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The Genetic Landscape of Human Infertility: A Comprehensive Review

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ABSTRACT

***Background**: Infertility affects approximately one in seven couples worldwide and arises from a heterogeneous interplay of chromosomal abnormalities, monogenic defects, polygenic susceptibility, epigenetic dysregulation, mitochondrial dysfunction, and environmental factors, yet a large proportion of cases still lack a clearly defined genetic etiology. **Objective**: To synthesize current evidence on the genetic, epigenetic, and mitochondrial determinants of male and female infertility, and to examine how these discoveries inform diagnostic evaluation, clinical management, and ethical, legal, and social frameworks. **Methods**: A narrative review of the literature was conducted using searches of major biomedical databases and targeted snowballing to identify original research, reviews, and professional guidelines on chromosomal, monogenic, polygenic, epigenetic, and mitochondrial mechanisms in human infertility, as well as their clinical translation into genetic testing, preimplantation genetic testing, and counseling. **Results**: Sex-chromosome aneuploidies, Y-chromosome microdeletions, and an expanding set of monogenic defects explain substantial fractions of severe male factor infertility and primary ovarian insufficiency, while GWAS have revealed complex polygenic architectures for polycystic ovary syndrome and endometriosis. Epigenetic and mitochondrial perturbations influence gamete competence and ART outcomes, and genetic testing and preimplantation genetic testing are increasingly embedded in guidelines, though access, variant interpretation, and ethical concerns remain challenging. **Conclusion**: The genetic landscape of human infertility is broad and rapidly evolving; integrating chromosomal, monogenic, polygenic, epigenetic, and mitochondrial insights into personalized reproductive care requires continued gene discovery, multi-ancestry research, robust counseling, and ethically grounded policy.*

Keywords
Infertility; Genetics; Azoospermia; Primary ovarian insufficiency; Polycystic ovary syndrome; Endometriosis; Epigenetics; Mitochondrial DNA; Preimplantation genetic testing

INTRODUCTION

Infertility is a major global public health concern, affecting approximately one in seven couples worldwide and imposing substantial psychological, social, and economic burdens on affected individuals and societies (1). Historically, infertility was often approached as an idiopathic condition or attributed to anatomical, endocrine, or infectious causes, with limited recognition of the extensive genetic underpinnings. Over the last two decades, advances in cytogenetics, molecular genetics, and genomics have reframed infertility as a complex, heterogeneous condition in which chromosomal abnormalities, monogenic disorders, and polygenic susceptibility interact with environmental and lifestyle factors to shape reproductive outcomes (2,3). This evolving view has important implications for clinicians and patients, as it moves care from empirical treatment towards mechanism-based diagnostics, prognostication, and counseling.

From a clinical and translational perspective, the "population" of interest in this review comprises men and women experiencing infertility or subfertility across diverse etiologies and care settings, including couples presenting to fertility clinics, and individuals identified during routine reproductive counseling (1–3). The primary "interventions" considered are genetic and genomic approaches such as karyotyping, Y-chromosome microdeletion analysis, targeted gene panels, exome and genome sequencing, and assessment of epigenetic and mitochondrial markers that provide mechanistic insight into reproductive failure (2,4). In many real-world settings, these interventions are compared with "standard" infertility evaluation, which historically relied on hormonal assays, imaging, and limited genetic testing, or with the absence of any genomic assessment, particularly in low-resource contexts (3). The "outcomes" of interest extend beyond pregnancy rates and live birth to include improved etiologic diagnosis, risk stratification for offspring, guidance on assisted reproductive technology (ART) options, and the ethical, legal, and social implications of incorporating genomics into reproductive decision-making (2–4).

Despite rapid growth in the infertility genetics literature, several critical knowledge gaps remain. First, while the contribution of sex-chromosome aneuploidies and Y-chromosome microdeletions to severe male factor infertility is well-established, many patients with non-obstructive azoospermia or severe oligozoospermia still lack a defined genetic diagnosis even after extensive evaluation (5–10). Second, in women with primary ovarian insufficiency (POI) or unexplained reduced ovarian reserve, only a subset can currently be explained by known genes involved in oocyte development, folliculogenesis, or gonadotropin signaling, leaving a large proportion of cases genetically unresolved (18–27). Third,

genome-wide association studies (GWAS) have identified susceptibility loci for polycystic ovary syndrome (PCOS), endometriosis, and related traits, yet the translation of these polygenic signals into clinically useful risk prediction or targeted therapies remains limited, especially in non-European populations (4,28–31). Fourth, epigenetic dysregulation and mitochondrial dysfunction have emerged as important pathways influencing gamete quality, implantation, and ART outcomes, but their integration into standard clinical practice is still in its infancy and often hampered by methodological heterogeneity across studies (32–39). Finally, although guidelines from professional societies increasingly address genetic testing in infertility, there is ongoing debate around the scope and timing of testing, equity of access, and the ethical boundaries of technologies such as preimplantation genetic testing and potential germline interventions (40–48).

