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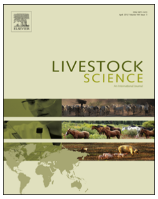

Meta-assembly of genomic regions and variants associated with female reproductive efficiency in cattle

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ABSTRACT

Decline in fertility in last few decades, especially in high milk producing dairy cows, is a major concern in many countries. Fertility is a compound trait of many events leading up to successful calving and subsequent lactation. Fertility traits in cattle have relatively low heritability. Recently a number of studies have searched for genomic regions and variants associated with various reproduction traits in cattle. We constructed a systematic meta-assembly of 35 QTL studies and separately for 23 genome-wide association studies (GWAS) related to female fertility in cattle representing over 101,000 genotyped individuals. We separately compiled and discussed additional candidate gene studies, fine-mapping studies, selection signatures and other novel potential biomarkers associated with female reproduction in cattle. Despite individual studies being low powered, inherent low heritability of fertility traits and low success of genomic selection for fertility traits, a substantial number of strong signals, causative mutations and biomarkers for fertility have been identified throughout the genome. A number of embryonic lethal mutations and haplotypes have been identified using novel approaches. These markers can be used for population screening, genomic-assisted mating plans, and can be incorporated in a marker assisted framework for genetic improvement in the fertility. The studies investigating the role of epigenomic markers are in the early stages, and may provide important biomarkers in near future. Novel approaches linking metabolomic and epigenetic markers, and high resolution genome content to high quality phenotypes will assist in our understanding of the genetic architecture of complex traits underlying fertility in cattle.

1. Introduction

Decline in fertility over the last few decades especially in high milk producing dairy cows, is a major concern to dairy industries world-wide. The calving rate of the modern dairy cow is declining at approximately 1% per annum (Royal et al., 2000). The decline in fertility has resulted in long-term declines of conception rates from 66% in 1951 to less than 50% in 1975 (Butler and Smith, 1989) to less than 44% in Holstein Friesian dairy cows across 14 Irish seasonal spring-calving dairy farms between the years 1990 and 2001 (Evans et al., 2006). The decline in fertility is associated with approximately one day increase per year in calving interval in Holstein dairy cows as observed in multiple countries (Rajala-Schultz and Frazer, 2003; Mee, 2004; Hare et al., 2006b; Atashi et al., 2012) and increased calving-to-conception intervals (de Vries and Risco 2005). Long-term herd life also declined as the mean number of parities for Holsteins declined from 3.2 for those first calving in 1980 to 2.8 for

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those first calving in 1994 (Hare et al., 2006a). The decline in overall fertility appears to be associated with the intensification of production and selection of animals with higher levels of milk production coupled with unfavourable genetic and environmental correlations between milk yield traits and fertility, and higher metabolic demands placed on cows for increased milk production.

Given the importance of cattle and in particular the Holstein breed in world milk production, this review primarily focuses on genetic architecture and factors underlying fertility in dairy cattle, with the inclusion of relevant studies from beef cattle.

1.1. Genetic variation in fertility

Fertility traits in cattle have relatively low heritability. Mark (2004) and VanRaden et al. (2004) reviewed the genetic parameters used in several countries for genetic evaluations and found that heritability estimates for different fertility traits to be small (0.01 to 0.07). Haile-Mariam et al. (2008) reported heritability estimate of 0.02 and 0.03 for calving interval in seasonal and year-round calving systems, respectively, in Australian Holstein Friesian. Whilst under experimental farm conditions heritability estimates of 0.16 and 0.11 for calving to first heat and calving to first service in Holstein Friesian in Ireland, the United Kingdom, the Netherlands and Sweden were reported by Berry et al. (2012). The estimates of genetic parameters on specific component traits for fertility are limited as well as those associated with heifer fertility since most reports concern cows in lactation. Despite the low heritability estimates for fertility traits, underlying genetic variation is often quite substantial but masked by large sources of undefined environmental variation, as well as difficulties with phenotypic expression and measurement of the component traits which make up fertility.

1.2. Trait definition and phenotypic expression

Fertility is a complex trait with many events leading up to successful reproduction. The key stages and sub-component traits relate to onset and expression of oestrus, ovulation, fertilization, embryo establishment, maintenance of pregnancy, parturition and neonatal survival. Each of the components are known to be under different genetic control (Kropp et al., 2014). Compounding the difficulty of fertility investigations is the expression and routine measurement of fertility traits. Current genetic evaluation for fertility in dairy cattle in most countries is mainly based on calving interval as calving date is easily recorded. However, calving interval is a censored trait where cows that do not calve again are excluded from genetic evaluations. Analysing a compound trait like calving interval by a single phenotypic measure is common practice but of limited utility in the detailed understanding of events contributing to the decline in fertility. Successful re-calving is the result of a chain of events including resumption of oestrous cycles post-partum, regular cycling and ability to conceive when inseminated, maintenance of pregnancy and parturition. The measurement of the component traits in large scale herd recording is limited despite the obvious value in the identification and understanding the factors contributing to the decline in fertility.

1.3. Scope for marker assisted selection

DNA markers provide an opportunity to gain insight into genomic mechanisms affecting fertility and an avenue for the application of DNA markers in the genetic improvement of fertility traits in cattle through marker assisted selection (MAS). MAS for fertility is particularly attractive since it favours traits which have low heritability, are difficult to measure, are sex limited, are expressed late in life and have high economic value. An extensive number of studies have been undertaken to find the genomic regions and variants associated with various reproduction traits in cattle. Early studies focussed on discovery of quantitative trait loci (QTL) based on microsatellite markers genotyping in pedigreed resourced populations (Khatkar et al., 2004; Hu et al., 2013). With the availability of SNP chips and DNA sequencing in bovine, a number of recent studies have focussed on genome-wide association studies (GWAS) in cattle (Hu et al., 2013; Zhang et al., 2012; Fortes et al., 2013a). The main assumption in the application of GWAS is that at least one of the SNPs on the panel is in linkage disequilibrium (LD) with causative mutations or quantitative trait nucleotides (QTNs). Given the extent of LD in cattle (Khatkar et al., 2008), current marker densities (especially 800K SNPs) seem sufficient to discover most significant associations. Furthermore, imputation provides another avenue to increase the marker density for GWAS and genomic selection applications (Khatkar et al., 2012). Fertility traits being complex traits are, in general, considered to be controlled by a large number of genes, each with very small individual effects (Wiggans et al., 2011). However, a number of individual recessive mutations have been discovered with marked unfavourable effects on fertility (Nicholas and Hobbs, 2014). A number of studies have used a candidate-gene approach and other novel approaches such as homozygote deficient haplotypes to discover such variants. The main limiting factor in the detection of significant genomic factors contributing to fertility has been the power and size of individual studies, with most being underpowered and leading to false positive associations and an under reporting of genes with small effect. In order to overcome this limitation we have undertaken a meta-assembly of all information available to us on genomic investigations on female fertility and herd life in cattle.

We first constructed a systematic meta-assembly of the QTL studies related to female fertility in cattle. We then separately prepared a meta-assembly of GWAS studies. Finally we compiled candidate gene studies, fine-mapping studies, and selection signatures/selective sweeps not included in the above two meta-assemblies.

2. Construction of meta-assembly of genomic studies on female fertility in cattle

2.1. Meta-assembly of QTL studies

QTL studies related to female fertility were extracted from the online AnimalQTLdb database (Hu et al., 2013). In total 35 studies, which covered the whole genome, were

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