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# Current Approach to Genetic Causes of Male Infertility and Genetic Counseling

## Erkek İnfertilitesinin Genetik Nedenlerine Güncel Yaklaşım ve Genetik Danışmanlık

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**ABSTRACT**

Generally, infertility is defined as the inability of couples who have had unprotected and regular intercourse for at least 12 months or longer to conceive naturally. When all societies in the world are examined, infertility is an important health problem affecting approximately 48 million couples, and it also has socio-cultural, economic, and psychological effects. While 8-12% of reproductive age couples have infertility problems, when gender-related reasons are examined, 20-30% of these reasons are male, 20-30% are female, and 25-40% are together with couples. While the etiology of 60% of male infertility causes has not been clarified yet, congenital urogenital anomalies are the most common causes, and genetic causes are the second most common cause among the known causes. While investigating genetic etiology in patients, chromosomal anomalies and Y microdeletions are at the forefront; however, the importance of monogenic causes has increased as some known genes have been associated with infertility because of familial segregation studies and the whole exome analyses with the development of new generation sequencing technologies. In this review, genetic causes of male infertility, diagnosis, and treatment approaches for genetic causes were examined by the current literature, and the importance of providing the proper genetic counseling to infertility patients was mentioned.
**Keywords:** Genetics; male; infertility; genetic counseling.

**ÖZ**

Genel olarak infertilite, en az 12 ay veya daha uzun süre korunmasız ve düzenli cinsel ilişki yaşayan çiftlerin doğal yollarla gebe kalamaması olarak tanımlanmaktadır. Dünyadaki tüm toplumlar incelendiğinde, infertilite yaklaşık olarak 48 milyon çifti etkileyen önemli bir sağlık sorunu olmanın yanı sıra, sosyo-kültürel, ekonomik ve psikolojik etkileri de bulunmaktadır. Üreme çağındaki çiftlerin %8-12'si infertilite problemi yaşarken, cinsiyete bağlı sebepler incelendiğinde, bu nedenlerin %20-30'unu erkek cinsiyet, %20-30'unu kadın cinsiyet ve %25-40'ını çiftler beraber oluşturmaktadır. Erkek cinsiyet kaynaklı infertilite nedenlerinin %60'ının etiyolojisi henüz aydınlatılmamışken, bilinen nedenler arasında doğumsal ürogenital anomaliler en sık nedenler ve genetik nedenler ise ikinci sıklıktaki nedenlerdir. Hastalarda genetik etiyoloji araştırılırken kromozomal anomalileri ve Y mikrodelesyonları ön planda izlenmektedir, ancak, yeni nesil dizileme teknolojilerinin gelişmesiyle birlikte yapılan ailesel segregasyon çalışmaları ve tüm ekzom analizleri sonucunda bilinen bazı genlerin infertilite ile ilişkilendirilmesiyle monogenik nedenlerin önemi artmıştır. Bu derlemede, erkek infertilitesinin genetik nedenleri, genetik nedenlere yönelik tanı ve tedavi yaklaşımları güncel literatürle uyumlu bir şekilde incelenmiş ve infertilite hastalarına doğru genetik danışmanlığın sağlanmasının öneminden bahsedilmiştir.
**Anahtar kelimeler:** Genetik; erkek; infertilite; genetik danışmanlık.

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## INTRODUCTION

Infertility, with its general definition, is the inability to conceive naturally after at least 12 months or more of unprotected and regular sexual intercourse (1). When all societies in the world are examined, infertility is a severe problem which an estimated 48 million couples are affected by (2), which has medical, psychological, economic, and socio-cultural effects and has affected societies in every period of history, the cause of which is still unsolved. Although the prevalence of infertility in reproductive ages varies between 8% and 12%, it is responsible for infertility of 20-30% in men, 20-30% in women, and 25-40% in both sexes (3). Considering the importance of having a child in the majority of cultures, infertility, which is very common, is a significant health problem that affects the society and family socio-cultural structure and causes substantial economic loss for most societies.

When the etiological causes of male infertility are examined, it is 10.7% congenital urogenital anomalies, 5.9% obstruction of the seminal tract, 4.4% severe sexual dysfunction, 3.4% oncological diseases, 6.6% other testicular factors, 7.8%, known genetic factors, 1.3% of them are known as secondary hypogonadism. Today, the cause of 60% has not been revealed (4). Since many factors cause male infertility, patients should be examined in pairs, if possible, and evaluated with a detailed anamnesis in which all systems are questioned.

In the anamnesis, family history, consanguineous of the couples, history of unsuccessful pregnancy, and known chronic diseases should be carefully examined. If the condition is suspected to be inherited genetically, the inheritance pattern should be revealed, and the cause of the disease should be clarified by performing a complete systemic examination. Before the genetic examination, a spermiogram should be performed; psychological, structural, autoimmune, oncologic, and endocrinologic causes should be excluded, and necessary radiographic imaging, hormonal, and biochemical tests should be evaluated. While examining the patient's spermiogram, sperm count, motility, and morphology must be assessed and classified by WHO 2010 criteria (5, Table 1).

