Getting beyond the notion of genes in reproductive medicine

David F. Albertini

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Revolutions in the quest for new knowledge take on many appearances. In biology and medicine, there has been no shortage of breakthroughs that forever change the way we think about a given topic once a new set of observations are collected and shared with colleagues whose ambitions are aimed in a similar direction. The broad spectrum of disciplines comprising our collective scientific enterprise continue to seek and obtain “truths” to the benefit of humankind as preventive, diagnostic, and treatment strategies evolve from where they resided 10, 50, or 100 years ago.

The march forward in what we perceive as the quest for new knowledge is inextricably linked to advances in technology. In the distant past, the roots of discovery rested firmly in the hands of those able to keenly observe and associate using nothing more than the naked eye. Introducing microscopes ushered in the next era of observation and analysis that brought to the surface both cell theory and the cellular basis of disease. Fast forward to the mid twentieth century, when the electron microscope arrived on the scene. An entirely new landscape of the inner workings of cells, tissues, and the assorted pathogens amongst us revealed a level of organization and complexity that both enhanced and revolutionized our powers of observation and conceptualization when it came to matters of life and death. Enter the world of molecular genetics, and the landscape of biology and medicine has taken up residence in an ever-expanding universe of new knowledge that students of human health and disease will be wedded to for years to come.

Capsule As we sink ever more deeply into the realm of bioinformatics, looking beyond traditional genetics becomes a welcomed imperative for those seeking insights into the fundamental complexities that underscore our successes and failures when it comes to human reproduction.

D. F. Albertini (✉)
3088 Kansas Life Science Innovations Center,
Kansas City, KS, USA
e-mail: dalbertini@kumc.edu

Research in reproductive medicine is following this inevitable course of action. One need only look so far as the breakthroughs afforded by GWAS studies; the discovery of new and unexpected genes plying their trades at the depths of basic processes involved in our ability to make or break good gametes or those gone sour in the embryos so derived; and the insights emerging from the high-resolution mapping of some of our old favorites like the genes for hormone receptors—the long-respected driving force behind so much that is reproductive physiology! It is with this latter theme in mind that we take a close look at genes, new and old, that are the target for sophisticated studies into the origins and consequences infertility in the male.

Featured on our cover this month is an electron micrograph of a human sperm that even the student of oncogenes might recognize as being “just not right”. This image is but one example of maligned sperm present in an ejaculate taken from a patient diagnosed with idiopathic hypergonadotropic hypogonadism. As reported by Collodel and colleagues from the University of Siena in this issue of JARG, the group of patients upon which this study is based displayed a range of SNP variations in either the FSH or LH receptor genes, accounting for their commonly elevated levels of FSH and LH. While standard semen analyses further showed some degree of pathology, it was only after a thorough analysis of sperm at the ultrastructural level that evidence of spermatogenic failure and apoptosis became evident, underscoring the clinical signs of subfertility. Two concepts emerge from this work. First, the authors make a clear case for extending future studies beyond the realm of genetics in order to accurately phenotype disease conditions such as this whose penetrance could only be appreciated by the use of the electron microscope relative to conventional light microscope evaluations in the andrology laboratory. Second, no common etiology at a genetic level will be forthcoming without what is likely to require deep sequencing approaches to better resolve the alterations observed in different segments of the LHR or FSHR polymorphisms that contributed to the complex phenotypes noted.

Finally, if our readership is wondering about how our perceptions of the genetic causes of male infertility are playing out with the technology we have in hand, then look no further than the five papers that follow the study mentioned above. These papers query the contribution of the mitochondrial DNA polymerase finding a lack of association, as does another paper examining methylation changes in an infertile population of men. On the positive side, Modi's group identifies a role for the progesterone receptor in subfertile males electing to undergo ICSI. And for the traditionalists amongst you, contributions assigning a role for segregation errors in patients carrying Robertsonian translocations and identifying the origins of numerical aberrations using high-resolution FISH fill out a menu of options that will likely elicit more of a sense of

bemusement that the level of confidence we would like to be able to offer our patients in guiding their appointment with parenthood.

Getting to know our genomes in a linear sense is fast becoming a market with which those bearing diseases of reproduction or other disorders will soon be on display as variations of a genetic theme. Indeed, having the "knowledge" of genomes is an important step in the direction of identifying the causes of infertility and other reproductive disorders. But the time may well have arrived to consider looking upon our genes on a different level in order to better comprehend the etiologies of fecundity-challenging events that impose themselves via genetic, epigenetic, and/or environmental factors that do more than cause a mutation here and there.