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Review

Investigating the Genetic Basis of Unexplained Infertility and Potential Chromosomal Abnormalities

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Abstract

Infertility affects millions globally, with 10-15% of couples experiencing unexplained cases. Despite advancements in medicine, the cause remains unknown, causing emotional distress. Recent research suggests a genetic basis for this issue. This review aims to provide a better understanding of the underlying genetic factors contributing to unexplained infertility and potentially identify genetic markers that could aid in the diagnosis and treatment of this condition. A literature review was conducted to understand the genetic basis of unexplained infertility. Relevant articles from databases like PubMed and Google Scholar were analyzed, covering topics like genetics, chromosomal abnormalities, genetic markers, and fertility, resulting in 50 articles. The literature review revealed that there is a strong correlation between unexplained infertility and chromosomal abnormalities. Several studies have

reported an increased rate of chromosomal abnormalities in couples with unexplained infertility compared to those with normal fertility. Around 10% of couples with unexplained infertility had chromosomal abnormalities, with the most common being translocations. A higher rate of chromosomal abnormalities in couples with unexplained infertility who had a history of recurrent miscarriages. The review reveals a significant genetic component to unexplained infertility, with chromosomal abnormalities in affected couples indicating underlying genetic factors. Further research is needed to identify specific genetic markers for diagnosis and treatment, potentially leading to personalized treatment options. Genetic counseling and testing should be considered for couples with recurrent miscarriages to identify potential abnormalities and provide appropriate support.

Keywords
Unexplained infertility; genetic basis; chromosomal abnormalities; genetic markers; genetic testing

1. Introduction

Unexplained infertility is a diagnosis given to couples who are unable to conceive despite undergoing thorough fertility investigations, including assessing the female partner's ovulation and the male partner's sperm analysis, and ruling out any structural or hormonal abnormalities. It is estimated that approximately 10-15% of couples experience unexplained infertility, making it a common and frustrating diagnosis for many couples trying to conceive [1].

The term "unexplained" implies that there is no apparent reason for the couple's infertility. However, this does not mean that there is no underlying cause. Recent research suggests that genetic factors may play a significant role in unexplained infertility [2]. Therefore, it is crucial to investigate the genetic basis of unexplained infertility to provide couples with a more accurate diagnosis and potentially offer targeted treatment options.

It is well-established that genetics plays a significant role in fertility, with numerous genes and chromosomal abnormalities linked to infertility [3, 4]. One of the most common genetic causes of unexplained infertility is chromosomal abnormalities. Chromosomes are thread-like structures found in the nucleus of cells, and they contain our genetic information in the form of DNA. Any deviation from the average number or structure of chromosomes can significantly impact fertility. Chromosomal abnormalities can be inherited from one or both parents or occur spontaneously during the formation of reproductive cells [5]. The most common chromosomal abnormalities associated with unexplained infertility are balanced translocations and inversions. A balanced translocation occurs when two chromosomes exchange genetic material without losing or gaining genetic material [6]. This can lead to infertility as it can disrupt the normal development of embryos [6]. Inversions, on the other hand, occur when a segment of a chromosome breaks off and reattaches in the opposite direction. This can also result in infertility due to potential disruptions in the genetic code [7, 8]. Another chromosomal abnormality associated with unexplained infertility is aneuploidy. Aneuploidy is the presence of an abnormal number of chromosomes in a cell. In the case of unexplained infertility, aneuploidy can often be found in

embryos, leading to implantation failure or early miscarriage [9]. “The importance of investigating the genetic basis of unexplained infertility lies in the fact that it can provide answers and potential treatment options for couples.

Furthermore, studies have also shown an increased prevalence of submicroscopic chromosomal abnormalities in couples with unexplained infertility [10]. These are small changes in the genetic code that traditional genetic testing methods cannot detect. However, these abnormalities can still have a significant impact on fertility and may be the underlying cause of unexplained infertility in some couples.

1.1 Search Strategy

A comprehensive search strategy was employed to gather relevant literature on the genetic basis of unexplained infertility and potential chromosomal abnormalities. Electronic databases such as PubMed, Embase, and Web of Science were searched using keywords such as “unexplained infertility”, “genetics”, “chromosomal abnormalities”, and “genetic markers”. In addition, reference lists of relevant articles were manually searched for additional studies.

1.2 Inclusion Criteria

The following inclusion criteria were applied to the selection of studies:

1. Studies published in English.
2. Studies involving human subjects.
3. Studies exploring the genetic basis of unexplained infertility and potential chromosomal abnormalities.

2. Causes of Unexplained Infertility

2.1 Female Factors

One of the most common causes of unexplained infertility in women is ovulatory dysfunction [11]. Ovulation is the process in which a mature egg is released from the ovary and travels down the fallopian tube, where it can potentially be fertilized by sperm. Ovulatory dysfunction occurs when a woman's ovulation cycle is irregular or absent, making it difficult to release a healthy egg for fertilization [12]. This can be caused by a variety of factors, such as hormonal imbalances, polycystic ovary syndrome (PCOS), thyroid disorders, and excessive exercise or weight loss. In some cases, women may experience ovulatory dysfunction due to stress, which can disrupt the delicate balance of hormones in the body.

Another potential cause of unexplained infertility in women is structural abnormalities in the reproductive system [13]. These abnormalities can include uterine fibroids, endometriosis, and adhesions in the pelvic area. Uterine fibroids are non-cancerous growths that form in the uterus and can interfere with the implantation of a fertilized egg [14]. Endometriosis is a condition in which the tissue that usually lines the uterus grows outside of it, causing inflammation and scarring that can damage the fallopian tubes and ovaries [15]. Adhesions, or scar tissue, in the pelvic area, can also block the fallopian tubes or interfere with the functioning of the ovaries, making it difficult for a woman to conceive [16].

Hormonal imbalances can also play a significant role in unexplained infertility [17]. A complex interplay of hormones regulates the female reproductive system, and any disruption in this balance can affect a woman's ability to ovulate and conceive. One common hormonal imbalance that can lead to infertility is a luteal phase defect, which occurs when there is a deficiency in the hormone progesterone [18]. This hormone is essential for maintaining a pregnancy. If there is not enough of it, the lining of the uterus may not be able to support a fertilized egg, leading to early miscarriage. Other hormonal imbalances that can contribute to unexplained infertility include high levels of prolactin, which can suppress ovulation [19], and low levels of thyroid hormones, which can disrupt the menstrual cycle and interfere with fertility [20, 21].

