# THE GENETICS OF MALE INFERTILITY

*"High technology approaches to fertility, including ICSI, are really a two edged sword: they allow us to treat severe male infertility, but they may alter natural selection in that decisions regarding sperm and eggs are made in the laboratory and not by nature."*
*— Dr. Paul Turek*

## How much of male infertility is genetic?

Among the 15% of couples who experience infertility, about 40% of the time the infertility is due to male "factors." About half of male infertility cases are due to defined reasons, including varicocele, infection, hormone imbalances, exposures such as drugs or medications, x-rays, tobacco use and hot tubs, blockage of the reproductive tract ducts, and previous surgery that has left scarring. Another cause of male infertility that has been underestimated in the past but is now gaining in importance is genetic infertility. The reason for its increased importance is that our knowledge about genetics is growing so quickly. Men who may have had unexplained infertility in the past may now be diagnosed with genetic causes of infertility through recently available testing. In fact, this field is progressing so quickly that genetic infertility has already become one of the most commonly diagnosed reasons for male infertility.

## Why does it matter if infertility has a genetic cause?

Developed in the early 1990's, assisted reproduction in the form of IVF and ICSI (intracytoplasmic sperm injection) is a revolutionary laboratory technique in which a single sperm is placed directly inside an egg for fertilization. This technique has opened the door to fertility for men who formerly had few available treatment options, as it allows men who were previously considered severely infertile or sterile the possibility of fatherhood. However, with ICSI sperm are chosen by laboratory technicians and not by nature and because of this, it is not clear what barriers to natural selection are altered. Thus, along with this technology comes the possibility of passing on to a child certain genetic issues that may have caused the father's infertility, or even more severe conditions. Another reason to know whether male

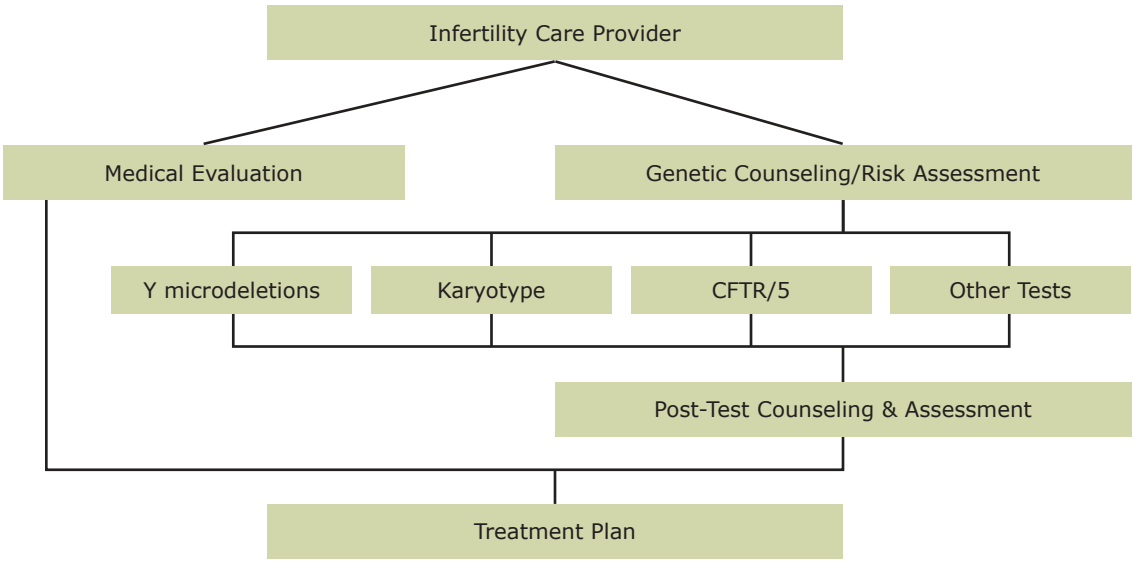
infertility is genetic or not is because classic treatments such as varicocele repair or medications given to improve male infertility. In fact, Dr Turek was one of the first to publish on this issue, showing that varicocele repair was not effective in improving fertility in men with genetic infertility. Because he recognized these issues early on, Dr. Turek, while at UCSF in 1997, founded the first formal genetic counseling and testing program for infertility in the U.S. Called the Program in the Genetics of Infertility (PROGENI), Dr. Turek's program has helped over 2000 patients at risk for genetic infertility to navigate the decision-making waters that surround this condition.

