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Identifying genes underlying quantitative traits

SS. Moore[1], M.R.S. Fortes[1], M. Kelly[1], Russell E Lyons[2], To Loan Nguyen[1], L. Dierens[2], Y. Li, and S.A. Lehnert

[1]The University of Queensland, Queensland Alliance for Agriculture and Food Innovation, Centre for Animal Science, Brisbane, Qld 4067, Australia.
[2]CSIRO, Animal, Food and Health Sciences, Queensland Biosciences Precinct, QLD 4067, Australia

Abstract

Quantitative Genetic approaches have been highly successful in animal improvement across all livestock species. More recently the addition of genomic information has, where the right criteria were met, further enhanced the approach. The best example is the Holstein dairy breed, where the addition of genomic profiling (using the Illumina BovineSNP50 beadchip), coupled with the existing phenotype recording system, has both improved the accuracy of selection and decreased the generation interval. The result has been a doubling of the rate of genetic gain in Holstein dairy cattle. Further to this, industry adoption of the technology in North America took less than 12 months from the availability of the single nucleotide polymorphism (SNP) chip. This is certainly an impressive piece of innovation; however significant barriers exist within the beef cattle sector, as each breed and population needs to have specific equations developed in order to calculate accurate GEBVs on any trait. A GEBV at best could achieve is the prediction power equivalent to the heritability of a phenotypic trait. This is compounded by the lower accuracy of the phenotypes assembled for developing GEBVs compared to the dairy industry. However successful this approach is to predicting GEBVs, the "Black Box" approach of treating every marker equally does not inform us about the underlying biology. While current GWAS approaches on the other hand have, with some notable exceptions, failed to identify genes of even moderate effect on whole animal phenotypes, it would seem that the interaction between genes is as important as the variation within the genes themselves. This paper examines possible approaches to improving the success in gene mapping and gene network analysis in tropically adapted *Bos indicus* cattle. Component traits such as fatty acid composition and reproductive traits will be used as successful examples.

Introduction

The use of genomic approaches to estimate genetic merit in cattle and other livestock has been a great success in a number of sectors (Goddard, et al., 2010; Saatchi, et al., 2011). The rate limiting step is no longer the availability of the technology, rather the cost of implementation, both in the cost of the genotyping, but more so the cost and logistics of collecting the necessary phenotypes. This in turn is determined by the structure of the industry and, depending on this, the value of individual breeding stock.

For example, the Holstein based dairy industry had a system in place for many years prior to the availability of single nucleotide polymorphism (SNP) chip technology for collecting relevant accurate phenotypes as well as an internationally agreed recording and evaluation system. The wide use of AI meant the superior bulls were very valuable and used widely across the entire industry. However, the time taken to "prove" a bull meant a long generation interval of around 5-7 years accompanied by a high cost of collecting the necessary phenotypes. It is easy to see why Genomic Selection was so quickly adopted in this industry. Shortening the generation interval alone through the availability of accurate Genomic Breeding Values allowed earlier distribution of semen from now proven young bulls. This resulted in a doubling of the rate of genetic gain along with substantial added savings as fewer bulls needed to have data collected on their daughters and grand daughters. All this for a DNA profile costing less than $200.00 per animal.

The poultry industry has also adopted genomics approaches. Despite the low value of the individual animals (around $0.01 per chick), the centralized structure of the industry makes it possible to implement genomic selection profitably. The same can be said for the swine breeding sector which falls somewhere between chickens and dairy cattle.

There have been significant challenges for implementing genomic selection across the beef industry. Some success has been achieved in the Angus breed, due to the number of animals, an intensive

production system allowing reasonably accurate phenotypic recording. Further the wide use of AI enables dissemination of superior genetics and hence increased value of superior bulls (Saatchi, et al., 2011). However the fact that GS has to be developed specifically for each breed or population means that the encouraging results from Angus cannot be directly applied across the whole industry. Despite this other breeds with larger populations and the ability to collect phenotypes look set to follow as more data is accumulated for each.