If oligospermia, asthenospermia, and teratozoospermia coexist, it is diagnosed as oligo-astheno-teratozoospermia (OAT). In terms of their etiology, 77.9% of mild oligospermia, 17.1% of azoospermia cases, and strikingly, approximately 0.1% of aspermia are idiopathic. The genetic cause of 25.8% of azoospermia cases can be revealed, while the genetic cause has been shown in only 1% of mild oligospermias (4). These results indicate that as the phenotype of the patients worsens, the causes of infertility are determined more clearly, and the weight of genetic causes increases compared to other reasons. It is essential to determine the cause of male infertility:

- Determining the cause of infertility in couples in the socio-cultural conditions in Turkey, arranging the treatment of patients for them and protecting them from unnecessary interventions, providing the proper treatment of the patient, and preventing unnecessary economic losses.
- A better understanding of the genes and mechanisms that cause infertility can prevent diseases and improve treatment possibilities.
- Evaluation and pre-detection of systemic diseases that may cause infertility and arranging the treatment and follow-up of the patients.
- Providing preimplantation genetic diagnosis (PGD) to infertile patients with monogenic and chromosomal causes and providing genetic counseling to the family regarding genetic diseases transmitted to the offspring.

As the sperm count decreases, the role of genetic etiology increases, and azoospermia is a disorder that causes the most severe infertility genetic causes are better known and are seen together as OAT syndrome in spermiogram. Azoospermia can be divided into obstructive azoospermia (OA) and non-obstructive azoospermia (NOA). OA develops due to obstruction in the ejaculation tract. Congenital bilateral absence of the vas deferens (CBAVD) or inflammation is the cause of other obstructive factors such as fibrosis. NOA is caused by sperm production and development disorders. NOA develops due to primary testicular failure, hypothalamus-pituitary-adrenal axis disorders (secondary testicular failure), and spermatogenesis defects (6). Chromosomal anomalies and causes that make sperm failure monogenic generally cause NOA, and mutations in *CFTR* and *ADGRG2* genes cause OA. If we look at azoospermia from a genetic point of view, the most common cause will be chromosomal anomalies, especially Klinefelter Syndrome. *AZFa*, *AZFb*, *AZFc* microdeletions of the Y chromosome, and *CFTR* mutations are the second and third most frequent reasons (7).

An important monogenetic group, including congenital hypogonadotropic hypogonadism (CHH) and disorders of sexual development (DSD), causes infertility accompanied by other system disorders. However, with the development of genetic techniques such as genome research and next-generation sequencing, the number of genes associated with spermatogenesis errors increases rapidly. Altogether, 104 genes associated with infertility and genitourinary development errors have been identified (8). The inheritance of these genes is quite complex and can be autosomal recessive (AR), autosomal dominant (AD), X-linked, and Y-linked, besides oligogenic and digenic inheritance patterns.

In this review, current developments and approaches in the genetic etiology of infertility will be explained. The causes will be examined under three main headings: quantitative disorders of spermatogenesis, qualitative disorders of spermatogenesis, and other reasons.

## QUANTITATIVE DISORDERS OF SPERMATOGENESIS

Quantitative defects of spermatogenesis due to primary testicular disorders are thought to have a range of clinical manifestations, from azoospermia (no spermatozoa in the ejaculate) to oligozoospermia (<39 million spermatozoa per ejaculate), as well as different histological implications. These histologic types of testicular tissue can

**Table 1.** Assessment of spermiogram analysis

| Variables | Normal | Pathologic |
|---|---|---|
| Volume (ml) | 1,5-6,8 | <1,5: Hypospermia<br>0: Aspermia |
| Concentration (million/ml) | 15-213 | <15: Oligospermia<br>0: Azoospermia |
| Vitality (%) | 58-91 | <58: Necrospermia |
| Total motility (%) | 40-78 | <40: Asthenospermia |
| Morphology (%) | 4-44 | <4: Teratospermia |

be present: Sertoli cell-only syndrome (SCOS), spermatogenic arrest at various stages of germ cell maturation (spermatogonia, spermatocyte, and spermatid), and hypospermatogenesis. Also, men with quantitative defects of sperm production have different follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels, testis volume, and degree of androgenization (9).

Other classifications of azoospermia are OA and NOA, and both of them have very different etiologies and treatments (10).

According to Lee et al. (11), the causes of azoospermia were divided into two major categories, chromosomal and extrachromosomal. In the category of chromosomal defects, there were chromosomal inversions, translocations, micro/macrodeletions of the Y chromosome, and numerical chromosomal anomalies, also known as aneuploidies non-chromosomal defects; there were epigenetic changes in the genome and included defects of the sperm mitochondrial genome. There are also several monogenic causes. Although the information on monogenic grounds of NOA is limited, established, and recently reported NOA genes associated with transcriptional and endocrine regulators of reproduction, guardians of meiosis have been notified (12).

Herein we represent several syndromes associated with quantitative disorders of spermatogenesis.

