The infertile male patient with a genetic cause

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The infertile male patient with a genetic cause

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Case History: A couple was referred to an assisted reproduction techniques (ART) clinic with a 7-year history of primary male factor infertility. The 31-year-old male partner had two abnormal semen analyses (SA) at an accredited laboratory before referral. His sperm concentration was 1.5 million/mL, with 5% total motility and 1% normal forms (strict criteria) on both occasions. A repeat SA at the ART clinic confirmed the previous findings. The female partner’s workup was normal. Their provider suggested intracytoplasmic sperm injection (ICSI) as an option to achieve fertility, but before consenting to the procedure, the couple wanted to know the possibility of their male offspring inheriting the infertility phenotype. They were particularly concerned because the man’s two brothers also had abnormal SA and infertility.

Background

Genetic abnormalities are estimated to contribute to 15–30% of male factor infertility [1]. Genetics influence fertility on many levels, impacting everything from the execution of the spermatogenic process to the regulation of hormones and the quality of sperm itself [2]. Consequently, an understanding of the impact of genetics on fertility is essential for clinicians to manage and counsel an infertile couple. The genetic background of male infertility is an expansive area of research and this chapter aims to introduce some of the most common genetic defects affecting fertility and to provide functional examples to guide the treatment and counseling of infertile couples.

Chromosomal abnormalities

Chromosomal abnormalities cause approximately 5% of male factor infertility and 15% of infertility in azoospermic patients [1]. In particular, Klinefelter syndrome occurs in about 5% of men with severe oligozoospermia and 10% of azoospermic men [3]. This condition is discussed further in Chapter 81.

Y chromosome abnormalities

Almost 95% of the Y chromosome is male specific and has no counterparts on other chromosomes [4]. It is critical for fertility because it contains coding sequences for the process of spermatogenesis and the development of the testes [2]. In addition, the
Y chromosome has no partner to use as a repair template which makes it susceptible to the loss of genetic material and to the propagation of errors [5]. The determination of specific relationships between genetic mutations and infertile phenotypes is complicated because different genetic mutations on the Y chromosome can produce equivalent fertility issues [6].

Y microdeletions are a frequent genetic cause of male infertile phenotypes [2], especially in azoospermic and severely oligozoospermic men [7]. The role of these mutations is expanded upon in Chapter 88.

**Autosomal chromosome abnormalities**

Abnormalities on autosomal chromosomes are also under investigation for roles in male infertility. Patients with congenital bilateral absence of the vas deferens (CBAVD) are infertile as a result of a structural defect that causes a disconnection between the epididymis and the ejaculatory duct. CBAVD occurs in about 1% of all infertile men and in 6% of males with obstructive azoospermia [1]. The CFTR gene, located on chromosome 7, is mutated in 60–90% of CBAVD patients and it codes for the cystic fibrosis transmembrane conductance regulator protein. Individuals with cystic fibrosis often have defects in the pancreatic exocrine system and other ductal abnormalities. Men with CBAVD usually have one mild mutation in combination with a severe mutation, or two mild mutations in the CFTR gene that cause the defect [2]. The severe mutation F508del occurs in 60–70% of patients with CBAVD [8].

Clinically, CBAVD patients present with normal size testes because the process of spermatogenesis is unaffected. However, palpation of the scrotum reveals the absence of the vasa on both sides. Transrectal ultrasound may also be useful to diagnose irregularities in the seminal vesicles [9]. If the female partner is not a carrier for the CFTR mutation, intracytoplasmic sperm injection (ICSI) combined with testicular sperm extraction (TESE) is effective for men with CBAVD because they still have normal sperm production [1]. In cases when both partners carry the mutation, it is strongly suggested that preimplantation genetic diagnosis (PGD) be performed to ensure that the mutation is not passed to offspring (see Chapter 6) [10].

X chromosome abnormalities

The X chromosome is another area actively investigated in infertility research. There are many X-linked genes with suspected involvement in the formation of gametes [11] or which are expressed in the testis [12]. Kallman syndrome is the most frequent cause of X-linked hypogonadotropic hypogonadism (HH) in infertile males [13]. HH is characterized by decreased output of gonadotropin releasing hormone (GnRH) [13] due to the failure of migration of GnRH neurons during development [14]. GnRH is essential for fertility because it regulates the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary gland. These hormones regulate androgen levels and the process of spermatogenesis [15].

The genetic defect responsible for the X-linked form of Kallman syndrome is a mutation of the KAL1 gene which codes for the cell adhesion molecule involved in the migration of the GnRH neurons, asomin 1 [14]. A less common form of the disease can occur from the loss of information on the X chromosome because of structural defects [16]. Kallman syndrome patients present with a variety of physical phenotypes because of the varying severity of the disease and can exhibit symptoms ranging from delayed or absent puberty to infertility [13]. Most patients have short penises, small testes and a lack of circulating gonadotropins in their blood because of the absence of GnRH. Additionally, patients with Kallman syndrome may be anosmic as a result of the developmental failure of the olfactory bulb and may have other congenital abnormalities, such as facial asymmetry, cryptorchidism and cleft palate [13]. However, hormone replacement therapy and gonadotropin stimulation treatment can be used to activate spermatogenesis in these males [17]. A recent study of patients treated with hormone replacement therapy has shown a reversal of HH after treatment was completed [18]. This finding is especially encouraging because it suggests that these men may no longer need assisted reproduction techniques (ART) in the future to achieve fertility [13].

