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Genetic abnormalities of male infertility

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Abstract

Infertility represents a major public health concern, affecting approximately 15% of couples worldwide, with male factors contributing to more than half of all cases. Optimizing clinical management therefore necessitates a comprehensive understanding of the underlying pathophysiological mechanisms, not only to refine diagnostic stratification but also to advance therapeutic strategies—particularly in the context of medically assisted reproduction. Nevertheless, for a long time, no causal explanation was found in almost half of the cases of male infertility. This mainly concerns the most severe cases, where the available treatments remain ineffective. Scientists believed that in idiopathic infertility there are often underlying genetic causes. But the patients were under-explored and the genetic tests carried out were essentially limited to karyotype and old molecular biology techniques. Recently, the development and cost reduction of next-generation sequencing has enabled the identification of dozens of genes implicated in male infertility.

This summary review of the literature reports the various chromosomal and gene abnormalities strongly correlated with syndromic and non-syndromic male infertility, depending on the level of impairment (central, primary testicular or post-testicular); and according to the nature of the abnormalities found in the spermogram – spermocytogram. Its results help to predict the chances of success of treatments and make it possible to better assess the potential risks to the health of the patient and his possible offspring in order to provide adequate genetic counseling.

Keywords: Male infertility; Spermogram; Genetics; Next generation sequencing; Congenital hypogonadotropic hypogonadism

1. Introduction

Infertility has emerged as a major public health concern, currently affecting approximately one in six couples worldwide, with isolated or combined male factors implicated in at least half of all cases. Notably, average sperm production has declined by nearly 50% over the past five decades, underscoring the growing burden of male reproductive dysfunction. Male infertility is therefore increasingly recognized as a multifactorial condition arising from complex interactions among genetic determinants, infectious or inflammatory processes, and environmental exposures. Despite these advances, nearly half of affected cases remain classified as idiopathic, reflecting substantial gaps in our understanding of the molecular and cellular mechanisms governing male reproductive capacity [1].

Assisted reproductive technology (ART) is primarily palliative, with little effort to understand and specifically treat the dysfunctions responsible for couples' infertility. Despite its successes, nearly half of the couples who seek ART fail to achieve pregnancy. These failures often result from an alteration of spermatogenesis producing spermatozoa incompatible with fertilization and/or embryonic development. Accurate genetic diagnosis is therefore important to better understand spermatogenesis, improve currently available treatment, increase the chances of adopting the best course of action for affected patients, and provide adequate genetic counseling. However, these genetic abnormalities

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are inconstant, complex and differ according to the anatomical level and mechanism of impairment. In this regard, a distinction is made between primary testicular insufficiency and pre- or post-testicular infertility.

2. Testicular insufficiencies

They correspond to a primary disorder in the course of spermatogenesis. The alteration can affect the quality and/or the quantity of the spermatozoa. In this category, cases with hypergonadotropic hypogonadism are observed, showing an increased level of FSH and decreased inhibin B [1]. Although male infertility is multifactorial, genetic factors predominate in this category. This is corroborated by the high number of genes (n ≥ 1000) expressed specifically in the testicles and necessary for spermatogenesis [2].

2.1. The severe quantitative reduction in the number of spermatozoa

This accounts for the majority of infertility cases. depending on the intensity of the disorder, manifests as severe oligozoospermia (OS) (spermatozoa concentration ≤ 5 million/ml of sperm) or so-called secretory non-obstructive azoospermia (ANO). The latter represents approximately 60% of azoospermia and affects 0.5% of men in the general population. OS and ANO can be linked to:

2.1.1. Chromosomal abnormalities:

They are present in 7% of infertile men. Their incidence is therefore higher than in the general population. Note that the frequency of karyotype abnormalities is inversely proportional to the number of spermatozoa: 20% in ANO, 5% in oligozoospermia and less than 1% in normospermia [3].

Chromosome number abnormalities

- Klinefelter Syndrome

Klinfelter Syndrome is the most common chromosomal abnormality in males, with incidence of 1 in 500 male births. It is the most common genetic cause of infertility. It is the leading genetic cause of infertility, accounting for more than 70% of chromosomal abnormalities observed in infertile men and about 15% of ANO cases. It is often diagnosed late during an infertility investigations. The 47,XXY karyotype predominates [4] (Figure 1). Mosaic formulas are diagnosed in about 10% of cases, usually corresponding to milder clinical forms, the formula 47,XXY/46,XY is most often encountered [5].

In Klinfelter Syndrome (47,XXY), testicles are normal in size at puberty onset, then undergo developmental arrest followed by bilateral regression of size around the ages15-16 becoming firm and insensitive by ages 18-20. Final testicular volume is that of an olive (less than 2 cm in length), secondary to peritubular fibrosis and progressive deterioration of Sertoli cells and the germ lines, often resulting in apoptosis of spermatogonia and spermatocytes, leading to azoospermia [6].

In healthy individuals, during prophase 1 of meiosis, the X and Y chromosomes pair at two regions PAR1 and PAR2 forming the XY body. The unpaired chromatin then undergoes transcriptional inactivation, repressing some genes that could have a toxic effect on the course of meiosis and allowing adequate meiotic progression (meiotic silencing). In contrast, in Klinefelter Syndrome, the two homologous X chromosomes pair aren't included in the XY body, and aren't repressed and can therefore produce gene products that are potentially deleterious to the spermatocyte [5].

Although 90% of adult Klinfelter Syndrome males are azoospermic, some exhibit only oligozoospermia and achieve successful pregnancy without ART. The spermatozoa found in these patients likely originate from normal germ lines in mosaic contexts. Fluorescent in situ hybridization (FISH) of spermatozoa shows sex chromosome aneuploidy rates between 1.5% and 7.5%. In homogeneous forms, spermatozoa can sometimes be extracted during early puberty via testicular microdissection (TESE) and cryopreserved. Indeed, spermatogenesis can persist in a heterogeneous way at the level of residual foci. However, sex chromosome aneuploidy rates in these spermatozoa can reach 50% [6].

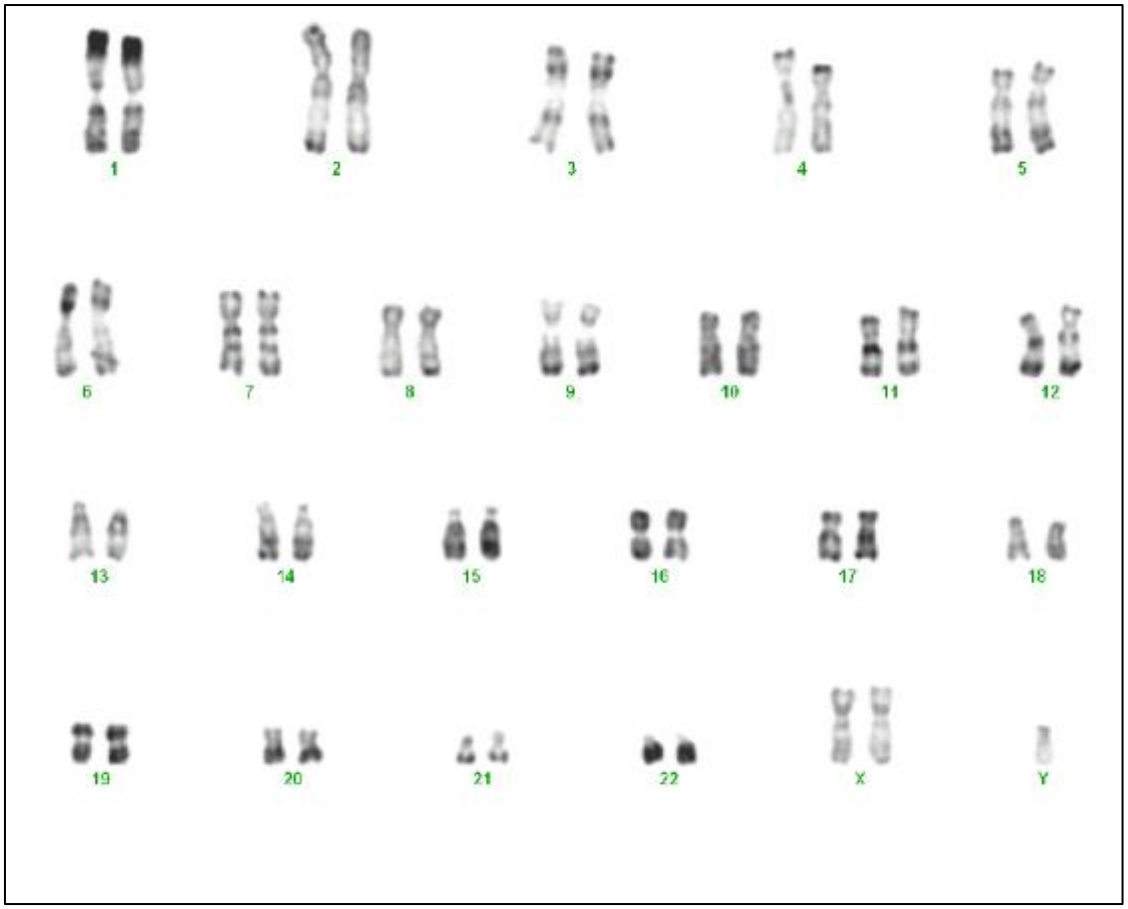


Figure 1 R-band karyotype result in a patient with infertility and azoospermia revealing Klinefelter syndrome: The chromosomal formula is 47,XXY