**Klinefelter Syndrome**

Klinefelter syndrome is the most common form of male hypogonadism, with a prevalence of 0.2% healthy male population (13). Klinefelter syndrome is detected in 14% of azoospermic men. However, there are classical findings of eunuchoid body structure, sparse beard growth, less body hair, gynecomastia, small testicles, and azoospermia. Slender stature with relatively long legs is typical for Klinefelter syndrome. Half of the patients have nondisjunction in first paternal meiosis (due to lack of normal Xp-Yp recombination in the pseudoautosomal region). During the oogenesis, it can occur either in meiosis-1, which is affected by maternal age, or meiosis-2. Ninety-five percent of patients with Klinefelter Syndrome have a 47,XXY karyotype; 5% of the cases are mosaic (such as 46,XY/47,XXY) (14). In addition, endocrinology consultation (for hormone replacement in case of indication) is necessary for patients with Klinefelter syndrome. Spermatogenesis may defect to varying degrees, but males are usually sterile. Sperm can be obtained by performing micro-testicular sperm extraction (micro-TESE) with successful surgical intervention in 69% of the patients. Some recent studies emphasize that cryopreservation of prepubertal spermatogonial stem cells may be beneficial in these patients (15).

**XX Male Syndrome**

XX male is a rare sex chromosomal disorder in infertile men and occurs in about 1 in 20,000 newborn males. Approximately 80% of 46,XX testicular DSD cases are SRY-positive as a result of translocation from the Y chromosome to the X chromosome (16). Most patients with SRY-positive 46,XX DSD, have a male phenotype with small testes and may have cryptorchidism or hypospadias, azoospermia resulting in primary infertility, and gynecomastia with normal cognitive development. Postpubertal testicular histology of SRY-positive XX men shows atrophy and hyalinization of the seminiferous tubules, but the testicles are also devoid of germ cells. In men with XX-male syndrome, patients with reduced testosterone production should receive appropriate replacement therapy. Currently, there is no therapy for infertility of men with XX-male syndrome. Patients with reduced testosterone production have to obtain appropriate testosterone replacement therapy (17).

**47,XYY Syndrome**

In a report covering the chromosome analyses performed between 1961 and 2014 in Denmark in 2020, the total prevalence of males diagnosed with 47,XYY syndrome was 9 per 100,000 males (239 47,XYY males among a population of 2.79 million males, 9% of expected) (18,19). Nevertheless, the maximum average prevalence was 18 47,XYY males per 100,000 newborn males (18% of predicted); these patients have non-disjunction of the Y chromosome in meiosis 2. Spermatogenesis can be affected in a variable range from normal to severe failure. Although no obvious physical anomaly is observed in their phenotypes, half of the cases have an intelligence score of 10-15 points below the average, and attention deficit and hyperactivity are remarkable. In addition, individuals with this genotype have more educational and behavioral problems than 46,XY individuals (14). However, a review of 50 years of literature published in 2015 also concludes that there is no appreciable evidence that patients with XYY syndrome have an antisocial or aggressive behavior disorder (20).

**Y Chromosome Deletions**

Genes responsible for testicular development and initiation and maintenance of spermatogenesis in adulthood are located on the human Y chromosome. (13). In the Y chromosome, which contains 60 million bases, very few of them are expressed as functional genes. Although there are 27 genes identified, 9 of them are located in the short arm (p) of the chromosome and 18 in the long arm (q) arm of the chromosome. Azoospermia factor (AZF), one of the most studied regions related to male infertility, is located in Yq and consists of three independent regions as *AZFa*, *AZFb*, and *AZFc* located in Yq. *AZFa*, *AZFb*, and *AZFc* residues are primarily expressed in testes and play an essential role in spermatogenesis. Deletions in *AZF* loci cause spermatogenesis defects (oligospermia, azoospermia, etc.) with the deletion of one or more candidate genes in these regions. Some of the candidate genes in the *AZF* regions are *USP9*, *DBY*, *DAZ*, and *RBMY*. After 20 years from the first molecular definition of the *AZF*, Yq deletion screening has now become a routine test for infertile males in many countries to identify the cause of male infertility. It is known that this test reveals a serious spermatogenesis defect and helps to determine the success rates of sperm retrieval in the use of assisted reproductive techniques and to predict the success of these technics (14).

**Other Chromosomal Abnormalities**

Common autosomal chromosomal changes are Robertsonian type translocations, reciprocal translocations, paracentric inversions, and marker chromosomes are ten times more often in patients with oligozoospermia (4-8%) than in patients with normozoospermia (9). These patients should be informed about PGD in those who have undergone in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI).

In addition, fluorescence in situ hybridization (FISH) studies and investigation of aneuploidy in semen in patients with normal/abnormal chromosomal results are important to decide whether PGD should be performed before ICSI. The isodicentric Y chromosome, which is considered another structural chromosomal anomaly, is one of the most common structural anomalies of the Y chromosome and may lead to a major OA clinic. Most of these anomalies disappear during cell proliferation, and cells with dicentric Y chromosomes are found in mosaic. The phenotypic findings of these patients are affected by the structure of the dicentric Y chromosome, the fracture site, and the degree of mosaicism, resulting in a reasonably wide range ranging from Turner syndrome-like women to infertile men (14). It has been reported that men with Down syndrome have impaired spermatogenesis and loss of function in Sertoli and Leydig cells. Although these individuals seem to have normal puberty that starts at an average age, the decrease in testicular volumes after puberty and an increase in gonadotropin production are indicators of gonadal dysfunction, which decreases with age. In addition, other studies have shown that the sperm count is abnormally low in men with Trisomy 21, suggesting that the resulting azoospermia or oligospermia may be related to damage to the spermatogenesis process (21).