**Epigenetic abnormalities**

Epigenetics, or modifications to the genetic code that do not change the basic coding sequence of nucleotides, are another critical area to consider when evaluating male infertility. Studies examining the
relationships of single gene polymorphisms and infertile phenotypes suggest that infertility is most likely a multifactorial disease [19]. The intricate process of spermatogenesis is vulnerable to the accumulation of errors at each step and the resulting sperm must be correctly programmed to communicate genetic and epigenetic information to the developing embryo [20].

One epigenetic error that can have negative consequences on fertility is aberrant imprinting, or the specific methylation of sections of the DNA sequence. Imprinting controls which genes from the maternal and paternal genomes are expressed in the developing embryo and it is critical for normal embryonic development [21]. The relation of imprinting to infertility is under debate because of conflicting research findings. Some studies have not found a significant difference in imprinting between infertile and normal men [22,23]. Others have demonstrated abnormal DNA methylation patterns in oligozoospermic men and in men with abnormal replacement of histones by protamines during the repackaging of chromatin [24–27].

The use of ART in men with imprinting disorders is controversial because it is still uncertain whether epigenetic errors are transmitted to subsequent generations. However, it is plausible that if abnormally methylated regions were not reset or removed they could be passed on to offspring [19]. ART also allows the utilization of immature sperm whose epigenetic code may not be totally established for fertilization [21]. The use of ART in infertile men has been associated with a greater incidence of imprinting disorders such as Beckwith–Wiedemann syndrome and Angelman syndrome in offspring [28–30], but it is unclear whether this is a negative consequence of ART or the use of sperm from men with abnormal epigenetic coding.

**Management options**

Hypogonadotropic hypogonadic men with Kallman syndrome respond well to hormone (gonadotropin) replacement therapy, which stimulates spermatogenesis in these azoospermic men and can restore fertility, often without the need for ART [17,18].

Infertile men with testicular (nonobstructive) azoospermia or severe oligozoospermia (<5 million/mL) should be offered karyotyping and screening for Y chromosome microdeletions before undergoing ICSI. The results will inform the genetic counseling offered to them regarding the chances of transmission of infertility to their male offspring, as well as the need for PGD in cases of chromosomal abnormalities such as balanced translocation carriers.

Almost all men with post-testicular (obstructive) azoospermia resulting from CBAVD have two mutations of the CFTR gene, and their female partners should be screened for the common CFTR mutations in their particular population. If she was found to be a carrier, then it is strongly suggested that PGD be performed to ensure that the mutation is not passed to offspring [10].

It must be recognized that ART surmounts the barriers of natural selection mechanisms and can use suboptimal sperm to produce a viable zygote [1]. Although this is a major scientific achievement, it also introduces the possibility of propagating genetic defects to subsequent generations. All couples undergoing ART for male factor infertility should be counseled about the possibility of transmitting the infertile phenotype to their male offspring.

**Prevention**

Although many genetic defects causing infertility are present in patients from birth, environmental agents and toxins have been implicated as causes of DNA damage and de novo mutations [31]. For instance, although smoking has not been conclusively linked to infertility, chromosomal and DNA damage have been correlated with the exposure of germ cells to tobacco smoke [32]. Physical agents such as irradiation and heat have both been found to cause DNA damage [31,33] and oxidative stress [34,35]. The chromatin integrity of sperm can also be compromised through exposure to chemical agents such as chemotherapy drugs [36], environmental toxins such as pesticides [37], and heavy metals [38]. However, the effect of these stressors on offspring is still unclear and the impact of environmental toxins on fertility is variable because an individual’s ability to repair damage is related to other factors such as past exposure and lifestyle [31]. In general, infertility patients should be advised to avoid or limit exposure to agents that could negatively impact their fertility.
**Key points**

**Challenge:** Male factor infertility patient with a genetic cause.

**Background:**
- Genetic abnormalities are estimated to contribute to as much as 15–30% of male factor infertility.
- Chromosomal abnormalities (such as Klinefelter syndrome) cause 5% of male factor infertility in general, and 15% of infertility in azoospermic patients.
- Y microdeletions are a frequent genetic cause of male infertility, especially in azoospermic and severely oligozoospermic men.
- 6% of men with obstructive (post-testicular) azoospermia have CBAVD and carry two CFTR mutations, with the risk of transmitting cystic fibrosis.
- Kallman syndrome is the most frequent cause of X-linked HH in infertile males.
- Epigenetic abnormalities may have an effect on male fertility.

**Management options:**
- Infertile men with testicular (nonobstructive) azoospermia or severe oligozoospermia should be offered karyotyping and screening for Y chromosome microdeletions before undergoing ICSI.
- Screen for CFTR mutations in female partners of CBAVD males before undergoing ICSI.
- Perform PGD in cases of balanced chromosomal translocation carriers or where both partners are carriers of CFTR mutations.
- In men with HH, gonadotropin replacement therapy is needed.
- Appropriate genetic counseling.

**Prevention:**
- Infertility patients should avoid or reduce exposure to harmful environmental agents (e.g., smoking) to limit the chance of de novo genetic mutations.

**References**

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