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Mendelian genetics of male infertility

Kathleen Hwang[1], **Alexander N. Yatsenko**[2,3], **Carolina J. Jorgez**[1], **Sarmistha Mukherjee**[1], **Roopa Lata Nalam**[2], **Martin M. Matzuk**[2,3,4], and **Dolores J. Lamb**[1,4]

[1]Scott Department of Urology, Baylor College of Medicine, Houston, Texas

[2]Department of Pathology, Baylor College of Medicine, Houston, Texas

[3]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas

[4]Department of Molecular and Cell Biology, Baylor College of Medicine, Houston, Texas

Abstract

Infertility is defined as the inability of a couple to conceive despite trying for a year, and it affects approximately 15% of the reproductive-age population. It is considered a genetically lethal factor, as the family lineage stops at that individual with no progeny produced. A genetic defect associated with an infertile individual cannot be transmitted to the offspring, ensuring the maintenance of reproductive fitness of the species. However, with the advent of assisted reproductive techniques (ART), we are now able to overcome sterility and bypass nature's protective mechanisms that developed through evolution to prevent fertilization by defective or deficient sperm.

Keywords

mendelian genetics; male infertility; asthenozoospermia; oligospermia

Introduction

The causes of male factor infertility are multifactorial, with estimates reaching 50% due to, or contributed by, genetic abnormalities (Table 1, Refs. 2–11).[1] Although the majority of the genetic causes of male infertility are still unknown, genetic defects, such as cystic fibrosis, have important implications for offspring conceived through intracytoplasmic sperm injection (ICSI). However, in the absence of a comprehensive clinical evaluation, many of these genetic etiologies may go undiagnosed.

The foundation of diagnosis for males is the routine semen analysis (SA), where sperm concentration, motility, morphology, and the presence of other cells are evaluated. Indicators of patency and function of the male genital tract are assessed including semen volume, liquefaction time, pH, and the presence or absence of fructose. While the routine SA evaluates the ejaculate for abnormalities in the sperm number, morphology, and motility, it only provides clues and suggestions to indicate the need to pursue further testing. Current genetic testing performed for male infertility includes karyotype, *CFTR* gene analysis, PCR

Address for correspondence: Dolores J Lamb, Baylor College of Medicine, One Baylor Plaza, N730, Houston, TX 77030. dlamb@bcm.edu.

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testing for Y-chromosome microdeletions, and sperm FISH analysis for specific chromosome aberrations.

The primary goals of the evaluation of the male presenting with infertility are to identify etiological conditions that can be reversed with resulting improvement of fertility status, medically significant and potentially dangerous diagnoses underlying the male's infertility, genetic etiologies that may have implications for the patient and/or his offspring; and irreversible conditions that may be best managed with the use of assisted reproductive techniques (ART) or the recommendation of donor insemination or adoption. The genetic basis of male infertility, although relatively poorly understood, may ultimately represent one of the most clinically important aspects of male infertility (Table 2, Ref. 12). However, with the advent of IVF/ICSI, while these hurdles of infertility can be overcome, the underlying causes of infertility–defective genes–have the potential to be transmitted to offspring.

When faced with the evaluation of a man with azoospermia, the focus should be placed on deciphering between whether the azoospermia is a result of abnormal spermatogenesis or obstruction (Fig. 1).

In Mendelian recessive inheritance, each parent contributes one of two mutant alleles for a disease trait. However, if a mutant allele has a dominant effect, it requires inheritance of only one parental allele. If the genotypes of both parents in a genetic cross are known, Mendel's principles of segregation and independent assortment can be used to determine the distribution of phenotypes expected for the population of offspring.

Endocrinopathies and male infertility

There are relatively few diagnosed genetic causes of male infertility. Diagnoses are largely descriptive and reflect the lack of understanding of the factors that regulate sperm production, maturation, and function. Endocrine factors are one of the components that are relatively well-established and have become an essential component of the male evaluation, with either an abnormal physical examination suggestive of a disorder in testosterone production and action, an abnormal semen examination, or evidence of impaired sexual dysfunction (Table 3). However, true endocrinologic causes of male infertility are relatively uncommon, being present in less than 3% of cases[13] (Table 4).

The hypothalamic–pituitary–adrenal (HPA) axis, and the hormonal reproductive system, that is, the hypothalamic–pituitary–gonadal (HPG) axis, are intimately interlinked. The HPG axis is an important mediator of infertility. Stress can inhibit the HPG axis and negatively impact fertility. Abnormal development of the HPG axis can result in acquired hypogonadotropic hypogonadism (IHH) and Kallman syndrome (KS). Finally, spontaneously occurring mutations in the genes involved in the HPG axis, can also contribute to infertility.[14,15]

Kallmann syndrome (MIM308700) is a rare condition characterized by isolated hypogonadotropic hypogonadism (HH) and anosmia due to agenesis of the olfactory bulb; it occurs in approximately 1 in 10,000–60,000 live births.[16] A subset of Kallmann syndrome, inherited in an X-linked fashion, is caused by a mutation of the *KAL1* gene, which produces a cell adhesion molecule.[17–19] Autosomal dominant inheritance is caused by mutations in *FGFR1*, *FGFR8*, *PROKR2*, and *PROK2* genes.[20–22] In about 75–80% of KS patients, the causative gene is unknown.