In addition to these specific factors, some general risk factors can increase a woman's chances of experiencing unexplained infertility. These include advanced age (over 35), a history of pelvic infections or sexually transmitted diseases, and a family history of infertility [22]. Lifestyle factors such as smoking, excessive alcohol consumption, and being overweight or underweight can also contribute to unexplained infertility.

2.2 Male Factors

Sperm abnormalities are one of the leading causes of unexplained infertility in men. Sperm abnormalities are deviations from the typical structure, function, or number of sperm cells. These abnormalities can include low sperm count, poor sperm motility (movement), and abnormal sperm morphology (shape). Low sperm count, or oligospermia, is when a man has less than 15 million sperm per milliliter of semen. Poor sperm motility, also known as asthenospermia, is when sperm cannot move correctly and, therefore cannot reach the egg for fertilization [23]. Abnormal sperm morphology, or teratospermia, is when sperm have an abnormal shape and cannot fertilize an egg. These abnormalities can be caused by various factors such as genetic disorders, hormonal imbalances, infections, and lifestyle choices such as smoking and excessive alcohol consumption.

Structural abnormalities in the reproductive system can also contribute to unexplained infertility in men [24]. These abnormalities refer to physical problems with the male reproductive organs that can affect fertility. The most common structural abnormality is a varicocele, which is an enlargement of the veins within the scrotum. This can lead to a decrease in sperm quality and quantity. Other structural abnormalities include blockages in the vas deferens (the tube that carries sperm from the testicles to the urethra), which can prevent sperm from reaching the semen, and structural problems with the testicles, such as undescended testicles or testicular torsion, which can affect sperm production and quality [25]. These structural abnormalities can occur from birth or develop later in life due to infections, injuries, or surgeries.

Hormonal imbalances can also play a role in unexplained male infertility [24]. Hormones are chemical messengers that regulate various bodily functions, including sperm production. An imbalance in hormone levels can affect the production of sperm, leading to decreased sperm count and quality. The most common hormonal imbalance in men is a testosterone deficiency, which is the primary male sex hormone. Low testosterone levels can affect sperm production, decreasing sperm count and motility [26]. Other hormonal imbalances that can contribute to unexplained infertility include problems with the thyroid gland, which can affect hormone levels, and high levels of prolactin, a hormone that regulates sperm production.

2.3 Other Possible Causes

Environmental factors, including toxins found in everyday products like cleaning agents, cosmetics, and pesticides, have been linked to reproductive problems in both men and women [27]. Pesticides disrupt hormonal balance, while heavy metals, industrial chemicals, and air pollution affect sperm and egg quality, making fertilization difficult. Lifestyle factors like diet, exercise, and substance use influence unexplained infertility. Obesity, excessive exercise, and substance use can lead to hormonal imbalances and infertility [28], affecting ovulation and sperm production [29]. These factors can damage genetic material in sperm and eggs, causing conception difficulties [30, 31]. Age-related factors, such as decreased ovarian reserve, increased chromosomal abnormalities, and age-related conditions like diabetes and hypertension, can significantly contribute to unexplained infertility in women and men [32]. These factors make it difficult to conceive, leading to higher risks of miscarriage and infertility [33].

This review was done under the guidelines and approval of the Research, Ethics and Grants Committee of the Faculty of Basic Medical Sciences, Adeleke University, Ede, Nigeria.

3. Role of Genetics in Unexplained Infertility

The exact cause of unexplained infertility is not fully understood, but there is growing evidence that genetics may play a role. Several studies have suggested that certain genetic variations may contribute to the development of unexplained infertility [10, 34, 35]. For example, a study found that women with a specific variation in the FSHR gene were more likely to experience unexplained infertility [36]. This gene produces follicle-stimulating hormone (FSH), which plays a crucial role in the menstrual cycle and ovulation. Another study identified a genetic variant in the ESR1 gene, which is involved in the production of estrogen, as a potential risk factor for unexplained infertility in women [37]. In addition to these specific genetic variations, there is evidence that unexplained infertility may have a multifactorial genetic basis. This means that a combination of genetic variations, rather than a single gene, may contribute to the development of this condition. A study also found that women with unexplained infertility were more likely to have inherited variations in multiple genes related to hormone production and reproductive function [38].

3.1 Genetic Inheritance Patterns

One potential factor that has been increasingly recognized as a contributor to unexplained infertility is genetics. Genetic factors play a crucial role in fertility and can be responsible for various reproductive disorders, including unexplained infertility [39]. In this paper, we explore the role of genetics in unexplained infertility and specifically look at the three main inheritance patterns - autosomal dominant, autosomal recessive, and X-linked - that can contribute to this condition. Before delving into the specific inheritance patterns, it is essential to understand the basics of genetics and how it relates to infertility. DNA is made up of genes, which are the instructions for the development and function of our bodies. These genes are inherited from our parents and can influence our physical and physiological characteristics, including fertility. Any changes or mutations in these genes can lead to reproductive disorders, including unexplained infertility.

3.1.1 Autosomal Dominant Inheritance

Autosomal dominant inheritance is a genetic pattern in which a single copy of a mutated gene from one parent is enough to cause a disorder. In other words, if one parent carries the mutated gene, there is a 50% chance of passing it on to their child [40]. This means a child has a 50% chance of inheriting the disorder and a 50% chance of not inheriting it.

In the context of unexplained infertility, several autosomal dominant disorders can contribute to the condition. One such example is polycystic ovary syndrome (PCOS), which affects about 10% of women of reproductive age and is a common cause of infertility [41]. Hormonal imbalances, irregular or absent menstrual cycles, and multiple cysts on the ovaries characterize PCOS. While the exact cause of PCOS is not fully understood, it is believed to have a vital genetic component, with studies showing that women with a family history of PCOS are more likely to develop the disorder.

Another example of an autosomal dominant disorder that can contribute to unexplained infertility is endometriosis. This condition occurs when the tissue that lines the inside of the uterus grows outside of it, leading to inflammation, scarring, and sometimes even damage to the reproductive organs. Endometriosis has been linked to several gene mutations that can be inherited from one parent, making it a potential underlying cause of unexplained infertility [42].