The situation in more extensive or commercial production systems is not as favorable towards genomic selection approaches. In the Northern Australian system as an example, it is extremely difficult to collect accurate phenotypes, AI is not widely adopted and bull inventory often hard to control. To address some of these issues, the Cooperative Research Centre for Beef Genetic Technologies (Beef CRC) invested in creating a genotype and phenotype database for Brahman and Tropical Composite cattle bred in Northern Australia (Barwick et al., 2009; Fortes et al., 2013). Nevertheless, the implementation of genomic selection in these extensive, multi-breed conditions remains a challenge.

We propose that there is an urgent need to understand the biology underlying economically important traits. The "Black Box" approach to quantitative and genomic selection will not help in this, as it does not have the ability to tag chromosomal segments housing informative genes. The quantitative trait loci (QTL) mapping or genome-wide association studies (GWAS) approach however has been somewhat disappointing in their ability to identify genes of even moderate affect (Ron et al., 2007).

The modest success of GWAS, despite increasingly dense genomic information, can be attributable to a number of factors. As Brenner (Brenner et al., 2010) points out, sequencing the genome is like sending a man to the moon. Getting him back is the tricky bit. We understand the sequence structurally but interpreting the sequence in the context of the complex physiology of a man or a cow (getting back) remains the problem. Even when simple traits are studied it is often only after the discovery of the causal gene that the molecular pathway becomes clear. With so called complex traits the phenotypes are often hard to measure accurately, reflect the whole animal state at just one point in time, and can be expressed differently in different genetic backgrounds. The situation has led to the suggestion that Fischer's contention (Fisher, 1918) of an infinite number of genes may be correct, however as Brenner (Brenner et al., 2010) points out "the whole may be greater than the sum of the parts studied in isolation but the very existence of biological organisms tells us that it cannot be greater than the sum of its parts and their interactions".

We have approached the problem in the context of beef cattle production by examining the individual component traits, which are closer to single cell or organ performance rather than whole animal or even herd performance. Two examples will be presented, (1) percentage of Oleic acid in a mix of *Bos taurus* and *Bos indicus* cattle as an example of a trait which is closely aligned with a defined molecular pathway. (2) Reproduction performance, which has been broken down into traits such as scrotal circumference at various time points, age at puberty for females and post partum anestrus. The cattle have been either Brahman or Tropical Composites, restricting somewhat the variation in genetic background.

Methods

Animals

Animal Care and Use Committee approval was not required because data used were obtained from existing phenotypic databases and DNA storage banks established by the Commonwealth Research Centre for Beef Genetics technologies (Beef CRC). Previous work was conducted under approval granted by the J M Rendel Laboratory Animal Experimental Ethics Committee (CSIRO, Queensland) as per approvals TBC107 and RH225-06.

Oleic acid composition

The cattle were part of the Australian Cooperative Research Centre for Beef Genetic Technologies (Beef CRC I). Phenotype data from 1,206 cattle were used. The overall design of the program was described previously by (Upton et al., 2001). A more detailed description of the animals measured for fatty acid composition was provided by (Kelly et al., 2013). Fatty acid composition of the

lipids in subcutaneous adipose tissue samples were determined by gas-liquid chromatography, essentially as described previously (Smith et al., 1998; Kelly et al., 2013).

Reproduction traits

Phenotypic data from 3,185 cattle, Brahman and Tropical Composite, were used for the current study (details on numbers of genotyped animals are in the following section). These cattle are part of the extensively phenotyped population bred by the Beef CRC. These cattle and their phenotypes have been described in detail previously (Burns et al., 2013; Corbet et al., 2013; Barwick et al., 2009; Johnston et al., 2009). In short, we used data from the growth and reproduction experiments of the Beef CRC, which included Brahman cows, their male offspring as well as Tropical Composite cows and their male offspring. Phenotypes of interest for this study were reproductive traits in males and females, which are components of overall fertility. In males, Scrotal Circumference (SC) and Percent Normal Sperm (PNS) were measured at 12, 18 and 24 months of age. In females, we observed puberty defined as Age at first Corpus Luteum (AGECL), and Post Partum Anoestrous Interval (PPAI), after the first calving.

