Finding of parental consanguinity in men with infertility facilitates the discovery of specific genetic causes for nonobstructive azoospermia

In the spectrum of diagnoses encountered by specialists in male infertility, the finding of nonobstructive azoospermia is likely the most devastating one to divulge to a patient. With this diagnosis, there is a relatively high chance that no sperm will be found despite extensive efforts. Further compounding this is the fact that a reason "why" they have this condition is able only to be elucidated in roughly 25% of patients with confirmatory genetic testing revealing Y chromosome microdeletions, Klinefelter syndrome, or the exceedingly rare azoospermia-causing Robertsonian translocations (1). Unfortunately, this is the extent of widely available genetic tests that are available to detect instances of nonobstructive azoospermia that are caused by distinct genetic defects with minimal environmental influence.

Work on defining single genetic defects that can lead to nonobstructive azoospermia was limited mostly to the extension of the work on mouse knockout models that lead to impaired spermatogenesis. As an example, attempts at finding human patients with nonobstructive azoospermia and mutations in genes previously known to cause defects in meiosis, and, therefore, sperm production, in mice, led to the discovery of mutations in the gene *TEX11* as a likely candidate for a genetic cause for nonobstructive azoospermia (2). More recently, the study of families with parental consanguinity and offspring with azoospermia has become the closest we can get to assessing the potential role of homo or hemizygous loss-of-function mutations in human subjects with azoospermia. The reason for this is that unions of relatives significantly increase the chances of very rare recessive mutations achieving homozygosity in their offspring, thus increasing the density of genes that may lead to nonobstructive azoospermia through different mechanisms (3). The potential value of using parental consanguinity as a model to discover azoospermia causing mutations is highlighted by Ozman et al. (4) in this issue of *F&S Reports*. In this study, they found that parental consanguinity was present in 33% of patients in their cohort with nonobstructive azoospermia. This was higher than the rate of consanguinity in their country overall (24%). Furthermore, another key finding was that in those patients with a history of parental consanguinity, 19.7% of them had infertile siblings, compared with 6.6% of patients without this family history. This highlights the potential for heritable genetic defects to be more prevalent in those families with consanguinity leading to several members with infertility. Last, patients with a history of parental consanguinity tended to have the histologic finding of maturation arrest (66%), compared with those without (21.6%), pointing to the potential presence of genetic defects leading mostly to meiotic errors in those with parental consanguinity. These last two points have allowed researchers to use next-generation sequencing techniques such as whole-exome sequencing, combined with homozygosity mapping and subsequent genomic database scanning for rare variants in genes that are putatively involved in spermatogenesis, to discover gene variants/mutations that are likely to cause azoospermia (5). Ultimately, studying multiple consanguineous families with several members with infertility using these techniques may broaden the scope of knowledge that we have and improve the menu of genetic testing we can offer patients to achieve some degree of peace of mind and a formal causative diagnosis. This last component, causation, likely will be enhanced by developing knockout mouse models of these candidate genes, if none are currently available.

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