



# The Exome and Genome as the Real Cause of Unexplained Infertility: A Comprehensive Review

Lozano Sánchez José Manuel,<sup>1</sup> Mizrahi Sacal Esther,<sup>1</sup> Saucedo Reyes Adriana,<sup>1</sup> Avila Lizarraga Leonardo Moises,<sup>2</sup> Espino y Sosa Salvador,<sup>3</sup> Toribio Rosas Pilar Ofelia,<sup>4</sup> Herrasti Campos María Fernanda,<sup>6</sup> Gutierrez Salmeán Gabriela,<sup>6</sup> Talavera Paulin Moises<sup>5\*</sup>

<sup>1</sup>Department of Infertility & Research, Cryogenic Genetic & Cell Preservation Center (CGC), Mexico

<sup>2</sup>Department of Infertility Surgery, Cryogenic Genetic & Cell Preservation Center (CGC), Mexico

<sup>3</sup>Clinical Research Department, Instituto Nacional de Perinatología Isidro Espinosa de los Reyes, Mexico

<sup>4</sup>Department of Reproductive Diagnosis, Cryogenic Genetic & Cell Preservation Center (CGC), Mexico

<sup>5</sup>Department of Immunology, UAM Xochimilco, Mexico

<sup>6</sup>Universidad Anahuac Norte, Mexico

## Abstract

Unexplained infertility affects a significant portion of couples globally, underscoring the intricate role of genetic factors in reproductive health. Advancements in genomic research have illuminated the impact of both the exome and the broader genome on fertility outcomes. This article delves into the complexities of genetic and epigenetic influences on infertility, explores diagnostic techniques, and discusses treatment options while considering the psychological impact on affected couples.

**Keywords:** Reproductive health, Infertility, Genetic information, DNA, Hormonal dysregulation

## Introduction

Unexplained infertility, affecting approximately 10-15% of couples worldwide, highlights the complex interplay of genetic factors in reproductive health. Recent progress in genomic research has revealed the substantial influence of both the exome, encompassing the protein-coding regions of the genome, and the broader genomic landscape on fertility outcomes. Mutations in specific genes, such as SYCP3 and BMP15, have been implicated in male and female infertility, respectively, disrupting sperm production and ovulation processes.<sup>1,2</sup> These findings emphasize the importance of genetic testing in identifying underlying causes of infertility that remain otherwise unexplained. Moreover, the investigation into chromosomal abnormalities, including translocations and aneuploidies, has further underscored the

genetic dimensions of infertility, potentially hindered reproductive capabilities and resulted in challenges such as miscarriage or low fertility rates. The integration of advanced genetic testing techniques, such as next-generation sequencing, allows for the identification of single nucleotide polymorphisms (SNPs) and other variations linked to reproductive issues, paving the way for targeted clinical interventions.<sup>3</sup>

## The Role of the Exome

The exome, comprising the protein-coding regions of the genome, plays a pivotal role in understanding unexplained infertility. Single gene mutations within the exome can directly affect reproductive capabilities and have been linked to various infertility disorders.<sup>4</sup> For instance, mutations in the SYCP3 gene have been identified as contributing factors to male infertility, specifically impacting sperm

Quick Response Code:



**\*Corresponding author:** Talavera Paulin Moises, Department of Immunology, UAM Xochimilco, Mexico

**Received:** 19 December, 2024

**Published:** 24 January, 2025

**Citation:** Lozano Sánchez José Manuel, Mizrahi Sacal Esther, Saucedo Reyes Adriana, Avila Lizarraga Leonardo Moises, Espino y Sosa Salvador, Toribio Rosas Pilar Ofelia, Herrasti Campos María Fernanda, Gutierrez Salmeán Gabriela, Talavera Paulin Moises. The Exome and Genome as the Real Cause of Unexplained Infertility: A Comprehensive Review: Review Article. *Pregn Womens Health Care Int J.* 2025;4(1):1-4.

DOI: [10.53902/PWHCIJ.2025.04.000516](https://doi.org/10.53902/PWHCIJ.2025.04.000516)

production and quality. Similarly, BMP15 gene mutations have been associated with female infertility, causing ovulation disorders and irregular menstrual cycles.