3.1.2 Autosomal Recessive Inheritance

Autosomal recessive inheritance is another genetic pattern in which both parents must pass on a mutated gene for a child to develop a disorder [43]. In this case, the child must inherit two copies of the mutated gene - one from each parent. This means that even if one parent carries the gene, their child has a meager chance of developing the disorder. However, if both parents carry the gene, there is a 25% chance of their child inheriting the disorder.

In terms of unexplained infertility, several autosomal recessive disorders can play a role. One such disorder is primary ciliary dyskinesia (PCD). This rare genetic disorder affects the functioning of cilia, tiny hair-like structures that help move eggs and sperm through the reproductive system [44]. PCD can lead to fertility problems due to the impaired movement of eggs and sperm, making it a possible cause of unexplained infertility [45]. Another example is congenital adrenal hyperplasia (CAH), a condition that affects the production of hormones in the adrenal glands [46]. CAH can cause irregular menstrual cycles, which can lead to difficulty conceiving. While it is not a direct cause of infertility, it can contribute to unexplained infertility in some cases.

3.1.3 X-Linked Inheritance

X-linked inheritance is a genetic pattern in which a mutated gene is carried on the X chromosome. Females with two X chromosomes are less likely to develop disorders caused by X-linked mutations [47]. However, males only have one X chromosome, which means they are more likely to develop disorders caused by X-linked mutations [47]. In the context of unexplained infertility, one example of an X-linked disorder that can play a role is Klinefelter syndrome. This condition occurs in males when they have an extra X chromosome, leading to hormonal imbalances and infertility. While some men with Klinefelter syndrome may still be able to father

children, they are more likely to experience fertility issues, making it a potential cause of unexplained infertility.

3.2 Potential Genetic Causes

3.2.1 Single Gene Mutations

Single gene mutations refer to a change in an individual's genetic code caused by a change in a single gene. These mutations can be inherited from one or both parents or occur spontaneously. Studies have shown that mutations in specific genes can lead to reproductive disorders, resulting in unexplained infertility [10, 34]. For example, mutations in the SYCP3 gene have been linked to male infertility, explicitly affecting sperm production and quality [48, 49]. Similarly, mutations in the BMP15 gene have been associated with female infertility, leading to ovulation disorders and irregular menstrual cycles [50]. In addition to these specific gene mutations, there is evidence that variations in the DNA sequence of many genes involved in fertility can contribute to unexplained infertility [51]. These variations, known as single nucleotide polymorphisms (SNPs), alter the gene's function and can lead to reproductive problems [52]. For instance, a study found that women with variations in the FSHR gene, which plays a crucial role in ovarian function, have a significantly higher risk of unexplained infertility [53, 54].

3.2.2 Chromosomal Abnormalities

Chromosomal abnormalities refer to structural or numerical changes in the chromosomes, which can lead to reproductive disorders and unexplained infertility. These abnormalities can occur spontaneously or be inherited from one or both parents. Studies have shown that individuals with chromosomal abnormalities, such as translocations, inversions, or deletions, are at a higher risk of experiencing unexplained infertility [10, 55]. These abnormalities can impact fertility by affecting hormone production, sperm or egg quality, or the ability of the fertilized egg to implant in the uterus. One specific chromosomal abnormality that has been linked to unexplained infertility is a balanced translocation, where two different chromosome segments exchange material without any loss or gain of genetic material [56]. This chromosomal rearrangement can lead to an increased risk of miscarriage and may also affect the development of the embryo, resulting in unexplained infertility.

3.2.3 Epigenetic Factors

Environmental factors like diet, stress, and toxins can influence epigenetic factors, which do not involve DNA sequence changes. These modifications can significantly impact reproductive health and contribute to unexplained infertility [57-59]. Studies show that unexplained infertility in women and men can be attributed to abnormal DNA methylation patterns in sperm [57, 58, 60]. Male unexplained infertility is linked to histone modification, a protein that organizes DNA in the cell nucleus [57]. Abnormalities in histone modifications can affect sperm fertilization and disrupt ovarian function, contributing to infertility [57]. Research on the epigenetic basis of male unexplained infertility is promising as it provides a potential explanation and opens new avenues for treatment and management. Identifying and addressing epigenetic factors could lead to more successful treatment outcomes for couples struggling with this condition [57, 60].

In addition to these epigenetic mechanisms, there is evidence that lifestyle and environmental toxins such as bisphenol A (BPA) and phthalates can contribute to unexplained male infertility through epigenetic changes [61, 62]. For example, exposure to certain environmental chemicals or toxins has been linked to alterations in sperm DNA methylation and histone modifications [61, 62]. Similarly, lifestyle factors such as smoking, alcohol consumption, and poor diet have been associated with changes in epigenetic markers in sperm.

Overall, unexplained infertility is a condition that could be influenced by genetic factors such as mutations, chromosomal abnormalities, and epigenetic modifications. It can be a combination of environmental and lifestyle factors. Other factors like age, hormonal imbalances, and medical conditions can also contribute. Understanding these causes can help identify high-risk individuals.

4. Investigating the Genetic Basis of Unexplained Infertility

4.1 Genetic Testing

Genetic testing has become an essential tool in investigating the genetic basis of unexplained infertility. Recent advancements in genetic testing have shed light on the genetic basis of unexplained infertility [63]. This paper discussed the various genetic tests used to investigate unexplained infertility, namely karyotype analysis, chromosomal microarray (CMA), and next-generation sequencing (NGS).

4.1.1 Karyotype Analysis

Karyotype analysis is a genetic test that examines the number and structure of an individual's chromosomes. This test is typically performed on blood samples and involves growing and staining cells to visualize the chromosomes under a microscope. Karyotype analysis is helpful in identifying chromosomal abnormalities, such as structural rearrangements or aneuploidy [64]. These abnormalities may include balanced translocations, inversions, or deletions in either partner [65-67]. A balanced translocation occurs when two chromosomes exchange pieces of genetic material without any loss or gain of genetic material. This can result in a normal karyotype, but the individual may still be at risk of producing unbalanced gametes, leading to recurrent miscarriages or infertility [68]. Karyotype analysis can identify these structural rearrangements and provide insight into the genetic basis of unexplained infertility.

