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THE USE OF GENETIC AND GENOMIC TECHNOLOGIES TO IMPROVE REPRODUCTIVE PERFORMANCE IN CATTLE

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This paper reviews existing and emerging genetic and genomic technologies to improve performance in farm animals with a focus on reproduction in dairy and beef cattle. It covers three inter-related areas and provides an outlook on impact of emerging technologies on reproductive biology and theriogenology. Conventional quantitative genetics and animal breeding strategies will continue to be an important basis on which to improve animal's genetic merit for desirable reproductive characteristics in herds. The genetic and phenotypic trends in many cattle breeding countries show that substantial progress has been made in improving milk and meat production. However, the consequences of genetic selection for milk and meat production on reproduction (and health / disease resistance) are very unfavourable (Kadarmideen, Thompson and Simm 2000, Kadarmideen, Thompson, Coffey et al. 2003). Modern animal breeding programs are now aimed at arresting the decline in reproductive ability of animals by optimising selection for production and reproduction, simultaneously via Total Merit Selection Index (Kadarmideen and Simm 2002).

Advances in molecular genetics have led to identification of genes or genetic markers controlling variation in reproductive ability of animals. Many chromosomal regions (quantitative trait loci or QTLs) have been identified for various reproductive traits on 26 of 30 bovine chromosomes. These QTLs can be incorporated in predicting genetic merit as per the methods of Meuwissen, Hayes, Goddard (2001). Currently selection and breeding decisions based on this approach are practiced by many breed societies and genetic companies around the world. An alternative form of identifying genes affecting reproduction is candidate gene approach which exploits variation within genes known to affect reproduction (for instance, GnRH, PRL, BPL, STAT genes etc.). Recently completed bovine genome sequencing and assembly projects (The Bovine Genome Sequencing and Analysis Consortium 2009) have led to the paradigm shift in QTL and candidate gene approaches. Currently, the genome-wide association studies (GWAS) uses 50000 or more dense genetic markers called Single Nucleotide Polymorphisms (SNP) to accurately detect genes for reproduction; these SNP discoveries are used in predicting genome-wide merit of animals and conducting 'genomic selection'. The genomic selection predicts the performance of an animal (at birth) given their genotypes at SNPs without ever recording a phenotypic observation. Hence it has huge impact on cost of traditional progeny testing schemes and length of time to make selection decisions (Schaeffer 2006).

Functional genomics and systems genetics (based on microarray gene expression profiling or MGEP) helps detect and annotate differentially expressed (DE) and co-expressed (CE) genes and construct underlying gene networks of reproduction. For instance, we have used these approaches to unravel the biology and genomics of sheep resistance to gastrointestinal

nematode (GIN) infections as well as sheep muscle growth and development (Kadarmideen, Watson-Haigh, Andronicos 2010). The same approaches can be applied for reproductive traits. For instance, animals with clearly distinct reproductive outcomes or characteristics could be used to identify DE and CE genes. GWAS and MGEP are often practiced as independent approaches to study reproductive phenotype; the power to unravel the biology of reproduction is greatly increased if both MGEP and GWAS are jointly conducted in *genetical genomics* framework. Recently, we have applied this integrated approach in identification of loci regulating expression GnRH and GnRH-receptor genes in inbred strains of mouse; this has implications for livestock species.

In the near future, there will be further revolution in genomics due to transition from Sanger sequencing (called first generation sequencing) to next generation sequencing or NGS (Metzker 2010); The NGS techniques are rapidly replacing microarrays due to inventions of a number of robust sequencing technology platforms and falling cost for generating sequence-based data. In addition to gene expression studies, NGS offers detection of cSNPs, novel and rare transcripts, novel protein isoforms, alternative splice sites, ncRNA, and allele specific expression in one single experiment. NGS will continue to rapidly open new applications in the biological sciences and scientists will have to adapt to these challenges. The scientists working in the areas of computational and systems biology, statistical genomics and bioinformatics, in particular, would need to keep up with these rapidly evolving new technologies.

Last but not the least veterinarians will play a crucial role in generating good quality and quantity of reproduction related data in cattle using new herd and animal level monitoring and management devices (e.g. heat detection and hormonal activity meters, intra-uterine devices, ovarian ultra sound scans etc.). Such phenotyping will be a basis for applying any novel genetic/genomic technologies and hence to have an impact in cattle reproduction.