Genotyping

For genotyping, DNA was extracted from blood samples of each animal. Animals were genotyped using one of 4 different SNP chips: the Illumina 7k chip was used for most of the oleic acid experiment, the BovineSNP50 bead chip (Matukumalli et al., 2009) version 1 was used to genotype females of the reproduction set; the BovineSNP50 bead chip version 2 was used to genotype males of the reproduction set; and the high-density SNP chip was used to genotype 917 samples (representative sires and dams of the Beef CRC). All SNP chips were processed according to the manufacturer's protocols (Illumina Inc., San Diego, CA). Repeated samples were included in the genotyping for quality assurance and the Bead Studio software (Illumina Inc., San Diego, CA 2006) was used to determine genotype calls. Genotype edits were carried out as previously reported (Hawken et al., 2012; Kelly et al., 2013; Fortes et al., 2012; Fortes et al., 2013). After BovineSNP50 genotyping, sires and selected representative animals of the Beef CRC populations (those 917 samples) were genotyped with the high-density SNP chip (~770,000 SNP; Illumina Inc., San Diego, CA) to allow for genotypic imputation. Complete high-density genotypes were imputed using the BEAGLE 3.2 program (Browning & Browning 2010) for all samples, as described previously (Fortes et al., 2013; Fortes et al., 2013b].

For oleic acid GWAS, 1,206 cattle were used and these were from three breed-types: *Bos indicus* (Brahman), *Bos taurus* (4 breeds) and tropically adapted composites (2 breeds). Details were described previously (Kelly et al., 2013).

For the reproduction traits GWAS, 843 Brahman cows, 866 Tropical Composite cows, 1,115 Brahman bulls and 1,085 Tropical Composite bulls were genotyped with SNP chips. Further, to test a possible causative mutation on BTA14, all females and Brahman males were tested for the SNP rs109231213, previously associated with stature in dairy cattle (Karim et al., 2011). This SNP is a *G* to *C* mutation that was mapped to the 3-UTR region of the *PLAG1* gene, and we used a TaqMan assay to genotype animals for this SNP, following published methodology (Karim et al., 2011). Results for the *PLAG1* analysis were first described by Fortes et al. (2013b) and are presented here as an example of fine-mapping following GWAS results.

Initial GWAS showed a QTL on chromosome X for male fertility (Fortes et al., 2012; Fortes et al., 2013). To test for possible causal mutations on two candidate genes located in this QTL on chromosome X we genotyped 1,476 cattle. Phenotypic data from 1,124 Brahman and 352 Tropical Composite (1,476) bulls were used for this fine-mapping experiment. Candidate genes were the androgen receptor (*AR*) and *TEXT11*. Genotyping was performed by allelic discrimination using custom TaqMan SNP Genotyping Assays and following the manufacturer's instructions. Briefly, 5 µl PCR reactions were carried out containing 2.5 µl TaqMan Universal PCR Master Mix (Applied Biosystems, New Jersey, USA), 10 ng DNA template and 0.25 µl TaqMan® Assay primers and FAM/VIC labelled probes by Applied Biosystems as Assays-by-Design™ (Applied Biosystems, Foster City, CA, USA). All thermal cycling experiments were performed in 384 well plates on a Gene Amp 9700 (Applied Biosystems). Amplification conditions consisted of 50°C for 2 min, 95°C for 10 min followed by 40 cycles of 95°C for 30 s and 60°C for 1 min, and finally 25°C until removed from the thermal cycler. End-point reads

were then performed on the Applied Biosystems ViiA™ 7 Real-Time PCR System, and allelic discrimination analysis was performed using ViiA™ 7RUO software (Life Technologies, CA, USA).