- Jacob's syndrome (47,XYY)

Its frequency is about 1 in 1000 births male birth. Although most affected men are fertile, this syndrome is the 2nd cause of gonosomal abnormalities after Klinfelter Syndrome. Its frequency is four times higher in infertile men than in the general population [7]. Infertility may result from altered XY body formation. No increased risk has been shown for offspring of 47,XYY patients. FISH studies reveal that most spermatozoa have balanced karyotypes, suggesting systematic elimination of the extra Y chromosome during meiosis or degeneration of abnormal cells [8].

- Mixed gonadal dysgenesis (mosaic 45X/46XY)

45,X/46,XY mosaicism is rare. Lashkari et al studied 49 infertile men with 45,X/46,XY mosaicism without Y-chromosome structural abnormality. 43% had azoospermia, while 8% showed normal spermogram [9].

Abnormalities of chromosomal structure

- Balanced rearrangements.

They are 10 times more common in infertile men than in men in the general population. They are found in more than 1.5% of patients with azoospermia and are also implicated in recurrent miscarriages. When they do not prevent the pregnancy from being carried to term, they are generally the cause of neurodevelopmental disorders, a dysmorphic and/or malformation syndrome [10]. Unlike aneuploidies, most structural abnormalities are more likely to be passed on from a carrier parent. The transmitted chromosome is either identical to the parental rearrangement or derived from it [11]. Unlike the CGH array test, karyotyping allows visualization of chromosome morphology and thus the demonstration of balanced chromosomal rearrangements. The karyotype is therefore essential for the assessment of ANO or OS, or even repeated spontaneous abortions [11].

- Translocations

Robertsonian translocations are found in 0.9% of infertile men. Subfertility in these carriers is partly linked to a disturbance of the meiotic segregation of the involved acrocentric chromosomes, which form a trivalent that can generate 8 different segregation outcomes: 85% of normal or chromosomal balanced spermatozoa (alternate segregation), 14% of spermatozoa unbalanced by adjacent segregation (4 different forms) and less than one percent of spermatozoa which are either carriers of the 2 acrocentrics with the chromosomal derivative, or completely lacking (segregation 3:0) [12]. This low rate of unbalanced spermatozoa in the ejaculate is explained by their tendency to go into apoptosis [13].

Reciprocal Translocations are present in 0.6% of infertile men. During meiosis 1, the chromosomal derivatives organize themselves between homologs by forming a quadrivalent and separate according to different modes of segregation: alternate, adjacent 1, adjacent 2, 3:1, or much more rarely 4:0 [11]. Unlike Robertsonian translocations, the rate of unbalanced sperm produced by patients with reciprocal translocations is highly variable depending on the size and locus of translocated segments, as well as the number and distribution of chiasma. Therefore, when the 1q21, 6p21, 16q21 and 17q11.2 regions are involved in a reciprocal translocation, infertility risk is very high since they contain genes involved in the processes of spermatogenesis, capacitation, mobility, an acrosomal function [14].

At the breakpoints of the trivalents or quadrivalents of translocated chromosomes, some spermatocytes 1 exhibit asynapsis regions undergoing inclusion in the XY body where meiotic silencing occurs. These unpaired sequences inappropriately undergo inactivation that can lead to a considerable reduction or even abolition of the level of transcription of genes necessary for basic cellular functions or meiotic progression, leading to meiotic arrest [15].

Furthermore, asynapsis or heterosynapsis within trivalent and quadrivalent meiotic configurations can interfere with normal chiasma formation in chromosomes not directly involved in the rearrangement. This disruption compromises proper bivalent alignment on the metaphase I plate and impairs accurate chromosome segregation at anaphase I. Such an “interchromosomal effect” promotes secondary meiotic errors, leading to an increased burden of sperm aneuploidy and further exacerbating gametic imbalance [16].

- - Inversions

In patients with a chromosomal inversion, meiotic segregation usually produces normal spermatozoa or carriers of the initial balanced inversion. However, crossing-over can occur within the pairing loop, especially when the inverted segment is large. In this case, if it is a pericentric inversion, this leads to chromosomes with duplicated or deleted segments on each arm [17]. And if it is a paracentric inversion, we note an acentric fragment formation which will be lost; and an unstable dicentric chromosome that can break randomly, or even block spermatocyte 1 at anaphase [18].

- Unbalanced structural anomalies

Small supernumerary chromosomal markers

These are much more common in infertile men with ANO or OS (0.12%) than in the general population. In relation to infertility, 21 of the 24 human chromosomes have been implicated in the formation of these markers. About 72% of them originate from acrocentric chromosomes, particularly from chromosome 15. The unpaired chromatin of the chromosomal marker associates with the XY body leading to meiotic arrest and severe spermatogenesis defects, thus explains oligozoospermia and significantly increased frequency of aneuploidy in spermatozoa [19].

The 46.XX testicular Disorder of Sexual Differentiation (chapel syndrome)

This is rare cause of male infertility has an incidence of approximately 1 in 25,000 newborns. Sterility results from absence of the AZF regions. Although these cases are often sporadic, familial cases have also been reported. Patients can be classified into two groups:

- 46.XX "SRY positive" formula (80 %): caused by translocation of the Y chromosome region containing the SRY locus onto the X chromosome or on an autosome during paternal meiotic recombination. This can be easily demonstrated by FISH or PCR. External genitalia and masculinization are usually normal [20].
- 46.XX “SRY negative” formula (20 %): diagnosed at birth due to possible insufficient virilization of the external genitalia, manifested by hypospadias, micropenis or cryptorchidism. These disorders can be explained either by the presence of a discrete mosaic of the Y chromosome restricted to gonads or by bi-allelic inactivating mutations in gene suppressing the male pathway in the XX gonads, such as the RSPO1 gene located in 1p34.3

whose mutation is associated with palmoplantar hyperkeratosis with an increased risk of squamous cell carcinoma of skin [21].

Other causes include heterozygous duplication at 17q24.3 locus at the activating region upstream of the *SOX9* gene, which leads to the expression of a transcription factor leading to testicular differentiation even in the absence from SRY. Similarly, duplication or gain-of-function mutations of *SOX3* (Xq27.1), an activator of *SOX9,* can cause sex reversal in 46,XX individuals [22].

- Other structural abnormalities of the Y chromosome

The euchromatic region proximal to the long arm of the Y chromosome (Yq11) comprises three sub-regions called "azoospermia factors": AZFa, AZFb and AZFc. They contain genes essential for spermatogenesis. Infertility is explained by recurrent, partial or complete large multi-gene interstitial micro deletions in the AZF regions. Such deletions are found in 3 to 9% of infertile men and more than 10% of men with ANO. Therefore, its research is indicated when the concentration of spermatozoa is less than 5 million/ml [23] (Figure 2).

Complete deletions of AZFa eliminate two genes, *USP9Y* and *DDX3Y*, and are associated with ANO in the setting of "Sertoli cells alone" syndrome. This is the most severe testicular phenotype characterized by the complete absence of all germ cells in the seminiferous tubules [24].