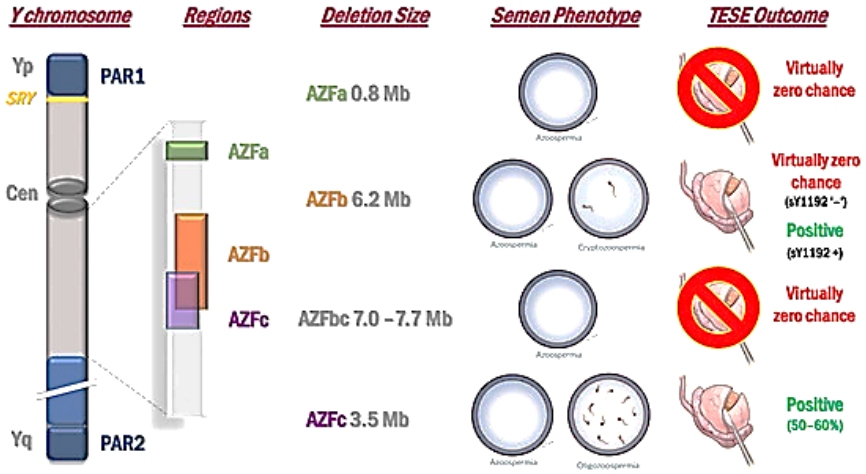

Figure 1: Schematic of Y Chromosome AZF Regions (AZFa, AZFb, AZFc) and consequences of deletions

This narrative review addresses these gaps by synthesizing current evidence on the genetic architecture of human infertility, spanning chromosomal abnormalities, monogenic conditions, and complex polygenic contributions in both men and women (2–4). We summarize key chromosomal and Y-linked defects in severe male factor infertility, catalog validated monogenic causes of spermatogenic failure and POI, and review GWAS-identified loci in PCOS and endometriosis with attention to implicated biological pathways (5–14,18–31). We further examine the roles of epigenetic and mitochondrial mechanisms in gamete competence and ART outcomes, highlighting how these non-classical mechanisms intersect with inherited genetic risk (32–39). In parallel, we discuss how genetic discoveries are being translated into routine clinical workflows, including genetic counseling, diagnostic testing, preimplantation genetic testing, and fertility preservation, and we critically appraise related ethical, legal, and social implications (40–48). The overarching objective of this review is to provide clinicians, reproductive scientists, and policymakers with an integrated, clinically oriented overview of the genetic landscape of human infertility and to identify priority areas for future research and responsible implementation. Accordingly, our guiding research question is: How do chromosomal, monogenic, polygenic, epigenetic, and mitochondrial mechanisms collectively shape the etiology, diagnosis, and clinical management of male and female infertility, and what are the key translational and ethical challenges in integrating this knowledge into personalized reproductive medicine?

MATERIALS AND METHODS

This work was conducted as a narrative review aiming to provide a conceptually coherent, clinically oriented synthesis of the genetic landscape of human infertility. The review approach was chosen because the literature spans diverse study designs, including basic mechanistic experiments, observational cohorts, case series, GWAS, and expert guidelines, which are not easily amenable to a single meta-analytic framework (2,3). The focus was on integrating mechanistic insights with clinical implications rather than estimating pooled effect sizes, making a narrative strategy more appropriate to address the broad translational questions outlined in the introduction (2–4).

To identify relevant literature, a comprehensive search of major biomedical databases was undertaken, including PubMed/MEDLINE, Scopus, and Web of Science, complemented by targeted searches in Google Scholar for recent or highly cited articles. Searches covered publications from January 2000 up to the most recent available year in which key landmark articles and guidelines were published, with additional backward citation tracking for seminal pre-2000 genetic and cytogenetic studies that remain clinically influential (5–7,26,39–41). Search terms combined controlled vocabulary and free-text words related to infertility and genetics, including but not limited to “infertility,” “male infertility,” “female infertility,” “azoospermia,” “primary ovarian insufficiency,” “Y chromosome microdeletion,” “AZF region,” “NOBOX,” “BMP15,” “GDF9,” “FSHR,” “polycystic ovary syndrome,” “endometriosis,” “genome-wide association study,” “epigenetics,” “DNA methylation,” “mitochondrial DNA,” “preimplantation genetic testing,” and “ethical, legal and social implications” in various combinations (2,3,5–7,18–20,28–32,37–43,46–48). No formal language restrictions were imposed during the initial search, but the final synthesis focused on articles available in English.

Eligible publications included original research articles, systematic and narrative reviews, consensus statements, and professional guidelines that provided primary or synthesized data on genetic, epigenetic, or mitochondrial contributors to human infertility in men or women, or that addressed the clinical translation or ethical dimensions of reproductive genetics (2–4,5–10,18–20,28–32,37–43,46–48). Studies restricted entirely to non-human animal models without clear translational relevance were generally excluded, except where specific experiments provided critical mechanistic insights that have directly informed understanding of human infertility genes, such as murine knockout models for key oocyte or follicular genes (20,21). Case reports and small case series were considered when they described novel monogenic causes or exceptionally informative phenotypes, particularly in the context of emerging infertility genes (11–14,18–23,25,26).