1. Conventional quantitative genetics and animal breeding strategies for improving reproductive performance in cattle

The key to genetically improve performance of animals is to keep accurate records of their performance for (genetic) evaluation and selection of best animals / culling worst animals. Hence, performance recording of cattle is crucial and are now conducted using state-of-the-art information technology tools and purpose built computer databases that are routinely implemented by national recording organisations and various breed societies. Veterinarians play an important role in assisting accurate and consistent reporting of disease, health or reproductive problems by farmers / producers to national recording organisations and various breed societies. The performance recording is standardized in most industrialized countries as per the guidelines of International Committee on Animal Recording (ICAR); this is more so for dairy cattle than beef cattle. Pedigree recording is also crucial for genetic evaluation as these methods predict future performance of animals based on performance of its relatives.

Quantitative genetics method is a well proven method to improve reproductive performance and productivity. Development of selection index principles in animal breeding programmes in

early 1940's (Hazel and Lush 1943) followed by application of Best Linear Unbiased Prediction (BLUP) of animal's genetic merit from early 1970's (Henderson 1975) have had major impact in animal breeding and it continues to do so. These methods accurately quantify transmittable genetic merit of animals or breeding potential (estimated breeding values or EBVs; expected progeny differences or EPDs) for economically important traits and are expressed in real units of measurement (e.g. percent pregnancy or non-return rates). To assess the relative superiority of a bull or a cow, the animal's EBV is compared with those reported by a breed average. With continuing advances in statistical and computing technology, quantitative geneticists successfully refined and modified BLUP methodology. This has led to accurate predictions of genetic merit of cattle and hence accurate selection of best animals for a range of desired traits simultaneously via Total Merit Index (TMI).

One of the traditional quantitative genetics approaches that does not require DNA genotyping but is aimed at detecting evidences of segregating major genes based only on phenotype and pedigree in BLUP framework is called complex segregation analysis [Janss et al. 1995]. It uses mixture (polygenetic and monogenetic) effect models and detects major genes, if present in the data. Stringent statistical tests are conducted for *Mendelian* transmission at the major gene to rule out environmental and polygenetic effects. These approaches are more often applied in detecting major genes for clinical diseases & reproductive and auto-immune disorders in bio-medical sciences than agricultural sciences. Examples of such segregation analysis applied to large animal populations for the analysis of production and health traits include cattle [Ilahi and Kadarmideen 2004, Karacaören et al. 2006], pigs [Kadarmideen and Janss 2005 and 2007, Kadarmideen and Ilahi 2005] and poultry [Hagger et al. 2004].

There has been very high emphasis on milk and meat production in dairy and beef cattle production programs over many decades (understandably due to food security issues after the Second World War). The genetic and phenotypic trends in many cattle breeding countries show that substantial progress has been made in improving milk and meat production. However, the consequences of genetic selection for milk and meat production on reproduction (and health / disease resistance) were very unfavourable, as seen in antagonistic genetic correlations between production versus "functional" traits (Kadarmideen et al. 2000 and 2003). Evidences are provided from various developed countries to support this trend. Hence it is important to arrest the decline in reproductive ability of animals. Modern animal breeding programs have taken these issues seriously by optimising selection for production and reproduction, simultaneously (Kadarmideen and Simm 2002).

As mentioned earlier conventional genetic/breeding approaches to make genetic improvement in reproduction rely heavily on availability of good quality and quantity cattle reproduction data, which could only be achieved with good collaboration between veterinarians, artificial insemination companies or stud breeders and recording organisations (Kadarmideen 2003). Recording for cow fertility should address two essential components: first the cyclicity- how early the cow comes to heat after calving; and the second, the ability to conceive at the first mating or insemination and to maintain the pregnancy (Kadarmideen 2003). These two components would reflect most biological phenomenon underlying reproduction in cattle. Because heat observations are difficult to observe and record in field conditions, number of

days between calving and first mating or insemination and conception successes or non-return rates (NR) should be used in genetic evaluations. Until full-scale recording and reliability of mating and insemination records improves, some indirect fertility traits can be used (example, calving interval or body condition scores). There is definitely an economic sense to putting more emphasis on reproduction in breeding program because TMI that includes reproduction show 38% more profit than the TMI that does not include reproductive traits (Kadarmideen and Simm 2002).