Complete deletions of AZFb remove all copies of the *HSFY, EIF1AY, KDM5D, RPS4Y2, PRY* and *RBMY1* genes. They are associated with azoospermia following an arrest of meiotic maturation of germ cells [25].

The AZFc region contains the *CDY1* and *BPY2* genes as well as palindromic duplications of the DAZ (deleted in azoospermia) gene organized into two clusters comprising four genes: *DAZ1, DAZ2, DAZ3* and *DAZ4.* These four copies of the DAZ gene are expressed in spermatogonia where they encode an RNA-binding protein important for spermatogenesis. Recurrent AZFc deletion accounts for approximately 6% of severe spermatogenesis defects. Large deletions of the AZFc interval, alothoug partial since they do not remove all the copies of the multi-copy encoding genes, have only a modest negative effect on male fertility, explaining the occurrence of infertile men whose the fathers carried the same deletion [26].

The AZFc region is more vulnerable to deletions because it is composed of repeat sequences and palindromes. AZF micro deletions constitutes 70% of AZF microdeletions, followed by AZFb (14%), AZFa (6%), and AZFb+c and AZFa +b+c (10%) [23].

Another relatively frequent structural anomaly of the Y chromosome is the isodicentric Y [idic(Y)], which is the result of a break in the juxtacentromeric region followed by a duplication of the fragment containing the centromere. This rearrangement may be missed on conventional karyotyping. Ring Y chromosomes are also observed.

Rearranged Y chromosome is unstable and is often lost during successive mitoses resulting in a 45.X cell line, the extent of mosaicism varies across tissues and individuals. The frequency of the 45,X/46,X,r(Y) mosaic is estimated at 1.5 per 10,000 births [27].

- Other copy number variations (CNV)

These CNVs are rare and represent a minor risk factor for azoospermia or oligospermia. Examples include:

  - The deletion of the short arm of chromosome 9, encompassing DMRT1 gene involved in testicular development, observed in 0.38% of infertile patients [28].
  - The deletion in Xp11.23 of a 100 kb segment containing the SPACA5 gene coding for an acrosome-associated protein.

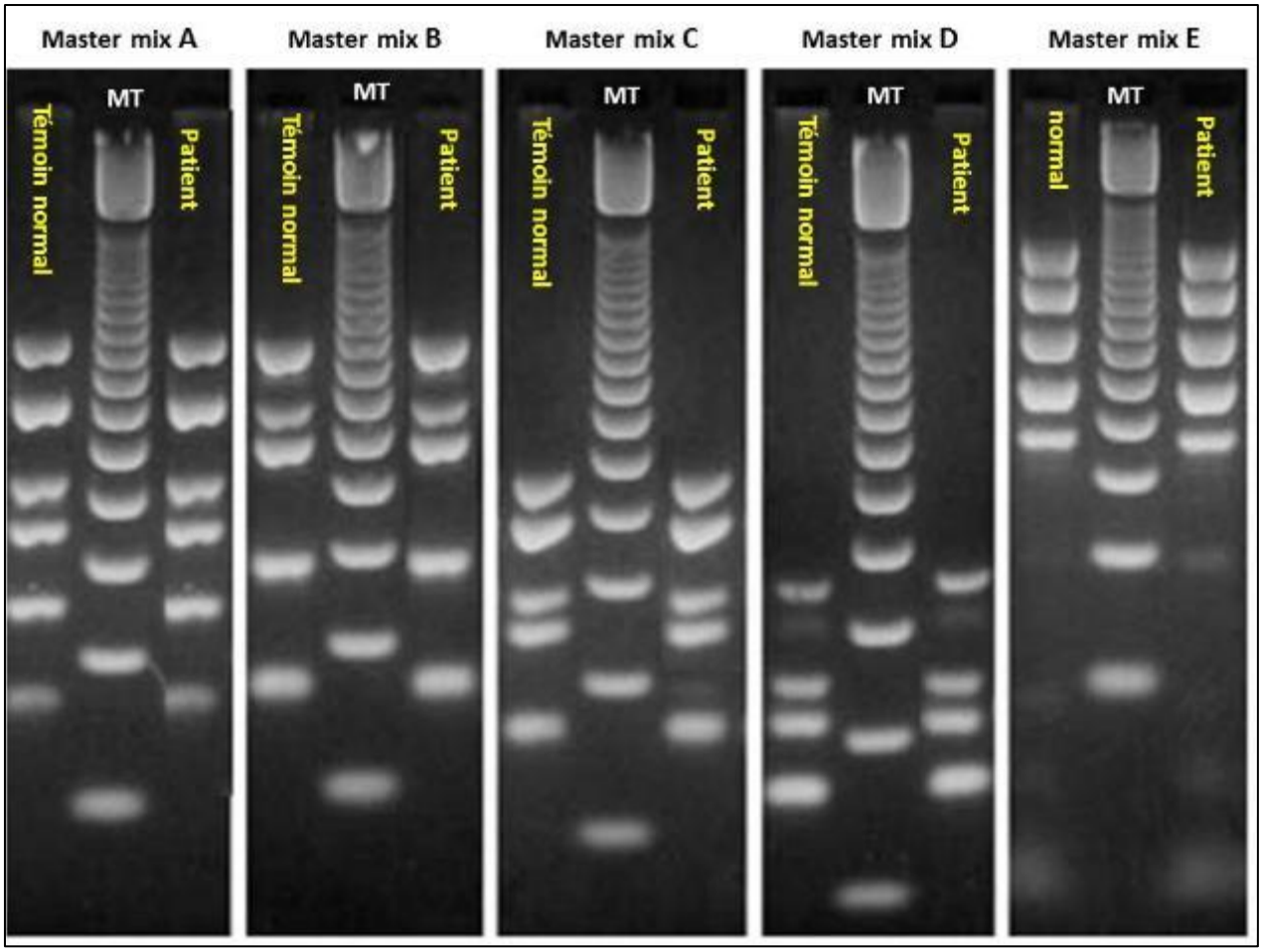


Figure 2 Result of the search for the micro deletion of the AZF regions in an infertile patient presenting azoospermia with a normal karyotype: All 20 loci are amplified at the level of the 5 multiplex PCR reactions, indicating the absence of micro deletion in this patient

2.1.2. Monogenic abnormalities

Causes linked to the X chromosome

Partial Androgen Insensitivity Syndrome: Typical presentation includes severe hypospadias, micropenis, and bifid scrotum with or without testes. It is linked to missense mutations of the AR gene in Xq11.12 coding for androgen receptors.

The *TEX11* gene (Xp11) is involved in chromosome pairing and recombination during meiosis. "Loss of function" type mutations such as c.1838-1G>A; c.792+1G>A; c.1837+1G>C and p.Asp435Leufs*10 leading to meiotic arrest are found in 1% of azoospermic men, which is relatively high. The p.Thr218_Lys296del mutation causes maturation arrest. However, it may permit progression to post-meiotic stages in some seminiferous tubules, producing oligozoospermia and enabling transmission. [29].

The *USP26* gene (Xq26.2) encodes ubiquitin-specific protease 26, which is important for spermatogenesis. The c.1737G>A mutation and its cluster mutations including 370–371insACA, 494T>C, and 1423C>T are risk factors for oligoasthenoteratozoospermia (OATS) and male infertility [30].

Autosomal recessive causes

These are rare homozygous or compound heterozygous bi-allelic "loss of function" type mutations in genes expressed in the testicles:

The *FSHR* (2p16.3) encodes the FSH hormone receptor. The polymorphisms c.919A>G (rs6165G allele) and c.2039A>G (genotype rs6166 GG) impair Sertoli cells stimulation by FSH and lead to a pre-meiotic blockage of spermatogonia [31].

The *SRD5A2* gene (2p23.1) encodes type 2 5 α-reductase which converts testosterone into its active form, dihydrotestosterone. The rs13395648TC genotype and the combination of the TC and CC genotypes of the gene are associated with lower semen volume compared to the TT genotype. Regarding the rs632148 variant, subjects with the GC genotype or the combination of GC and CC genotypes have lower sperm motility compared to those with the GG genotype. The c.591G>T mutation leads to an enzymatic deficiency causing infertility which can be associated with sexual ambiguity [32].

The *LHCGR* gene (2p16.3) encodes the LH and HCG hormone receptor. Several mutations of this gene lead to variable degrees of resistance to the LH hormone. In partial forms, patients have slightly reduced testicular volume but mature Leydig cells are absent or rare. Sometimes infertility is associated with micropenis and/or hypospadias.