Statistical Analysis

Oleic acid composition

The additive effect of each SNP was estimated by regression in a mixed model analysis using Wombat (Meyer et al., 2011) and fitting the following model:

$$y_i = X\beta + Z\mu + s_j + e_i$$

where y_i is the percentage of Oleic acid in subcutaneous beef fat of the i animal, X is an incidence matrix relating the observations and fixed effects in β. While Z is an incidence matrix linking the observations to the random additive polygenic effects (μ). The term s_j is the additive association of the SNP (fitted as a random effect in the model) and lastly $e_{i,}$ is the random residual error term for animal i. The fixed effects used in the GWAS analysis of all traits were the herd of origin, sex, year/season and HCW*Slaughter day.

Reproduction traits

Genome-wide association studies were performed with high-density SNP for each trait separately. Genotype calls were coded as 0 for the homozygote of the A allele, 1 for the heterozygote and 2 for the homozygote of the B allele. Alleles A and B were defined according to top/bottom rules from Illumina.

A mixed animal model similar as above was used to examine the marker-trait association.

Where $\mathbf{S}_k$ in the vector of genotypes for the *k*-th SNP across all animals; a_{jk} represents the additive association of the *k*-th SNP on the *j*-th trait.Fixed effects included in the model were contemporary group (i.e. cohorts of cattle born in the same year and raised together) and trait specific fixed effects detailed before (Hawken et al., 2012; Fortes et al., 2012; Fortes et al., 2013). Age (in days) at the time of trait measurement was used as a linear covariate for SC, PPAI and PNS. Solutions for the effects in the model as well as variance components were estimated using Qxpak5 (Perez-Enciso et al., 2011) for bulls and using ASReml software (Gilmour et al., 2002), as detailed previously (Hawken et al., 2012; Fortes et al., 2012; Fortes et al., 2013). Association tests were performed one SNP at a time and one phenotype at a time.

The same models used in the GWAS were used to test the association between the *PLAG1* SNP and each trait (Fortes et al., 2013b).

Test for Admixture

Further, we performed admixture tests for BTA14 and chromosome X. Details for BTA14 were published before (Fortes et al., 2013b), but for the X chromosome results are presented here for the first time. To determine whether there was a general increase in the proportion of *Bos taurus* alleles across the genome or in the X chromosome in animals carrying the *G* allele of the *TEX11* SNP we performed an admixture text. The *Bos taurus* percentage of each animal was estimated using either all 50k autosomal SNP or all X chromosome SNP using Admixture (Alexander et al., 2009). To test for more localized admixture, the origin of 10 SNP haplotypes was estimated across the X chromosome using the methodology described in (Bolormaa et al., 2011). The *Bos taurus* reference animals included 3,666 male animals from three breeds (Angus, Shorthorn Murray Grey and Hereford) and 1,032 Brahman bulls were used as the *Bos indicus* reference. The mean and standard deviation of *Bos taurus* proportion was then calculated for animals carrying the *A* or *G* allele of the most significant TEX11 SNP.

Results and discussion

Oleic acid composition was considered as a model trait, which is linked to a discrete set of metabolic pathways. The top locations observed in GWAS were on chromosome 19 and 23 (Figure 1). Further investigation of the regions underlying these peaks revealed strong candidate genes, fatty acid synthase and steroyl Co-A desaturase. These genes have been found to be associated with differences in fatty acid composition across a large range of breeds from Angus to Wagyu (Meyer et al., 2011; Alexander et al., 2009; Zhang et al. 2008, Powell et al., 2010; Uemoto et al., 2010; Zhang et al., 2010b; Mannen, 2011; Matsuhashi et al., 2011; Orru et al., 2011; LI et al., 2012; Uemoto et al. 2012; Yokota et al., 2012), thus illustrating the utility of traits which are more closely linked to cellular pathways. These "intermediate" phenotypes can be used as stepping stones for investigating more complex, whole animal traits. In this example, oleic acid composition is an intermediate phenotype for investigating fat metabolism.