Androgen insensitivity syndrome (AIS, MIM300068) is an X-linked disorder caused by mutations in the androgen receptor (*AR*) gene (MIM313700), resulting in end-organ resistance to androgens. More than 800 different *AR* gene mutations, resulting in AIS have been reported. However, the mutation–receptor structure–function relationship is not yet

fully understood. Thus, the phenotypes resulting from these mutations are not always predictable. The vast majority of androgen receptor mutations are single base substitutions, while deletions or insertions are rare. Most of these mutations are located in a few "hot spots" in the ligand-binding domain of the AR protein. About two thirds of these androgen receptor mutations are inherited in an X-linked fashion. The remainders of these mutations are either germ line or somatic *de novo* mutations. Somatic mutations can result in somatic mosaicism, where both mutant and wild-type receptors are expressed in different proportions.[23]

AIS is a disorder affecting sexual differentiation in variable severity, ranging from phenotypic females (complete AIS, CAIS) to defective spermatogenesis in otherwise normal males (partial AIS, PAIS, or minimal AIS, MAIS) depending on the type and localization of these mutations.[24,25] Haploinsufficiency of the *AR* gene due to complete or partial gene deletions or nonsense and frameshift mutations usually lead to complete AIS. Splicing mutations or missense mutations, on the other hand, can result in diverse phenotypes that are impossible to predict. Alternative factors that can influence the phenotype include defects in the protein coactivators and corepressors, somatic mosaicism, and the length of polyglutamine (PolyGln) repeats in exon 1. There are at least 864 mutations known, of which 724 associated with AIS have been reported in the *AR* mutation database (www.mcgill.ca/androgendb). Until now, only 91 mutations have been reported in exon 1 of the *AR* gene in patients suffering from any form of AIS, despite the fact that it encodes for more than half of the AR protein. Interestingly, many patients presenting with clinical features of AIS do not have documented mutations in the *AR* gene and may have alternative defects in androgen signaling pathway. For example, defects in coregulators such as transcriptional intermediary factor 2 (*TIF2*)[26–28] and AR coactivators[29] are also implicated in the pathogenesis of AIS. Reduced AR transcription was also found in patients with AIS.[30] Several mutations have been identified in the *AR* gene linked to endocrine dysfunction. Most of these mutations are due to loss-of-function of AR activity.

Systemic genetic disorders/syndromes

The expansion of the CAG trinucleotide repeats encoding the polyglutamine (PolyGln) tract, including the amino terminal transactivation domain of the AR protein, is involved in various neurodegenerative disorders. Spinal and bulbar muscular atrophy (SBMA, MIM313200) or Kennedy's disease (Kennedy-Alter-Sung disease) is a rare inherited X-linked neurodegenerative disorder of motor neurons.[31,32] SBMA usually affects males in the third decade. It is characterized by muscle cramps, fasciculations followed by weakness, and atrophy of the proximal limb and bulbar muscles.[33–35] The severity of the disease correlates with the increased number of CAG repeats of the *AR* gene. Expansion over 38–62 repeats leads to degeneration of facial, hypoglossal, and spinal motor neurons with neurogenic wasting of the corresponding skeletal muscle. Clinically, patients with SBMA present with progressive AIS, severe oligozoospermia, infertility, testicular atrophy, and gynecomastia.[32,36,37]

SBMA is a member of a new class of trinucleotide repeat disorders (or PolyGln-related) and inherited neurodegenerative diseases[38,39] that include Huntington's disease (HD), several spinocerebellar ataxias (SCAs),[40] and dentatorubral-pallidoluysian atrophy (DRPLA).[41,42] These conditions are caused by gain-of-function mutations leading to accumulation of abnormal proteins with the PolyGln tract that produce neurotoxic effects and cause cell death of motor neurons,[38] mostly in the anterior horns of the spinal cord and in the bulbar region of the brain stem.

Frequently, A[43] and myotonic dystrophy (DM) (MIM160900) are associated with idiopathic azoospermia.[44] DM is caused by a CTG trinucleotide repeat expansion in the 3′-untranslated region of the DM protein kinase gene (*DMPK*, MIM605377, 19q13.3). However, the results are controversial since one report found more than 18 repeats at the DM locus in azoospermia patients, and not in controls,[45] while others have failed to find any differences.[44] A less frequent cause of DM is an expansion of the CCTG repeat in intron 1 of zinc finger protein 9 (*ZNF9*, MIM116955, 3q13.3).[46]

Rare instances of isolated HH can also result from rare dominant or recessive mutations in *GNRHR*, *KISS1R*, *NROB1*, *LEPR*, *TAC3*, and *TACR3* affecting the various components of the HPG axis.[15] The effect of inactivating mutations of *GNRHR* has been associated with impaired LH/FSH secretion, HH, and delayed puberty in both males and females. Male patients present with microphallus and undescended testes in childhood. Inactivating mutations of LH receptors have also been described in both sexes. In men, the phenotype ranges from female genitalia to micropenis. Testicular biopsies show various degrees of Leydig cell hypoplasia with resultant oligozoospermia. Isolated selective LH hormone deficiency has been described in consanguineous families due to mutations in the luteinizing hormone β (LHB) gene, resulting in hypogonadism in both sexes.[47] Recently, a polymorphism in the promoter of the follicle stimulating hormone β (FSHB) gene, which is associated with hypogonadism has been identified in a young Estonian cohort.[48]

Prader-Willi syndrome (PWS) (MIM176270) is a complex genetic disorder caused by deficiency of one or more paternally expressed imprinted transcripts within chromosome 15q11-q13, affecting 1:25,000 live births. Thus, PWS is not usually inherited in a Mendelian fashion. PWS is characterized by hypothalamic dysfunction resulting in hypogonadism associated with delayed puberty, obesity, hypotonia, developmental delay, behavioral abnormalities, short stature, and genital abnormalities that include cryptorchidism, scrotal hypoplasia, and microphallus.[49,50] PWS is a phenotypically variable disorder with regards to sexual maturation. Pubertal variability is common in most of the individuals who are unable to complete puberty, likely due to degeneration of GnRH secreting neurons.[50,51] Fertility has not been documented in any male PWS patients to date. PWS infertility could be a result of multiple factors, including low pituitary-testicular axis hormones including FSH, LH, estradiol, testosterone, and inhibin B.[52,53] PWS patients have low sexual libido with testicular histology varying from normal to Sertoli cell only.[54]