**Other Single Gene Disorders**

Some of the genes that will be evaluated in this section lead to hormonal dysregulation and some of them cause spermatogenesis defects and cause male infertility. Kallmann syndrome is a disease with hypogonadotropic hypogonadism (HH) that can be evaluated in this group, and the genes responsible for some of the cases are; *KAL-1*, *FGFR-1*, *PROK-2*, *PROKR-2*, *CHD-7*, and *FGF-8* (1). Furthermore, many genes can cause non-syndromic male infertility, which can progress with ambiguous genitalia and cause sex chromosome phenotype mismatch, and a group of these genes is associated with hormone biosynthesis defects. In addition to these, LH receptor defects, Androgen receptor defects (*AR* gene), hemizygous mutation of the *SRY* gene, hemizygous "duplication" in the *NR0B1* (*DAX1*) gene, a homozygous mutation in the *DHH* gene, heterozygous mutations in the *MAP3K1* and *NR5A1* genes are among the causes of monogenic fertility. Although cystic fibrosis (CF) is a multisystem disease characterized by abnormal mucus production, it is one of the major causes of obstructive infertility in men. Ninety-eight percent of men diagnosed with CF are infertile. Insufficient development of seminal vesicles or congenital bilateral absence of the vas deferens (CBAVD), accounts for 1.2-1.7% of all male infertility can be seen in these patients. Testicular functions and spermatogenesis are expected to be intact in these patients and assisted reproductive techniques are used to approach infertility problems. In addition, the expected phenotype in infertile individuals differs depending on the types of variants detected in CF patients (6).

## QUALITATIVE SPERM DISEASES

Structural defects of sperm can be detected with a simple spermiogram and divided into subtypes. In general, it is thought that environmental, epigenetic, and genetic factors affect the morphology of sperm together. However, the effect of genetic causes is powerful in patients with OAT or with specific morphology. We will examine the qualitative sperm diseases under four subtitles globozoospermia, macrozoospermia, acephalic sperm syndrome (ASS), and multiple morphological abnormalities of the flagella (MMAF) (22).

**Globozoospermia**

Globozoosperm is briefly sperm with a round head without an acrosome. Since it does not have an acrosome, it cannot penetrate the zona pellucida and so causes infertility. If all of the sperm counts are globozoospermia, it is called type 1; if 20-90% of the sperm count is globozoospermia, it is called type 2 globozoospermia. Globozoospermia accounts for 0.1% of infertile men. The most common cause is intragenic deletions and point mutations of the *DPY19L2* gene, explaining 60-80% of the cases (9).

The *DPY19L2* gene stabilizes the acrosome, supporting the nuclear membrane of the acroplaxoma, elongation of the sperm head in the development of normal sperm morphology, and acrosome formation. In recent studies, point mutations in the *SPATA16* and *PICK1* genes have been detected in cases of unexplained globozoospermia. The *SPATA16* and *PICK1* genes are involved in vesicle transfer from the Golgi body to the acrosome and acrosome biogenesis (23). In addition, *ZPBP1*, *SPINK2*, and *CCDC62* are candidate genes involved in the pathogenesis of globozoospermia; mutations of their genes have been reported in some cases, sperm structures mimicking globozoospermia have been shown in mutant mouse studies, and they have been shown to play an essential role in acrosome biogenesis (24). The *GOPC* gene, which is associated with these genes, is one of the candidate genes that may have an effect on the etiology of infertility (25). In type 1 globozoospermia patients, artificial oocyte activation is provided by ICSI, and in type 2 globozoospermia, sperm with a solid structure is selected, and fertility is provided by ICSI (23).

**Macrozoospermia**

Macrozoospermia is defined as detecting nearly 100% sperm with macrocephalic multiflagella in semen analysis. The most common cause of macrozoospermia is the homozygous c.144delC variant in exon 3 of the *AURKC* gene (26). Although this variant explains 85% of the cases, the remaining etiology is elucidated as homozygous or compound heterozygous variants with nonsense mutations such as p.Y248* seen in exon 6 (27). The *AURKC* gene is necessary for accurate chromosomal segregation and cytokinesis, and its mutations result in tetraploid sperms as a result of errors during meiotic division. In patients with macrozoospermia, the *AURKC* mutation must be analyzed before performing assisted reproduction tests. ICSI is not recommended since all sperm will be polyploid if a mutation is detected. If the mutation is negative, sperm FISH should be performed to evaluate the euploid sperm ratio, and PGD is recommended in cases with a moderate aneuploid sperm ratio (26).