4.1.2 Chromosomal Microarray (CMA)

Chromosomal microarray (CMA) is a genetic test that can identify small deletions and duplications in the genome. Unlike karyotype analysis, CMA can detect changes in the number of copies of genetic material, known as copy number variations (CNVs). CMA uses advanced technology, such as single-nucleotide polymorphism (SNP) arrays or comparative genomic hybridization (CGH), to analyze DNA from a blood or tissue sample [69, 70]. Studies have shown that CMA can detect CNVs in approximately 7-10% of couples with unexplained infertility [71, 72]. These CNVs may disrupt genes involved in fertility and reproduction, leading to impaired sperm or egg development. For example, a study found a deletion in the NR5A1 gene in a couple with unexplained infertility, which is known to play a crucial role in ovarian development [73]. CMA can

also identify CNVs associated with developmental disorders, which may be the underlying cause of unexplained infertility in some cases.

4.1.3 Next-Generation Sequencing (NGS)

Next-generation sequencing (NGS) is a revolutionary genetic testing method that allows the rapid and cost-effective analysis of a large amount of DNA sequence data. NGS can identify small and large genetic variations, including single nucleotide variants (SNVs), insertions, deletions, and CNVs [74]. This technique can also analyze multiple genes simultaneously, making it a powerful tool for investigating the genetic basis of unexplained infertility. Studies have shown that NGS can identify pathogenic variants in genes related to fertility and reproduction in couples with unexplained infertility [75, 76]. These variants may include mutations in genes involved in the development of the reproductive organs, hormone production, or sperm and egg maturation. For example, a study found a homozygous mutation in the WEE2 gene in a couple with unexplained infertility, leading to impaired oocyte maturation [77]. NGS can also identify variants in genes associated with syndromic forms of infertility, such as polycystic ovary syndrome (PCOS) or Kallmann syndrome [78].

4.1.4 Fluorescence in Situ Hybridization (FISH)

FISH is a molecular technique that uses fluorescent probes to label specific DNA sequences within a cell. It can detect smaller chromosomal abnormalities, such as microdeletions or duplications, that may not be visible on a karyotype analysis. FISH is often used to investigate specific regions of chromosomes that are known to be associated with infertility, such as the Y-chromosome microdeletions in males [79].

4.1.5 Genome-Wide Association Studies (GWAS)

GWAS is a method that compares the genetic makeup of large populations to identify genetic variations associated with a particular trait or disease [80]. This technique has successfully identified genetic variations associated with common diseases such as diabetes and cancer. In the context of infertility, GWAS could potentially identify novel genetic variations that contribute to unexplained infertility [81].

4.2 Family History and Genetic Counseling

Family history plays a crucial role in understanding the genetic basis of unexplained infertility. Many genetic conditions are known to run in families, and unexplained infertility may be one of them. Couples with unexplained infertility need to discuss their family medical history with their healthcare provider to identify any potential genetic risk factors. For example, if a woman's mother or sister experiences unexplained infertility, it may indicate a genetic predisposition to this condition [82]. Furthermore, a family history of other reproductive disorders, such as endometriosis or polycystic ovary syndrome (PCOS), may also increase the risk of unexplained infertility [20]. These conditions have a known genetic component, and individuals with a family history of these disorders may be more likely to develop unexplained infertility.

Genetic counseling is a valuable tool for couples with unexplained infertility. A genetic counselor is a healthcare professional trained in genetics who can help couples understand the genetic basis of their condition and provide personalized recommendations for family planning. Genetic counseling for unexplained infertility may involve a thorough review of the couple's medical history, including any family history of reproductive disorders or genetic conditions. The genetic counselor may also recommend genetic testing to identify potential genetic risk factors. This testing may involve analyzing specific genes related to reproductive function or conducting a comprehensive genetic screening to identify any inherited genetic conditions. The genetic counselor can provide personalized recommendations for family planning based on the results of genetic testing and the couple's family history. For example, suppose a genetic variation is identified as a potential cause of unexplained infertility. In that case, the genetic counselor may recommend specific fertility treatments or assisted reproductive technologies (ART) that may be more effective in overcoming this genetic barrier [83].

4.3 Role of Pre-Implantation Genetic Testing

Advances in genetic technologies have allowed for a deeper understanding of the role of genetics in human reproduction. One such technology that has shown promise in investigating the genetic basis of unexplained infertility is pre-implantation genetic testing (PGT) [84, 85].

PGT is a procedure that involves the analysis of embryos created through *in vitro* fertilization (IVF) for genetic abnormalities before they are implanted into the uterus [86]. This testing can be performed for a variety of genetic conditions, including those that can contribute to infertility. PGT allows for selecting healthy embryos for implantation, increasing the chances of a successful pregnancy. There are several ways in which PGT can aid in the investigation of unexplained infertility. First, it can identify genetic abnormalities that may be responsible for recurrent pregnancy loss or failed IVF cycles [86]. By analyzing the embryos before implantation, PGT can identify chromosomal abnormalities, genetic mutations, or other genetic factors that may be preventing the successful implantation or development of the embryo.

Moreover, PGT can also aid in the diagnosis of genetic disorders that can cause infertility [87]. Some genetic conditions, such as Fragile X syndrome or Turner syndrome, can affect reproductive health and cause infertility. PGT can detect these conditions in embryos, allowing couples to make informed decisions about their reproductive options and seek appropriate medical interventions [88].

PGT also has the potential to improve the success rates of IVF [89]. By selecting healthy embryos for implantation, the chances of a successful pregnancy are increased. This is especially important for couples with unexplained infertility, as it can help overcome any undetected genetic factors that may be hindering their ability to conceive.

However, there are some concerns surrounding the use of PGT in investigating unexplained infertility. The procedure is expensive and not widely accessible, making it an option only for couples who can afford it. There are also ethical considerations to take into account, such as the potential for the selection of embryos based on non-medical traits, leading to concerns about eugenics.

5. Potential Chromosomal Abnormalities in Unexplained Infertility

5.1 Structural Chromosomal Abnormalities

Recent research has suggested that chromosomal abnormalities may play a role in unexplained infertility, particularly structural abnormalities such as translocations, deletions and duplications, and inversions.