Chromosome abnormalities

Klinefelter's syndrome is the most common cause of hypogonadism and infertility in males (1 in 500). The classic Klinefelter's syndrome is associated with a 47, XXY karyotype due to maternal or paternal meiotic nondisjunction. Maternal nondisjunction is associated with advanced maternal age.[55] A variety of mosaic patterns constitute nearly 15% of the cases, most common being 46,XY/47,XXY and the remainder of cases are due to polysomy of X chromosome (48, XXXY or 49,XXXXY). Rare cases of Klinefelter syndrome are caused by isochromosome Xq i (Xq), or X-Y translocations in 0.3–0.9% of males with X chromosome polysomies.[56,57] Clinically, patients with this syndrome present with azoospermia or severe oligozoospermia, gynecomastia in late puberty, atrophy and hyalinization of the seminiferous tubules, and elevated urinary gonadotropin levels.

CFTR and reproductive tract obstruction

Cystic fibrosis transmembrane conductance regulator (*CFTR*) gene-related disorders encompass a disease spectrum from focal male reproductive tract involvement in congenital bilateral absence of the vas deferens (CBAVD) to multiorgan involvement in classic cystic fibrosis. *CFTR*-related disorders are inherited in an autosomal recessive manner. Severe

dysfunction of the *CFTR* gene causes cystic fibrosis (CF), a life-threatening disease manifesting with progressive lung disease. CBAVD, resulting in primary obstructive azoospermia is a well-recognized cause of male infertility.

The *CFTR* gene (MIM602421) is located on the long arm of chromosome 7q31.2 and contains 27 coding exons that spread over 230 kb.[58] Its normal allele produces a 6.5-kb mRNA that encodes a 1480-amino acid integral membrane protein that functions as a regulated chloride channel in a variety of epithelial cells. The most common gene mutation is a 3-bp deletion, resulting in loss of a phenylalanine at amino acid position 508 of the CFTR polypeptide (ΔF508); this mutation accounts for about 30–80% of all mutant alleles depending on the ethnic group.[59] CBAVD commonly results from the combination of two mutant alleles, one allele with severe *CFTR* mutation and a second allele with either a mild *CFTR* mutation or the common splicing mutant allele 5T.[60]

Young's syndrome (MIM279000) is a condition characterized by respiratory infections, ranging from simple bronchitis to bronchiectasis, and obstructive azoospermia secondary to inspissated secretions, although spermatogenesis is unaffected. Due to the similarities, parallels to CBAVD secondary to mutations in the *CFTR* gene were noted; however, further investigations concluded that classical Young's syndrome was unlikely associated with defects in *CFTR*.[61,62]

Men without clinically apparent pulmonary manifestations of CF may have CBAVD. Hypoplasia or aplasia of the vas deferens and seminal vesicles may occur either bilaterally or unilaterally. CBAVD does not pose a health risk per se to the affected men, and testicular development, function, and spermatogenesis are usually normal. CBAVD is commonly identified during evaluation of infertility or as an incidental finding at the time of a surgical procedure, such as orchidopexy. However, the genetic fundamental basis of CBAVD has a significant impact on ART. For fathers with CBAVD, spermatogenesis may be normal, though it is imperative to determine whether the female partner is a carrier of the *CFTR* mutation as their offspring will be at increased risk of transmitting infertility to their male offspring or cystic fibrosis to both male and female offspring.

The treatment options include both microsurgical epididymal sperm aspiration (MESA) and testicular sperm extraction (TESE), or donor sperm in conjunction with ICSI to treat men with obstructive azoospermia (Fig. 1). Genetic counseling is standard in family planning for male factor couples with CBAVD.

Sperm motility defects

Asthenozoospermia (AZS) or reduced sperm motility is defined by the proportion of motile spermatozoa in semen (usually <40%). It is one of the four major semen defects found in at least half of infertile men. AZS is one of the phenotypes present in primary ciliary dyskinesia (PCD) (MIM242650), a predominantly autosomal recessive condition characterized by ciliary dysfunction and impaired mucociliary clearance that causes respiratory tract infections and infertility. The most severe form, Kartagener's syndrome (KS), presents in combination with *situs inversus* (MIM244400). The incidence of PCD is estimated at 1:16,000 births with KS accounting for 50% of the cases. A high percentage of PCD males are infertile, and the majority of cases of KS are due to immotility or dysmotility of the spermatozoa; however, the penetrance of the defect varies among individuals. PCD is caused by different structural abnormalities in dynein arms of axoneme, the internal structure of cilia and flagella responsible for their motility. The axonemal structure is highly conserved through evolution and consists of a complex made of a central pair of two microtubules and nine outer-doublet microtubules with attached inner and outer dynein arms (9 + 2 structure).[63] There are more than 250 genes involved in the structure, assembly, and

regulation of a cilium; however, only three genes have been associated with PCD: *DNAI1* (MIM603332; 9p21-p13), *DNAH5* (MIM603335; 5p15.2), and *DNAH11* (MIM603339; 7p21). Recent screening in 90 non-syndromic AZS patients and 200 controls revealed one mutation in each of the three dynein genes in seven patients, all inherited from their mothers.[64]