The *TEX15* (8p12) is involved in chromosome pairing and recombination during meiosis as well as DNA repair. Bi-allelic nonsense mutation (c.2130T>G, p.Y710*) causes meiotic arrest, and consequently azoospermia/oligozoospermia [33].

The *MEI1* (22q13.2) encodes meiotic double-strand break formation protein 1, essential for the formation of chromosomal synapses. Its mutation c.C3307T (p.R1103W) leads to meiotic arrest and azoospermia [34].

The *FANCM* gene (14q21.2) encodes a component of the central Fanconi anemia complex that is expressed in germ cells and Sertoli cells. It then ensures chromosomal stability during mitosis and meiosis. Mutations have been described: c.1946_1958del; c.4387−10A>G; 1778delG; 1663G>T and c. 1972C>T. They cause a “Sertoli cells alone” syndrome resulting in azoospermia. They have also been associated with an increased risk of familial breast and ovarian cancer [35].

The *M1AP* gene (2p13.1) encodes the protein associated with meiosis 1. Its mutations lead to meiotic arrest and oligo-azoospermia. These include the nonsense mutation c.676dup (p.Trp226LeufsTer4); and the homozygous missense mutation c.1166C>T (p.Pro389Leu) [36].

The *STAG3* gene (7q22.1) encodes a meiosis-specific subunit of the cohesin complex. This complex is a large protein ring with DNA scavenging ability that ensures sister chromatid cohesion and allows proper synapse and segregation of homologous chromosomes during meiosis. Some mutations cause premature ovarian failure in women. c.1262T>G (p.Leu421Arg) and c.1312C>T (p.Arg438Ter) mutations cause infertility due to meiotic arrest. Indeed, spermatocytes I are blocked at the zygotene stage and show significant chromosomal aberrations [37].

The *TEX14* gene (17q22) encodes a protein exclusively expressed in the testicles which is necessary for intercellular bridge formation in germ cells and for spermatid survival. The exon-16 deletion c.2668_2678del produces a frameshift and a premature stop codon yielding a truncated protein and meiotic arrest [38].

The *XRCC2* (7q36.1) is one of the 5 paralogs of the *RAD51* gene necessary for homologous recombination during meiosis. Its homozygous mutation c.41T>C (p.Leu14Pro) leads to meiotic arrest and azoospermia in men and premature ovarian failure in females [39].

About 10% of cases of Fanconi anemia are said to be "occult" because diagnosis is delayed until adulthood, often when solid cancer appears. Bi-allelic mutations in *FANCA* gene have been identified in azoospermic patients with “Sertoli cells only” syndrome but without overt anemia. This gene located at 16q24.3 codes for proteins involved in the correction of double-stranded DNA lesions [40].

Mulibrey dwarfism is a very rare pre and post-natal growth retardation characterized by craniofacial dysmorphism, a small rib cage likely to cause respiratory problems, frequent type 2 diabetes and a risk of developing Wilms tumor. Constrictive pericarditis is the most serious anomaly. This disease is more common in Finland. It is due to mutations in the *TRIM37* gene located at 17q22, coding for a peroxisomal protein. From mid-puberty, affected individuals develop hypergonadotropic hypogonadism with small testes and severe oligoasthenozoospermia or azoospermia [41].

Causes with dominant transmission

These are rare heterozygous variants located in certain genes that are weakly associated with infertility. Their negative effect on fertility is minimal and typically requires interaction with other variants in different genes to manifest. This

seems logical, as variants with a strong negative impact on male fertility would be rapidly eliminated from the population. The following genes have been identified:

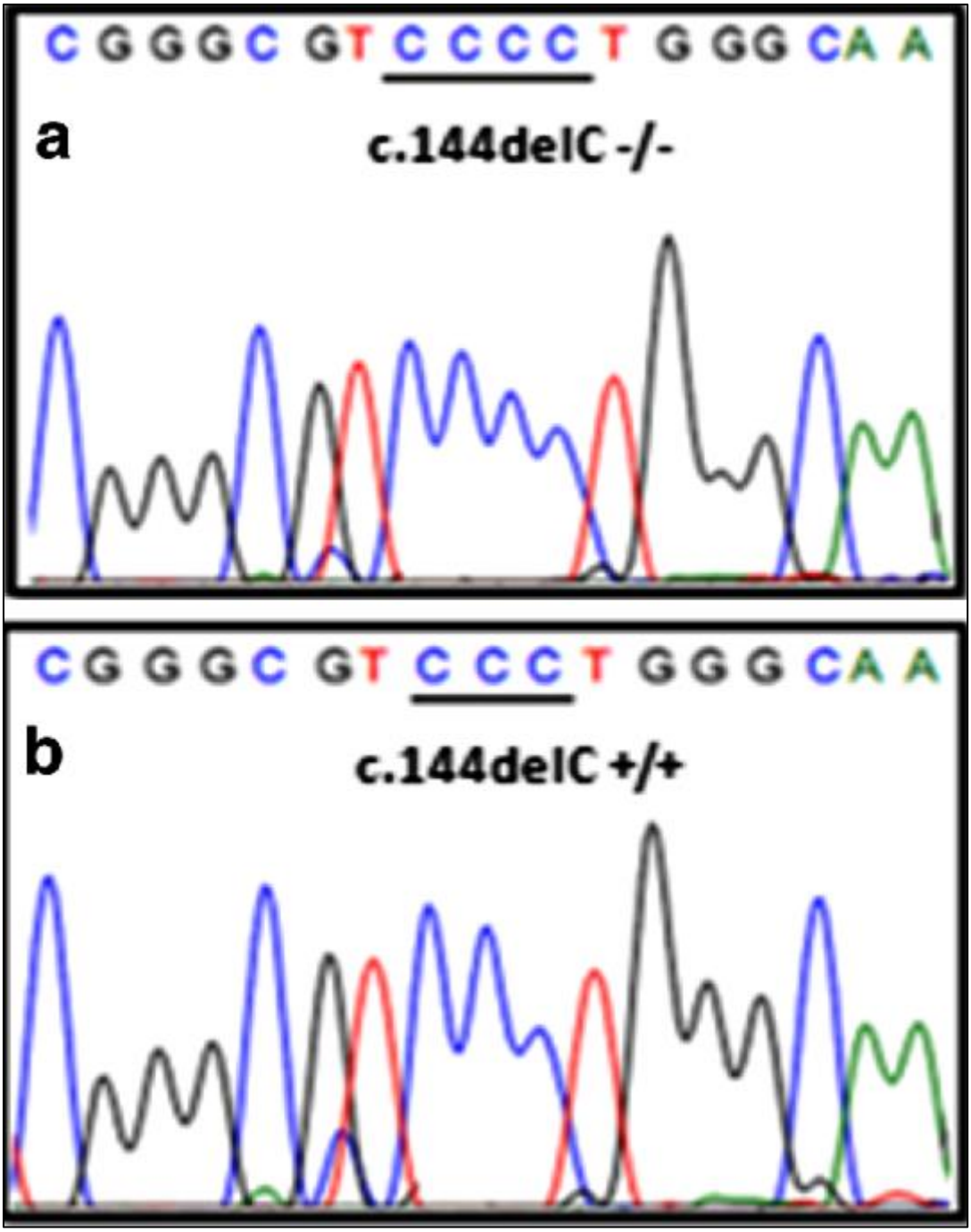
- The *NR5A1* gene (located at 9q33.3) encodes the transcription regulator *SF1* necessary for gonadal development. Missense mutations of this gene are found in 0.6 to 4% of men with ANO or OS related to premeiotic arrest [42].
- The *GATA4* gene (located at 8p23.1) codes for a transcription factor that interacts with the *NR5A1* or *WT1* genes to regulate the transcription of genes necessary for the determination and the testicular development; and the functioning of Sertoli and Leydig cells. Usually, *GATA4* mutations cause disorders of sex development with ambiguity. Nevertheless, some of these mutations have been found in infertile men with ANO [43].
- The *KLHL10* gene (located at 17q21.2) is expressed in the cytoplasm of elongated spermatids. Several heterozygous mutations have been described such as the missense mutations p.A313T and p.Q216P which lead to impaired homodimerization with the wild-type protein causing asynchronous maturation and a partial degeneration of late spermatids. The consequence is OS and infertility [44].
- The *SYCP2* gene (located at 20q13.33) and the *SYCP3* gene (located at 12q23.2) code for proteins of the central axis of the synaptonemal complex. Mutations c.3067_3071del (p.Lys1023LeufsTer2); c.2022_2025del (p.Lys674AsnfsTer8); c.2793_2797del (p.Lys932SerfsTer3) of *SYCP2* disrupt synapsis and increase apoptosis, leading to azoospermia/cryptozoospermia. The *SYCP3* c.643delA mutation introduces a premature stop codon, truncating its C-terminal coiled region, which disrupts co-expression with its wild-type homologous for *SYCP3* fibers formation. This leads to a failure of the chromosomal synapse, an arrest at the zygotene stage and an increase in apoptosis which results in azoospermia and small testes. Additional mutations (e.g., c.548T>C, c.553-16_19del, c.657T>C) have been identified in recurrent miscarriage cases due to abnormal splicing and truncated protein products [45].
- The *APOA1* gene (located at 11q23.3) encodes Apolipoprotein A1 mainly produced by the intestines and liver, and incorporated into HDL (60%) and chylomicrons (12%). Heterozygous mutation causes a rare hereditary amyloidosis affectiong the kidneys, liver and testicles in young patients. Testicular involvement occurs in 68.2% of patients. Infertility is characterized by ANO, frequently associated with macro-orchidism and hypergonadotropic hypogonadism [46].
- Muckle-Wells syndrome is a rare autoinflammatory condition characterized by recurrent episodes of systemic inflammation (fever, rashes, arthralgia). Its main complications are sensorineural deafness and amyloidosis. It is caused by the heterozygous p.R258W mutation in *NLRP3* (1q44), which causes excessive caspase-1 activation and of interleukin-1b secretion. Most affected individuals present with oligozoospermia and even azoospermia; however, IL-1-targeted therapies do not improve fertility [47].
- The *INSL3* gene (located at 19p13.11) encodes an insulin-like hormone secreted by Leydig cells. The *LGR8/GREAT* gene encodes the *INSL3* receptor. This signaling pathway mediates development and shortening of the gubernaculum testis independently of androgen action. Mutations in either gene account for approximately 7% of bilateral cryptorchidism cases and may result in failed spermatogenesis, including azoospermia [48].

