Genetic causes and chromosomal abnormalities in male infertility

Why genetics matters in male infertility

Spermatogenesis is a highly coordinated biological sequence that begins with spermatogonial stem cells and ends with mature sperm capable of fertilizing an egg. This sequence requires normal testicular development, endocrine signaling, meiotic chromosome pairing, DNA repair, sperm maturation, and unobstructed transport through the reproductive tract. Genetic changes can interfere with any of these steps.

In clinical practice, genetic causes are most strongly suspected when semen analysis shows azoospermia, meaning no sperm seen in the ejaculate, or severe oligozoospermia, usually defined as a very low sperm concentration. Genetic evaluation is also considered when there are small testes, elevated follicle-stimulating hormone, delayed puberty, recurrent pregnancy loss in a couple, multiple failed assisted reproduction cycles, or congenital absence of the vas deferens.

It is also helpful to distinguish between obstructive and non-obstructive patterns. In obstructive azoospermia, sperm may be produced in the testes but cannot reach the ejaculate because of blockage or absence of ducts. In non-obstructive azoospermia, sperm production itself is severely impaired.

Genetic findings are particularly common and clinically meaningful in non-obstructive azoospermia and severe sperm count abnormalities.

Klinefelter syndrome: an extra X chromosome and impaired spermatogenesis

Klinefelter syndrome is one of the most common chromosomal causes of male infertility. The classic karyotype is 47,XXY, although mosaic forms such as 46,XY/47,XXY also occur. The additional X chromosome can disrupt testicular development and seminiferous tubule function, often leading to small firm testes, elevated gonadotropins, low or low-normal testosterone, and markedly reduced sperm production.

Many men with Klinefelter syndrome are not diagnosed until fertility evaluation. Some have typical pubertal development and normal erectile or ejaculatory function, which can make the diagnosis unexpected and emotionally difficult. Others may have symptoms related to androgen deficiency, such as reduced energy, decreased muscle mass, lower libido, or gynecomastia. These features vary widely.

From a fertility perspective, the important point is that azoospermia is common, but it does not always mean there is no possibility of biological fatherhood. In selected patients, sperm may be found with testicular sperm extraction, particularly microdissection testicular sperm extraction performed by experienced teams. If sperm are retrieved, IVF with intracytoplasmic sperm injection may be considered. Decisions should include counseling about genetic risks, hormonal health, and realistic expectations.

Y-chromosome microdeletions and AZF regions

The Y chromosome contains genes essential for normal sperm production. Microdeletions, which are too small to be seen on a standard karyotype, may remove genes within azoospermia factor regions known as AZFa, AZFb, and AZFc. These deletions are a major reason why Y-chromosome microdeletion testing is recommended in many men with non-obstructive azoospermia or severe oligozoospermia.

The location of the deletion matters. Complete AZFa deletions are typically associated with Sertoli cell-only patterns and a very poor chance of sperm

retrieval. Complete AZFb deletions also generally carry a poor prognosis because meiosis is often arrested. AZFc deletions tend to have a more variable phenotype; some men have azoospermia, while others have severe oligozoospermia, and sperm retrieval may be possible in selected cases.

A crucial counseling point is inheritance. If a man with a Y-chromosome microdeletion has a male child through assisted reproduction, the deletion may be transmitted to that son, potentially causing infertility later in life. This does not automatically determine what a couple should do, but it makes pre-treatment counseling essential. Couples may discuss IVF with ICSI, donor sperm, embryo testing options where appropriate, and the ethical dimensions of transmitting infertility risk.

Structural chromosomal rearrangements

Some men have the correct total amount of chromosomal material but arranged in an atypical way. Balanced translocations, Robertsonian translocations, inversions, and other structural rearrangements can interfere with meiotic pairing and segregation. This may reduce sperm count, increase abnormal sperm morphology, or contribute to recurrent pregnancy loss due to embryos with unbalanced chromosomal content.

A balanced rearrangement may not cause obvious medical problems in the carrier, which is why it can remain undetected until fertility testing or pregnancy loss evaluation. A standard karyotype is the main test used to identify large-scale chromosomal number or structure abnormalities. It can detect sex chromosome aneuploidy such as 47,XXY and balanced structural rearrangements, but it will not detect small Y-chromosome microdeletions.