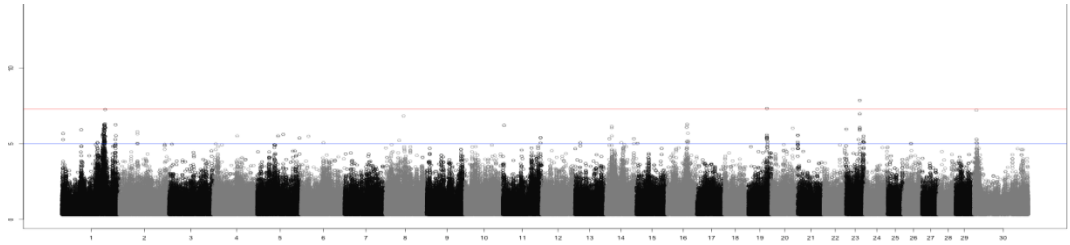

Figure 1. Manhattan plot of association between C18:1c9 SNP.

Reproductive traits were broken down into the following components: Scrotal Circumference (SC) at 12, 18 and 24 months, Percent Normal Sperm (PNS) at 12, 18 and 24 months, Age at first Corpus Luteum (AGECL), and Post Partum Anoestrous Interval (PPAI). Previous results from the Beef CRC have identified multiple QTL for these traits on various chromosomes (Hawken et al., 2012; Fortes et al., 2012; Fortes et al., 2013). Fortes et al. (2013b) further examined the QTL on BTA14 and found evidence for pleiotrophic effects of genes in the region. Effects were seen on IGF1 concentration in blood, hip height, feed intake, and age at puberty in males (SC of 20cm) and females (AGECL). Some of these traits were antagonistic, for example younger age at puberty and smaller frame size. A strong candidate gene (PLAG1) was identified from previous studies (Karim et al., 2011; Littlejohn et al., 2012; Nishimura et al., 2012; Pryce et al., 2012 e Utsunomiya et al., 2013), although other strong candidate genes do exist in the region. Further to this, strong evidence was found of that the favorable haplotype for female reproductive traits was of *Bos taurus* origin (Fortes et al., 2013b).

An examination was carried out of the QTL region on chromosome X affecting SC and PNS at various ages. The broad QTL region suggested the possibility that two genes may be present in the region that influence one or both traits. Two genes were examined, the Androgen Receptor (*AR*) and Testes Expressed 11 (*TEX11*).

Brahman cattle were "graded up" in both the USA and Australia. In other words the small number of animals introduced into each country the founders necessitated the crossing of Brahman bulls with various *Bos taurus* breeds then backcrossed to achieve a required proportion, usually $15/16^{th}$ Brahman origin. The result of this is that the Australian Brahman genome contains on average around 10% *Bos taurus* content (Bolormaa et al., 2011). The QTL regions of BTA14 and BTAX in Brahman cattle both contained a slightly higher than background level of Taurine content. Further examination of the regions indicated that the alleles having a positive effect on reproductive traits were of *Bos taurus* origin. With approximately 80% of haplotypes in this region in animals carrying the favorable allele being of *Bos taurus* in origin.

Tropical adaptation enables *Bos indicus* cattle to survive in the harsh and seasonal conditions such as experienced in the Northern Australian landscape. This however comes at a cost, animals grow slower and are reproductively less efficient that *Bos taurus* animals, which usually inhabit more manageable and milder environments. How far the *Bos indicus* cattle can be pushed to improve economically

advantageous traits or what is the maximum advantage that can be gained from cross breeding schemes remains uncertain. What is interesting is that of the two QTL examined here affecting reproductive traits, the favorable alleles in both are of *Bos taurus* origin. During the "grading up" process it could be speculated that alleles fixed in *Bos taurus* animals and favorable for reproduction would self-select. Further selective pressure through practices such as culling empty cows or selecting for SC (a trait present in the current breeding program in Australia) would further increase the frequency of these alleles. It is tempting to speculate on how many *Bos taurus* derived haplotypes might be favorably influencing production traits in Brahman cattle.

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