Sperm motility requires an increase in the concentration of intracellular calcium ions.[65] Several calcium channel genes residing in the sperm may be responsible for infertility. The *CATSPER* gene family (*CATSPER1–4*) is a unique cation channel expressed exclusively in sperm. *CATSPER2* (MIM607249) (expressed in the sperm and inner ear) together with *STRC, KIAA0377*, and *CKMT1B* are associated with deafness-infertility syndrome (DIS) (MIM61102) due to a homozygous contiguous gene deletion at 15q15.3. Four families have been identified with homozygous deletions in this area that cause deafness and sperm dysmotility.[66,67] *CATSPER1* (MIM606389; 11q12.1), a gene responsible for infertility in mice due to lack of sperm motility, has been mutated in infertile men of two consanguineous families.[68,69] Two separate insertion mutations that lead to frameshifts and a premature stop codon in *CATSPER1* were found in three infertile Iranian men, and absent in 576 Iranian controls.[68]

SPAG16 (MIM612173; 2q34), which encodes a protein from the axoneme central apparatus, is associated with ciliary dyskinesia and mouse infertility due to impaired sperm motility.[70] In humans, two fertile males heterozygous for the *SPAG16* mutation were reported with only one having sperm count and motility levels significantly below the normal range. *SPAG16* likely influences the stability of protein interactions in the sperm axoneme; however, it may be not significant enough to cause infertility.[71]

Another family of proteins important for axoneme stability and structure are the tektins, playing a fundamental role in ciliary movement. A screening of 90 nonsyndromic AZS patients for *TEKT2* (MIM608953; 1p35.3-p34.1) revealed a heterozygous mutation in one patient that was maternally inherited.[72] Dysplasia of the fibrous sheath (DFS) is a genetic sperm defect with hypertrophy and hyperplasia of random fibrous sheath associated with classical dynein arm deficiency in spermatozoa. Mutations in the cyclic-dependent protein kinases *AKAP3* (MIM604689; 12p13.3) and *AKAP4* (MIM300185; Xp11.2), the most abundant structural proteins of the sheath, were found in an AZS patient indicating the importance of motility of the sperm for fertility.[73] These are examples of Mendelian inheritance of nonsyndromic male infertility. Most of the mutations are heterozygous displayed by the variable penetrance.

Currently, there are numerous mouse models described that manifest asthenozoospermia (Table 5). These models provide growing evidence that a myriad of the gene products influence spermatozoal motility in mammals, and defects in many human genes could result in spermatozoal immotility. Moreover, recent proteomic studies estimate that several hundred genes encode structural proteins of the flagellum, the axoneme fibrous sheath, outer dense fibers, and enzymes of the glycolytic machinery in spermatozoa and could therefore be considered as additional gene candidates for AZS in human males.[74,75]

Sperm count and morphology defects

Oligozoospermia (OZS), or reduced sperm count, is one of the most common categories of semen defects and is found in nearly half of infertile men. According to the World Health Organization, OZS is defined as a sperm concentration with less than 20×10^6 sperm/mL.[125] However, several prominent studies indicate that the diagnosis of OZS must reflect the inherent intra- and inter-individual variability of sperm concentration, and therefore OZS should be divided into subcategories that are more specifically defined, that is, severe OZS

with concentration < 1×10^6 sperm/mL, moderate OZS with $1–10 \times 10^6$ sperm/mL, and mild OZS >10×10^6 to 20×10^6 sperm/mL.[126–128] Other major semen categories are absence of sperm (azoospermia) and morphology defects (teratozoospermia). Clinically, azoospermia overlaps with severe oligozoospermia. To date, only a limited number of genes are associated with low sperm count and male infertility.

One of the first successful studies reported is an association of nonsense mutations in *SYCP3* with azoospermia and severe OZS in infertile patients.[129] *SYCP3* encodes a DNA-binding protein and is an important structural component of the synaptonemal complex, which mediates the synapsis of homologous chromosomes pairing during meiosis in male germ cells. The *Sycp3* knockout mouse model exhibits meiosis arrest during spermatogenesis and resultant azoospermia and male infertility.[130] The patients selected for this analysis represented a highly selected group of men with a meiotic arrest phenotypically similar to that observed in the mouse model.

Likewise, mutations in two related genes, *CREM* and *FHL5* (formerly ACT, activator of CREM in testis), were shown to be responsible for azoospermia and OZS in men.[131,132] *CREM* encodes a testis-specific transcription factor, cAMP responsive element modulator protein, and a CREM recognition site was found in the promoters of many testis-specific genes. *Crem* knockout mice show round spermatid arrest leading to male infertility.[133,134] FHL5 protein contains a four-and-a-half LIM (FHL) domain that binds to CREM as a cofactor and modulates its activity. The *Flh5* knockout mouse model demonstrates severe OZS and abnormal cell morphology, resulting in subfertility.[135]

Similarly, investigation of *PRM1* gene mutations in infertile patients with severe OZS, abnormal morphology, and DNA damage revealed nonsense and missense alterations.[136–138] *PRM1* encodes protamine 1, which functions to compact, stabilize, and protect the DNA-protein complexes in the nucleus during spermatid development. The study was prompted by the *Prm1* haploinsufficiency effect in mice, which causes abnormal sperm compaction, DNA damage, OZS, and male infertility.[139] Recently, *NALP14* mutations were identified in patients with AS and severe OZS.[140] The study was initiated by delineation of gene-candidate disrupted by chromosome aberrations identified in patient with OZS.[141] The gene was mapped to the chromosome 11p15 region. *NALP14* displays testis-specific expression and encodes protein that plays important roles in apoptosis.