When a structural rearrangement is found, reproductive counseling becomes especially important. Options may include natural conception with prenatal diagnostic testing, IVF with preimplantation genetic testing for structural rearrangements, donor gametes, or adoption. The best path depends on the specific rearrangement, reproductive history, age-related factors, personal values, and the couple’s tolerance for uncertainty.

CFTR variants and congenital absence of the vas deferens

Not all genetic male infertility is due to impaired sperm production. In congenital bilateral absence of the vas deferens, the testes may produce sperm, but sperm cannot enter the ejaculate because the vas deferens is absent or incompletely formed. Semen volume may be low, and semen pH or fructose results may suggest ejaculatory duct or seminal vesicle involvement.

This condition is strongly associated with variants in the CFTR gene, the same gene involved in cystic fibrosis. Some men with congenital absence of the vas deferens do not have classic cystic fibrosis symptoms, so the fertility finding may be the first clue. Because CFTR-related conditions are inherited in an autosomal recessive pattern, testing the reproductive partner is often recommended if a CFTR variant is found.

If both partners carry clinically significant CFTR variants, there is a risk of a child being affected by cystic fibrosis or a CFTR-related disorder. Sperm retrieval from the epididymis or testis combined with IVF and ICSI may be technically possible, but genetic counseling is central before proceeding.

Single-gene and syndromic causes

Beyond the well-known chromosomal causes, many single-gene conditions can affect male fertility. Examples include disorders of gonadotropin-releasing hormone secretion, such as congenital hypogonadotropic hypogonadism and Kallmann syndrome, primary ciliary dyskinesia affecting sperm motility, androgen receptor abnormalities, and genes involved in meiosis or sperm flagellar structure. Some are rare, but modern sequencing has increased recognition of monogenic causes.

These conditions may present with broader clinical clues. Anosmia or reduced smell can suggest Kallmann syndrome. Chronic sinus or lung disease with immotile sperm can suggest primary ciliary dyskinesia. Ambiguous genitalia, undervirilization, or unusual hormone patterns may suggest androgen signaling disorders. A detailed medical history and physical examination remain important even in the era of genetic testing.

Gene panels or exome sequencing may be considered when standard testing is unrevealing but suspicion remains high, particularly in severe non-obstructive azoospermia, familial infertility, syndromic features, or unexplained severe

sperm motility defects. However, sequencing can produce uncertain results, so pre-test and post-test counseling are vital.

When genetic testing is considered

Testing is individualized, but several patterns commonly prompt evaluation. A reproductive urologist or fertility specialist may consider a karyotype and Y-chromosome microdeletion test in men with non-obstructive azoospermia or severe oligozoospermia. CFTR testing is often considered when congenital bilateral absence of the vas deferens is suspected. Additional testing may be guided by hormone results, testicular volume, family history, recurrent pregnancy loss, or syndromic findings.

Common components of evaluation may include:

Semen analysis, usually repeated to confirm azoospermia or severe sperm abnormalities.
Reproductive hormone testing, including FSH, LH, testosterone, prolactin, and sometimes estradiol or inhibin B.
Physical examination focused on testicular size, vas deferens presence, varicocele, and signs of androgen deficiency.
Karyotype for chromosome number and structural abnormalities.
Y-chromosome microdeletion testing for AZF region deletions.
CFTR testing when absence of the vas deferens or obstructive azoospermia is suspected.

No single test explains all male infertility. Results must be interpreted alongside the clinical picture, because the same semen result can have different causes and different treatment implications.

Implications for treatment and family planning

A genetic diagnosis can be emotionally heavy, but it can also reduce uncertainty. It may explain why sperm counts are extremely low, whether sperm retrieval is likely to succeed, and whether a condition could be transmitted to children. This information can help couples make decisions before undergoing physically, emotionally, and financially demanding treatment.

For some diagnoses, such as complete AZFa or AZFb deletions, the chance of finding sperm may be extremely low, and couples may discuss donor sperm or other family-building options earlier. For AZFc deletions or Klinefelter syndrome, sperm retrieval may be considered in selected cases, but outcomes vary. For chromosomal rearrangements, embryo or prenatal testing may be part of counseling. For CFTR-related obstructive azoospermia, partner testing is essential to clarify reproductive risk.

Importantly, fertility genetics is not only about achieving pregnancy. Some diagnoses have broader health implications, including testosterone deficiency, metabolic risk, bone health, or cystic fibrosis carrier status in relatives. A coordinated approach involving reproductive endocrinology, reproductive urology, genetics, and primary care can support both fertility goals and long-term health.