**Acephalic Sperm Syndrome**

Observation of a high rate of headless sperm in the spermiogram is called ASS, and it is a rare severe type of teratozoospermia. Headless flagellar structures and only the head structure of the sperm can be observed during the examinations. In addition, the presence of isolated flagella

or the presence of tailless head structures with flagella can give an idea about the origin of the pathology (28). Since Sertoli cells will phagocytize head structures in testicular pathologies, the rate of headless sperm is significantly increased in semen analysis, whereas in epididymal pathologies, almost the same number of flagella and head will be seen since flagella and head structure will separate later. Improper attachment of the implantation pit and basal layer, defective or incomplete connection structures due to the absence of pericentriolar granular material, migration of flagella to the caudal end, and defective regulation of flagella formation play a role in the pathogenesis of acephalic sperm (29,30). ASS was first described in 1981 (31), and the factors in its genetic etiology could not be clarified until 2016. In 2016, the AR inheritance pattern was determined by familial segregation analyses in men with more than 50% acephalic sperm in semen analysis, and then 16 pathogenic variants were detected in the *SUN5* gene by whole-exome sequencing. The *SUN5* protein is an essential protein that provides the head and tail connection of the sperm. Homozygous or fused heterozygous frameshift, missense, nonsense mutations, and deletions of sequences encoding the transmembrane, SUN, and conserved coil-coil region of this protein have been shown to cause infertility. Today, *BRDT*, *PMFBP1*, *TSGA10*, *DNAH6*, *HOOK1*, *CEP112*, and *ACTRT1* (32) genes have also been associated with ASS. Biallelic mutations that lose function in these genes cause infertility through the mechanisms mentioned in the pathogenesis of ASS. Successful pregnancy and healthy delivery have been achieved in patients with mutations in the *SUN5*, *PMFBP1*, *TSGA10*, *HOOK1*, and *CEP112* genes with ICSIs performed by selecting sperm without flagella (33).

**Multiple Morphological Abnormalities of the Flagella**

In human sperm, the flagellum is the organelle that provides the necessary motility to successfully reach the oocyte and fertilize in the female genital tract. It is generally examined in three parts: the midpiece consisting of flagella, mitochondrial sheath, and outer dense fiber, the principal piece covered with fibrous sheath, and the terminal piece containing only axonemes. The most important structure of the flagella is the microtubular complex, which is organized in the form of 9+2, and this structure provides the main movement of the sperm. The microtubular complex consists of a pair of central microtubular nuclei and nine pairs of type A and type B microtubules around it, and these pairs slide over each other with the help of arms made of dynein protein. In addition, peripheral pairs are held together by nexin-dynein complexes, while peripheral microtubules are connected to the central nucleus by proteins called radial rays. Dynein is a multiprotein ATPase complex divided into the inner dynein arm (IDA) and the outer dynein arm (ODA) (34,35). Any mutation affecting these structures can result in faulty head-tail or midpiece, principal piece connectivity, abnormal mitochondrial sheath structure, excessive folding of the flagellar structure, and residual cytoplasmic residues. As a result of mutations, tailless, short-tailed, and bizarre morphology sperms can be detected in the spermiogram; these disorders are called MMAF. The genetic etiology of MMAF was not clarified until 2014, and currently, 18 genes account for the cause of 30-60% of patients (35). In the study in which the first genetic etiology was revealed, the homozygous p.G3930Afs* variant and three different homozygous variants were detected in the *DNAH1* gene in 4 patients with strong consanguinity in 20 patients in North Africa, and these mutations were shown to cause MMAF in mice (36). In subsequent studies, mutations of *DNAH1*, *DNAH2*, *DNAH6*, and *DNAH17* genes that impair the function of IDA and ODA, mutations of *CFAP43*, *CFAP44*, and *CFAP65* genes that affect the IDA-related T/TH complex, mutations of the *CFAP70* gene that cause errors in the role of the ODA-related *CFAP70* complex in intraflagellar transport, mutations of the *WDR66* gene that cause defects in peripheral and central microtubule transduction of the radial beam complex, mutations of the *FSIP2* gene that disrupt the organization of periaxonemal structures; Mutations of the *CEP135* gene, which causes defects in the biogenesis of the centrosome and centrioles, mutations of the *TTC21A*, *TTC29* and *CFAP69* genes that cause intraflagellar transport errors, and mutations of the *QRICH2* gene, which is located in the ubiquitin-proteasome pathway and causes protein degradation, have been shown to be clinically associated with MMAF. In addition, it should be kept in mind that *AK7* and *ARMC2* genes, whose functions are not clearly known but shown by whole-exome sequencing in segregation studies, may also play a role in the pathogenesis of MMAF (37). It has been demonstrated that frameshift, missense, and nonsense mutations and deletions of 18 genes causing loss of biallelic function lead to clinical trials. In the literature, it has been shown that successful pregnancy is achieved by the ICSI method in couples with *DNAH2*, *DNAH6*, *DNAH17*, *CFAP43*, *CFAP44*, *CFAP65*, *CFAP70*, *CEP135*, *TTC29*, and *SPEF2* mutations. Successful pregnancy could not be achieved in patients with mutations in the *DNAH17* gene, and in patients with *CFAP65* mutation, although successful pregnancy was achieved, all of them resulted in abortion (35).

## OTHER CAUSES OF INFERTILITY

Hypothalamo-pituitary-gonadal axis dysfunction is one of the important causes of male infertility. Developmental anomalies in this axis are called hypogonadism and are basically classified as hypergonadotropic (primary) and hypogonadotropic (secondary). Since the primary problem of hypergonadotropic hypogonadism is in the gonads, it progresses with high LH, FSH, and low testosterone levels. Its etiology includes infection, radiotherapy, cryptorchidism, autoimmune, liver and kidney diseases, trauma, and genetic causes. The most common genetic cause of hypergonadotropic hypogonadism is Klinefelter syndrome in men.

