Genetics causes of bovine male reduced fertility: environment and genetics meeting in the AHR gene

Rotem Vainberger[1,2], Zvi Roth[2], Alisa Komsky-Elbaz[2], Dorit Kalo[2], Tanya Kogan[2,3], Moran Gershoni[2]

1. Department of Ruminant Science, Institute of Animal Sciences, Agricultural Research Organization, The Volcani Center, Rishon LeZion, 7505101, Israel
2. Department of Animal Sciences, Robert H. Smith Faculty of Agriculture, Food and Environment, the Hebrew University, Rehovot, 76100, Israel
3. SION Artificial Insemination and Breeding Center, Hafetz-Haim, Israel.

Breeding programs for farm animals have led to significant progress in many livestock traits. However, such progress was not achieved for fertility-associated traits. This is likely due to the high heterogeneity of these traits, which involves multiple environmental and genetic variables. Typically, breeding indexes include female but not male fertility. Thus, identifying markers predicting male fertility is expected to facilitate improvement in overall herd fertility. Here, we aimed to discover genetic causes in bulls' sub-fertility. We reduced the subfertility etiological heterogeneity by producing and analyzing high-throughput phenotypic and genomic data. First, we identified bulls that presented significantly reduced conception rates; then, bulls (n=20) underwent genotype-based kinship analysis (nSNP=50K) and clustered according to their familial affiliation. This analysis revealed that the cohort of subfertile bulls is mainly composed of four familial clusters. Thereafter, we performed an in-depth semen physiology analysis to identify the precise semen fertilization malfunction. Measurements included acrosome activity, sperm membrane integrity, mitochondrial membrane potential, sperm genomic stability, and the response of sperm to oxidative stress (representing environmental stressors). The analysis pointed to one family cluster (n=4) in which all the bulls present a similar aberrant phenotype of significantly higher ROS production upon exposure to oxidative stress. That several bulls of the same descent were found to share a similar cellular response might suggest a similar genetic etiology. In support of this, a whole genome sequence analysis (WGS) of the subfertile and control bulls identified a polymorphism (MAF ~ 2.5%) in the gene Aryl Hydrocarbon Receptor (AHR) which carried by all the affected bulls (n= 4) and was absent in control (n=14). AHR is a transcription factor that enables the adaptation of cells to cellular metabolism and environmental changes. Similar to our findings, polymorphism in human AHR is associated with men's infertility and seminal oxidative stress. Therefore, it is suggested that, upon validation, the AHR allele could serve as a marker for bull fertility.