One noteworthy alternative approach for the OZS research is the RNA-based study of human kelch-like 10 (*KLHL10*) in infertile OZS patients.[142] It employs the presence of stable mRNAs in human ejaculate spermatozoa. Our investigations focused on the detection of missense and splicing *KLHL10* mutations in male germline mRNAs obtained from semen samples of OZS infertile men. We identified seven *KLHL10* missense and splicing mutations out of 550 (1.2%) OZS patients examined. A concurrent study of 400 normozoospermic controls did not reveal these described *KLHL10* mutations. Using reverse transcription-polymerase chain reaction (RT-PCR), we demonstrated that the splicing mutation caused a frameshift of the *KLHL10* open reading frame. Pathogenic effects of the identified *KLHL10* missense mutations were confirmed using a functional assay, an *in vitro* yeast 2-hybrid screen, which showed abnormal protein dimerization of mutant proteins. These findings were consistent with earlier mouse studies. KLHL10 is germ cell-specific protein involved in protein ubiquitination and is critical for maturation of mouse spermatozoa. Male mice heterozygous for a deletion in the *Klhl10* gene demonstrate a failure of spermatozoal maturation, resulting in severe oligozoospermia.[143,144]

Despite a low frequency of described gene defects in OZS, significance of mutations in *SYCP3*, *CREM1*, *FLH5*, *NALP14*, *PRM1*, and *KLHL10* were supported by statistical and/

or functional evidence. However, many other investigations report limited statistical or functional evidence to support the pathological roles of the gene mutations in oligozoospermia; these include *DDX25, PRM2*, *PRM3*, *TNP1*, *TNP2*, *UBE2B*, *USP26*, *FKBP6*, mitochondrial *ATPase8*, and *ATPase6*.[136,138,145–151]

Teratozoospermia (TZS) is a condition characterized by the presence of sperm with abnormal morphology that affects fertility in males. Despite its relatively high occurrence, the progress toward understanding TZS has been slow. To date, there are only a few dozen genes that exhibit abnormal spermatozoal morphology in mouse knockout models,[12] and even fewer genes show an association with TZS in infertile men.

One of the encouraging discoveries in the genetics of TZS and male infertility has been reported recently. Using a conventional identical-by-descent genetic approach, researchers reported that a testis-expressed gene, aurora kinase C (*AURKC*), is responsible for TZS in 10 patients with male infertility.[152] The study demonstrated that all male patients carried same founder mutation, homozygous single-nucleotide deletion in the *AURKC* gene. These patients presented with nearly 100% morphologically abnormal spermatozoa, including oversized irregular heads, abnormal midpiece and acrosome, up to six flagella, and large-headed multiflagellar polyploid spermatozoa. In addition, AURKC protein plays an important role in meiotic division during spermatogenesis in mice.[153]

In another report, investigation focused on globozoospermia, rare form of TZS with characteristic round-headed spermatozoa that lack an acrosome and showed that the gene *SPATA16* is responsible for globozoospermia in three related male infertile patients.[154] The study described three affected brothers from a consanguineous family, in which each brother is homozygous for mutation in the *SPATA16*. The gene is testis-specific and SPATA16 specifically located in cytoplasm and involved in acrosome formation.[155] However, a follow-up study of unrelated patients with complete or partial globozoospermia failed to identify *SPATA16* mutation, highlighting the common difficulty in identifying genetic mutations in such highly heterogeneous etiology as TZS.

Y chromosome microdeletion

The Y chromosome comprises 60 million base pairs with a short arm (Yp) and a long arm (Yq). The sex determining region (SRY) is located on Yp and is an essential member of the group of genes that ultimately determines the fate of the bipotential gonad.[156] The Y chromosome contains vital components needed for male differentiation and sperm function. The azoospermia factor region (AZF) on the long arm of the Y chromosome (Yq) is responsible for sperm development. The male-specific Y is the chromosomal material that bridges the two polar pseudoautosomal regions and is unique in the human genome. It comprises approximately 95% of the Y chromosome and houses multiple genes that help drive spermatogenesis such as *DAZ, USP9Y, RBMY1*, and *BPY2*.[157] The AZF region is subdivided by location into AZFa, AZFb, and AZFc, which correspond to proximal, middle, and distal portions of the chromosome.[5] Deletions in these locations are responsible for varying degrees of spermatogenic dysfunction. Entire microdeletions of AZFa or AZFb regions of the Y chromosome portends an exceptionally poor prognosis in sperm retrieval, such that microscopic sperm extraction is predictably negative.[158]

Depending on the severity of the deletion, a microdeletion in AZFc can result in a spectrum of spermatogenic deficiency including oligospermia and azoospermia.[158] Deletions in the Y(q) are too small to be detected with a karyotype and thus are termed microdeletions. These deletions are identified using polymerase chain reaction techniques to analyze sequence tagged sites. Indications for testing AZF microdeletions are sperm concentrations less then 5 million/mL. Importantly, male offspring of patients with Y microdeletions will

inherit the abnormal gene, rendering them likely to be infertile. Thus, ICSI with preimplantation genetic diagnosis (PGD) should be discussed.

Conclusions

As additional mouse models are created and high throughput screening approaches are used, we are beginning to understand more about the Mendelian genetics of male infertility. While it is difficult to fully understand the impact of Mendelian genetics on male infertility, the quick evolution of advanced reproductive therapies has allowed the achievement of biological paternity by men, who, by nature's standard, would have never been permitted to procreate. IVF/ICSI has allowed the technical potential for these men with severe male factor infertility the ability to father children. However, finding a genetic basis and understanding this mishap before proceeding with any surgical or *in vitro* technology allows appropriate counseling of the couple with regard to immediate and long-term issues not only for the parents, but also for the future offspring that they should be aware of before moving forward.

