59]

4.2 Unbalanced lncRNA Level Leading to Fertility Problems

Harmful DNA methylation (such as the extra methylation of H19) blocks the development of germ cells [49-51]. Some lncRNAs, such as Malat1, act as miRNA sponges to compete away miRNAs that manage genes involved in spermatogenesis [52]. When lncRNAs prevent the proper function of splicing, Prc1-AS1 prevents the correct formation of sperm [53].

Research now links LINC00662 and similar RNAs in seminal plasma, providing possible noninvasive tools for diagnosing breast cancer. If lncRNAs in sperm can be regulated with CRISPR during gene therapy, this might restore normal sperm production [22]. The practical use of bacteriophages in medicine warrants further exploration. While speculative at this stage, the possibility of using CRISPR-based approaches to modulate dysregulated lncRNAs (e.g., restoring normal H19 expression) could be explored in future preclinical studies, but significant technical and safety challenges remain [51].

Most lncRNA studies in male infertility remain exploratory, often based on small RNA-seq cohorts and lacking functional follow-up experiments. The clinical relevance of many reported lncRNAs, therefore, remains preliminary [52].

5. PIWI-Interacting RNAs (piRNAs) and Spermatogenesis

A type of small non-coding RNA known as PIWI-interacting RNAs (piRNAs) connects to PIWI proteins in the PIWI subfamily of Argonaute proteins [54]. The function of these molecules helps to keep the genome undamaged, silence transposable elements, and regulate gene expression when cells become sperm [55]. In the testes, spermatogenesis is precisely controlled to produce one sperm cell from two spermatogonial stem cells, and piRNAs play a significant role in sperm because they help preserve fertility [56]. Many of the characteristics that set piRNAs apart from other small RNAs are their size, the way they are produced, and their association with PIWI proteins [57].

piRNAs direct PIWI proteins to shut down TEs by altering their DNA and adding or removing certain histone modifications [58]. Lack of piRNAs will increase TE genomic activity, which can damage DNA and introduce defects in meiosis. Pachytene piRNAs are reported to be important for spermiogenesis [29].

Another protein, MIWI (Piwi-like protein), takes in pachytene piRNAs and supports the elongation step of spermatids [59]. In haploid spermatids, piRNA-PIWI complexes either destroy or block the production of target mRNAs [59]. The TDRD6-piRNA pathway helps regulate spermiogenesis by eliminating unnecessary transcripts [59]. Restoring piRNA pathway function represents a theoretical therapeutic strategy for some forms of non-obstructive azoospermia, but this remains purely conceptual and will require major advances in delivery and targeting technologies [56].

Failure of piRNA-mediated transposon silencing leads to DNA damage and meiotic arrest at the pachytene stage, resulting in germ cell apoptosis and the azoospermic phenotype commonly observed in affected patients. Human data on piRNA pathway alterations are particularly limited, and functional evidence linking specific piRNA defects to spermatogenic failure is still predominantly derived from murine models [57, 58].

5.1 Dysregulation of piRNAs and Male Infertility and Clinical Implications

Defects in piRNA pathways are linked to Azoospermia (lack of sperm) due to meiotic arrest, Teratozoospermia (abnormal sperm morphology) from defective spermiogenesis, and Hybrid sterility in some species due to piRNA-mediated incompatibilities [45, 60, 61]. piRNA expression profiles may diagnose male infertility and serve as biomarkers for infertility [62]. Restoring piRNA function could treat certain forms of infertility. piRNAs are essential for spermatogenesis by maintaining genomic stability, regulating meiosis, and ensuring proper sperm maturation. Their dysfunction contributes to male infertility, highlighting their potential in diagnostics and therapy [63].

6. Circular RNAs (circRNAs) in Testicular Function

circRNAs are special endogenous non-coding RNAs because they are made as circles by back-splicing of pre-mRNA transcripts [64]. Whereas linear RNAs are destroyed by exonucleases, circRNAs are more stable because they lack 5' and 3' caps [65]. CircRNAs are found at higher levels in the testis, where they support sperm formation, production of hormones, and functions of non-sperm cells [42, 66, 67]. There is now growing evidence that circRNA imbalance is connected to male infertility and problems with the testes [68]. There are mainly three methods by which testicular circRNAs are formed. (a). Exon skipping is the most frequent reason for circular RNA production in spermatogenic cells, according to [22, 42]. (b). Many Sertoli cells use intron pairing for circularization according to [69, 70]. (c). QKI and FUS-controlled proteins can lead to RNA circularization then regulated by RNA-binding proteins (RBPs) in Leydig cells [64]. Proof-of-concept studies in mice using engineered circRNAs have suggested the potential to correct certain gene defects. Whether similar approaches could eventually be translated to humans remains an open question for future research [61].

