Identification of Paternal Factors Compromising Pregnancy Establishment and Reproductive Outcomes in Bovine Model

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The artificial insemination (AI) is the driver of efficiency in cattle breeding via the use of genetically superior sires through genomic selection aimed at improving production traits of their progeny. This biotechnological approach has significant impact on economy, production and environment and thus is widely, and increasingly applied worldwide. However, optimizing the production traits involves the use of a small number of often closely related sires causing reduced fitness and fertility. Detailed field AI service records enabled us to identify 85 AI bulls with acceptable sperm quality but substandard fertility outcomes. Genome sequencing revealed that these sires carry rare, homozygous single nucleotide polymorphisms in the genes known to regulate preimplantation embryo development and/or impact sperm quality. Genome sequenced bulls were sorted into subgroups based on the prevailing sperm morphological defect (e.g., knobbed acrosome, nuclear vacuoles, midpiece defects) and the rare, deleterious gene variants shared by all bulls within each group were identified. Our interest is currently focused on phenotype characterization of five carrier bulls with sperm nuclear vacuoles (NVs) phenotype that share mutations in fertility-associated genes PEG3, MSL3, PIR, EP400 and TDRD9. We developed a state-of-the-art high throughput sperm phenotyping pipeline including cell imaging, image-based flow cytometry, proteomics and protein structure modeling. Preliminary results have mapped the localization of the above proteins of interest in the spermatozoa, spermatids and testis of wild-type, non-carrier bulls and our biological control (NV spermatozoa from bull with testicular injury). The expression of mutation-affected proteins is being determined in spermatozoa of NV sires harboring the corresponding deleterious mutations, with anticipation of revealing the changes in sperm function and morphology. Results of this research will advance the understanding of spermatogenesis and link idiopathic infertility etiologies underlying pregnancy failure due to heritable paternal factors, with implication for more efficient livestock breeding, accommodating challenges listed in The Dublin Declaration of Scientists on The Societal Role of Livestock. Moreover, study results are also likely to transfer to human reproductive medicine, particularly the area of pregnancy establishment of recurrent pregnancy loss.

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