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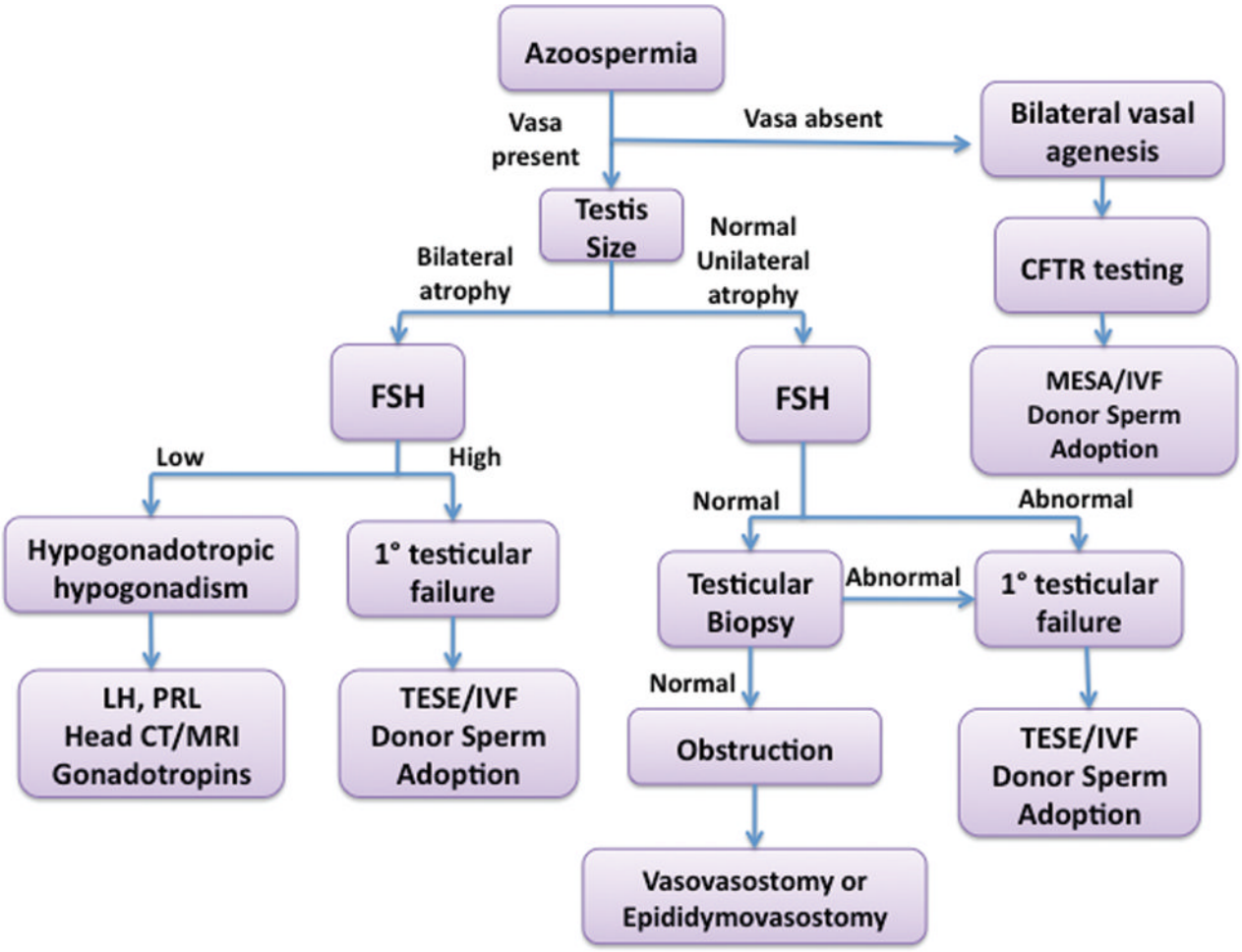

Figure 1.

Evaluation of patient with azoospermia. CFTR, cystic fibrosis transmembrane conductance regulator gene; FSH, follicle stimulating hormone; IVF, *in vitro* fertilization; MESA, microsurgical epididymal sperm aspiration; LH, luteinizing hormone; TESSE, testicular sperm extraction; PRL, prolactin.

Table 1

Frequency and associated phenotypes of the most common genetic abnormalities in male infertility

Reference	Genetic abnormality	Phenotype	Prevalence (%)
Foresta *et al.*[11]	Chromosomal aberrations	Azo → normospermia	2–10
Foresta *et al.*[4]	Klinefelter's syndrome	Azo → severe oligospermia	5–10 azoospermia 2–5 severe oligospermia
Mau-Holzmann *et al.*[6]	Other sex chromosome	Azo → normospermia	0.1–0.2
De Braekeleer *et al.*[2]	Robertsonian translocations	Azo → severe oligospermia	0.5–1.0
De Braekeleer *et al.*[2]	Reciprocal translocations	Azo → severe oligospermia	0.5–1.0
Kuroda-Kawaguchi *et al.* [5]	Y chromosome microdeletions	Azo → severe oligospermia	5–10
Vogt *et al.* [8]	AZF*a*	Azo-SCOS	0.5–1.0
Vogt *et al.*[8]	AZF*b*	Azo-spermatogenic arrest	0.5–1.0
Ferlin *et al.*[10]	AZF*c*	Azo → severe oligospermia	3–7
Vogt *et al.*[8]	AZF*b*+*c*	SCOS/spermatogenic arrest	0.5–1.0
Vogt *et al.*[7]	Partial AZF*c* deletion Gene mutations	Azo → normospermia	3–5
Foresta *et al.*[4]	CFTR	Obstructive azo	60–70 5% in infertile men
Ferlin *et al.*[9]	AR	Azo-oligospermia	2–3
Bogatcheva *et al.*[3]	INSL3-LGR8	Cryptorchidism	4–5

Azo = Azoospermia

Table 2

Genetic basis of human male infertility defects: spermatogenesis and sperm function

