Genetics of Male Infertility

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KEYWORDS

• Y chromosome microdeletion • Klinefelter syndrome • CBAVD • Germline mutation • Male infertility

KEY POINTS

- Much of idiopathic male infertility is likely to have a genetic cause.
- Men who have nonobstructive azoospermia or severe oligospermia with total motile count less than 5 million should have a karyotype and Y chromosome microdeletion.
- Klinefelter syndrome (47,XXY) is the most common chromosomal abnormality with a frequency of 1:600 males and has a wide spectrum of clinical presentation.
- Men with an *AZFa*, *AZFb*, *AZFb/c* microdeletion uniformly have complete absence of spermatogenesis.
- If a male has congenital bilateral absence of the vas deferens, it is critical to offer him and his partner genetic testing for cystic fibrosis mutations as well as genetic counseling.

INTRODUCTION

Approximately 1 in 6 couples in the Western world is not able to conceive spontaneously after 1 year of unprotected intercourse; in nearly half of these couples, the male partner has 1 or more semen parameters below the WHO cutoffs for normozoospermia.[1–4] Although the sequencing of the human genome in 2003 heralded a new era of genetic medicine, it will likely take decades to realize the potential of this project. Male infertility, in part due to the nature of the condition, remains largely unexplained. The cause of most cases of male infertility or subfertility remains unknown; monogenic disorders (eg, cystic fibrosis [CF], Kallman syndrome), cytogenetic abnormalities (eg, Klinefelter syndrome [KS; 47,XXY]), and Y chromosome deletions account for only up to 30% of cases.[5] The proportion of the remaining male factor cases that can be attributed to genetic causes is currently unknown, but it is likely that aberrations in many additional genes underlie a significant proportion of male infertility/subfertility because sperm production requires the coordinated action of thousands of genes, and knocking out any 1 of hundreds of genes in mice results in subfertility phenotypes in males.[6] However, discovering such genes in humans has proved challenging.[1–3,5,6]

Based on studies of animal models, however, it is likely that genetic variation that alters gene expression or function accounts for a significant proportion of male subfertility. For example, knock outs of or mutations in hundreds of genes cause subfertility phenotypes in male mice.[6] This is not surprising given that sperm development and maturation require the coordinated action of thousands of genes. However, identifying the variation and specific genes that are essential for reproductive success in humans has been extremely challenging for 2 reasons. First, because of the nature of the condition, it is virtually impossible to conduct genome-wide family-based studies of infertility, approaches that have been successful for identifying genes for many conditions with monogenic, and even some with complex genetic causes. Second, male infertility is a heterogeneous condition that can result from aberrations of many different genes. This is due in part to strong selection pressure against transmission of these genetic variants. As a result, candidate gene association studies (or even genome-wide association studies [GWAS]) of cases (infertile) and control (fertile) men would not likely be successful because only a small proportion of the cases are expected to share the same genetic abnormality.

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This is shown by the relative paucity of specific genetic variants and genes that are robustly associated with male infertility.[7–20]

Our lack of success in explaining approximately 50% to 70% of male infertility is nowhere more apparent than in our interactions with infertile men. These men want an answer to what caused their infertility. Currently, we cannot provide this in most instances. Furthermore, technological advances such as intracytoplasmic sperm injection (ICSI) and microsurgical testicular sperm extraction (microTESE) allow us to bypass the problem and bring with them another set of questions from patients that we cannot answer.[21,22] When considering ICSI, many patients want to know what are the chances they will pass on the genetic cause of their infertility to their offspring, as well as the potential for nonreproductive effects from these genes. These are questions that currently cannot completely answered completely. Although studies suggest that assisted reproductive technologies do not seem to result in a significantly higher rate of birth defects after risk factors such as maternal age are controlled for, the role of sperm quality in reproduction is just beginning to be unraveled.[23]

In 2012, Kong and colleagues[24] published a seminal paper in *Nature* showing that the de novo mutation rate for each generation is driven largely by paternal age with paternal sperm mutation rate doubling for every 16-year increase in paternal age. Increased paternal mutations from advancing age of fathers explained 30% of the increase in autism and schizophrenia over the time period of this study. The mechanism driving this is believed to be increased de novo mutations resulting from decreased fidelity of DNA replication in spermatogenesis with advancing paternal age. These mutations result in a higher mutation rate in sperm, which are then passed on to offspring and can manifest as diseases such as schizophrenia or autism.

Studies such as that of Kong and colleagues[24] and recent work by Wang and colleagues,[25] which sequenced the entire genome of individual sperm, herald a paradigm shift in our ability to develop the next generation of genetic tools to understand and possibly treat the underlying cause of male infertility. Tools such as this provide the ability to interrogate the reproductive potential of individual sperm, unfortunately, at this time, this cannot be done without destroying them. However, this technology holds incredible potential to determine the reproductive potential of an individual sperm.

Voltaire said, “with great power comes great responsibility.” In many ways, ICSI and microTESE have given us incredible power to treat male infertility. With this power, comes the ethical and moral responsibility to understand the genetic causes of male infertility for our patients and their offspring. Much of the potential of the Human Genome Project will be brought to bear on the genetic causes of male infertility.

This article examines some basic concepts that are prerequisite to any examination of the genetic causes of male infertility and reviews who should be evaluated and the current tools for genetic evaluation as well as their limitations. An overview of state of the art research in the field and what the landscape will look like in 2034 are presented.

PHENOTYPE DEFINITIONS

Studying the genetics of male infertility is complex because many of the tools of genetic analysis such as linkage mapping, family studies, and complex pedigree analysis are rendered useless by the nature of the condition. Furthermore, male infertility exists on a spectrum and is likely the result of the contribution of 100s if not 1000s of genes to a man’s overall reproductive potential.[2] To study this or any other genetic condition, accurate phenotyping is essential. To determine the precise genetic cause of male fertility, robust definitions that can clearly differentiate men into similar groups for analysis are essential. If this often overlooked but critical step cannot be completed, our efforts are doomed to failure. Although significant progress is being made in genomic, proteomic, and metabolomics biomarkers of male infertility, the limiting factor in this work is lack of accurate phenotyping of these men from a clinical and molecular standpoint (**Table 1**).[26] Another key component of accurately phenotyping men is to define accurate inclusion and exclusion criteria to establish a uniform cohort of men for analysis (**Table 2**).

Previous investigators have focused on men with nonobstructive azoospermia (NOA) to identify a pure phenotype with a uniform condition.[9,14,20] Although this approach is appealing in that NOA is certainly a reproducible end point and clearly defines a population of patients, it has not been successful in identifying genetic causal variants that explain large portions of male infertility.[7–20] Much of this is believed to be due to racial and ethnic differences in genetic carrier frequencies and the 100s of genetic defects that can result in an NOA phenotype.[5] Given that most men do not realize their full reproductive potential, that birth outcomes are also dependent on female factors, and that semen analyses are notoriously variable, NOA provides an attractive phenotypic definition for male infertility.[27] The problem with using men with NOA as a phenotypic definition of male factor infertility is that significant numbers of men with

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