Screening proceeded in two stages. Titles and abstracts retrieved by the search strategy were reviewed to identify clearly irrelevant articles, such as those focused solely on contraception, pregnancy complications unrelated to infertility, or non-genetic aspects of reproductive health. Full texts of potentially relevant articles were then evaluated for inclusion against the conceptual scope of this review. When multiple overlapping reviews or guidelines addressed similar topics, priority was given to the most recent and comprehensive documents, while seminal earlier work was retained

when it provided foundational insights or nomenclature still used in contemporary practice (5–10,18–20,28–32,40–45). For guideline and consensus documents issued by professional societies, the most recent version at the time of drafting was preferentially included (40–45).

Data extraction and synthesis were performed using a thematic framework. Key information from each included article was charted into conceptual domains corresponding to the main sections of this review: chromosomal and Y-linked causes in male infertility; monogenic causes of spermatogenic failure and POI; polygenic architectures of PCOS, endometriosis, and related traits; epigenetic and mitochondrial mechanisms; and clinical translation including diagnostic testing, preimplantation genetic testing, and ethical, legal, and social considerations (2–4,5–14,18–32,32–39,40–48). For genetic loci and genes, extracted elements included gene name, encoded protein or pathway, predominant phenotype, representative evidence type (e.g., GWAS, linkage, candidate gene, functional study), and clinical implications (5–14,18–31). For epigenetic and mitochondrial studies, key extracted features included the type of epigenetic modification or mitochondrial measure, the reproductive outcome studied, and implications for ART or reproductive counseling (32–39). For guidelines and policy-oriented articles, the extracted information focused on recommended indications for testing, counseling considerations, regulatory boundaries, and unresolved ethical questions (40–48).

As this was a narrative rather than a systematic review with quantitative meta-analysis, no formal risk-of-bias scoring or pooled effect size calculation was undertaken. Instead, emphasis was placed on triangulating evidence from multiple independent lines of investigation, prioritizing replicated associations and genes with robust functional validation, and highlighting areas where evidence remains preliminary or conflicting (5–14,18–23,28–32,40–43). Potential selection bias was mitigated by casting a broad search across databases, using extensive snowballing from reference lists, and ensuring inclusion of both male and female infertility literature across chromosomal, monogenic, and complex genetic domains (2–4,5–10,18–32). Data integrity and reproducibility were supported by maintaining a structured extraction template for all included articles and by cross-checking key genetic entities, phenotypes, and guideline recommendations across multiple sources whenever possible (5–14,18–23,28–32,40–45). Ethical approval was not required because this review did not involve direct contact with human participants or use of individual-level identifiable data; all information was derived from previously published, peer-reviewed sources (2–4,5–48).

RESULTS

Y-chromosome microdeletions in the azoospermia factor regions illustrate a genotype–phenotype gradient: AZFa deletions are usually associated with Sertoli-cell-only syndrome and virtually no chance of sperm retrieval, AZFb deletions with meiotic arrest, and AZFc deletions with a spectrum from severe oligozoospermia to azoospermia, where TESE may still be successful (5–10). These patterns, summarized in Table 1, have led to karyotyping and AZF deletion testing becoming standard components of the diagnostic work-up in men with severe oligozoospermia or azoospermia, as reflected in contemporary guidelines (40,44).

Table 1. Major chromosomal and Y-linked causes of male infertility and clinical implications

Category	Specific abnormality / locus	Predominant phenotype	Key mechanistic feature	Clinical implications for diagnosis and management	Representative references
Sex chromosome aneuploidy	47,XXY (Klinefelter syndrome)	Non-obstructive azoospermia, hypergonadotropic hypogonadism, small testes	Germ cell loss, seminiferous tubule hyalinization	Routine karyotyping in severe male factor; TESE may retrieve sperm in subset; genetic counseling for offspring risk	(5–8,10)
Sex chromosome mosaicism	46,XY/47,XXY and related mosaics	Variable spermatogenic impairment	Mixed cell lineages with partial germ cell preservation	Consider mosaicism in milder phenotypes; influences TESE prognosis	(5–8,10)
Structural autosomal abnormalities	Balanced translocations, inversions	Oligozoospermia, recurrent pregnancy loss	Meiotic segregation errors, gamete imbalance	Karyotyping recommended; preimplantation genetic testing for structural rearrangements (PGT-SR) in affected couples	(2,3,40,43)
Y-chromosome microdeletions	AZFa deletions	Sertoli-cell-only syndrome, complete azoospermia	Loss of genes essential for early spermatogenesis	Very low likelihood of sperm retrieval; definitive etiology; counsel against repeated TESE attempts	(5–10)
Y-chromosome microdeletions	AZFb deletions	Meiotic arrest, severe azoospermia	Disruption of meiosis-related genes	Poor prognosis for sperm retrieval; informs ART planning	(5–10)
Y-chromosome microdeletions	AZFc deletions	Severe oligozoospermia to azoospermia	Deletion of multi-copy gene clusters (e.g., DAZ family)	Most frequent Y deletion; TESE may be successful; high transmission risk to male offspring	(5–10)
Combined Y-chromosome deletions	AZFbc, AZFabc	Profound spermatogenic failure	Extensive gene loss across AZF regions	Poor prognosis for sperm retrieval; strong indication for genetic counseling	(5–10)