Abnormal spermatogenesis	
ATM; ATMAC; ***DAZL; ERCC2****; GTF2A1L; JUN; NLRP14; NRB0B1;* ***POLG****; PRM1; PRM2;* ***SDHA****; SOX8; XRCC1;* ***YBX2***	
Azoospermia	
APOB*; ACSBG2;* ***ART3****; ATM; BOULE;* ***BPY2; BRCA2****; CDY1; CFTR; CREM; DAZ;* ***DDX25****; DDX3Y; DRFFY; ERCC1; ERCC2;* ***FASLG****; FHL5;* ***FKBP6; HNRNPC****; HSFY1; KLHL10; LAP3; MBOAT1; ME11; MLH1; MLH3;* ***MTR****; NLRP14; PRDM16;* ***RBMX****; RBMY1A1; RBMY1F; SPATA16; SYCP1; SYCP3; TAF7L; TGIF2LX; TSPY;* ***TSSK4****; UBE2B;* ***USP26****; UTP14C; USP9Y; UTY;* ***XPC; XPD; XRCC1****; YBX2; ZNF230*	
Oligozoospermia	
MT-*ATP6; EGF;* ***FASL****; H19 and MEST; KLHL10; PIGA; PRM1; PRM2;* ***SHBG; SDHA; TSSK4; UBE2B****; VASA*	
Asthenozoospermia	
AKAP3; AKAP4C; CATSPER2; ***DNMT3B***; *DHAH5; DNAH11; DNAL1; PDYN; GNA12*; Mitochondrial DNA; *MTHFR*; MT-*ND4; PIGA; POLG; PPM1G; PRKAR1A; SHBG; SPAG16; TEKT1; TEKT2; TPN1; TPN2; TXNDC3*; **T**	
mt DNA haplotypes	
Teratozoospermia	
AURKC; ***PRM1****; PVRL2; SPATA16; SP1*	
Oligoasthenozoospermia	
JUND; MT-*ND4; NALP14*	
Oligoasthenoteratozoospermia	
MTRR; IL1B; SABP	
Acrosome or Fertilization	
POIA3	
Varicocele effect	
MT-*ATP6*; MT-*ATP8; CACNA1C*; MT-*CO1*; MT-*CO2*; MT-*ND3*	
Chromosome defect	
Numerical sex chromosome (Klinefelter's; XXY–XXXXY)	
Structural chromosome (translocations, inversions or deletions)	
Y chromosome microdeletions, XX male or XY female	
Systemic Disorders Affecting Fertility	
Kartagener's syndrome	Sickle cell anemia (*HBB*)
Fanconi anemia (*FANCA*)	®-thalassemia
Myotonic dystrophy (*DMPK*)	Noonan (*PTPN11*)
DNA Damage	**Infertility**
GSTM1	*AR; GSTM1* ***KIT; KITLG;*** *IL1A; OAZ3;* ***PRM1;*** *TSPY;* ***TSSK4; USP26; YBX2***

Note: SNPs of unknown significance shown in bold. Adapted by permission from Macmillan Publishers Ltd: Matzuk & Lamb Nature Medicine 2008.[12]

Table 3

Endocrinopathies in male infertility

Hypergonadotropic hypogonadism
Classic (Klinefelter syndrome)
Isolated spermatogenic compartment failure/primary germ cell failure: postpubertal viral or bacterial orchitis, chemotherapeutic agents, idiopathic, secondary to exposure to environmental toxicants
Hypogonadotropic hypogonadism
Congenital (Kallman syndrome)
Acquired: tumor, infection, autoimmune, infiltrative diseases, pituitary infarction, and drug use
Defective androgen synthesis or response
5 α-reductase deficiency
Complete androgen insensitivity
Partial androgen resistance

Table 4

Distribution of final diagnostic categories found in a male infertility clinic

Category	Number	%
Idiopathic	1535	32.6%
Varicocele	1253	26.6%
Obstruction	720	15.3%
Normal female factor[b]	503	10.7%
Cryptorchidism	129	2.7%
Ejaculatory failure	95	2.0%
Endocrinopathies	70	1.5%
Drug/radiation	64	1.4%
Genetic[a]	56	1.2%
Testicular failure	52	1.1%
Sexual dysfunction	32	0.7%
Other	80	1.6%
Total	4589	100%

Adapted from Sigman M. 2009. Office evaluation of the subfertile male. In *Infertility in the Male*. L. I. Lipshultz, S. S. Howards, & C. S. Neiderberger, Eds.: 153–176. Cambridge University Press.

[a]Underestimation as most patients are not evaluated.

[b]Normal female factor indicates no clinically detected abnormalities in female partner.

Table 5

Mouse male infertility and motility models.