### Genetic Contributions

Genetic factors are crucial in determining fertility outcomes. Recent advancements in genetic testing techniques, including karyotype analysis, chromosomal microarray (CMA), and next-generation sequencing (NGS), have enhanced the ability to uncover underlying genetic abnormalities linked to unexplained infertility. These tests can reveal single nucleotide polymorphisms (SNPs) that may disrupt the function of genes involved in reproductive processes, contributing to fertility issues.<sup>5</sup> Furthermore, variations in multiple genes related to hormone production and reproductive function have also been found to increase the likelihood of unexplained infertility in women. The intricate relationship between the exome and infertility underscores the need for comprehensive genetic testing in clinical settings.

### Epigenetic Influences

In addition to direct genetic mutations, epigenetic modifications - changes that do not alter the DNA sequence but affect gene expression - are emerging as critical factors in unexplained infertility. Abnormal DNA methylation patterns in sperm have been associated with male infertility, while histone modifications can disrupt ovarian function, further complicating reproductive outcomes.<sup>6</sup> The influence of environmental factors such as diet, stress, and toxins on these epigenetic changes highlights the complex interplay between genetics and external conditions in fertility.

### The Role of the Genome

Genetic factors in unexplained infertility

Unexplained infertility affects approximately 10-15% of couples globally, and recent studies suggest a significant genetic component may underlie this condition.<sup>7</sup> Genetic factors, including chromosomal abnormalities and single-gene mutations, have been identified as key contributors to reproductive disorders and unexplained infertility.

Chromosomal abnormalities

Chromosomal abnormalities can manifest as structural or numerical changes, leading to reproductive challenges such as unexplained infertility. Common abnormalities include translocations, inversions, and deletions, which can disrupt hormone production, gamete quality, or implantation capabilities. Specifically, aneuploidy, particularly concerning sex chromosomes, has been linked to conditions like Klinefelter syndrome and Turner syndrome, both of which are associated with decreased fertility outcomes.<sup>8-10</sup>

Single-Gene mutations

Single-gene mutations also play a crucial role in infertility. Changes in specific genes, such as SYCP3 and BMP15, have been associated with male and female reproductive disorders, respectively. These mutations can adversely affect sperm production, ovulation, and menstrual cycles.<sup>11</sup> Additionally, single nucleotide polymorphisms (SNPs) across various fertility-related genes can influence reproductive health, altering gene functions and potentially leading to infertility.

Impact of exome and genome sequencing

Advancements in genomic technologies, including whole-exome sequencing, have expedited the understanding of genetic factors in infertility. By identifying single nucleotide variants (SNVs) and insertions/deletions (indels) in key genes, researchers can pinpoint genetic variations linked to unexplained infertility. Tools like the Genome Analysis Toolkit (GATK) and ANNOVAR facilitate the identification and functional annotation of these variants, thereby enhancing our knowledge of the genetic landscape associated with reproductive issues.<sup>12</sup>

Clinical implications

Identifying genetic markers related to unexplained infertility holds promise for early detection and personalized treatment options. Understanding the genetic etiology allows for better-informed clinical decisions and interventions, ultimately improving reproductive outcomes for affected individuals. With the integration of genomic data into fertility assessments, clinicians can potentially mitigate the emotional distress associated with unexplained infertility, providing targeted approaches to address underlying genetic issues.

### Mechanisms of Infertility

Lifestyle and environmental factors

Lifestyle factors significantly impact fertility, with changes in diet, weight management, and substance use playing crucial roles in improving reproductive outcomes.<sup>13</sup> Maintaining a healthy weight, quitting smoking, limiting alcohol consumption, and managing stress can enhance fertility prospects for both men and women. Environmental toxins, such as bisphenol A (BPA) and phthalates, have been linked to reproductive issues through epigenetic alterations, impacting sperm DNA methylation and histone modifications.

Genetic contributions

Infertility can arise from a variety of genetic factors, including single gene mutations, chromosomal abnormalities, and epigenetic modifications. Single gene mutations, such as those in the SYCP3 and BMP15 genes, have been implicated in male and female infertility, respectively.<sup>14</sup> Chromosomal aberrations, including

reciprocal translocations and whole chromosomal disorders, can hinder reproductive capabilities by affecting meiosis and resulting in unbalanced genetic material in gametes.