HH, on the other hand, is associated with the low synthesis of gonadotropes and low testosterone levels because of developmental and synthesis deficiency at the hypothalamo-pituitary level. HH is a rare cause of infertility and appears below 1% (38). If we do not consider invasive, infiltrative, ischemic, and traumatic causes, 50% of CHH is idiopathic. CHH may occur with pubertal tarda, absence of body hair, gynecomastia, cryptorchidism, and small testicular volume (39). In the early embryonic development stages, the gonadotrophin releasing hormone (GnRH) neurons migrate from the inner

part of the nasal epithelium to the forebrain, and in the following period, they move to their final location in the hypothalamus. Olfactory neurons also develop from the nasal plate close to the neurons that secrete GnRH, and as they migrate via similar pathways, anosmia or hyposmia is also observed in some of the CHH cases (38). CHH is divided into two major categories: Kallmann syndrome and normosmic hypogonadotropic hypogonadism (nHH). CHH may also be observed in association with Gordon Holmes, CHARGE, Waardenburg, Bardet-Biedl, and Prader Willi syndromes, such as Xp21 and Xp22.3 deletion. There have been identified more than 25 different genes related to Kallmann syndrome, 35 genes about CHH in the literature, and according to some of the studies, more than 60 genes of CHH. CHH shows AD, AR, X linked recessive (XLR), and oligogenic inheritance patterns. The genes involved in HH-related pathways were roughly classified as follows and then listed in Table 2 (9,38-43):

i. Genes associated with GnRH neuronal embryonic differentiation and migration: *CHD7*, *FGF8*, *FGFR1a*, *HESX1*, *WD11*, *SOX10*, *ANOS1* (*KAL*), *FGF17*, *IL17RD*, *DUSP6*, *SPRY4*, *FLRT3*, *KLB*, *PROK2*, *PROKR2*, *HS6ST1*, *SEMA3A*, *SEMA3AE*, *DCC*, *AMH*, *AMHR*, *IGSF10*, *SMC*, *NDNF*, and *FEZF1* genes. CHARGE, Kallmann syndrome with anosmia, combined pituitary hormone deficiency, and Waardenburg syndrome are in this group.
ii. Genes associated with GnRH neuron regulation: *DMXL2* (polyendocrinopathy polyneuropathy syndrome), *TAC3*, *TACR3*, *KISS1*, *KISS1R*, *GNRH1* genes (GnRH neuron pulsatile release), *GNRH1*, *GNRHR*, *FSHB*, *LHB* genes (pituitary gonadotropin secretion).
iii. Genes associated with HH and obesity-*LEP*, *LEPR* genes.
iv. X-linked adrenal hypoplasia and CHH-*NROB1* (*DAX1*) genes.
v. Genes related to gonadotropin secretion and activation-*PCSK1*, *LHB*, *FSHB*, *LHR*, and *FSHR* genes.
vi. HH associated genes with cerebellar ataxia-*POLR3A*, *POL3RB*, *OTUD4*, *RNF216*, *PNPLA6*, and *STUB1* genes.

***Kallman syndrome*** is a rare (1/30000) clinical entity and shows wide phenotypic and genotypic variability. The disease presents with CHH findings and hyposmia/anosmia. In addition to these major findings, renal developmental disorders, finger anomalies (polydactyly, syndactyly, camptodactyly), cleft or lip palate, abnormal eye movements, synkinesis, dental agenesis can also be seen. More than 20 genes have been identified in the etiology of this disease. *ANOS1* (*KAL1*), *FGFR1*, *FGF8*, *FGF17*, *IL17RD*, *DUSP6*, *SPRY4*, *FLRT3*, *KLB*, *PROK2*, *PROKR2*, *HS6ST1*, *CHD7*, *WDR11*, *SEMA3A*, *SEMA3E*, *IGSF10*, *SMCHD1*, *CCDC141*, *FEZF1* are the most common genes. These genes are related to neuronal migration pathways. The *ANOS1* (*KAL1*) gene is localized in Xp22.3 and encodes a protein called anosmin-1. This gene is attached to the cell membrane with heparan sulfate and is responsible for GnRH neuron adhesion and axonal migration (44). Anosmin is colocalized with the *FGFR1* gene. The *ANOS1* gene strengthens the FGF signal by interacting with the FGFR-FGF-HEPARAN sulfate proteoglycan complex on the cell surface, and this also provides GnRH neuronal migration. These genes, which are involved in different molecular pathways, ultimately affect the GnRH neuronal migration and cause anosmia/hyposmia and CHH clinic (39,44).

***CHARGE syndrome*** is a rare genetic syndrome that affects many parts of the body (1-8500/10000). The features of this syndrome are coloboma, heart defects, atresia choanae, genital, growth, and ear abnormalities. These patients may also present with HH findings, lip, cleft palate, and rarely tracheoesophageal fistula. Rarely do patients have scoliosis kyphosis, poly-oligodactyly. The *CHD7* gene is the genetic cause of this syndrome, responsible for chromatin remodeling. Point mutations, deletions, and rarely translocations are the main reasons for the patient's symptoms in different systems. Unlike anosmic HH, this syndrome is not accompanied by a loss of smell (45).