Mutant gene (*gene symbol*; alternate protein symbol)	Chr.	Reproductive phenotype	Fertility status	Ref.
Apolipoprotein B (*Apob*)	12	Oligoasthenozoospermia, decreased spermatozoan survival time and ability to fertilize ova	Infertile	76
Adenylate cyclase 3 (*Adcy3*)	12	Reduced sperm motility and defects in acrosome reaction	Subfertile	77
Adenylate cyclase 10 (*Adcy10*; soluble adenylate cyclase)	1	Abnormal sperm motility defect	Infertile	78
A kinase (PRKA) anchor protein 4 (*Akap4*)	X	Lack of progressive motility in spermatozoa	Infertile	79
ATP/GTP binding protein 1 (*Agtpbp1*; Nna1; pcd)	13	Spontaneous mutant; oligoasthenoteratozoospermia	Infertile	80,81
ATPase, Ca^{++} transporting, plasma membrane 4 (*Atp2b4; PMCA4*)	1	Defect in hyperactivated motility	Infertile	82,83
Bardet-Biedl syndrome 1 (*Bbs1*)	19	M390R knock in allele; absence of sperm flagella, motility defect	Infertile; Multiple defects	84
Bardet-Biedl syndrome 4 (*Bbs4*)	9	Absence of sperm flagella	Infertile, lethality variable;	85
Cation channel, sperm associated 1 (*CatSper1*)	19	Defects in hyperactivated motility and fertilization	Infertile	86,87
Cation channel, sperm associated 2 (*CatSper2*)	2	Defects in hyperactivated motility and fertilization	Infertile	86
Cation channel, sperm associated 3 (*CatSper3*)	13	Defects in hyperactivated motility and fertilization	Infertile	88,89
Cation channel, sperm associated 4 (*CatSper4*)	4	Defects in hyperactivated motility and fertilization	Infertile	88,89
CD59b antigen (*Cd59b*)	2	Teratozoospermia	Progressive infertility	90
Glycoprotein hormone α-subunit (*Cga*)	4	Hypogonadal due to FSH and LH deficiency	Infertile	91
F11 receptor (*F11r; JAM-A*)	1	Gene trap; decreased motility	Subfertile	92
Glyceraldehyde-3-phosphate dehy drogenase, spermatogenic (*Gapdhs*)	7	Motility defect	Infertile	93
Gene model 101 (*Gm101; PCDP1*)	1	Nm1054 mutant; lack of mature flagella, motility defect	Infertile, lethality;	94
Inositol polyphosphate-5-phosphatase (*Inpp5b*)	4	Asthenozoospermia, reduced ability of sperm to fertilize eggs, defects in fertilin β processing	Infertile	95
Lactate dehydrogenase C (*Ldhc*)	7	Rapid loss of motility, absence of hyperactivated motility, and capacitation defects	Variable infertility/subfertility	96
Low density lipoprotein receptor-related protein 8, apolipoprotein e receptor (*Lrp8*)	4	Defective osmotic regulation and motility in epididymal spermatozoa	Infertile	97
5, 10-Methylenetetrahydrofolate reductase (*Mthfr*)	4	Reduced sperm numbers and abnormal spermatogenesis	Infertile	98
NOL1/NOP2/Sun domain family, member 7 (*Nsun7*)	5	ENU mutant; decreased motility	Infertile	99
Proprotein convertase subtilisin/kexin type 4 (*Pcsk4; PC4*)	10	Sperm have impaired fertilization	Infertile	100
Phospholipase A2, group IVC (*Pla2g4c*)	7	Asthenozoospermia, decreased fertilization capacity	Subfertile	101
Phosphatidylglycero-phosphate synthase 1 (*Pgs1; ROSA22*)	11	Spermatid flagella defect	Infertile	102
Phospholipid transfer protein (*Pltp*)	2	Asthenozoospermia	Subfertile	103
Polymerase (DNA-directed), delta 4 (*Pold4*)	19	Immotile spermatozoa	Infertile lethality;	104
Protein kinase, cAMP dependent, catalytic, α (*Prkaca*)	8	Ranting, sperm motility defects	Lethality; Fertility not assessed	105

Mutant gene (*gene symbol*; alternate protein symbol)	**Chr.**	**Reproductive phenotype**	**Fertility status**	**Ref.**
Protein kinase, cAMP dependent regulatory, type I, α (*Prkar1a*)	11	Abnormal spermatozoa, oligozoospermia, decreased fertilization	Subfertile	106
Ros1 proto-oncogene (*Ros1*; c-ros)	10	Sperm motility defects	Infertile	107,108
Sirtuin 1 (*Sirt1; SIR2α*)	10	Failure of ovulation (F); azoospermia and asthenozoospermia (M)	Variable lethality; Infertile	109
Solute carrier family 9, member 10 (*Slc9a10; sNHE*)	16	Asthenozoospermia	Infertile	110
Sperm mitochondrion-associated cysteine-rich protein (*Smcp*)	3	129 background; defects in sperm motility and migration into the oviduct, defects in fertilization	Infertile	111
Sperm associated antigen 6 (*Spag6*)	16	Dysmorphic and immotile sperm	Infertile postnatal lethal;	112
Sulfotransferase family 1E, member 1 (*Sult1e1*)	5	Progressive defects in sperm motility (M); abnormal ovulation and cumulus expansion (F)	Subfertile	113,114
Transaldolase 1 (*Taldo1*)	7	Motility defect, defective sperm mitochondrial potential	Infertile	115
Transcription factor 21 (*Tcf21; Pod1*)	10	Male to female sex reversal (M); both sex gonadal agenesis, germ cell loss	Postnatal lethal	116
Tektin 2 (*Tekt2*)	4	Spermatozoa have defective motility and ultrastructure	Infertile	117
Tektin 3 (*Tekt3*)	11	Sperm motility defects	Fertile	118
Tektin 4 (*Tekt4*)	17	Sperm motility defects and ultrastructural defects in flagellum	Subfertile	119
Testis expressed gene 18 (*Tex18*)	10	Asthenoteratozoospermia	Subfertile	120
Transforming growth factor β1 (*Tgfb1*)	7	Decreased testosterone production due to decreased LH, infrequent intromission, absence of ejaculation (M), SCID background; decreased ovulation frequency due to impaired LH surge, decreased progesterone synthesis, preimplantation embryo defects (F)	Subfertile (F) Infertile (M)	121,122
Testicular haploid expressed gene (*Theg*; kisimo)	10	Transgene insertion; abnormal elongated spermatids, asthenozoospermia	Infertile	123
Voltage-dependent Anion Channel 3 (*Vdac3*)	8	Immotile sperm, axonemal defects as sperm mature	Infertile	124

Chr. abbreviates chromosome locations, and Ref. denotes corresponding references