5.1.1 Translocations

Translocations are structural chromosomal abnormalities that occur when a piece of one chromosome breaks off and attaches to another chromosome. This can result in a rearrangement of genetic material, leading to potential issues with fertility. There are two types of translocations - reciprocal and Robertsonian [90]. Reciprocal translocations occur when two chromosomes exchange pieces with each other. This can result in an unbalanced translocation, where there is either a gain or a loss of genetic material, or a balanced translocation, where there is no net gain or loss of genetic material [90]. In the case of unbalanced translocations, there may be an increased risk of miscarriage or the birth of a child with congenital disabilities.

Robertsonian translocations occur when two acrocentric chromosomes (chromosomes with a centromere near one end) fuse together. This type of translocation is often balanced and does not typically cause fertility issues [90]. However, there is a risk of unbalanced gametes being produced, which can lead to miscarriages or the birth of a child with genetic abnormalities. Studies have shown an increased prevalence of translocations in couples with unexplained infertility compared to the general population [91]. It is estimated that 4-6% of couples with unexplained infertility may have a chromosomal translocation [92]. Translocations can also be inherited from one or both parents, increasing the likelihood of infertility issues in subsequent generations.

5.1.2 Deletions and Duplications

Deletions and duplications are structural chromosomal abnormalities that involve the loss or gain of genetic material, respectively. These abnormalities can occur spontaneously or be inherited from a parent. In some cases, deletions and duplications may be too small to be detected by traditional genetic testing methods, making them difficult to identify as a cause of unexplained infertility. Deletions and duplications can disrupt essential genes involved in reproductive function, leading to issues such as irregular ovulation, impaired sperm production, and implantation failure [93]. Studies have shown a higher prevalence of deletions and duplications in couples with unexplained infertility compared to fertile couples, with a reported prevalence of 3.3% [94, 95].

5.1.3 Inversions

Inversions are chromosomal abnormalities where a segment of genetic material is reversed within a chromosome. These abnormalities can be inherited or occur spontaneously. Inversions can affect fertility by disrupting the regular pairing and separation of chromosomes during cell division, leading to chromosomal imbalances in gametes. Studies have shown a higher prevalence of inversions in women with unexplained infertility compared to fertile women [10, 96]. Inversions

may also be associated with recurrent miscarriages and implantation failure in assisted reproductive technologies [97]. However, the exact impact of inversions on fertility is still not well understood, and further research is needed to understand their role in unexplained infertility fully.

5.2 Numerical Chromosomal Abnormalities

Numerical chromosomal abnormalities refer to changes in the number of chromosomes in a cell. Usually, humans have 46 chromosomes, with 23 coming from each parent. However, sometimes errors can occur during cell division, resulting in an abnormal number of chromosomes. This can lead to aneuploidy, where there is an extra or missing chromosome, or polyploidy, with additional sets of chromosomes. These abnormalities can occur in any chromosome but are most commonly observed in the sex chromosomes (X and Y). Numerical chromosomal abnormalities can significantly impact fertility, as they can disrupt the normal development of reproductive cells or gametes [98]. Aneuploidy and polyploidy can occur in either sperm or eggs and when these abnormal gametes are involved in fertilization, they can result in chromosomally abnormal embryos [98]. These embryos are either unable to implant in the uterus or may lead to early miscarriages. One of the most well-known numerical chromosomal abnormalities associated with infertility is aneuploidy of the sex chromosomes, particularly the presence of an extra X chromosome in males (Klinefelter syndrome) and the absence of an X chromosome in females (Turner syndrome) [99]. These conditions can cause a range of reproductive issues, including decreased sperm production, low ovarian reserve, and early menopause. Individuals with Turner syndrome are also at a higher risk of having miscarriages and not having children with chromosomal abnormalities, except only in mosaic cases where there are chances. In addition to sex chromosome aneuploidies, there is growing evidence that aneuploidy in other chromosomes can also contribute to unexplained infertility. Studies have shown that women with recurrent miscarriages have a higher incidence of aneuploidy in their eggs compared to fertile women [100]. This suggests that aneuploidy in eggs may be a contributing factor to both recurrent miscarriages and unexplained infertility. Furthermore, polyploidy, where there are additional sets of chromosomes, has also been linked to infertility. While polyploidy is rare in humans, it has been observed in a small percentage of cases of unexplained infertility. Studies have shown that polyploidy in embryos can lead to implantation failure, early miscarriages, and even developmental abnormalities in offspring [98]. The prevalence of numerical chromosomal abnormalities in unexplained infertility highlights the importance of screening for these abnormalities in couples struggling with infertility. Chromosomal analysis, known as karyotyping, can be performed on both partners to identify any aneuploidies or polyploidies. This can help guide fertility treatment options and increase the chances of a successful pregnancy.

5.3 Importance of Balanced Chromosomal Abnormalities

Balanced chromosomal abnormalities can cause fertility issues, recurrent miscarriages, and a higher risk of having a child with congenital disabilities or developmental delays. For example, women with balanced translocations have a higher risk of miscarriage and may have difficulty conceiving due to the rearrangement of genetic material. In men, balanced chromosomal abnormalities can lead to sperm abnormalities and male infertility [101]. Therefore, identifying and understanding these abnormalities is crucial for couples planning to have children.

The presence of balanced chromosomal abnormalities can significantly impact the success of assisted reproductive techniques, such as in vitro fertilization (IVF). During IVF, genetic testing is often performed on the embryos to identify any chromosomal abnormalities before implantation [97]. If a balanced chromosomal abnormality is detected, it can affect the success of the IVF cycle and increase the risk of miscarriage or birth defects in the offspring. Furthermore, these abnormalities can also affect natural conception. In cases where one partner has a balanced chromosomal abnormality, there is a higher risk of miscarriage, stillbirth, and birth defects in the offspring. This is because, during the formation of reproductive cells, the parent's genetic material with the balanced chromosomal abnormality can become unbalanced, leading to an unbalanced chromosomal abnormality in the offspring.

