J Assist Reprod Genet (2014) 31:129–130
DOI 10.1007/s10815-014-0192-5

EDITOR'S COMMENTARY

Searching for genomic answers to recurrent pregnancy loss—barking up the wrong tree?

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Published online: 15 February 2014

Several months ago I attended a seminar entitled "What does our genome encode?" To finally hear that the bulk of our genomes have uses in unpredictable ways was encouraging. After all, unlike most of the organisms that populate our planet, mammals in general and humans in particular have brought to the genomics discussion table a most perplexing and puzzling situation. While plants and invertebrates engage>90 % of their genomes in protein-encoding genes and domains that regulate gene activity–with the balance ascribed to "junk DNA"–we humanoids have taken an apparently alternative tack by endowing a meager 2 % of our genomes as protein-encoding and designating the 98 % balance as junk! But what is one person's junk may be turning into another's gold.

The search for meaning to the so-called junk DNA has taken on a new and exciting connotation, in large part owing to the National Human Genome Research Institute project ENCODE (ENCyclopedia Of DNA Elements). Project ENCODE is bringing to light the nuances and sophistication of nuclear DNA that has gone into the making of human genomes. With ever-greater precision and technological bravado, the regulatory roles of what was previously thought to be useless stretches of our genomes are being recognized and placed into a three-dimensional landscape occupied by the bits and pieces that make up our protein-encoding genes amidst a mass of DNA elements that act as switches for our genes. Not only is the dissection of this genomic superstructure casting rhyme and reason for the bulk of our genomes, it is turning out that the very features that make an erythrocyte distinct from a neuron, and an adipocyte distinct from a spermatozoon, have a basis in the ways that DNA elements are organized in that specific cell types acquire and maintain a nuclear architecture unique to their designated developmental fate. With powerful insights of this kind playing into the everyday practice of human genetics, the question immediately arises as to what the benefit will be to have a patient's complete genetic code staring physicians in the face when asked for guidance for a given health condition.

For the 5,000 or so human disorders for which a specific gene or chromosomal abnormality can be identified, clinical-grade deep genomic sequencing will become cost-effective and a necessary guiding light for counseling and treatment strategies of the future. But what about multigenic disorders and the ever-increasing examples of inherited diseases for which there is no clear Mendelian basis? Without pandering to the epigeneticists amongst our readership, it is time for a sobering examination of the facts as they fit into the practice of reproductive medicine.

Our issue this month brings to the surface a focus, sadly of futile proportions, on the problem of recurrent pregnancy loss. Few situations face couples desiring a child with the combination of frustration, inadequacy, and hopelessness as those experiencing recurrent pregnancy loss (RPL). Surely, somewhere at the interface between genetics and human ARTs there will be an enabling advance for those couples with RPL to realize their dreams of having a child, by natural or artificial means.

The search for candidate genes contributory to RPL continues as an exercise in futility for many. And JARG has seen its share of the reports hoping to bridge that gap between cause and effect that has eluded scientists and clinicians to date. This month is no exception. The anticipated quest for polymorphisms linked to RPL continues in the guise of genes for *AMH, SULF1, p53*, and an old favorite *HLA-G*. And

Capsule Despite striking advances in sequencing technology that will make personal genomes commonplace components of medical records, recurrent pregnancy loss continues to evade explanation on a genetic level much to the chagrin of health care providers and affected patients.

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traditional cytogenetics, as it has in the past, offers important clues to the puzzle that is RPL. But what will it take to make the diagnosis, and subsequent counseling, failsafe and efficient for these couples? With a pathogenesis linked to inflammation, too many gene candidates could be invoked on either the maternal or fetal side for straightforward resolution and, moreover, we remain ignorant as to the extent to which this disorder may or may not find its roots in the genetic quality of the ovum itself. The latter prospect is not too farfetched when viewed in the context of a case report published several years ago.

Fisher and colleagues reported on a 29-year-old woman with four consecutive pregnancy losses, the last three being confirmed molar pregnancies (What a difference an egg makes. Lancet 2011; 378:1974). Two mutations were mapped in the gene *NLRP7* that turns out to be involved in maternal imprinting in the oocyte (although it is expressed in other tissues such as the uterus) indicating a likely causative role in the patient's history of pregnancy loss and the need for oocyte donation as a treatment strategy. Indeed, oocyte donation was successful, illustrating the utility of this approach for women bearing *NLRP7* mutations. Moreover, *NLRP7* as an agent of maternal imprinting points to both a genetic and epigenetic mechanism at least in the etiology of patients with recurrent hydatidiform moles. It seems ever more likely that the traditional genotype-phenotype link is eroding and that, as in this case, the search for a cause to RPL will end with a better understanding of the balance between the 2 % of protein-coding genes and that other 98 % of not-so-junky genomic stuff.

Getting down to a level of genetic micromanagement that will serve the needs of the reproductive medicine community remains a task of enormous proportions. Deciphering gene networks as functional entities–or how well does your junk DNA play with protein-encoding DNA–is an ongoing endeavor awaiting completion. Intercalating your epigenetics with your genetics is also active area of investigation and one that by definition will have to focus on the gametes, given their pivotal place in the management of epigenomes over the reproductive lifespan. Add to this the technology explosion, and you have what the media have enjoyed exploiting since last December 19, when the journal *Cell* published the paper "Genome analyses of single human oocytes" (Hou et al., Cell 155: 1492–1506, 2013.http://dx.doi.org/10.1016/j.cell.2013.11.040). Armed with a powerful new sequencing approach known as MALBAC, the first and second polar body genomes–and female pronuclei in some cases–were mapped in single human oocytes, providing for the first time details of female meiosis never before observed. With all the momentum behind PGS for use in human ARTs, it should come as no surprise that this kind of approach will open a gateway for a level of genetic analysis not even suspected as little as a year ago. With some luck and the compilation of technologies now being enacted, in conjunction with our evolving conceptualizations of human genetics, the problem of recurrent pregnancy loss might finally have an explanation.