***ANIMAL***

**Review: Genomics of Bull Fertility**

Jeremy F. Taylor, Robert D. Schnabel and Peter Sutovsky

*Chromosomal aberrations and structural variants*

Chromosomal aberrations involving gross structural rearrangements such as large translocations, insertions, deletions and inversions have been known for some time to directly affect meiosis, gametogenesis, and the viability of zygotes and embryos (Raudsepp and Chowdhary, 2016). These mutations are also inherited in a non-Mendelian manner in the sense that they cause copy number variation (CNV) within individuals. While a bull that carries a Robertsonian translocation of chromosomes 1 and 29 may be normal in the sense that he carries two copies of all autosomes, the translocation may result in the unbalanced assortment of copies of chromosomes 1 and 29 into his gametes resulting in an imbalance in some embryos which may be fatal. In total, 47 different centric fusions of bovine chromosomes have been reported involving all chromosomes except 17 and 26 (Raudsepp and Chowdhary, 2016). Of these, the Robertsonian 1:29 translocation is the most common with an average frequency of about 1.2% in cattle and is responsible for a 5-10% reduction in fertility in carriers (Raudsepp and Chowdhary, 2016). Presumably, the centric fusions that involve other chromosome pairs also results in reductions in fertility due to the imbalance in chromosome numbers in gametes following meiosis. Reciprocal translocations involve the exchange of small chromosome segments between non-homologous chromosomes and are thought to be the second most common of the structural rearrangements in cattle (Raudsepp and Chowdhary, 2016). Of these, a translocation involving a ~500 kb chromosomal segment involving *KIT1* on chromosome 6 to chromosome 29 has been shown to be responsible for color-sidedness in cattle (Durkin et al. 2012). However, whether any of the known translocation events results in any effect on fertility is not known.

A major constraint to studying the effects of structural and copy number variants on cattle fertility is the difficulty in detecting the presence of novel variants and then accurately assaying their genotypes (copy numbers and genomic organization) in sufficient numbers of animals to enable suitably powered association studies. The use of next generation sequence data, in particular, with the paired-end sequencing of large insert fragment libraries may allow the detection of translocations and large CNVs but with relatively high false positive and negative discovery rates (Bickhart et al., 2015). Nevertheless, a study involving the whole genome sequence data of 75 individuals has shown that there is significant variation in the copy number of the fertility related genes prolactin-related protein family (PRP) and pregnancy associated glycoprotein (PAG) within cattle (Bickhart et al., 2016). Intensity data generated in the collection of high-throughput SNP chip genotypes can also be used to detect CNVs in a high-throughput manner, albeit with issues of resolution in terms of the size of the duplicated regions that can be detected. This approach also suffers from high false positive and negative discovery rates, but was used by Xu et al. (2016) to characterize CNVs in the Bovine HapMap panel representing 300 animals from 8 breeds including European and African taurines and indicines. By performing three pairwise comparisons among European taurine, African taurine and the indicine groups, the study identified 78 CNV regions that were differentiated between the groups. These regions overlapped with genes involved in traits related to parasite resistance, immunity response, body size, fertility, and milk production.

**References**

Bickhart DM, Hutchison JL, Xu L, Schnabel RD, Taylor JF, Reecy JM, Schroeder S, Van Tassell CP, Sonstegard TS and Liu GE 2015. RAPTR-SV: a hybrid method for the detection of structural variants. Bioinformatics 31, 2084-2090.

Bickhart DM, Xu L, Hutchison JL, Cole JB, Null DJ, Schroeder SG, Song J, Garcia JF, Sonstegard TS, Van Tassell CP, Schnabel RD, Taylor JF, Lewin HA and Liu GE 2016. Diversity and population-genetic properties of copy number variations and multicopy genes in cattle. DNA Research 23, 253–262.

Durkin K, Coppieters W, Drögemüller C, Ahariz N, Cambisano N, Druet T, Fasquelle C, Haile A, Horin P, Huang L, Kamatani Y, Karim L, Lathrop M, Moser S, Oldenbroek K, Rieder S, Sartelet A, Sölkner J, Stålhammar H, Zelenika D, Zhang Z, Leeb T, Georges M and Charlier C 2012. Serial translocation by means of circular intermediates underlies colour sidedness in cattle. Nature 482, 81–84.

Raudsepp T and Chowdhary BP 2016. Chromosome aberrations and fertility disorders in domestic animals. Annual Review of Animal Biosciences 4, 15-43.

Xu L, Hou Y, Bickhart DM, Zhou Y, Hay EH, Song J, Sonstegard TS, Van Tassell CP and Liu GE 2016. Population-genetic properties of differentiated copy number variations in cattle. Scientific Reports 6, 23161.