2.2. Abnormalities of sperm morphology or function

Individuals with specific monomorphic teratozoospermia are more likely to have a common genetic origin.

Large-headed multi-flagellar spermatozoa (Macrozoospermia)

Macrozoospermia is globally rare but relatively common in North Africa. It is characterized by the presence of large-headed spermatozoa (greater than 70% in the so-called complete forms) and multiflagelled ones. Approximately 85% of patients carry bi-allelic mutation of *AURKC* (located at 19q13.43) which encodes a protein involved in the control of meiotic spindle assembly and corrects inappropriate kinetochore-microtubule attachments [49]. The c.144delC exon-3 mutation represents ~87.7% of detected mutation it results in an unstable truncated transcript (Figure 3). The nonsense mutation c.744C>G (p.Y248*) accounts for approximately 10.5%. Other rare mutations have been reported, such as a missense mutation in exon 6 (p.C229Y), and an intronic mutation c.436-2A>G in the consensus splice site of acceptor of exon 5. These mutations lead to the production of spermatozoa with chromosomal imbalance (aneuploidy and polyploidy) preventing embryonic development, making ART contraindicated. Although chromosome separation fails during meiosis, spermiogenesis proceeds, frequently producing tetraploid spermatocytes [50].



a: fertile control. b: patient with macrozoospermia showing a homozygous c.144delC mutation.

Figure 3 Sanger sequencing of exon 3 of the AURKC gene

2.2.1. Globozoospermia

Complete globozoospermia features nearly 100% round-headed spermatozoa lacking an acrosome and unable to bind or penetrate the zona pellucida. It is associated with impaired histone-to-protamine transition, high DNA fragmentation, and reduced or absent PLCζ, resulting in poor ART outcomes [51]. 70% of cases are due to biallelic alterations in *DPY19L2* (located at 12q14.2) and expressed mainly in spermatids; it encodes a protein located in the inner nuclear membrane opposite the acrosomal vesicle, essentialfor acrosome anchoring during spermiogenesis. A recurrent 200 kb deletion affecting the entire gene accounts for ~80% of pathogenic alleles. Less frequently, punctual mutations have been found, especially in a critical region between exons 8 to 11 such as p.R290H and p.R298C [52].

Around 3% of cases are linked to biallelic *SPATA16* mutations (c.848G>A (p.R283Q), and less frequently a deletion including its exon 2); *SPATA16* is located on chromosome 3 and codes for a protein located in the Golgi apparatus involved in acrosome biogenesis, and its mutations may result in multi-headed or multiflagellated sperm [53].

2.2.2. Acephalic spermatozoa

Affected men typically show predominantly isolated flagella with few detached heads. Bi-allelic mutations in *SUN5* gene (located 20q11.21) such as: c.381delA (p.V128Sfs7*); c.675C>A (p.Y225X) and c.88 C>T (p.R30X) are responsible for about 50% of cases. *SUN5* encodes a protein located in the inner nuclear membrane of elongated spermatids and spermatozoa in head-flagellum junction. It is involved in the formation of LINC complexes linking the nucleus to the cytoskeleton [54].

The *PMFBBP1* gene (located at 16q22.2) encodes a protein located in spermatozoa at the head-neck connection that connects the implantation fossa and the basal body. It would regulate the expression of the outer dense fiber proteins ODF1 and ODF2. Bi-allelic nonsense mutations of *PMFBBP1*: c.1462C>T (p.Gln488*); c.2404C>T (p.Gln802*); c.2725C>T (p.Arg909*); vs. 2092delG (p.Ala698Profs*7); c.361C>T (p.Gln121Ter) and c.414+1G>T splice mutation have been reported. They would disrupt the cooperation of *PMFBP1* with *SUN5* and *SPATA6*, resulting in a headless spermatozoa syndrome [55].

The *TSGA10* gene (located at 2q11.2) encodes a fibrous sheath protein of spermatozoa. Its c.211delG (p.A71Hfs*12) and c.545dupT (p.Ala183Serfs*10) mutations result in the production of a truncated protein causing misdisposition of the mitochondrial sheath [56].

2.2.3. Multiple Morphological Abnormalities of the Flagellum (MMAF)

A proteomic analysis has identified more than 700 flagellum-specific proteins, many of which are axonemal components. These findings underscore the remarkable complexity of flagellar structure and biogenesis and suggest that numerous genes may be implicated in flagellar abnormalities and/or asthenozoospermia.

The specific MMAF phenotype is characterized by astheno-teratozoospermia resulting from a mosaic of flagellar defects, including absent, coiled, curved, angulated, irregular, or short flagella [57]. In approximately 30% of patients presenting with this phenotype in th absence primary ciliary dyskinesia (PCD), the *DNAH1* gene is mutated. Located at 3p21.1, *DNAH1* encodes a heavy chain of the inner dynein arms of the axoneme, contributing to the stabilization of the radial spokes and, consequently the central pair complex. Loss or dysfunction of *DNAH1* leads to severe axonemal disorganization, often with a “9+0” structure corresponding to the absence of the central pair. Given the critical role of the central pair in maintaining overall flagellar architecture, its absence is considered a key pathophysiological mechanism underlying the MMAF phenotype. Severe axonemal disorganization may also result from defective anchorage of radial spokes. Additional ultrastructural abnormalities include abnormal extension of outer dense fibers 3 and 8 into the principal piece, distortion of the fibrous sheath, and absence of the mitochondrial sheath. Despite these defects, spermatozoa of patients with *DNAH1* gene mutations have good nuclear quality and low aneuploid counts, and favorable outcomes have been reported following intracytoplasmic sperm injection (ICSI) [58].