Table 2. Selected monogenic causes of male infertility

Gene	Mode of inheritance	Principal function/pathway	Main clinical phenotype	Key evidence type (human ± model)	Clinical considerations	References
TEX11	X-linked	Meiotic recombination and synapsis	Non-obstructive azoospermia with meiotic arrest	Human exome sequencing, functional studies in mouse models	Candidate gene testing in idiopathic azoospermia; counseling for X-linked transmission	(11–14)

Gene	Mode of inheritance	Principal function/pathway	Main clinical phenotype	Key evidence type (human ± model)	Clinical considerations	References
FANCM	Autosomal recessive	DNA damage repair, homologous recombination	Azoospermia or severe oligozoospermia	WES in infertile men, overlap with cancer susceptibility	Links infertility with cancer predisposition; consider shared counseling	(13,14)
MLH3	Autosomal recessive	Mismatch repair, meiotic crossing-over	Meiotic arrest, spermatogenic failure	Genetic association and functional evidence	Supports role of DNA repair pathways; potential inclusion in panels	(13,14)
BRCA2	Autosomal dominant / recessive (context-dependent)	Homologous recombination, genome stability	Severe spermatogenic failure, cancer risk	Case series, familial studies, oncology–reproduction bridge	Dual counseling for infertility and hereditary cancer risk	(13,14)
CFTR	Autosomal recessive	Chloride channel, epithelial ion transport	Congenital bilateral absence of vas deferens (CBAVD), risk of cystic fibrosis in offspring	Linkage and mutation studies, large cohorts	Routine CFTR testing in CBAVD; partner testing; reproductive counseling	(15–17,40–42)
ADGRG2	X-linked	Epithelial transport in male reproductive tract	X-linked CBAVD with normal CFTR	Exome sequencing, functional characterization	Explains CFTR-negative CBAVD; informs X-linked inheritance counseling	(41,42)

Table 3. Selected monogenic causes of female infertility and primary ovarian insufficiency (POI)

Gene	Function / pathway	Phenotype spectrum	Evidence base	Clinical implications	References
NOBOX	Oocyte-specific transcription factor	POI, disrupted folliculogenesis	Murine knockouts, human loss-of-function mutations	Explains a subset of idiopathic POI; potential for targeted gene panels	(18–22)
BMP15	Oocyte-derived growth factor (TGF-β family)	POI, altered follicular development	Human mutations, functional studies	Dose-sensitive effects; informs recurrence risk counseling	(23–27)
GDF9	Oocyte-derived growth factor (TGF-β family)	POI, ovulatory dysfunction	Human variants, animal models	Often combined with BMP15 variants; implications for ovarian reserve assessment	(23,27)
FSHR	FSH receptor, gonadotropin signaling	Ovarian dysgenesis, hypergonadotropic hypogonadism	Linkage, mutation analyses	Demonstrates receptor-level causes of infertility; supports hormonal phenotyping with genetic testing	(25,26)
FOXL2	Transcription factor in granulosa cells	POI, Blepharophimosis–Ptosis–Epicanthus Inversus Syndrome	Human mutations, functional data	Syndromic POI; importance of integrating ocular and reproductive phenotypes	(18,19)

Table 4. Polygenic architecture of PCOS and endometriosis

Condition	Representative loci / genes	Putative biological pathways	Key associated traits	Translational implications	References
PCOS	DENND1A, THADA, FSHB	Gonadotropin signaling, androgen biosynthesis, metabolic regulation	Hyperandrogenism, oligo-anovulation, insulin resistance, obesity	Potential for polygenic risk scores; insight into metabolic–reproductive interface	(4,27,28)
Endometriosis	WNT4, GREB1, ESR1, FN1	Sex-steroid hormone signaling, tissue remodeling, immune response	Pelvic pain, subfertility, disease stage-specific burden	Identification of therapeutic targets; stage- and ancestry-specific risk stratification	(29–31)
Cross-trait	Shared loci between endometriosis and metabolic or immune traits	Inflammatory and metabolic pathways	Co-occurring disease states (e.g., pain syndromes, obesity)	Supports pleiotropy; suggests need for integrated care	(30,31)

Table 5. Epigenetic and mitochondrial mechanisms in infertility

Mechanism	Sex / context	Key findings	Clinical or ART-related implications	References
Sperm DNA methylation	Male infertility, ART	Altered methylation at imprinted and developmental genes in infertile men	Potential biomarkers of sperm quality; relevance for embryo development	(32–34)
Histone retention patterns	Male infertility	Aberrant histone retention linked to impaired spermatogenesis	May influence chromatin packaging and embryo competence	(32,33)
Oocyte imprinting errors	Female infertility, ART	Aberrant methylation at imprinted loci (e.g., H19, SNRPN) associated with reduced implantation	Concern for imprinting disorders; need for careful ART monitoring	(34–36)
ART-associated epigenetic variation	ART-conceived offspring	Slightly increased risk of imprinting disorders (e.g., Beckwith–Wiedemann, Angelman syndromes)	Requires risk–benefit counseling; absolute risk remains low	(35,36)