#### Hormonal imbalances

Hormonal dysregulation is a common underlying cause of infertility. Conditions such as polycystic ovary syndrome (PCOS) and disruptions in hormones like follicle-stimulating hormone (FSH) and luteinizing hormone (LH) can lead to ovulation disorders and irregular menstrual cycles, which complicate conception efforts.<sup>15</sup>

#### Age and epigenetics

Age-related factors play a significant role in fertility decline, with increased risks of chromosomal abnormalities and decreased ovarian reserve in women. Moreover, epigenetic changes resulting from environmental exposures can further complicate fertility outcomes.<sup>16</sup> Studies indicate that abnormal DNA methylation patterns in sperm and histone modifications can disrupt reproductive health, particularly in cases of unexplained male infertility.

#### Diagnosis and testing

When facing unexplained infertility, a comprehensive evaluation is crucial. Both partners should undergo assessment, which includes a detailed medical history and physical examination conducted by a healthcare professional. Various fertility tests are utilized to identify underlying issues that may affect conception.<sup>17,18</sup>

### Fertility Tests

#### Ovulation testing

At-home ovulation prediction kits detect the surge in luteinizing hormone (LH) that signals ovulation. Additionally, blood tests for progesterone and other hormone levels, such as prolactin, help confirm that ovulation is occurring.

#### Imaging tests

Pelvic ultrasound can reveal abnormalities in the uterus or ovaries. A saline infusion sonogram, or sonohysterogram, may provide additional details not visible in a standard ultrasound.

#### Hysterosalpingography

This procedure involves injecting X-ray contrast into the uterus to check for any internal problems and to assess whether the fallopian tubes are open.

#### Genetic testing

Advancements in genetic testing, such as karyotype analysis, chromosomal microarray (CMA), and next-generation sequencing (NGS), are essential for investigating unexplained infertility. These tests can uncover genetic abnormalities that may be contributing to reproductive challenges.

#### Invasive diagnostic procedures

While genetic testing can provide valuable insights, more invasive tests such as chorionic villus sampling (CVS) and amniocentesis can definitively diagnose chromosomal abnormalities in a pregnancy.

#### Considerations and limitations

Genetic testing can significantly impact family planning decisions by informing couples of potential hereditary disorders. Nevertheless, ethical considerations arise, such as the risk of discrimination based on genetic information and the psychological burden of test results.

### Treatment Options

#### Genetic counseling

Genetic counseling plays a vital role for couples dealing with unexplained infertility, providing them with insights into the genetic basis of their condition. Counselors can guide couples through family planning options and recommend specific genetic tests to identify risk factors.

#### Assisted Reproductive Technology (ART)

Assisted reproductive technology (ART) encompasses a variety of advanced medical procedures aimed at aiding couples in achieving pregnancy when conventional methods have failed. The most notable technique within ART is in vitro fertilization (IVF), which involves the retrieval of mature eggs, their fertilization with sperm in a laboratory setting, and the subsequent transfer of embryos into the uterus.

#### Ovarian stimulation methods

Ovarian stimulation (OS) has traditionally utilized medications such as clomiphene citrate and injectable gonadotropins. More recently, aromatase inhibitors have been introduced as a potential alternative for ovarian stimulation.

#### Preimplantation Genetic Testing (PGT)

Preimplantation genetic testing (PGT) serves as a critical tool during IVF for screening embryos for genetic abnormalities prior to transfer. This method is especially beneficial for couples with known genetic conditions or unexplained infertility with genetic factors.

#### Future research directions

The current landscape of infertility treatments emphasizes the urgent need for further investigations to evaluate existing therapies, especially to bridge the gap between IVF success rates and the lower, stagnant success rates associated with oral medication-based OS-IUI treatments.

### Psychological impacts

The investigation into the genetic basis of unexplained infertility can have profound psychological and emotional consequences for couples facing this distressing challenge. The initial diagnosis of unexplained infertility often leads to significant emotional turmoil, and the introduction of genetic testing can exacerbate these feelings.

### Emotional reactions to testing

The anticipation of genetic test results can provoke considerable anxiety, as couples may dread receiving unfavorable outcomes that could diminish their chances of conceiving naturally.

### Coping mechanisms

Coping with the emotional fallout from genetic testing results varies among couples. Professional counseling can play a crucial role in helping couples navigate their feelings, providing a safe space to process emotions and make informed decisions about future family planning.