The *CFAP43* gene (10q25.1) and the *CFAP44* gene (3q13.2) encode cilia- and flagella-associated proteins containing 9 WD repeat domains. Bi-allelic mutations in *CFAP43* have been identified in approximately 13% of MMAF cases and include: c.3661-2A>-; p.Arg300Lysfs*22; p.Thr526Serfs*43; c.3541−2A>C; c.2658G>A; c.2680C>T; c.3352C>T; c.1240_1241delGT and c.3882delA. Bi-allelic mutations in *CFAP44* account for approximately 8% of MMAF cases and include: c.2935_2944del (p.D979*); c.T1769A (p.L590Q); c.2005_2006del (p.M669Vfs*13); c.G3262A (p.G1088S) and c.C1718A (p.P573H); c.1387G>T; c.3175C>T; c.4767delT; c.2818dupG and c.1890+1C >T [59].

Bi-allelic mutations in *CFAP65*, located at 2q35, are responsible for approximately 7% of MMAF cases. Reported variants include c.1775delC (p.Pro592Leufs*8); c.3072_3079dup (p.Arg1027Profs*41); c.1946delC (p.Pro649Argfs*5); c.1580delT (p.Leu527Argfs*31); c.4855C>T (p.Arg1619*); c.5270T>A (p.Leu1757*) and c.5341G>T (p.Glu1781*) [60].

The *CFAP69* gene, located at 7q21.13, encodes a protein required for flagellar assembly and stability. Bi-allelic mutations, including c.860+1G>A and c.763C>T (p.Gln255Ter), account for approximately 2.5% of MMAF cases [61].

The *CFAP251* gene at 12q24.31 encodes a protein involved in flagellar development, and bi-allelic mutations in this gene are estimated to cause approximately 5% of MMAF cases [62].

The *CFAP91 (MAATS1)* gene, located at 3q13.33, encodes a binding partner of WDR66 within the calmodulin- and radial spoke–associated complex. This protein is essential for normal flagellar structure and function. Bi-allelic mutations, including c.682+1G>A and c.124G>C (p.Asp42His), result in severe defects of the central pair and radial spoke complexes and are thought to account for approximately 3.6% of MMAF cases [63].

The *DNAH17* gene, located at 17q25.3, encodes a β-type heavy chain component of the outer dynein arms that co-localizes with *DNAH8* and α-tubulin along the sperm flagellar axoneme. Notably, *DNAH17* expression is restricted to spermatozoa and is absent from motile epithelial cilia. Therefore, bi-allelic mutations of *DNAH17* do not cause PCD, but rather AMMF and/or asthenozoospermia.. Ultrastructural analyses of affected spermatozoa reveal partial loss of both peripheral microtubule doublets and the central pair complex [64].

The *TTC29* gene, located at 4q31.22, is highly and preferentially expressed in the testis and encodes a tetratricopeptide repeat containing protein involved in intraflagellar transport. Homozygous truncating mutations in *TTC29* are estimated to account for approximately 3.8% of MMAF cases [65].

The *QRICH2* gene at 17q25.1 encodes a protein required for stabilizing components involved in sperm flagellum biogenesis. Homozygous mutations, including c.3501C>G (p.Tyr1167Ter) and c.4614C>G (p.Tyr1538Ter), have been identified in approximately 1% of patients with the MMAF phenotype [66].

The *FSIP2* gene, located at 2q32.1, encodes a protein associated with fibrous sheath formation that interacts with the anchoring protein AKAP4, which is essential for flagellar assembly. Bi-allelic mutations such as c.16246_16247insCCCAAATATCACC (p. T5416fs*7); c.17323C>T (p.Q5774*); c.910delC; c.16389_16392delAATA; c.2282dupA and c.1606_1607insTGT; 1607_1616delAAAGATTGCA would be responsible for about 5% of AMMF [67].

Finally, the *ARMC2* gene, located at 6q21, plays a role in the assembly and/or stability of the central pair of the axonemal complex. Bi-allelic mutations, including c.1023+1G>A; c.2279T>A; c.2353_2354delTT; c.1284_1288delACAAA; and c.421C>T, are responsible for approximately 3% of MMAF cases [68].

2.2.4. The absence/defect of the annulus

The *SEPT12* gene located at 16p13.3 encodes a member of the Septins family forming homofilaments and heterofilaments constituting the annulus by binding and hydrolyzing GTP. A stable Septin complex is required for flagellum differentiation by interacting with α- and β-tubulin. Heterozygous mutations of *SEPT12* have a negative dominance effect because they alter the formation of Septin filaments with wild-type proteins. The p.Thr89Met mutation in exon 3 reduces the hydrolytic activity of GTP, while the p.Asp197Asn mutation in exon 6 interferes with GTP binding and leads to the formation of a defective annulus and a curved flagellum [69].

2.2.5. Isolated asthenozoospermia

The *TAT1* gene encodes SLC26A8, a monovalent and/or divalent anion transporter localized to the equatorial segment of the sperm head and the annulus of spermatozoa. This transporter interacts with the CFTR channel forming complexes to stimulate its transport activity represented by chloride and bicarbonate fluxes necessary for sperm motility and capacitation. Heterozygous missense mutations, including p.Glu812Lys and p.Arg954Cys, lead to reduced SLC26A8 expression levels or mislocalization of the protein. These alterations promote instability and proteasomal degradation of the SLC26A8–CFTR complex, thereby impairing capacitation and resulting in asthenozoospermia [70].

The *CATSPER1* gene encodes one of the four α-subunits forming the pore of the CATSPER channel, which is located on the plasma membrane of the principal piece of the sperm flagellum. Upon stimulation by progesterone, this channel mediates calcium influx, a critical step in sperm capacitation and hyperactivation. Homozygous *CATSPER1* mutations, including c.539_540insT and c.948_949insATGGC, result either in truncated proteins lacking all transmembrane domains and the channel pore or in complete absence of the protein, thereby leading to asthenozoospermia [71].

2.2.6. Failed oocyte activation syndrome

The *PLCZ1* gene located at 12p12.3 codes for phospholipase C Zeta in the spermatozoon which triggers calcium oscillations and oocyte activation during fertilization. Its bi-allelic mutations cause defective calcium signaling and impaired early embryonic development [72]. In addition, absence or malformation of the acrosome—particularly observed in globozoospermia—results in reduced levels or complete absence of PLCZ1 protein, further contributing to defective oocyte activation [51].

2.2.7. Syndromic infertility linked to asthenozoospermia

Primary ciliary dyskinesia (PCD)

The sperm flagellum shares common structural elements—most notably the axoneme—with motile cilia present in epithelial cells of the respiratory tract, fallopian tubes, choroid plexus, and cerebral ventricles. PCD is a multi-systemic disorder caused by motility defects of cilia and flagella, its incidence is estimated at 1 per 15,000 births. It is mainly characterized by recurrent respiratory tract infections with, symptoms ranging from chronic rhinosinusitis to bronchiectasis. In 50% of cases, PCD is associated with situs inversus due to dysfunction of motile cilia in the embryonic node, thus disturbing the laterality of the organs (Kartagener's syndrome). More rarely, hydrocephalus may occur as a consequence of impaired ependymal ciliary motility, resulting in obstruction of cerebrospinal fluid flow [57].

Although numerous genes have been implicated in PCD, only a subset is associated with male infertility. In affected individuals, spermatozoa are typically immotile and may present with a multiple morphological abnormalities of the flagellum (MMAF) phenotype, characterized by ultrastructural defects such as absence of dynein arms, loss of radial spokes, or microtubular transpositions.

The *SPEF2* gene, located at 5p13.2, encodes a protein that interacts with components of radial spoke heads and intraflagellar transport, both of which are essential for flagellar assembly. Bi-allelic mutations, including c.910C>T (p.Arg304*); c.3400delA (p.Ile1134Serfs*13) and c.3240delT (p.Phe1080Leufs*2) result in a combined PCD and MMAF phenotype [73].

The *CCDC39* gene (3q26.33) encodes a protein involved in the assembly of inner dynein arms and radial spokes. Bi-allelic mutations (e.g., c.983T>C; p.Leu328Pro) cause severe axonemal disorganization, including mislocalization of peripheral microtubule doublets, displacement or absence of the central pair, and loss of inner dynein arms and nexin links. Affected patients present with oligo-asthenozoospermia, a narrowed midpiece, and a shortened flagellum [74].

