

Are there genetic factors associated with male infertility?

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The genetic basis of male infertility probably represents one of the most important, yet under emphasized, causes of male infertility. The current diagnoses of male infertility are largely descriptive, i.e., cryptorchidism or failure of testicular descent, testicular failure, idiopathic infertility (the cause is unknown). These diagnoses reflect a relatively poor understanding of the processes regulating the development and function of the male genital tract, the process of spermatogenesis, ejaculation and fertilization. Each of these processes is complex with the expression of thousands of genes thought to be required and accordingly difficult to study. Yet the genetic causes of infertility should be an area of importance in reproductive medicine. Assisted reproductive technologies have been developed to overcome sterility allowing otherwise infertile couples to become biologic parents (Chapter 21). These technologies include in vitro fertilization (IVF, test tube babies), intracytoplasmic sperm injection (ICSI) used together with IVF and preimplantation genetic diagnosis to attempt to select embryos free of specific genetic diseases. Yet in depth thought about these techniques suggests that they are used to circumvent natural evolutionary pressures. In essence, an infertile male represents the end of that genetic line. In nature, infertility is a “genetic lethal” condition as the defective genes causing infertility (and perhaps genetic syndromes) cannot be passed on to future generations. Assisted reproductive technologies now bypass this evolutionary checkpoint.

What are the genetic problems currently known causing male infertility? If we consider the most simple examination of genetic information, inspection of the chromosomes by a karyotype analysis is the most superficial, but certainly a very important assessment. A karyotype is similar to looking at the volumes of an encyclopedia in the library. The number of volumes are checked and whether large portions are missing. With this approach, a number of genetic defects are recognized. Certainly chromosome abnormalities (both numerical and structural) account for a significant percentage of male infertility. With no additional diagnostic or physical evaluation, nearly 6% of infertile men will be found to have a chromosome defect. For example, Klinefelter syndrome (a chromosome defect with extra X chromosomes present—XXY, XXXY or XXXXY) accounts for about 14% of non-obstructive azoospermia (no sperm in the ejaculate due to a sperm production problem) (Chapter 17).

Klinefelter syndrome is an example of a numerical chromosome defect in

which a whole chromosome is gained or missing. More complex chromosome defects can be present with the individual having a mixture of cells or mosaicism (XY, XO, XYY, and so on). Structural chromosome defects in which part of a chromosome is missing, duplicated or misplaced (analogous to missing or duplicated chapters, chapters out of order or backwards) such as translocations, inversions, duplications, deletions can cause male infertility as well. For example, Y chromosome microdeletions, in which the missing portion is too small to be visualized on karyotype analysis but evident with more advanced molecular diagnostic tools (analogous to missing pages in a chapter) are present in about 8-12% of men with severe infertility such as non-obstructive azoospermia and a lower percentage of oligospermic men (low sperm count in the ejaculate).

At the level of individual genes, mutations or deletions can certainly be present as well. This is an area of active research investigation and much of our knowledge comes from studies in animal models. Disruption of genes encoding proteins involved in sex determination, sex development, steroid or protein hormone biosynthesis, metabolism or receptor action, genes involved in the paracrine (cell-cell) signaling in the testis by growth factors, cytokines and their receptors, genes involved in structural aspects of spermatogenesis and cell-cell interactions, the formation and function of the sperm and fertilization can cause male infertility. A challenge to investigators is the complexity of the signaling processes regulating these important steps required for fertility, making dissection of specific defects difficult in individual patients. However, as discussed below, there are several examples that provide important insights into the significance of defining these defects.

Men with obstruction of the male reproductive excurrent ductal system associated with congenital bilateral absence of the vas deferens (CBAVD) are now known to have mutations in the gene for the cystic fibrosis transmembrane regulatory protein or CFTR, which encodes an ion channel that pumps chloride out of cells. The most common mutations of the CFTR gene are those associated with cystic fibrosis. The observation that cystic fibrosis patients had co-existing CBAVD led investigator to ask if CBAVD patients who do not have cystic fibrosis had mutations in the same gene. The CFTR gene is huge with over 1300 different mutations identified to date. Not surprisingly, the mutations causing cystic fibrosis differ (“severe” mutations) from those causing CBAVD (“mild” mutations). Men with CBAVD may have mutation in only one allele or two mild mutations in each allele. Alternatively, a severe cystic fibrosis mutation may be found on one allele with a mild one on the other. 5T allele polymorphism in a non-coding region (intron 8) of the CFTR gene, commonly found in CBAVD men in association with a CFTR mutation in the other allele, can result in decreased amount of CFTR protein synthesized.

Assisted reproduction with surgical sperm retrieval for ICSI is practically the only hope for these men to father genetic children. For the CBAVD male it is assumed he has a mutation in the CFTR gene. The spouse is usually tested for the most common mutations causing cystic fibrosis (about 30-50 out of ~1300 mutations). Accordingly, even when the spouse was tested “negative” for CFTR mutation, unless the couple undergoes expensive evaluation of the entire sequence of the CFTR gene, they remain at risk (albeit lower if the most common mutations are not present in the female partner) of conceiving a child with cystic fibrosis or CBAVD. In the past, before this genetic cause of CBAVD was identified, couples underwent assisted reproduction with the risk of the birth of an affected child. The CBAVD-CFTR story represents an example of a technology (the assisted reproductive technologies) being developed before the clinical consequences of the method was understood.

Finally, because these assisted reproductive technologies overcome infertility, are they safe for the offspring? Generally, the children appear relatively healthy although there is an increased incidence in low birth weight and birth defects (particularly those affecting the genitourinary system) requiring surgical correction. There is a slight increase in the incidence of genetic imprinting disorders, such as Beckwith-Wiedemann. The majority of the children born seem healthy. Obviously, long-term studies of the safety and efficacy of these procedures are required.

For infertile couples, understanding the cause of their infertility is important. It allows them to make educated decisions regarding their choices to use assisted reproductive technologies, to use donor sperm, adopt or remain childless. This is particularly important when a genetic cause of infertility is known, as the defect can be transmitted to the offspring. In addition, because some genetic causes of infertility may also cause systemic abnormalities in the infertile male (or the offspring), in the future, advanced genetic testing to diagnose the cause of infertility will be of critical importance.

Suggested reading

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