***Waardenburg syndrome*** is a rare genetic disease that is the most common syndromic cause of hearing loss and progresses with loss of pigmentation in the hair, skin, and eyes (1/40000). The eyes have iris heterochromia and hypopigmentation. *EDN3*, *EDNRB*, *MITF*, *PAX3*, *SNAI2*, and *SOX10* genes play a role in its etiology. *SOX10* genes are essential for infertility. *SOX10* is the gene transcription factor responsible for neuronal migration during early embryonic developmental stages. Rarely, *SOX10* mutations can also cause anosmic HH (46).

***Gordon Holmes syndrome*** is a rare syndrome characterized by neurological symptoms and HH (prevalence is unknown). Patients present with delayed puberty findings, cerebellar findings such as dysarthria, and balance problems. *RNF216*, *OTUD4*, *PNPLA6*, and *STUB1* gene mutations are involved in the etiology of the disease (47).

## GENETIC COUNSELING IN MALE INFERTILITY

Genetic counseling; for the individual who comes to receive counseling to understand the effect of genetics on diseases, it is an interactive process that helps students understand and adapt to the medical, psychological, and familial impact of the current medical condition. In this process, the individuals' personal medical history and family histories should be examined by removing their detailed pedigrees. Individuals should be told about the possible causes of their current situation, the tests that can be done to determine these causes, and what kind of a period awaits them on the way to diagnosis. While informing about the current situation or results of the patient, the results and options should be presented with full transparency, and the individual should be allowed to make their own choices. A genetic counseling process should proceed in confidence and should never be directive. In addition to all these, recent developments in assisted reproductive technologies and their widespread use have been useful for couples with infertility. Using IVF and ICSI technologies, men with infertility can have their biological children. Clinicians following the patient should be aware of this, and necessary guidance

**Table 2.** Genes, function, and clinical phenotypes related to hypogonadism

| Genes | OMIM | Inheritance | Clinical Phenotype | Gene Function |
|---|---|---|---|---|
| *ANOS1(KAL)* | 300836 | XLR | HH 1 with or without anosmia | Growth and migration of GnRH neurons |
| *FGF8* | 600483 | AD | HH 6 with or without anosmia | Formation and migration of GnRH neurons |
| *FGFR1* | 136350 | AD | HH 2 with or without anosmia | Formation and migration of GnRH neurons |
| *HESX1* | 60182 | AD, AR | GH deficiency, pituitary dysplasia | Interacting other genes, product TF, development of the forebrain |
| *SOX10* | 602229 | AD | Waardenburg syndrome type 2E, 4C | Cell migrations from the spinal cord to specific regions |
| *CHD7* | 608892 | AD | CHARGE, HH 5 with or without anosmia | Regulating of chromatin remodeling and GnRH neuron specification |
| *WDR11* | 606417 | AD | HH 14 with or without anosmia | GnRH neuron specification and regulating GnRH production |
| *FGF17* | 603725 | AD | HH 14 with or without anosmia | GnRH neuron and gonadotroph differentiation and fate specifications |
| *IL17RD* | 606807 | AD, AR, DD | HH 18 with or without anosmia | GnRH neuron and gonadotroph differentiation and fate specifications |
| *SEMA3AE* | 608166 | AD | CHARGE syndrome | Development of the olfactory system and the migration of GnRH neurons |
| *SEMA3A* | 603961 | AD | HH 16 with or without anosmia | Development of the olfactory system and the migration of GnRH neurons |
| *PROK2* | 607002 | AD | HH 4 with or without anosmia | Migration and development of both GnRH and olfactory neurons |
| *PROKR2* | 607123 | AD | HH 3 with or without anosmia | Migration and development of both GnRH and olfactory neurons |
| *FLRT3* | 604808 | AD | HH 21 with or without anosmia | GnRH neuron and gonadotroph differentiation and fate specifications |
| *DUSP6* | 602748 | AD | HH 19 with or without anosmia | GnRH neuron and gonadotroph differentiation and fate specifications |
| *SPRY4* | 607984 | AD | HH 17 with or without anosmia | GnRH neuron and gonadotroph differentiation and fate specifications |
| *HS6ST1* | 604846 | AD | HH 15 with or without anosmia | Guiding cell communications during neural development and |
| *NDNF* | 616506 | AD | HH 25 with or without anosmia | GnRH neuron migration and development of the olfactory scaffold |
| *FEZF1* | 616030 | AR | HH 22 with or without anosmia | Transcription repressor and guidance GnRH neurons and olfactory axons |
| *DMXL2* | 616113 | AR | PNEPS with HH | Regulation exocytosis vesicles of GnRH neurons and gonadotrophs |
| *TAC3* | 162330 | AR | HH 10 with or without anosmia | Expressed in the hypothalamus, GnRH neuron activation, and networking |
| *TACR3* | 162332 | AR | HH 11 with or without anosmia | Expressed in the hypothalamus, GnRH neuron activation, and networking |
| *KISS1* | 603286 | AR | HH 13 with or without anosmia | Regulation of GnRH neuron activation and hormone secretion |
| *KISS1R* | 604161 | AR | HH 8 with or without anosmia | Regulation of GnRH neuron activation and hormone secretion |
| *GNRH1* | 152760 | AR | HH 12 with or without anosmia | Direct secretion and action of GnRH |
| *GNRHR* | 138850 | AR | HH 7 with or without anosmia | Direct secretion and action of GnRH |
| *LEP* | 164160 | AR | Obesity with HH | Afferent to GnRH neurons |
| *LEPR* | 614963 | AR | Obesity with HH | Afferent to GnRH neurons |
| *NR0B1(DAX1)* | 300473 | XLR | Adrenal hypoplasia with HH | GnRH neuron and gonadotroph differentiation and fate specifications |
| *PCSK1* | 162150 | AR | Obesity with HH | Gonadotropin secretion and action |
| *LHB* | 152780 | AR | HH 23 with or without anosmia | Gonadotropin secretion and action |
| *FSHB* | 136530 | AR | HH 24 with or without anosmia | Gonadotropin secretion and action |
| *LHCGR* | 152790 | AR | Leydig cell hypoplasia with HHG | The receptor of luteinizing hormone and chorionic gonadotropin |
| *POLR3A* | 614258 | AR | 4H syndrome 7 with HH | Encoding RNA polymerase catalytic subunits |
| *POLR3B* | 614366 | AR | 4H syndrome 8 with HH | Encoding RNA polymerase catalytic subunits |
| *OTUD4* | 611744 | AR | Gordon Holmes and HH | Playing a role in the ubiquitin-proteasome system |
| *RNF216* | 609948 | AR | Gordon Holmes and HH | Playing a role in the ubiquitin-proteasome system |
| *PNPLA6* | 603197 | AR | Boucher-Neuhauser, Gordon Holmes | Coding NTE protein, contributes to membrane stabilization, and release of hormones from PG |
| *STUB1* | 607207 | AR | Spinocerebellar ataxia 16 with HH in some families | Playing a role in the ubiquitin-proteasome system |

