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Male infertility biomarkers and genomic aberrations in azoospermia

Jason R. Kovac, M.D., Ph.D. and Dolores J. Lamb, Ph.D.

Scott Department of Urology, Center for Reproductive Medicine, and the Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas

TO THE EDITOR

Estimates indicate that 15%–30% (or more) of male factor infertility is due to whole-organism genetic abnormalities, and large numbers of genes have already been discovered to play important roles (1, 2). Numerous methods have yielded new genetic discoveries, with the karyotype, fluorescent in situ hybridization, comparative genomic hybridization, and microarrays all contributing (1). All identified genetic aberrations are further complicated by epigenetic modifications (i.e., methylation and protamination), as well as individual differences and environmental influences that make diagnosis and treatment frustrating (1). Unfortunately, in many men, the results of multiple investigations often yield inconclusive or slightly abnormal results, with a subsequent diagnosis of idiopathic infertility.

A biomarker has been defined as a distinctive biological indicator of a process, event, or condition that can be objectively measured, evaluated, and compared (1). In this context, a recent study by Malcher et al. (3) examined 27 testicular biopsy specimens from 18 men in an attempt to determine genetic biomarkers for male factor infertility. Using a Gene-Chip Human Gene 1.0 ST array (Affymetrix), testicular tissues were classified into categories based on their histopathology and compared with controls with real-time polymerase chain reaction to confirm expression. In infertile men, differential expression levels of several genes (i.e., AKAP4, ODF1, PRM1, PRM2, LRWD1) were identified (3). The authors compared the expression levels of several specifically selected genes that demonstrated a minimum change (four-fold) in relation to the infertile subgroup (UBQLN3, FAM71F1, CAPN11, SPATA3, GGN, and SPACA4) (3). These genes, along with others, were then proposed to be candidates for biomarkers of spermatogenic failure in men with azoospermia.

The authors have correctly classified their results as an identification of novel male factor infertility biomarkers; however, this may be too simplistic a view. Indeed, the primary criticism of the manuscript rests with the tissues that the authors have elected to study. They compare testicular samples from azoospermic patients without germ cells (Sertoli cell–only disease) with those from patients with normal spermatogenesis (controls). Given that spermatocytes and round spermatids have very high rates of RNA synthesis (4), their presence in the control samples impacts the relative amount of gene RNA captured. Thus, the authors are not truly examining the genetic regulation of infertility but are instead classifying cellular heterogeneity and documenting the genetic composition of Sertoli cells

and germ cell RNA. Accordingly, a number of the genes already known to be expressed in spermatogenesis could serve this same purpose (1).

While the caveat that the genes identified are biomarkers is written within the Malcher manuscript, they could not be obtained from a blood sample. Instead, patients would need testicular biopsies and direct tissue homogenate analysis—eliminating a major reason why a biomarker would be beneficial. A more effective approach to identifying biomarkers would be to focus on the conserved pathways involved in nonobstructive azoospermia through analysis of fibroblasts. This would better classify the actual genetic defects involved in male factor infertility.

In summary, the genes presented in this study (discovered via testicular biopsy and perhaps the result of a few rare sperm) are coupled with a complicated and expensive microarray technique to paint an unclear picture as to how they improve current management techniques. Indeed, the ability to identify foci encompassing rare sperm that are then micro-dissected and physically identified in the biopsy specimen remains the gold standard. However, there is no doubt that specific biomarkers could be used with great utility to improve patient diagnosis. While the work of Malcher et al. (3) contributes to the quest, the genetic pathways underlying male factor infertility remain to be elucidated.

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