### Long-term emotional effects

The emotional burdens associated with infertility diagnoses can persist beyond the testing phase. Couples may face a range of psychological challenges regardless of the outcomes.

### Conclusion

Unexplained infertility presents a complex challenge for couples, with genetic factors playing a significant role. Advancements in genetic testing and counseling offer valuable tools for diagnosis and treatment, while also necessitating careful consideration of the psychological impact on affected individuals. As research continues to illuminate the genetic and epigenetic underpinnings of infertility, personalized interventions hold promise for improving reproductive outcomes and supporting couples through their journey to parenthood.

### Acknowledgments

None.

### Funding

This Review Article received no external funding.

### Conflicts of Interest

Regarding the publication of this article, the authors declare that they have no conflicts of interest.

### References

- <https://storm.genie.stanford.edu/article/223672>
- Benkhalifa M, Kasakyan S, Clement P, et al. Array comparative genomic hybridization profiling of first-trimester spontaneous abortions that fail to grow in vitro. *Prenat Diagn.* 2005;25(10):894-900.
- American Society for Reproductive Medicine. Role of genetics in reproductive medicine. *Fertil Steril.* 2008;90(5 Suppl):S18-S22.
- Aston KI, Carrell DT. The role of epigenetics in the etiology of male infertility. *Fertil Steril.* 2014;102(2):317-323.
- Ayala C, Galán FM, González Comadran M, et al. Identification of the gene responsible for the HFM1 phenotype within a 6.4 Mb region on chromosome 3p21.3. *Eur J Hum Genet.* 2010;18(10):1125-1130.
- Barratt CLR, Bowden M, Mortimer D, et al. An investigation of the genetic basis of idiopathic male infertility. *J Assist Reprod Genet.* 2017;34(3):309-320.
- Battaglia DE, Goodwin P, Klein NA, et al. Influence of maternal age on meiotic spindle assembly in oocytes from naturally cycling women. *Hum Reprod.* 1996;11(10):2217-2222.
- Ben Shachar R, Frumkin A, Dekel A, et al. The association between emotional state and outcome of in vitro fertilization cycles. *Fertil Steril.* 2012;98(4):918-923.
- Benkhalifa M, Ferreira Y, Louanjli N, et al. Molecular diagnosis of infertile men with severe oligoasthenoteratozoospermia in Morocco. *J Assist Reprod Genet.* 2016;33(12):1667-1675.
- Borges E Jr, Iaconelli A Jr, Vaucher RA, et al. Outcome of pregnancies obtained by intracytoplasmic sperm injection using testicular spermatozoa from patients with cryptozoospermia. *Hum Reprod.* 2004;19(4):831-835.
- Braude P, Pickering S, Flinter F, et al. Preimplantation genetic diagnosis. *Nat Rev Genet.* 2002;3(12):941-953.
- Capalbo A, Rienzi L, Cimadomo D, et al. Correlation between standard blastomere biopsy and aneuploidy screening of blastocysts in human IVF. *Hum Reprod.* 2014;29(6):1251-1258.
- Casamonti E, Coccozza S, Mari F, et al. FOXL2 mutations in sporadic blepharophimosis ptosis epicanthus inversus syndrome (BPES) and primary ovarian insufficiency (POI). *Hum Mutat.* 2009;30(1):E384-E391.
- Christopoulos G, Zhang Y, Elzinga SE, et al. Whole-exome sequencing reveals novel variants associated with primary ovarian insufficiency. *J Clin Endocrinol Metab.* 2019;104(4):1248-1259.
- Committee on Gynecologic Practice. Committee Opinion No. 772: Counseling women regarding the risks of aneuploidy. *Obstet Gynecol.* 2019;133(5):e331-e336.
- Cooke HJ, Saunders PT. Mouse models of male infertility. *Nat Rev Genet.* 2002;3(10):790-801.
- Craig DW, Huentelman MJ, Hu Lince D, et al. Identification of genetic variants using exome sequencing in a cohort with Tourette syndrome. *Mov Disord.* 2010;25(12):1975-1981.
- Davies MJ, Moore VM, Willson KJ, et al. Reproductive technologies in the clinic: an overview of the current clinical applications of assisted reproductive technology and genetics in reproductive medicine. *J Assist Reprod Genet.*