Chapter 36
Genetic factors likely cause a large percentage of male infertility

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The genetic basis of male infertility probably represents one of the most important, yet under emphasized, cause 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) (Chapters 32, 33). 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 35). 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 37).

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. One such defect is a Robertsonian translocation that results when two different number chromosomes with a very long and a very short arm recombined together during the production of sperm or eggs. It is easy to see on a karyotype analysis. Individuals with this type of structural chromosome defect are at risk of infertility, pregnancy loss or having a child with a significant birth defect. Another important structural chromosome defect is a 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 oligozoospermic 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 while some of our knowledge comes from studies in animal models, today we have a much better understanding of the human genes impacting some forms of male infertility. 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 (Chapter 4), genes involved in structural aspects of spermatogenesis and cell-cell interactions, the formation and function of the sperm and fertilization can cause male infertility. While identifying specific defects in most infertile men remains difficult in individual patients, there are some areas where great

progress has been realized. 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. CBAVD patients who do not have cystic fibrosis also can have mutations in this 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 factor couple, both partners should be tested for mutations causing cystic fibrosis even if the spouse tests "negative" for *CFTR* mutation, 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. An additional gene that causes CBAVD has recently been identified, adhesion G protein coupled receptor G2 (*ADGRG2*), which causes an X-linked form and can be associated with unilateral renal agenesis.

Two major areas for which there is a significant increases in our understanding of the genetic basis of male infertility are poor sperm shape (morphology) and poor sperm motility. A subset of infertile men may have normal sperm concentration/density and motility but, for example, head defects where the sperm have a round head rather than being shaped somewhat like a tennis racket. This is because they may have a misplaced, atrophied, or absent acrosome. The acrosome resembles a "sock" over about 75% of the top of the sperm head which contains the enzymes needed to be liberated when the sperm has to traverse the egg investments to eventually penetrate the egg for fertilization (Chapter 25). Defects of two genes (among others), *DPY19L2* and *SPATA16*, can cause round-headed sperm. Other men have tail defects due to gene defects affecting the internal structures

within the sperm tail/flagellar and these genes encode proteins needed for subcellular sperm structures such as the outer and inner dense fibers, the dynein arms and other parts of the tail.

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 Beckwidth-Wiedemann. The majority of the children born seem healthy (Chapter 38). Obviously, long-term studies of the safety and efficacy of these procedures are required. There is a concern that some infertile men have health risks associated with their infertility. These men may have a higher risk of developing malignancies at early ages or have increased mortality and morbidity. Although the genetic or genomic defects linking infertility with health risks are not clearly defined, it is an area of intense investigation (Chapter 64).

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 is of critical importance.

Suggested reading

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