One of the most significant concerns with balanced chromosomal abnormalities is the risk of passing them on to offspring [102]. In some cases, individuals with balanced chromosomal abnormalities may not show symptoms or have a mild phenotype, making it challenging to identify the condition without genetic testing. However, when these individuals have children, there is a 50% chance that the offspring will inherit the balanced chromosomal abnormality [103]. This can lead to fertility issues and an increased risk of miscarriage or birth defects in the next generation. In addition, individuals with balanced chromosomal abnormalities may also have an increased risk of having children with unbalanced chromosomal abnormalities [103]. This is because, during the formation of reproductive cells, the genetic material can become unbalanced, resulting in an unbalanced chromosomal abnormality in the offspring. This can lead to serious health issues, such as developmental delays, intellectual disabilities, and birth defects.

Identifying and understanding balanced chromosomal abnormalities is crucial for couples planning to have children [92]. Genetic counseling and testing can help identify these abnormalities and provide information about the risk of passing them on to offspring. This can help couples make informed decisions about their reproductive options, such as prenatal testing or using donor gametes to reduce the risk of passing on the abnormality. In cases where a balanced chromosomal abnormality is detected, several options are available to help reduce the risk of passing it on to offspring. Preimplantation genetic testing (PGT) can be performed during an IVF cycle to identify any chromosomal abnormalities in the embryos before implantation. This can help increase the chances of a successful pregnancy and reduce the risk of passing the abnormality to offspring. In some cases, couples may also opt for assisted reproductive techniques, such as using donor gametes or pursuing adoption.

6. Impact of Investigating the Genetic Basis of Unexplained Infertility

6.1 Psychological and Emotional Impact

The diagnosis of unexplained infertility can already be a traumatic experience for couples, and the addition of genetic testing can further compound their emotional distress. The possibility of discovering a genetic cause for their infertility can bring about a range of emotions, including fear, anxiety, and guilt [104]. One of the main concerns for couples is the fear of receiving an unexpected genetic test result. This can lead to feelings of hopelessness and despair, as the couple may feel that their chances of conceiving naturally are diminished. They may also worry about the potential impact of a genetic condition on their future children. On the other hand, a positive genetic test result may also bring about a mix of emotions. While it may provide a sense of relief

for some couples, knowing the cause of their infertility may also bring about feelings of guilt and self-blame [104]. They may also worry about the potential implications of the genetic condition on their future children. Couples may also experience a sense of loss and grief upon receiving a genetic test result. This is especially true if the result indicates that they will not be able to have biological children or if there is a high risk of passing on a genetic condition to their offspring. This can be a significant blow to their dreams of starting a family and can have a profound impact on their mental well-being.

The process of coping with genetic testing results can be challenging for couples. They may experience various emotions, and their reactions may vary depending on the test outcome. Some couples may find it helpful to seek support from family and friends, while others may prefer to keep the information private. Counseling can also be a valuable resource for couples struggling to cope with genetic testing results [105]. A trained therapist can help them process their emotions, provide support and guidance, and assist them in making informed decisions about their future family planning. Couples may also turn to alternative coping mechanisms, such as joining support groups or engaging in self-care activities. Couples need to find healthy ways to manage their emotions and navigate the challenges that come with genetic testing results.

The results of genetic testing can have a significant impact on a couple's decision-making process for future family planning [106]. For some couples, a positive test result may mean that they will need to explore alternative options for conceiving, such as assisted reproductive technologies or adoption. This can be a difficult and emotionally taxing decision for couples, as it may involve letting go of their dream of having biological children. On the other hand, a negative test result may give couples a sense of relief and hope for conceiving naturally. However, it is essential to note that a negative test result does not guarantee a successful pregnancy, and couples may still need to consider other fertility treatment options. The decision to undergo genetic testing for unexplained infertility is a personal one, and each couple must carefully weigh the potential outcomes and make the decision that is best for them. Couples must have access to accurate information and support to help them make informed decisions about their future family planning.

6.2 Improved Diagnosis and Treatment

One of the primary benefits of investigating the genetic basis of unexplained infertility is the potential for improved diagnosis [107]. Traditionally, the diagnosis of unexplained infertility has been made through a process of elimination, where all other known causes have been ruled out. This can be a lengthy and costly process, and it often leaves couples without a clear explanation for their infertility. However, with genetic testing, it is now possible to identify specific genetic factors that may be contributing to the couple's infertility. For example, research has shown that mutations in the FMR1 gene, which is responsible for the production of a protein essential for the development of eggs and sperm, may be linked to unexplained infertility [39, 108]. By identifying these mutations, healthcare professionals can provide a more accurate diagnosis and potentially develop targeted treatment options.

6.2.1 Targeted Treatment Options for Unexplained Infertility with Genetic Factors

Another significant impact of investigating the genetic basis of unexplained infertility is the development of targeted treatment options. With a better understanding of the genetic factors involved in infertility, healthcare professionals can tailor treatment plans to address these specific issues. This personalized approach has the potential to improve the success rates of fertility treatments and reduce the time and cost associated with ineffective treatments. For instance, for couples with mutations in the FMR1 gene, targeted treatments such as in vitro fertilization (IVF) with preimplantation genetic testing (PGT) can be used to select and transfer embryos without the mutation, increasing the chances of a successful pregnancy [109]. In cases where a problem with the sperm is identified, such as DNA fragmentation, targeted treatments such as intracytoplasmic sperm injection (ICSI) can be used to bypass this issue and increase the chances of fertilization.

Interestingly, the diagnosis of unexplained infertility is often a diagnosis of exclusion, meaning that it is made after all known causes of infertility have been ruled out. This includes testing for hormonal imbalances, structural abnormalities, and other medical conditions. However, with the emerging evidence of genetic factors contributing to unexplained infertility, a thorough genetic evaluation should also be considered in the diagnostic process [110]. This is especially important as genetic testing is becoming more accessible and affordable, making it a valuable tool in the diagnosis of infertility.