XLR: X linked recessive, AD: autosomal dominant, AR: autosomal recessive, DD: developmental delay, HH: hypogonadotropic hypogonadism, GH: growth hormone, CHARGE: coloboma, heart defects, atresia of choanae, retardation of growth or development, genital or urinary defects, PNEPS: polyendocrinopathy polyneuropathy syndrome, HHG: hypergonadotropic hypogonadism, GnRH: Gonadotropin releasing hormone, TF: transcription factors, NTE: neuropathy target esterase, PG: pituitary gland

and planning should be provided for patients within appropriate indications. If we go into detail about some of the causes of male infertility that we have explained above;

i. Men with Klinefelter syndrome (including mosaic (47,XXY/46,XY) individuals) have hypogonadism, which affects the patient's spermatogenesis process and testosterone production. This situation causes individuals to encounter masculinization deficiency and azoospermia in their spermiograms. When the sperm samples obtained from individuals with Klinefelter syndrome are examined, the picture we usually encounter is haploid sperm morphology. Still, the use of PGD and FISH methods increases the chances of these individuals obtaining a healthy embryo in Klinefelter syndrome. In addition, the literature has reported that natural pregnancy can be achieved in these individuals, and most of the known cases consist of mosaic cases (47,XXY/46,XY) or non-mosaic (47,XXY) cases with younger age. In addition, micro-TESE, one of the assisted reproductive techniques used in these patients, offers more successful results in obtaining sperm than the conventional TESE method.

ii. Mutations in the *CFTR* gene cause congenital bilateral absence/dysfunction as mentioned above and are detected in 1-2% of infertile men. The majority of the mutations of this gene are point mutations, but there are rare cases where deletion and duplication are detected. In the light of this information, necessary studies should be planned by using appropriate molecular tests in individuals with clinical symptoms suggesting a mutation in the *CFTR* gene. In addition, the carrier status of the partner for *CFTR* mutations should be checked. Possible scenarios and options should be explained with the results, and if necessary, the couple should be directed to the relevant centers for PGD.

iii. Autosomal chromosomal abnormalities such as translocations can be detected, especially in cases with oligoasthenoteratozoospermia, and since this may cause unbalanced translocations in the fetus, it is recommended to use PGD in addition to the use of assisted reproductive techniques in these individuals. If there is an imbalance between non-homologous chromosomes in Robertson translocation, one of the translocation types, this can lead to monosomy and trisomies. If this imbalance is between homologous chromosomes, it is not expected that the pregnancy will continue healthy.

iv. The genetic etiology of the patient with infertility problems due to Y microdeletion and monogenic causes should be determined well. According to the mutation detected, joint councils with endocrinology and urology departments should be formed, and the treatment process of the patient should be carried out correctly. For example, it is possible to achieve fertility in a male patient with Kallman's syndrome with appropriate hormone replacement therapy at the right time and using assisted reproductive techniques. However, having a child with assisted reproductive techniques alone is insufficient for the family's treatment. The sons of patients with Y microdeletion may have the same deletion as their fathers and may encounter the same problem, or the child may inherit monogenic mutations and experience infertility or issues affecting other systems in isolation. Therefore, proper genetic counseling should be given to the family before pregnancy, and PGD options should be mentioned.

## CONCLUSION

When all these data and research are evaluated, infertility is one of the main issues negatively affecting public health. Although technology is developing extremely fast on the way to genetic diagnosis, there are still many undiagnosed infertility cases. In the approach to the infertility problem, after a detailed and careful clinical evaluation, appropriate genetic tests should be planned by choosing the proper methods, and appropriate genetic counseling should be given to the couples to achieve a healthy pregnancy in line with the test results.

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