Mitochondrial DNA copy number in cumulus cells	IVF cycles	mtDNA content in cumulus cells predicts embryo implantation potential	Candidate non-invasive biomarker of oocyte competence	(37)
Embryonic mtDNA copy number	Preimplantation embryos	Elevated mtDNA associated with reduced implantation potential	Reflects cellular stress; may guide embryo selection	(38)
Mitochondrial replacement therapy (MRT)	Women with mitochondrial disease	Pronuclear or spindle transfer can reduce transmission of pathogenic mtDNA	Raises germline modification and regulatory concerns	(39,46–48)

Table 6. Clinical translation of genetic findings in infertility

Domain	Intervention / tool	Typical indication	Expected yield/value	Guideline and practice context	References
Male infertility	Karyotyping, Y-microdeletion testing	Severe oligozoospermia or azoospermia	Identification of Klinefelter syndrome or AZF deletions; informs prognosis and counseling	Incorporated in AUA/ASRM and European best-practice guidelines	(5–10,40,44)
Monogenic diagnostics	Targeted gene panels, WES/WGS	Idiopathic NOA, syndromic infertility, POI	Detection of pathogenic variants in validated infertility genes	Growing use in tertiary centers; need for careful variant interpretation	(11–14,18–23,41,42)
Preimplantation genetic testing	PGT-M, PGT-SR, PGT-A	Monogenic diseases, structural rearrangements, aneuploidy risk	Reduces transmission of known pathogenic variants or rearrangements; may improve implantation in selected settings	Addressed in ASRM/ESHRE guidance; requires multidisciplinary counseling	(40,43–45)
Fertility preservation	Oocyte, embryo, ovarian/testicular tissue preservation	Gonadotoxic therapies, high genetic risk of gonadal insufficiency	Protects future reproductive potential	Supported by female fertility preservation guidelines	(45)
Counseling and ethics	Structured genetic counseling	All patients undergoing genetic/PGT testing	Informs patient understanding, consent, and reproductive decision-making	Emphasized in ethical and legal frameworks for reproductive genetics	(46–48)

The genetic architecture of male infertility is dominated by chromosomal and Y-linked anomalies and a growing catalogue of monogenic defects. Sex-chromosome aneuploidies, particularly Klinefelter syndrome (47,XXY), represent one of the most frequent known causes of non-obstructive azoospermia and are detected in a notable proportion of men referred for severe male factor infertility (5–8). Klinefelter syndrome and related mosaic karyotypes typically present with small testes, elevated gonadotropins, and azoospermia, but testicular sperm extraction (TESE) can recover sperm in a substantial subset of men, although success rates vary across cohorts (5–8,10).

Beyond large-scale chromosomal variants, monogenic defects have been increasingly recognized as causes of spermatogenic failure, especially with the advent of whole-exome sequencing. TEX11, an X-linked regulator of meiotic recombination and synapsis, is a paradigmatic example, with loss-of-function variants leading to meiotic arrest and non-obstructive azoospermia (11). Systematic reviews and clinical validity assessments have expanded the list of genes implicated in male infertility, including DNA repair genes such as FANCM, MLH3, and BRCA2, which link meiotic failure to pathways also central to cancer biology (13,14). The identification of CFTR mutations as the major cause of congenital bilateral absence of the vas deferens (CBAVD) and the subsequent discovery of ADGRG2-related X-linked CBAVD have further underscored the diversity of male infertility genes and have cemented CFTR testing as standard of care in men with obstructive azoospermia due to CBAVD (15–17,40–42). Table 2 highlights representative male infertility genes, their functional pathways, and clinical implications.

Female infertility similarly reflects a continuum from chromosomal to monogenic to polygenic etiologies. Turner syndrome (45,X) and related sex-chromosome abnormalities lead to gonadal dysgenesis and primary ovarian insufficiency (POI), but most women with POI have a normal karyotype, prompting the search for single-gene causes (18,19). Key oocyte and follicle-specific genes such as NOBOX, BMP15, and GDF9 have been linked to POI and impaired folliculogenesis through evidence from murine knockouts and human loss-of-function variants (20–23,27). NOBOX deficiency disrupts early follicular development and oocyte-specific gene expression, and heterozygous mutations can act in a dominant-negative manner, accounting for a meaningful subset of idiopathic POI cases (20–22). Similarly, variants in BMP15 and GDF9, both oocyte-derived growth factors within the TGF-β family, affect granulosa cell proliferation and oocyte maturation and have been shown to contribute to ovarian failure in a dose-dependent fashion (23,24,27). Inactivating mutations in the follicle-stimulating hormone receptor (FSHR) provide a classic example of receptor-level defects causing hereditary ovarian dysgenesis and hypergonadotropic hypogonadism, thereby directly linking gonadotropin signaling to infertility (25,26). These entities are summarized in Table 3.