2. Molecular genetics enhanced animal breeding strategies for improving reproductive performance in cattle

Identification of genes or genetic markers controlling variation in economically important quantitative traits, such as reproduction and complex diseases or disorders in animals has been practiced for over 20 years. The gene mapping or so called quantitative trait loci (QTL) mapping uses a few hundred multi-allelic microsatellite markers that are spread evenly and densely across the entire genome. QTL mapping is based on two steps: a) Creation of genetic linkage maps (in centiMorgan or cM units) based on recombination rates and/or distances using genetic markers. Analogy to linkage map is a large voluminous text book and markers are like page numbers on the book referring to a point in the genome and b) application of statistical modelling and analysis of genomic regions flanked by markers for their effect on range of traits (such as NR). For instance, investigating whether an animal carrying one form of a gene (allele) has more ability to be cycling regularly and have high NR than an animal carrying a different form of the gene (allele). These techniques have been extensively developed and applied in various livestock species for various traits and numerous QTLs have been found. For reproductive traits in cattle, there are several studies showing QTL or genomic regions that may contain genes affecting reproductive ability of cattle. For instance, Jemaa et al. (2008) found QTLs for NR traits on bovine chromosome 1 (68 - 98 cM), chromosome 2 (100-119 cM) and chromosome 3 (20-30 cM) and Holmberg et al. (2007) found NR QTLs on Chr 9 (25-30 cM). Hoglund et al (2009) lists several QTLs for various reproductive traits on all 26 chromosomes. Often, identification of causal genes is difficult but the genetic markers that are closely linked to or co-segregating with putative genes may be used to derive associations.

An alternative form of identifying genes affecting reproduction is candidate gene approaches. These approaches exploit variation within genes known to affect reproduction (for instance, GnRH, PRL, BPL, STAT genes etc.). The candidate gene approach looks at explaining variation in reproductive performance between animals because different animals carry different polymorphisms within a gene, each having different end result due to changes in protein and/or metabolites that produced by allelic variants. Some examples of detected candidate genes for reproductive traits include the study of Huang et al., (2009) for BPL, GHR PRLR genes, Kadarmideen et al., (2008) for PRL, Gpr54, FOS genes, Khatib et al. (2009) for *STAT1* and *STAT3* genes.

Whether it is a QTL based approach or candidate gene based approach, the identified gene information can be put into practical genetic improvement of reproduction. The incorporation of genetic marker in selection and breeding decisions of elite animals is called *marker assisted selection*. If marker information is incorporated in traditional BLUP EBVs then it is called *Marker*

Assisted breeding value estimation. These approaches and their impact on improving performance of animals are thoroughly discussed in Dekkers et al., (2004).

Bovine genome sequencing and assembly projects (The Bovine HapMap Consortium 2009 and The Bovine Genome Sequencing and Analysis Consortium and Elsik et al. 2009) have led to the end of low throughput gene mapping using microsatellites and a paradigm shift in QTL and candidate gene approaches. It is due to availability of high throughput genetic markers ranging from 50000 or more Single Nucleotide Polymorphisms (SNP). This number is expected to reach to 300,000 markers in the near future. These markers can be genotyped using high throughput Affymetrix or illumina GeneChips. The genome-wide association studies (GWAS) relate each one of those highly dense SNP markers with observed phenotypic traits (such as reproduction) in a “reference population” to identify SNP-QTLs across the genome that explains most genetic variation in phenotypes (Kruglyak 2008). Results of GWAS are then used in “Genomic Selection” of livestock in a “selection population” where estimated SNP effects are used predict the performance of an animal (at birth) given their genotypes at SNPs without ever recording a phenotypic observation, with an accuracy up to 70%. This dramatically changes traditional progeny testing schemes in cattle and other species because it eliminates the need to maintain and record performance of large number of animals from test bulls or sires for many years. In addition, GWAS still offers identification of major QTLs or candidate genes. This genome-wide genetic evaluation of animals is now practiced by livestock genetic evaluation industries and genomic companies (e.g. Pfizer Animal Genetics and Merial). This has become quickly adapted because the traditional genetic evaluation schemes suffer from the longer time span needed to prove genetic merit of animals and costs involved in progeny- or sib-testing schemes. In fact, Schaeffer (2004) claims, via empirical simulations, that the use of SNP GeneChip[®] arrays can cut down the cost of typical progeny testing in dairy cattle (and other animals) by astonishing 92% and the genetic improvement could be two-fold compared to normal conventional methods. However, it is important to address the lack of biological knowledge in these “gene discovery” or ‘genomic selection’ projects because of high number of false positives and biologically irrelevant SNPs. For instance, SNPs that are within the coding regions of genes which in turn are involved directly in producing proteins, metabolites or hormones affecting reproduction would need to be given higher weights than those that are peripherally involved. To this end, softwares such as FuncSNP (developed in our lab by Goodswen et al. 2010) that appropriately identifies functionally relevant SNPs for a given trait would be useful.