The miR-135a sponge function of circRNA_0004867 helps preserve the stem cells in developing sperm, circBoule works with DAZL protein to control the process of meiosis, and circSry in mice

helps to determine which sex an animal becomes [71-81]. The sponging of miR-145 by circLRP6 increases testosterone production. The expression of circRNA_004760 helps regulate cholesterol transport in Leydig cells. circRNA profiling studies are promising but currently rely on small discovery cohorts without large-scale replication or functional characterization of the most differentially expressed candidates. In Table 3, we see which circRNAs may be disturbed in various testicular disorders.

Table 3 Dysregulation in Testicular Disorders.

circRNA	Associated Disorder	Mechanism	Reference
circRNA_103827	Non-obstructive azoospermia	Sponges miR-34c-5p	[77, 82-86]
circRNA_104816	Varicocele-associated infertility	Binds IGF2BP1	
circRNA_0002035	Testicular germ cell tumors	Activates Wnt/ β -catenin	
circRNA_0000799	Cryptorchidism	Regulates INSL3 signaling	

circRNAs in seminal plasma may hold potential for simpler and less invasive diagnosis of infertility. Researchers identified circRNA traits that can distinguish between obstructive azoospermia and non-obstructive azoospermia. Cheng et al. used artificial circRNAs to treat spermatogenic failure and correct gene defects in mice. Interventions that involve circRNAs may be possible for people with low testosterone. In males, testicular circRNAs are key regulators involved in reproduction and have begun to be associated with germ cell, somatic cell, and endocrine functions. Because their expression patterns are consistent and well-controlled, they are suitable genes to explore for the treatment of male reproductive disorders. Future studies need to explore their detailed functional roles and how they might be used clinically [74].

circRNA profiling studies in testicular tissue and seminal plasma are promising, but most reports are based on small discovery cohorts without large-scale validation. Their potential as non-invasive biomarkers, therefore, requires further rigorous evaluation. Dysregulated circRNAs appear to influence SSC maintenance, meiotic progression, testosterone production, and germ cell apoptosis, contributing to spermatogenic failure, low testosterone, or abnormal sperm morphology [73, 74].

7. Conclusions

This review underscores the substantial yet underappreciated contribution of non-coding genetic variation to male infertility in the Chinese population. Non-coding regulatory variants, particularly haplotypes in protamine genes (PRM1/PRM2), KIT/KITLG pathway loci, and antioxidant gene interactions, consistently show stronger associations with spermatogenic impairment in Chinese cohorts than many individual coding variants. Concurrently, dysregulation of multiple non-coding RNA classes — including miRNAs, lncRNAs, piRNAs, and circRNAs — disrupts interconnected stages of spermatogenesis, ranging from maintenance of spermatogonial stem cell maintenance and meiotic progression to chromatin remodeling and sperm functional maturation. Notably, several population-specific patterns emerge in Chinese (predominantly Han) men, including distinct haplotype structures, allele frequency differences, and ncRNA expression signatures that differ from those commonly reported in European, Middle Eastern, or other Asian populations. Despite these promising associations, the current evidence base remains limited by relatively small sample sizes,

scarce independent replication, the paucity of large-scale genome-wide studies, and the near absence of functional validation experiments.

Looking ahead, the most promising and clinically relevant research directions include conducting large-scale, multicenter genome-wide association studies and whole-genome sequencing focused on non-coding regions in well-phenotyped Chinese men with idiopathic infertility. Systematic replication of the most consistent signals in independent Chinese and multi-ethnic cohorts, combined with rigorous functional validation of high-priority candidates using CRISPR-based editing, reporter assays, testicular organoids, and single-cell multi-omics approaches, should be prioritized. Equally important is the accelerated development and validation of non-invasive ncRNA biomarkers in seminal plasma and peripheral blood, particularly diagnostic panels capable of distinguishing obstructive from non-obstructive azoospermia or predicting potential for spermatogenic recovery. Finally, investigating gene–environment interactions — especially in relation to prevalent exposures in China such as air pollution, endocrine-disrupting chemicals, and lifestyle factors — will be essential to better understand how these modifiers influence the penetrance and expressivity of non-coding risk variants. Progress in these areas holds the greatest potential to advance mechanistic insight and support the development of more precise, population-informed diagnostic and, ultimately, therapeutic strategies for male infertility in China and beyond.

Author Contributions

Conceptualization; M.M, Data curation; M.M, Formal analysis; M.M, Funding acquisition; M.M, Investigation; M.M, Methodology; M.M, Project administration; M.M Resources; M.F, Software; Supervision; M.A.K, Validation; Visualization; M.F, Writing - original draft; Z.U.R and Writing - review & editing, M.M.

Competing Interests

The authors have declared that no competing interests exist.

Data Availability Statement

No additional data is attached to this manuscript.

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