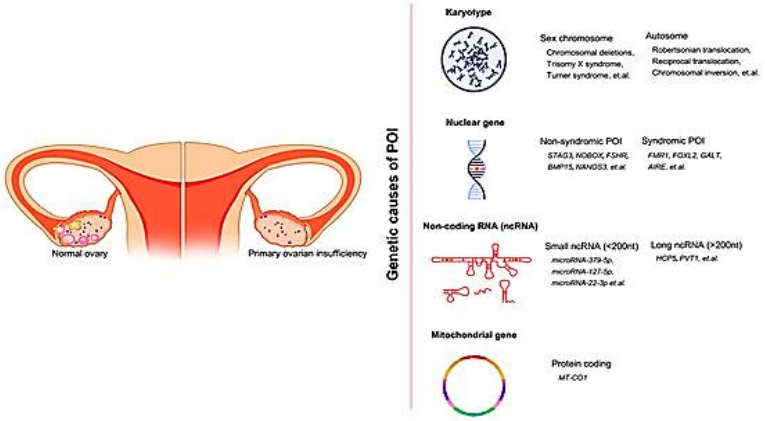

Figure 3. Four categories of genetic factors and corresponding examples are included.

Common female reproductive disorders such as PCOS and endometriosis represent the polygenic end of the infertility spectrum, with GWAS revealing dozens of susceptibility loci. For PCOS, large-scale meta-analyses have identified variants near DENND1A, THADA, FSHB, and other loci, implicating pathways in gonadotropin signaling, androgen biosynthesis, and metabolic regulation (4,27,28). Risk alleles in DENND1A have been functionally linked to increased androgen production in theca cells, and PCOS susceptibility variants overall show genetic correlations with obesity and insulin resistance, underscoring the metabolic component of the syndrome (27,28). For endometriosis, GWAS have highlighted loci near WNT4, GREB1, ESR1, and FN1, which collectively point to perturbations in sex-steroid signaling, tissue remodeling, and immune response (29–31). Cross-phenotype analyses have demonstrated shared genomic architecture between endometriosis and other disease states, reinforcing the concept that reproductive disorders are embedded within broader systemic networks (30,31). Table 4 synthesizes these polygenic findings and their translational implications.

Non-classical mechanisms, particularly epigenetic dysregulation and mitochondrial dysfunction, add additional layers of complexity. Epigenetic studies have shown that aberrant sperm DNA methylation and altered histone retention patterns are associated with impaired spermatogenesis and reduced embryo development potential in ART cycles (32,33). In women, disturbed methylation of imprinted genes such as H19 and SNRPN in oocytes and preimplantation embryos has been linked to lower implantation and pregnancy rates and to an increased, albeit still low, absolute risk of imprinting disorders in ART-conceived offspring (34–36). Mitochondrial DNA (mtDNA) copy number within cumulus cells and embryos has emerged as a candidate biomarker: reduced mtDNA in oocytes and cumulus cells correlates with poor embryo development, whereas elevated mtDNA in embryos has been associated with diminished implantation potential, possibly reflecting cellular stress responses (37,38). Mitochondrial replacement therapy through pronuclear or spindle transfer offers a proof-of-concept intervention for women with pathogenic mtDNA mutations but raises substantial ethical and regulatory questions given its impact on the germline (39,46–48). Table 5 summarizes key epigenetic and mitochondrial findings.

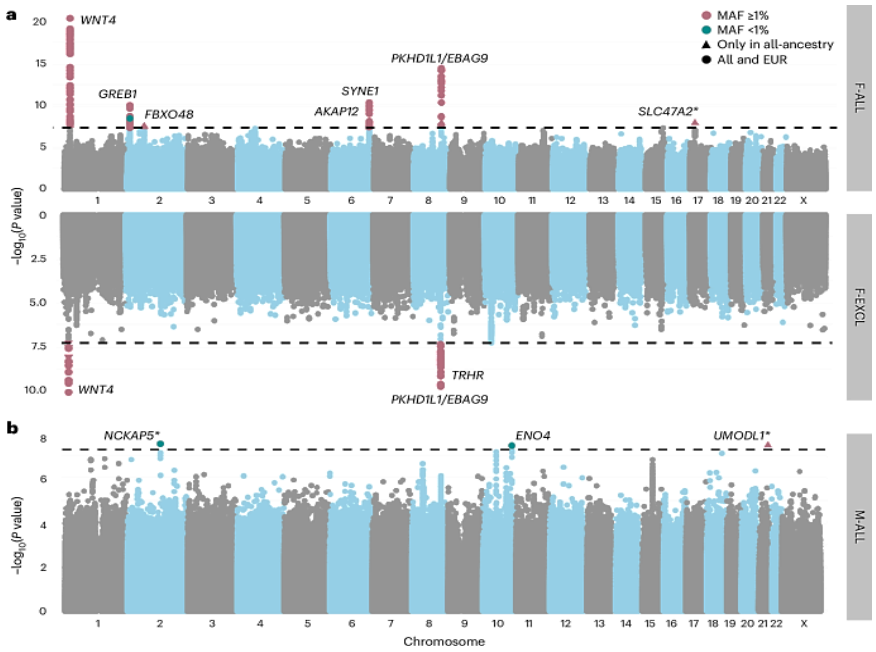

Figure4: Miami and Manhattan plots for selected infertility meta-analyses.