## How does one learn whether male infertility is genetic or not?

Men with infertility should be seen by a urologist for a thorough medical history, physical examination, and appropriate medical testing. If genetic infertility is a possibility, then a genetic counselor can help couples understand the possible reasons, offer appropriate genetic testing, and discuss the complex emotional and medical implications of the test results. The approach taken early on by Dr. Turek is outlined in Figure 1. Just like the medical diagnosis from a urologist or fertility specialist, information about family history plays a critical role in genetic risk assessment. This approach to genetic evaluation, termed non-prescriptive, has been the cornerstone of Dr. Turek's critically acclaimed clinical program that now has over a dozen publications contributing to our current knowledge in the field.  It is important to note that a lack of family history of infertility or other medical problems does not eliminate or reduce the risk of genetic infertility. In fact, a family history review will often be unremarkable. However, family history can provide crucial supporting information toward making a genetic diagnosis (such as a family history of recurrent miscarriages or babies born with problems). Dr. Turek has published that having a genetic counselor obtain family history information is much more accurate than simply giving patients a written questionnaire to fill out and bring to their visit. A genetic counselor can also discuss appropriate genetic testing options and review the test results in patients in a meaningful way.

When speaking to Dr. Turek's genetic counselor about genetic testing, keep in mind that he or she will not tell you what to do. Genetic counselors are trained to provide information, address questions and concerns, and support you in the decision making process. A genetic counselor does not assume which decisions are most appropriate for you.

*Figure 1.* *Dr. Turek's famous non-prescriptive clinical pathway for evaluating male genetic infertility, used for over 2000 patients since 1997.*




## What kinds of conditions suggest that the male infertility may be genetic?

Among the various infertility diagnoses that men have, some are more commonly associated with genetic causes. Diagnoses that can have genetic causes include men nonobstructive azoospermia (no sperm count), oligospermia (low sperm count), and congenital absence of the vas deferens. A list of some of the best-described causes of genetic male infertility and their frequencies and associated conditions are listed in Table 1.

*Table 1.* *Quick Reference for Genetic Risks associated with Common Male Infertility Diagnoses.*

| **Diagnosis** | **Chromosome Abnormality Risk** | **Y chromosome Microdeletion Risk** | **CF Mutation/5T Allele Risk** |
|---|---|---|---|
| Oligospermia (<5 million sperm/mL) | 2-7% | 6-8% | Same as general popul. |
| Nonobstructive Azoospermia | 15% | 13% | Same as general popul. |
| Congenital unilateral absence of vas deferens (CUAVD) 15% | Not increased* | Not increased* | Up to 50% |
| Congenital bilateral absence of vas deferens (CBAVD) | Not increased* | Not increased* | Up to 80% |

**It is possible to have sperm production problems that are masked by congenital or unexplained obstruction. If testicular or epididymal sperm quantities are normal, then there is no increased risk for chromosomal abnormalities or Y chromosome deletions. However, if sperm production is abnormal then these risks may be increased.*

### Nonobstructive azoospermia

Nonobstructive azoospermia is defined as zero sperm count in the ejaculate due to an underlying sperm production problem within the testicles. This is quite different from obstructive azoospermia in which sperm production within the testes is normal, but there is a blockage in the reproductive tract ducts that prevents the sperm from leaving the body. There can be changes in the levels of reproductive hormones, such as follicle stimulating hormone (FSH), observed with nonobstructive azoospermia. Most commonly, the FSH is elevated in this condition, which is an appropriate and safe hormone response by the pituitary gland to states of low or no sperm production. This diagnosis is associated with a 15% chance for having chromosome abnormalities (Figure 2) and a 13% chance for having gene regions missing on the Y chromosome (termed Y chromosome microdeletions, Figure 3). To detect these changes, blood tests are typically offered to men with nonobstructive azoospermia.

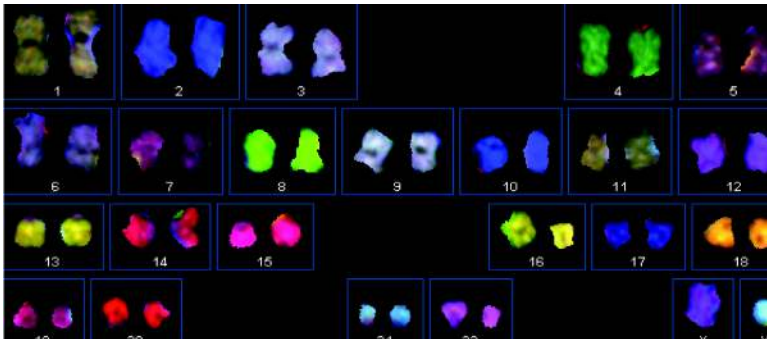


*Figure 2. An example of a human chromosomal analysis using spectral karyotyping.*

### Oligospermia

Oligospermia that places men at risk for genetic infertility occurs when the ejaculate contains a sperm concentration of <5 million sperm/mL semen. Similar to nonobstructive azoospermia, this is most commonly due to an underlying sperm production problem. With this diagnosis, there is a 2% risk for chromosome abnormalities and 6-8% risk of Y chromosome microdeletions. In general, the lower the sperm count, the higher the chance that a genetic cause is present. Again the appropriate testing includes a