Accurate diagnosis is crucial in determining the most effective treatment options for unexplained infertility with genetic factors. In the past, couples with unexplained infertility were often treated with empiric therapies, such as intrauterine insemination (IUI) and in vitro fertilization (IVF) [111]. While these treatments have been successful in some cases, they may not be the most appropriate option for couples with underlying genetic factors. For instance, mutations in the FSH receptor gene have been found to affect the response to ovarian stimulation, which is a crucial step in IVF treatment [112]. Therefore, an accurate diagnosis of this mutation would warrant a different approach to IVF treatment, such as using a higher dose of medication to stimulate egg production. Similarly, couples with unexplained male infertility and mutations in the androgen receptor gene may benefit from intracytoplasmic sperm injection (ICSI) rather than conventional IVF. Furthermore, accurate diagnosis can also help identify potential risks and complications that may arise during treatment. For example, couples with specific genetic mutations may be at a higher risk of developing ovarian hyperstimulation syndrome (OHSS) during IVF treatment [113]. Therefore, an accurate diagnosis would allow the healthcare team to monitor the patient closely and take necessary precautions to minimize the risk of OHSS. In addition to guiding treatment options, accurate diagnosis of genetic factors in unexplained infertility also has implications for genetic counseling and family planning. Couples with underlying genetic mutations that contribute to their infertility may pass on these mutations to their offspring, which can lead to future generations also experiencing fertility issues [114]. Therefore, genetic counseling is essential for these couples to understand the risks and make informed decisions about family planning.

6.2.2 Lifestyle Changes and Medical Interventions for Genetic Causes of Infertility

Lifestyle Changes. Lifestyle factors significantly impact fertility, and lifestyle changes can improve chances of conceiving [115]. Maintaining a healthy weight, quitting smoking, limiting

alcohol consumption, reducing stress, and having a balanced diet can improve fertility outcomes. Obesity, smoking, excessive alcohol consumption, stress management, and a balanced diet rich in antioxidants can also improve fertility [116].

Medical Interventions. Medical interventions for unexplained infertility with genetic factors include medications to address hormonal imbalances. Hormonal imbalances affect ovulation and sperm production, with ovulation-stimulating medications like clomiphene citrate and letrozole for women and gonadotropins for men [117, 118].

6.2.3 Surgical Interventions

In some cases of unexplained infertility with genetic factors, structural abnormalities of the reproductive system may be the underlying cause. These abnormalities can affect fertility by interfering with the sperm and egg's ability to meet and fertilize. In such cases, surgical interventions can correct the structural abnormality and improve fertility outcomes. For women, surgical procedures such as laparoscopy or hysteroscopy can remove fibroids, polyps, or scar tissue that may be causing blockages or hindering implantation [119]. In men, surgical procedures such as varicocele repair or vasectomy reversal can be performed to improve sperm production and quality [120].

6.2.4 Assisted Reproductive Techniques

Assisted reproductive techniques (ART) are advanced medical procedures used to help couples conceive when lifestyle changes, medical interventions, and surgical interventions fail [121]. These techniques, such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), can bypass underlying issues and increase the chances of pregnancy in cases of unexplained infertility with genetic factors. PGT and sperm DNA fragmentation testing can also help [122].

6.3 Success Rates of Treatment Options for Unexplained Infertility with Genetic Factors

In vitro fertilization (IVF) is the most commonly used fertility treatment for couples with unexplained infertility. It involves retrieving eggs from the woman's ovaries, fertilizing with the partner's or donor's sperm in a laboratory, and the transfer of resulting embryos into the woman's uterus. Various factors, including age, ovarian reserve, and the underlying cause of infertility, influence IVF success rates. In cases of unexplained infertility with genetic factors, the success rates of IVF may be affected by the type and severity of the genetic condition. A study by Ellakwa et al. [123] found that women with unexplained infertility and a chromosomal abnormality had significantly lower pregnancy rates (19.4%) compared to those without a chromosomal abnormality (41.8%).

Preimplantation genetic testing (PGT) is a technique used during IVF to screen embryos for genetic abnormalities before transfer. This option is handy for couples with known genetic conditions that their offspring can inherit. PGT can also be used to identify chromosomal abnormalities in embryos of couples with unexplained infertility. The success rates of PGT for unexplained infertility with genetic factors vary depending on the type and severity of the genetic condition. A study by Barad et al. [124] reported a 40% live birth rate in couples with unexplained infertility who underwent PGT for aneuploidy (abnormal number of chromosomes).

Intrauterine insemination (IUI) is a fertility treatment that involves placing washed and concentrated sperm directly into the woman's uterus during ovulation. It is a less invasive and less expensive option compared to IVF and is often used as a first-line treatment for unexplained infertility. However, the success rates of IUI for couples with genetic factors contributing to their unexplained infertility are relatively low. A study by da Silva Maranhão et al. [125] reported a live birth rate of 9.3% in couples with unexplained infertility who underwent IUI. This low success rate could be because IUI does not address potential genetic abnormalities in either partner.

Intracytoplasmic sperm injection (ICSI) is a technique used in IVF where a single sperm is injected directly into an egg to achieve fertilization. ICSI is often recommended for couples with male factor infertility, but it can also be used for couples with unexplained infertility. The success rates of ICSI for unexplained infertility with genetic factors have not been extensively studied. However, a study by Chen et al. [126] reported a significantly higher pregnancy rate (53.3%) in couples with unexplained infertility who underwent ICSI compared to those who underwent IVF (36.7%). This suggests that ICSI may be a more effective treatment option for couples with unexplained infertility and genetic factors.

6.3.1 Implications for Couples with Unexplained Infertility and Genetic Factors

The presence of genetic factors in unexplained infertility can significantly impact the success rates of various treatment options. Couples with unexplained infertility and known genetic conditions should be referred for genetic counseling to discuss the implications of their condition on fertility and their options for assisted conception. PGT can be helpful for identifying genetic abnormalities in embryos and increasing the chances of a successful pregnancy. However, it is essential to note that PGT is not a guarantee of a healthy pregnancy, and couples should be aware of the potential risks and limitations of the procedure.

7. Genetic Markers That Could Aid in the Diagnosis and Treatment of Unexplained Infertility

The use of genetic markers in the diagnosis and treatment of unexplained infertility shows significant promise in improving the outcomes for couples struggling to conceive. One of the most promising research areas in UI is the study of genetic mutations associated with the follicle-stimulating hormone receptor (FSHR). FSHR is a protein found on the surface of ovarian cells and plays a crucial role in the development and maturation of eggs. Studies have shown that mutations in the FSHR gene can impair fertility in women, including UI [127]. These mutations can affect the responsiveness of the ovary to FSH, leading to a decrease in the number and quality of eggs produced. Identifying these mutations through genetic testing could aid in the diagnosis of UI and also provide insight into potential treatment options.