Translation of these discoveries into clinical practice is proceeding on several fronts. In male infertility, routine use of karyotyping and Y-microdeletion testing for men with severe oligozoospermia or azoospermia is now embedded in European and AUA/ASRM guidelines, ensuring that a significant subset of patients receives a specific genetic diagnosis that informs prognosis, TESE expectations, and counseling regarding transmission risk to offspring (5–10,40,44). For both sexes, targeted gene panels and exome sequencing are being deployed in tertiary care settings to investigate idiopathic NOA, POI, and syndromic infertility, although challenges remain regarding variant interpretation and the balance between diagnostic yield and incidental findings (11–14,18–23,41,42). Preimplantation genetic testing modalities (PGT-M, PGT-SR, PGT-A) are increasingly used to prevent transmission of known monogenic diseases and structural rearrangements and, in selected contexts, to optimize embryo selection, but they require careful multidisciplinary counseling and alignment with ethical guidelines (40,43–45). Fertility preservation strategies, including oocyte, embryo, and gonadal tissue cryopreservation, intersect with genetic risk when patients face gonadotoxic therapies or carry variants predisposing to early gonadal failure (45). These translational domains and their policy context are presented in Table 6.

Ethical, legal, and social implications cut across the full spectrum of reproductive genetics. The expansion of genetic testing and PGT raises questions about responsible use, equity of access, potential stigma, and the boundaries of acceptable embryo selection (46–48). Discussions around gene editing and MRT illustrate the tension between preventing serious genetic disease and preserving societal consensus on germline modification, with most professional bodies currently advocating for tightly regulated research and cautious clinical use under stringent oversight (46–48). These dimensions are developed further in the Discussion.

DISCUSSION

The synthesis presented in this narrative review underscores that human infertility is best conceptualized as a genetically and epigenetically complex condition spanning chromosomal, monogenic, polygenic, mitochondrial, and environmental layers rather than as a homogeneous clinical endpoint. At the chromosomal level, sex-chromosome aneuploidies and Y-chromosome microdeletions remain among the most robustly characterized causes of severe male factor infertility, and their detection yields clear clinical benefits through improved prognostication and rationalization of invasive procedures such as TESE (5–10,40,44). The stratification of Y-chromosome deletions into AZFa, AZFb, and AZFc

regions, with distinct phenotypic and prognostic profiles, provides an exemplar of how cytogenetic discoveries can translate into highly actionable clinical algorithms and has motivated analogous efforts in delineating genotype–phenotype relationships in other infertility contexts (5–10). At the same time, a substantial fraction of men with non-obstructive azoospermia or severe oligozoospermia remain without a defined genetic cause, highlighting the need for continued gene discovery through exome and genome sequencing and for functional validation in relevant model systems (11–14,41,42).

For women, the expanding catalogue of genes implicated in POI and ovarian dysgenesis illustrates the power of combining human genetics with functional models to move beyond idiopathic diagnoses. Variants in NOBOX, BMP15, GDF9, FSHR, and FOXL2 collectively demonstrate that perturbations at multiple levels—from oocyte-intrinsic factors and oocyte–granulosa crosstalk to gonadotropin receptor signaling and granulosa-cell transcriptional control—can culminate in similar clinical phenotypes (18–23,25–27). However, even when monogenic causes are identified, the penetrance and expressivity of these variants can be variable, and many women with POI will harbor no clearly pathogenic variant in known genes, suggesting that additional genes, regulatory variants, and gene–environment interactions contribute to ovarian insufficiency (18–23,25–27). Clinically, these findings support the increasingly accepted view that women with early ovarian failure or a suggestive family history should be evaluated for genetic causes, not simply for reproductive planning but also for broader health surveillance, given the systemic consequences of estrogen deficiency (18,19,45).

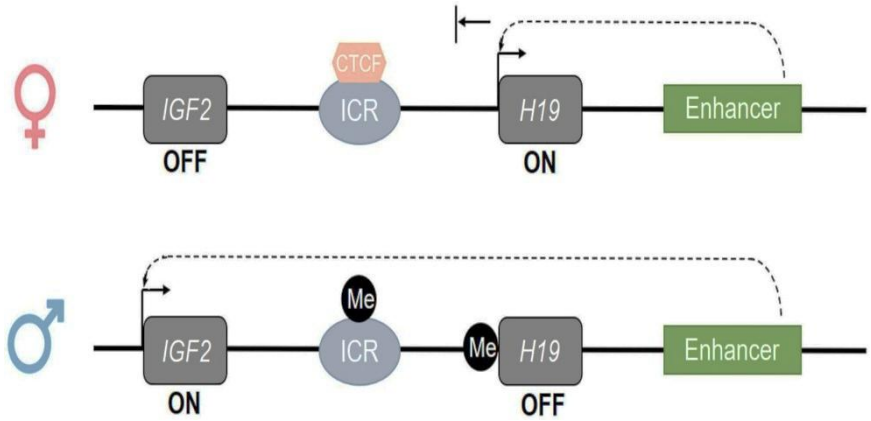

Figure5: Interplay between Genetics, Epigenetics & Environment in Infertility (conceptual diagram)