The *CCDC40* gene, located at 17q25.3, encodes a protein that functions together with *CCDC39* to establish the 96-nm axonemal repeat and ensure proper assembly of inner dynein arms and the dynein regulatory complex. Bi-allelic mutations of *CCDC40* such as: c.901C>T p.(Arg301*); c.2065_2068dup (p.Ala690Glyfs*67); c.2824_2825insCTGT; c.1989+1G>A; c.1416delG, c.1259delA lead to absence of inner dynein arms, abnormal central apparatus formation, and microtubular disorganization, resulting in reduced ciliary beat amplitude and impaired axonemal bending. Clinically, patients exhibit chronic respiratory infections, Kartagener syndrome in approximately half of cases, and infertility frequently associated with MMAF, and more rarely with isolated asthenozoospermia [75].

The *DNAAF4* gene located at 15q21.3 encodes a protein involved in the pre-assembly of axonemal arms and participates in the integration and stabilization of the intermediate chain, which is an integral part of both the inner and outer dynein arms. Its c.988C>T (p.Arg330Trp) mutation causes astheno-teratozoospermia [76].

The *MNS1* gene located at 15q21.3 encodes a protein that dimerizes and interacts with the *CCDC114* complex, contributing to docking of outer dynein arms in the axonemes of the vibratile cilia in respiratory epithelial cells and flagella of spermatozoa, and would also be present in the primitive embryonic nodal cilia. Homozygous nonsense mutations (p.Arg242*); c.407_410del (p.Glu136Glyfs*16) and c.603_604insG (p.Lys202Glufs*6) have been reported in men with situs inversus and astheno-teratozoospermia characterized by morphological abnormalities at the outer microtubule doublets leading to infertility. Interestingly, patients with PCD carrying mutations in the *CCDC114* gene have been described as normally fertile [77].

Compound heterozygous mutations in *ARMC4* (c.2095C>T; p.Gln699* and c.1679C>T; p.Ala560Val) have been identified in a patient with situs inversus and infertility due to loss of outer dynein arms and MMAF [78].

Other genes suspected to contribute to PCD-associated MMAF include *DRC1* [79], *CFAP74* [80], and *BRWD1* [81]. However, in most PCD cases, sperm flagella appear morphologically normal by light microscopy, arguing against a major role for many of these genes in teratozoospermia or MMAF. This is notably the case for the following genes:

- The *LRRC6* gene (8q24.22) encodes a cilia-and flagella-associated protein. Bi-allelic mutations such as c.749G>A (p.W250*); c.538C>T (p.R180*); c.64dupT (p.S22Ffs*19) and c.863C>A (p.P288H) have been reported in PCD patients, resulting in absence of both inner and outer dynein arms and causing sperm ultrastructural and motility defects [82].

- Mutations in *DNAAF6* (Xq22.3), including c.319_329del (p.Arg107fs) and c.290G>T (p.Gly97Val), result in absence of both inner and outer dynein arms, leading to asthenozoospermia and infertility [83].
- The *DNAAF2* gene (14q21.3) encodes a protein involved in cytoplasmic preassembly of dynein arm complexes prior to their transport to the ciliary compartment. Bi-allelic mutations: c.C156A (p.Y52X); c.C26A (p.S9X); c.C23A (pS8X); c.1214-1215insACGATACCTGCGTGGC (p.G406Rfs89X); c.T1901C (p.F634S) and c.C998T (p.A333V) have been identified in patients with PCD with akinetospermia [84].
- The *RSPH3* gene (6q25.3) encodes a protein expressed in respiratory epithelial cilia and sperme flagella, it plays a critical role in assembly of the central pair and radial spokes. 10% of PCD cases with central apparatus and radial spoke defects are attributable to bi-allelic *RSPH3* mutations, particularly c.616C>T (p.Gln206*). These cases exhibit near-complete absence of radial spokes and variable central pair defects, resulting in a mixture of immotile flagella and flagella with reduced-amplitude motility [85].
- The *CDC14A* gene (1p21.2) encodes a dual-specificity phosphatase located in cilia of inner ear cells, basal bodies and sound-transducing stereocilia. It is involved in regulation of kinocilium length, microtubule integrity, DNA double-strand break repair, and chromosome segregation. Bi-allelic *CDC14A* mutations are implicated in moderate to severe hearing loss. Nevertheless, male infertility is not constant. Only certain mutations such as: c.376delT; c.417C>G; c.934C>G; c.839-3C>G or c.959A>C have been associated with oligoasthenozoospermia or azoospermia [86].

Ciliopathies

Ciliopathies represent an expanding group of disorders caused by mutations in genes involved in ciliary structure and function. One of the most frequently implicated genes is *CEP290* (12q21.32), which encodes a centrosomal protein essential for ciliogenesis. Bi-allelic *CEP290* mutations give rise to a wide spectrum of overlapping phenotypes, including Leber congenital amaurosis, Senior–Løken syndrome, nephronophthisis, Joubert syndrome, Bardet–Biedl syndrome, and Meckel–Grüber syndrome. Cases of male infertility associated with asthenozoospermia or akinetospermia have been reported in patients with *CEP290* mutations; however, despite the identification of more than *100* pathogenic variants, no clear genotype–phenotype correlation has been established [87].

Autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited adult-onset renal disorder, most commonly caused by heterozygous inherited or de novo mutations in *PKD2* or *PKD1* located at 16p13.3. Patients with *PKD1* mutations frequently present with infertility associated with cystic dilatation of the genital tract, particularly the seminal vesicles. Sperm morphological abnormalities are common and include coiled or shortened flagella, absence of central microtubules, and irregular peripheral doublets. These defects may result from dysregulation of the Hippo signaling pathway, potentially promoting ciliary disassembly [88].

Deafness-Infertility syndrome

Bi-allelic contiguous gene deletions at 15q15.3 encompassing both *CATSPER2* and *STRC* cause a syndrome characterized by asthenozoospermia-associated infertility and non-progressive prelingual sensorineural hearing loss [89].

3. Pre-testicular causes

Congenital hypogonadotropic hypogonadism (CHH) is defined by a congenital deficiency in the production, secretion, or action of gonadotropin-releasing hormone (GnRH). It accounts for less than 2% of male infertility cases and results in impaired spermatogenesis associated with endocrine testicular insufficiency (hypo-Leydigism). CHH is frequently associated with developmental abnormalities such as cryptorchidism or micropenis and is most often characterized by absent puberty. In partial forms, puberty may be delayed or incomplete, leading to infertility.

CHH may occur in isolation or in association with deficiencies of other pituitary hormones. In approximately 50% of patients, CHH is accompanied by anosmia or hyposmia due to hypoplasia or aplasia of the olfactory bulbs, a condition known as Kallmann syndrome, which results from defective embryonic migration of GnRH neurons from the olfactory placode [90].

3.1. Genes involved in CHH with normal olfaction

These include:

- *GNRH1* (8p21.2), encoding GnRH [91];

- *GNRHR* (4q13.2), encoding the GnRH receptor in anterior pituitary gonadotroph cells [92];
- *FSHB* (11p14.1), encoding the β-subunit of follicle-stimulating hormone; and *LHB* (19q13.33), encoding the β-subunit of luteinizing hormone [93];
- *KISS1* and *KISS1R* (19p13.3), which encode kisspeptin-1 and its receptor, respectively, essential regulators of GnRH neuronal activity [94];
- Similarly, the *TAC3* gene encoding tachykinin-3, and the *TACR3* gene located at 4q24 and encoding its receptor are involved in the control of GnRH neurons [95],
- *SOX2* (3q26.33): Its heterozygous mutations are linked to septo-optic dysplasia associated with anophthalmia/microphthalmia. This pathology is defined by the triad: pituitary hormonal deficits, optic nerve hypoplasia, and cerebral midline malformations.

The *CCDC141* (2q31.2) encodes a cytoskeletal scaffold protein that links actin and microtubule components of the cytoskeleton that underlie a cell's shape and motility, with force-generating motor proteins. Its bi-allelic inactivating mutations alter the migration of GnRH neurons without affecting olfactory neurons [96].

3.2. Genes involved in Kallmann syndrome

Mutations in these genes either affect the neurogenic niche in the olfactory region and may also alter craniofacial development; or the migration of GnRH neurons:

A major subset of these genes encodes components of the fibroblast growth factor 8 (FGF8) signaling pathway, including *FGF8* (10q24.32) and its receptor *FGFR1* (8p11.23). FGF8–FGFR1 signaling is essential for the ontogenesis and survival of GnRH neurons during early forebrain development and plays a critical role in neural crest cell migration and olfactory stem cell maintenance. Heterozygous loss-of-function variants in *FGF8* or *FGFR1* are frequently associated with craniofacial defects, such as cleft lip and/or palate, as well as skeletal abnormalities, reflecting the pleiotropic developmental functions of this pathway [97].