3. Functional genomics and systems genetics enhanced animal breeding strategies for improving reproductive performance

Microarray gene expression profiling (MGEP) has become popular in livestock species in the last decade that uses high-throughput transcriptomic arrays (e.g. Affymetrix or Agilent arrays) containing up to 30000 gene transcripts to reveal underlying gene (co)regulation in a set of biological conditions. Most transcriptomics experiments are focused on detection and annotation of differentially expressed (DE) and co-expressed (CE) genes and construction of gene networks (for review of transcriptomics, see Kadarmideen and Reverter 2007). For instance, we have used these approaches to unravel the biology and genomics of sheep resistance to gastrointestinal nematode (GIN) infections as well as sheep muscle growth and

development (Kadarmideen et al. 2010a, and 2010b). These methods or techniques are the same for reproductive traits, where animals with clearly distinct reproductive outcomes or characteristics could be used.

While the above mentioned GWAS and MGEP are often practiced as independent approaches to study a disease or reproductive phenotype, the power to unravel the biology of such traits is greatly increased if both MGEP and GWAS are jointly conducted in the same population to study genetics of -omics variation (genetic variation in transcriptome; Kadarmideen et al. 2006). Until the invention of high-throughput -omic techniques, it has not been possible to identify genetic variation in these omics traits. *Genetical genomics* is a novel method in integrative systems biology that helps us to investigate the inheritance of such regulatory loci, so called *expression quantitative trait loci* or *eQTL*. Recently, we have identified eQTLs regulating expression GnRH and GnRH-receptor genes in inbred strains of mouse that have implications for livestock species (Kadarmideen 2008)

4. New genomics approaches to improve reproductive performance

Hybridization-based approaches typically involve incubating fluorescently labelled cDNA with custom-made microarrays (e.g. Agilent arrays) or commercial high-density oligo microarrays (Affymetrix arrays as described in previous section); these methods have several limitations, which include:

- a. reliance upon existing knowledge about genome sequence
- b. high background levels owing to cross-hybridization
- c. A limited dynamic range of detection owing to both background and saturation of signals
- d. comparing expression levels across different experiments is often difficult and can require complicated normalization methods

The main factors that enabled transition from Sanger sequencing (called first generation sequencing) to next generation sequencing (NGS) are inventions of number of robust sequencing technology platforms and falling cost for generating sequence-based data. The fundamentals of NGS technologies are reviewed by Metzker (2009 and 2010). These NGS approaches are quantitative in that they directly determine the entire sequence thereby more accurately estimating RNA expression levels in cells or tissues than microarrays. We can directly compare results between experiments. In addition to gene expression studies, NGS offers detection of cSNPs, novel and rare transcripts, novel protein isoforms, alternative splice sites, ncRNA, and allele specific expression in one single experiment. Computationally, RNA-Seq has an advantage in that it can capture transcriptome dynamics across different tissues or conditions without sophisticated normalization of data sets. Hence, the evolution of 'omic' science has come full circle with a new focus on next generation genome sequencing. In nutshell, NGS will continue to rapidly open new applications in the biological sciences and scientists will have to adapt to these challenges.

The generation of high-throughput -omics data (proteomic, metabolomic, metagenomic, transcriptomic, genomic and nutrigenomic data) have resulted in data deluge containing information on genes (& their sequences), metabolites, proteins, cellular dynamics and

organisms' responses to genetic and environmental perturbations. Systems biology, in practice, is a result of these new technologies that enables hugely comprehensive data at all levels of biological system to be collectively analysed using state-of-the art mathematical, computational biology and bioinformatic principles and tools. The principle of systems biology is that, in order to understand how an organism functions, (e.g. how human/animal grow, develop disease etc.,) we must study interactions at various levels both within and across biological systems but not in isolation. It is the vision of system biology to be ultimately able to link different processes within and between cells, tissues, organs, functions of the system and eventually up to the individual level traits to provide complete blueprint of functions. A branch of systems biology which focuses on integrating genetic factors (SNPs, QTLs etc) causing variation between individuals in intermediate -omic traits (whole genomic gene expression levels, metabolomic or proteomic levels etc) is called systems genetics. Livestock systems genetics will become increasingly important as more and more genes or QTLs affecting various intermediate traits are found in addition to SNPs or QTLs causing variation in complex polygenic traits measured on the animal itself such as reproduction traits. This 'systems genetics' would also include combining these data with information on signalling pathways and gene networks from other bioinformatic resources for a broader and deeper understanding of systems biology of complex traits. The most exciting development in genomics of reproduction will be to integrate NGS based transcriptomic and metabolomic investigations on reproduction with GWAS studies on reproduction.

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