The polygenic architecture of PCOS and endometriosis exemplifies the strengths and limitations of GWAS for reproductive disorders. On one hand, GWAS have successfully identified numerous susceptibility loci, highlighted key biological pathways, and revealed shared genetic architecture with metabolic and immune traits (4,27–31). The identification of DENND1A, THADA, and FSHB in PCOS and loci near WNT4, GREB1, ESR1, and FN1 in endometriosis has refined our understanding of how gonadotropin signaling, steroid hormone action, tissue remodeling, and immune response contribute to disease pathogenesis (4,27–31). These discoveries open avenues for targeted pharmacologic interventions and motivate integrated care models that address both reproductive and systemic manifestations, such as metabolic syndrome in PCOS and pain comorbidities in endometriosis (27–31). On the other hand, the clinical translation of polygenic findings remains limited. Polygenic risk scores for PCOS or endometriosis are not yet routinely used in practice, and most GWAS cohorts are skewed towards individuals of European ancestry, constraining generalizability and potentially exacerbating health disparities if tools derived from these data are applied uncritically to diverse populations (4,30,31). Future research must prioritize multi-ancestry GWAS and functional studies that move beyond locus discovery towards mechanistic clarity and therapeutic exploitation (4,28–31).

Epigenetic and mitochondrial insights further enrich this landscape but also raise new questions. Studies demonstrating altered sperm DNA methylation and histone retention in infertile men and imprinting disturbances in oocytes and ART-conceived offspring provide compelling evidence that epigenetic regulation is central to reproductive success (32–36). However, heterogeneity in assay platforms, sample preparation, and analytic pipelines complicates the comparison of results across studies, and causality is often difficult to disentangle from correlation (32–36). Similarly, mtDNA copy number in cumulus cells and embryos has emerged as a candidate biomarker, but its predictive performance and clinical utility are still being evaluated, and there is ongoing debate about how best to integrate mtDNA metrics into embryo selection algorithms without overfitting to small or context-specific datasets (37,38). Mitochondrial replacement therapy represents a particularly striking example of translational innovation, offering preventive potential for women with pathogenic mtDNA variants while simultaneously challenging ethical and regulatory frameworks due to its germline implications (39,46–48). Long-term follow-up data on children born after MRT remain limited, underscoring the need for robust registries and international collaboration (39,46–48).

The translation of genetic discoveries into everyday infertility practice is progressing but uneven. Genetic testing is now widely recommended for men with severe spermatogenic failure and for couples undergoing PGT for known monogenic disorders or structural rearrangements (40,43,44). Yet access to sophisticated genomic diagnostics remains constrained by cost, infrastructure, and expertise, particularly in low- and middle-income settings, where infertility care often competes with other pressing health priorities (1–3,40–45). Furthermore, even when testing is available, the high rate of variants of uncertain significance in multi-gene panels and exome sequencing can complicate counseling and risk communication, especially when penetrance and expressivity are not well defined (11–14,18–23,41,42). These challenges highlight the importance of multidisciplinary teams that include reproductive endocrinologists, clinical geneticists, genetic counselors, embryologists, and ethicists, as well as the need for up-to-date variant databases and consensus frameworks for interpretation.

Ethical, legal, and social questions permeate all aspects of reproductive genetics. The expansion of PGT and embryo selection raises concerns about potential drift towards non-medical selection, social pressure on couples, and the risk of reinforcing stigma around disability (46–48). Debates around germline genome editing and MRT focus on the balance between preventing devastating genetic diseases and preserving societal boundaries on heritable modifications, with most professional organizations currently endorsing a cautious, research-limited approach with strict governance (46–48). Equity of access is a recurrent theme: as genomic tools become more powerful, there is a real risk that only affluent patients

or health systems will benefit, thereby widening existing disparities in fertility care and reproductive autonomy (1–3,40–48). Addressing these issues will require not only technical advances but also inclusive policy-making, patient and public engagement, and attention to the cultural contexts in which reproductive decisions are made.Taken together, the evidence synthesized here argues for a future in which infertility evaluation and management increasingly incorporate layered genetic, epigenetic, and mitochondrial information, interpreted within a comprehensive clinical and ethical framework. To realize this vision, research priorities should include systematic discovery and validation of infertility genes across diverse populations; integration of multi-omics data to refine mechanistic models; rigorously designed studies to evaluate the clinical utility and cost-effectiveness of emerging tests; and longitudinal follow-up of offspring conceived using advanced genomic technologies (2–4,28–32,37–39,40–48). Only through such efforts can the promise of personalized reproductive medicine be translated into tangible, equitable benefits for infertile individuals and couples worldwide.

CONCLUSION

Human infertility arises from an intricate interplay of chromosomal abnormalities, monogenic defects, polygenic susceptibility, epigenetic dysregulation, mitochondrial dysfunction, and environmental influences, and the rapid expansion of genetic and genomic knowledge is transforming both etiologic understanding and clinical practice; by synthesizing evidence across male and female infertility, this narrative review highlights how established entities such as Klinefelter syndrome, Y-chromosome microdeletions, NOBOX- and BMP15-related POI, and PCOS and endometriosis susceptibility loci converge with emerging epigenetic and mitochondrial markers to define a broad genetic landscape that informs diagnostic evaluation, genetic counseling, and reproductive decision-making, while also exposing persistent gaps in gene discovery, limited representation of diverse populations, and profound ethical, legal, and social challenges that must be explicitly addressed to ensure that the benefits of reproductive genomics are realized in a responsible and equitable manner (1–4,5–14,18–23,27–39,40–48).

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