Another genetic marker that has shown promise in the diagnosis of UI is the presence of polymorphisms in the CYP19A1 gene, which encodes for the enzyme aromatase. Aromatase converts androgens to estrogens, a process essential for ovulation. Studies have shown that specific polymorphisms in the CYP19A1 gene can affect aromatase activity, leading to irregularities in the menstrual cycle and decreased fertility [128, 129]. Detecting these polymorphisms through genetic testing could help in the diagnosis of UI and guide treatment options such as hormonal therapy to regulate ovulation.

In addition to FSHR and CYP19A1, other genetic markers have also been linked to UI. These include mutations in the genes responsible for the production of estrogen and progesterone, as well as genes involved in the development and function of the ovaries and fallopian tubes [39]. Identifying these genetic markers could provide valuable information about the underlying causes of UI and guide treatment decisions.

Genetic markers not only have the potential to aid in the diagnosis of UI, but they could also play a crucial role in personalized treatment. Currently, the standard treatment for UI is assisted reproductive technology (ART), which includes procedures such as in vitro fertilization (IVF) and intrauterine insemination (IUI) [130]. These treatments can be expensive, time-consuming, and emotionally taxing. However, not all couples with UI may benefit from the same type of treatment. For example, if a couple has a genetic mutation that affects the production of estrogen, ART may not be the most effective treatment option. Instead, hormone therapy or surgery may be more beneficial. Genetic testing could help identify the most suitable treatment option for each individual, increasing the chances of a successful pregnancy.

Furthermore, the use of genetic markers in UI could also impact the fertility preservation field. Many women with UI may choose to freeze their eggs or embryos for future use. However, the success of these procedures is highly dependent on the quality and quantity of the eggs retrieved. Identifying genetic markers that affect the quality of eggs could help predict the success of fertility preservation and guide decisions about the number of eggs to be retrieved and stored.

8. Ethical Considerations

The investigation of the genetic basis for unexplained infertility requires careful regulation and upholding of fundamental ethical principles. These include the principle of autonomy, which allows individuals to make informed decisions about their genetic information. The principle of non-maleficence minimizes harm to individuals and their families, and the principle of justice ensures fair treatment and avoids perpetuating harmful societal beliefs or stigmatizing individuals with infertility.

9. Current Research and Future Directions

Genetic testing technology has advanced significantly in recent years, allowing for more accurate and comprehensive testing of an individual's genetic makeup. Traditional genetic testing methods, such as karyotyping, only analyze a small portion of an individual's genetic code and cannot always identify subtle genetic variations that may contribute to infertility. However, with the development of next-generation sequencing (NGS) techniques, researchers can now analyze an individual's entire genome, providing a more detailed and accurate picture of their genetic makeup. NGS technology has also significantly reduced the time and cost of genetic testing, making it more accessible and feasible for use in clinical settings. This has allowed for larger-scale studies to be conducted, leading to the identification of new genetic causes of unexplained infertility.

Through the use of NGS technology, researchers have been able to identify new genetic causes of unexplained infertility. One study found that a genetic mutation in the gene SYCP2 was associated with unexplained infertility in both males and females [131]. This gene is involved in the formation of sperm and eggs, and mutations in this gene can lead to abnormal sperm and egg

development, resulting in infertility. Another study identified a mutation in the gene DDX4, which is involved in developing egg cells, as a potential cause of unexplained infertility in females [132]. This mutation was found to cause a decrease in the production of mature eggs, leading to difficulty in conception. These studies highlight the potential of NGS technology in identifying new genetic causes of unexplained infertility. By understanding the genetic basis of infertility, researchers can develop targeted treatments and interventions to improve fertility outcomes.

The identification of new genetic causes of unexplained infertility has opened up the potential for personalized treatment approaches. With a better understanding of the underlying genetic factors contributing to infertility, researchers can develop targeted treatments that address the specific needs of each individual. For example, in the case of the SYCP2 mutation, targeted treatments could focus on improving sperm and egg development, potentially leading to successful conception. In the case of the DDX4 mutation, interventions could be developed to stimulate egg production and improve fertility outcomes [133]. Personalized treatment approaches can also potentially improve the success rates of assisted reproductive techniques, such as in vitro fertilization (IVF) [134]. By identifying genetic factors that may affect the success of these techniques, researchers can develop personalized protocols that increase the chances of a successful pregnancy.

The development of gene editing techniques, such as CRISPR-Cas9, has opened up new possibilities for correcting genetic mutations that may contribute to infertility [135]. This technology has been successfully used in animal models to correct genetic defects associated with male infertility. While this technology is still in its early stages, it holds promise for potential future treatments for individuals with genetic causes of infertility. While advancements in genetic testing technology have shown great promise in identifying new genetic causes of unexplained infertility and potential personalized treatment approaches, there is still much to be explored in this field. Future research should focus on expanding the use of NGS technology to identify additional genetic causes of infertility. This will require large-scale studies and collaborations between researchers and clinicians. Furthermore, researchers should also investigate the impact of environmental and lifestyle factors on infertility. While genetics play a significant role, these external factors can also contribute to fertility issues. Understanding the interplay between genetics and lifestyle factors will provide a more comprehensive understanding of infertility and inform personalized treatment approaches.

10. Conclusion

In conclusion, the investigation of the genetic basis of unexplained infertility is of utmost importance in understanding the underlying causes of this condition. The diagnosis of unexplained infertility can be frustrating for couples, as it means that no specific cause can be identified. However, it is essential to note that there is still hope for these couples to conceive with the help of assisted reproductive technologies, such as in vitro fertilization (IVF) or intrauterine insemination (IUI). These treatments can bypass many of the potential causes of unexplained infertility and increase the chances of a successful pregnancy. By identifying specific genetic factors, we can develop targeted treatments and interventions, improve diagnostic accuracy, and provide better patient counseling. Moreover, further research in this field can lead to the development of more personalized approaches to infertility treatment, increasing the chances of a

successful pregnancy for couples struggling with unexplained infertility. It is essential to continue investing in this area of research to improve the lives of individuals and couples affected by this complex and challenging condition.

Author Contributions

The review paper was conceptualised by OMO and AOO, while OMO, OAO, OOC and AOO prepared, edit and revised the Original manuscript. All authors have read and agreed to the published version of the manuscript.

Competing Interests

The authors declare no conflict of interest.

Data Availability Statement

All data relevant to the study are included in the article.

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