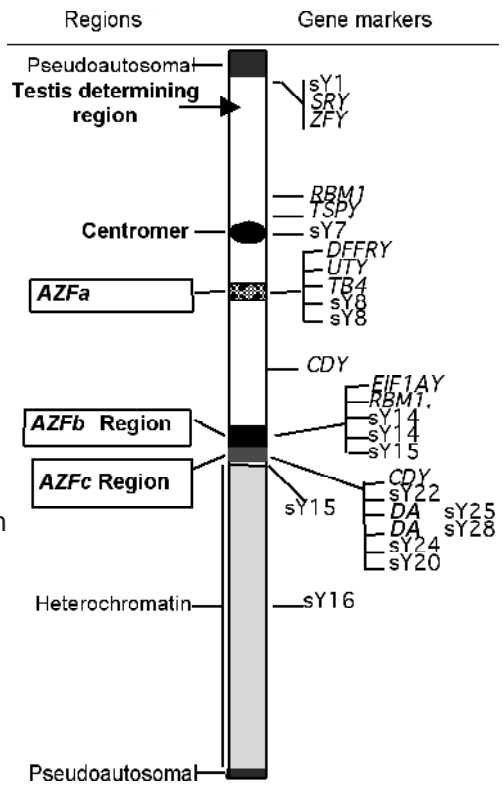



*Figure 3. A schematic diagram of the human Y chromosome showing genes and gene regions that can affect male infertility.*

karyotype and Y chromosome microdeletion analysis. Thus far, there are no established guidelines for applying these genetic tests in cases of low sperm motility (movement) or poor sperm morphology (shape).

### Congenital absence of the vas deferens (CUAVD, CBAVD)

Congenital absence of the vas deferens is characterized by the malformation or absence of the ducts that allow sperm to pass from the testicles into the ejaculate and out of the body during ejaculation. The duct that is affected in this condition is the vas deferens. This is the same duct that is treated during a vasectomy, a procedure for men who want birth control. Men with this condition are essentially born with a "natural vasectomy." This congenital condition is associated with mutations and/or variations in the genes for cystic fibrosis (the CFTR gene) in 70-80% men if the vas deferens is absent on both sides, but less than this if the duct is missing on only one side. For most men with this condition with a mutation in the cystic fibrosis gene, the missing vas deferens is the only problem that results from this genetic change and they do not have the full spectrum of symptoms associated with cystic fibrosis, the most common genetic disease in the U.S. and generally lethal in early adulthood.

### Unexplained obstruction or blockage

A less common reason for men to have a zero sperm count (azoospermia) than nonobstructive azoospermia is obstructive azoospermia. In essence, this is an unexplained zero sperm count due to a blockage of the reproductive tract ducts leading from the testicle to the ejaculate. Blockages are most commonly found in the epididymis but can also be located in the vas deferens or ejaculatory ducts. Most cases of obstructive azoospermia are amendable to surgical repair and naturally fertility is common. However, a high proportion of these men (47%) have mutations in the cystic fibrosis gene (CFTR) or harbor variations in the CFTR gene, termed 5T alleles. As such, genetic counseling and testing is also important in these patients.

These conditions represent only the most common genetic conditions encountered when evaluating men for genetic infertility. For this reason, consider reading Dr. Turek's recently published article that discusses most of the currently understood syndromes and conditions that are associated with infertility. It is also important to remember that if all genetic test results are normal, there is still a possibility that the infertility has a genetic cause. However, in many cases, medical science is currently unable to offer testing to detect it.

## What does having a Y chromosome microdeletion or a chromosomal abnormality mean for the health of children?

If a man has a chromosome abnormality identified as the cause of infertility, then depending on the chromosome abnormality detected, there may be a higher risk for children to be born with birth defects or mental impairment. This occurs as a result of a child inheriting from the father an imbalance in chromosome material. A genetic counselor can provide more detailed information about such potential risks, and offer other resources for individuals who have been diagnosed with a chromosome abnormality. There may be support organizations available to help men with genetic diagnoses and their partners cope with the impact of this information. Some couples find it helpful to talk to others in similar circumstances.

If a man is diagnosed with a Y chromosome deletion, then he will pass on that Y chromosome deletion to any son he conceives. To his daughters, he will pass on his X chromosome, instead of the Y chromosome. It is assumed that any son inheriting a Y chromosome deletion from his father will also have infertility. It is unclear whether the type and severity of the infertility will be different from the father's. So far, there have only been a few reports of sons born to fathers with Y chromosome deletions after conception by assisted reproduction. As expected, there has not been an increase in the rate of birth defects or other problems for these boys, although this group is still small in number, and too young to have fertility evaluations.

Transmission of CFTR mutations in cases of infertility due to congenital absence of the vas deferens is somewhat more complex than either Y microdeletions or a chromosome abnormality. This is because there are over 1400 described mutations in the CFTR gene and the impact of mutations differs depending on which one is present. In general, the partner of an affected man should be tested as well, so that the residual risk of a child having either congenital absence of the vas deferens or full-blown cystic fibrosis can be estimated.

National Society of Genetic Counselors - Locate a genetic counselor near you at (610) 872-7608.

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