The *ANOS1* gene (Xp22.31) encodes anosmin-1, a transiently expressed extracellular matrix glycoprotein that enhances FGF signaling through direct interactions with the FGFR–FGF–heparan sulfate proteoglycan complex at the cell surface. Disruption of *ANOS1* impairs olfactory axon guidance and GnRH neuron migration; clinically, bimanual synkinesis and unilateral renal agenesis are highly suggestive features of *ANOS1*-related disease [98]. The functional activity of anosmin-1 is further dependent on *HS6ST1* (2q14.3), which encodes heparan sulfate 6-O-sulfotransferase 1, a key enzyme required for proper heparan sulfate modification and effective FGF signaling [99].

Additional modulation of the FGF signaling axis is mediated by *IL17RD* (3p14.3) -encodes the interleukin-17 receptor- and *FGF17* (8p21.3). *FGF17* represents the second most important ligand of FGFR1c in GnRH neuron development, although it exhibits lower morphogenetic potency than *FGF8.* Both genes display spatiotemporal expression patterns overlapping with FGF8 and fine-tune FGFR1-dependent signaling through enhancer or inhibitory effects. Heterozygous mutations in *IL17RD* are associated with Kallmann syndrome, frequently accompanied by sensorineural hearing loss [100].

Neurodevelopmental transcriptional regulators also play a central role in GnRH neuron specification and migration. *CHD7* (8q12.2), which encodes a transcriptional cofactor of *SOX2,* is critical for early neurogenesis. Heterozygous *CHD7* mutations underlie CHARGE syndrome, a multisystem developmental disorder characterized by coloboma, cardiac anomalies, choanal atresia, growth delay, genital abnormalities, and ear malformations with deafness [101]. Similarly, *SOX10* (22q13.1), a transcriptional activator essential for neural crest development, is implicated in Waardenburg syndrome types 2 and 4, which combine congenital deafness with pigmentary and neurodevelopmental defects [102].

The prokineticin signaling pathway, comprising *PROK2* (3p13) and its receptor *PROKR2* (20p12.3), is another critical regulator of olfactory bulb development and GnRH neuron migration, with pathogenic variants resulting in impaired reproductive axis activation [103]. Likewise, axon guidance molecules such as semaphorin-3A *(SEMA3A,* 7q21.11) and its receptor plexin-A1 *(PLXNA1,* 3q21.3) are essential for olfactory system development and the neuronal control of puberty, further underscoring the tight coupling between olfactory wiring and reproductive maturation [104].

Finally, *WDR11* (10q26.12) encodes a protein that interacts with the *EMX1* transcription factor, a key regulator of olfactory neuron development. Heterozygous *WDR11* mutations reduce or abolish this interaction, thereby perturbing olfactory and GnRH neuronal development and contributing to the pathogenesis of Kallmann syndrome [105].

3.3. The genes involved in the combined pituitary hormone deficiency

Combined pituitary hormone deficiency (CPHD) represents an important genetic cause of congenital hypogonadotropic hypogonadism and is frequently associated with broader endocrine dysfunction. Among the key genes implicated, *POU1F1,* located at 3p11.2, encodes a pituitary-specific transcription factor essential for pituitary cell lineage commitment. Likewise, *PROP1*, located at 5q35.3, encodes a transcription factor that orchestrates early pituitary development by regulating the ontogenesis of gonadotropes, somatotropes, lactotropes, and caudomedial thyrotropes [106]. Pathogenic variants in these genes disrupt pituitary organogenesis and lead to variable combinations of growth hormone, gonadotropin, thyroid-stimulating hormone, and prolactin deficiencies.

3.4. The concept of oligogenic inheritance

Regardless of clinical presentation, pedigree analyses of hypogonadotropic hypogonadism (HH) consistently reveal incomplete penetrance and marked inter- and intrafamilial phenotypic variability, even among individuals carrying identical pathogenic variants. These observations have challenged the traditional Mendelian paradigm of HH as a strictly monogenic disorder. Accumulating evidence indicates that multiple rare variants in distinct genes can act synergistically to produce more severe or complex phenotypes, supporting an oligogenic mode of inheritance. Current estimates suggest that at least 20% of HH cases are oligogenic, while approximately 15% exhibit spontaneous reversal in adulthood, highlighting the contribution of gene–gene and gene–environment interactions [107]. This complexity significantly complicates risk assessment and genetic counseling, particularly with respect to transmission probability and phenotypic prediction.

4. Post-testicular obstructive causes

Post-testicular obstructive causes of male infertility result from physical or functional barriers that prevent the transport of spermatozoa from the testis to the ejaculate. Among men diagnosed with obstructive azoospermia, approximately 15–30% present with congenital bilateral absence of the vas deferens (CBAVD). In the absence of associated renal agenesis, a targeted genetic evaluation is indicated.

4.1. The ABCC7 gene (CFTR)

The *ABCC7* gene (*CFTR*), located at 7q31.2, encodes the cystic fibrosis transmembrane conductance regulator, an anion channel expressed at the apical membrane of epithelial cells lining exocrine glands. Disorders related to *CFTR* mutations follow an autosomal recessive inheritance pattern, and more than 2,000 variants have been described to date. Biallelic severe loss-of-function mutations abolish CFTR activity and cause classic cystic fibrosis, a condition in which CBAVD is observed in nearly all affected males. In contrast, combinations involving at least one mild allele that partially preserves channel function result in CFTR-related disorders, including idiopathic pancreatitis, bronchiectasis, and isolated CBAVD.

CFTR mutations are detected in approximately 80% of men with isolated CBAVD. These variants disrupt epithelial ion transport, leading to altered fluid composition, increased viscosity of secretions, and progressive obstruction of the male excurrent ducts. The vas deferens is thought to undergo early obstruction followed by degeneration or atrophy during infancy or early childhood [108]. Management of CBAVD relies on assisted reproductive technologies, most commonly involving microsurgical epididymal sperm retrieval for use in intracytoplasmic sperm injection (ICSI).

4.2. The *ADGRG2* gene

Pathogenic variants in the *ADGRG2* gene account for approximately 3% of CBAVD cases. Located at Xp22.13, *ADGRG2* encodes an adhesion class G protein–coupled receptor that is selectively expressed in the efferent ducts, where it plays a critical role in fluid reabsorption and maintenance of ductal patency [109]. Mutations in *ADGRG2* represent a distinct X-linked cause of obstructive azoospermia and should be considered in CFTR-negative patients.

5. Conclusion

The genetics of male infertility embodies a fundamental paradox: it concerns transmission of defects in a condition that intrinsically limits transmission. Historically, genetic evaluation of infertile men was largely restricted to karyotype analysis and screening for Y-chromosome microdeletions. However, the advent of high-throughput sequencing—particularly whole-exome and targeted gene panel approaches—has profoundly reshaped this field, enabling the identification of dozens of genes involved in spermatogenesis, sperm function, and reproductive tract development.

Beyond etiological clarification, genetic diagnosis has important clinical implications. It informs the assessment of long-term health risks, including susceptibility to systemic disorders such as pulmonary or oncological diseases; guides prediction of sperm retrieval success in azoospermic men; and, critically, allows evaluation of the genetic risks associated with the use of affected gametes in assisted reproductive technologies (ART). While ART has dramatically expanded reproductive options for infertile couples, the use of spermatozoa derived from severely impaired spermatogenesis raises concerns regarding the transmission of infertility or other genetic disorders, with potential consequences for the health of future generations.

A key challenge moving forward is therefore the identification of spermatozoa with optimal developmental competence while minimizing risks to the resulting offspring. We advocate for the systematic integration of recent genetic discoveries into routine diagnostic workflows. This review provides a framework for the development of targeted next-generation sequencing panels, particularly for cases of idiopathic infertility. Although the genetics of infertility initially lagged behind other medical disciplines, the pace of discovery has accelerated substantially—and the field is now poised for full clinical translation.

Compliance with ethical standards

Disclosure of conflict of interest

Authors don't have financial or non-financial interests to disclose.

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