Genome wide association study reveals new chromosome regions affecting age at first calving in Nellore cattle

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Resumo: Na era da seleção genômica, a identificação e o uso de marcadores genômicos como os SNPs permite predição e ganho em acurácia nos valores genéticos genômicos estimados (GEBV) para características de importância econômica. Os objetivos deste estudo foram estimar parâmetros genéticos para idade ao primeiro parto (AFC), fazer predições genômicas em bovinos Nelore, bem como identificar QTLs associados aos SNPs mais relevantes. Os dados fenotípicos consistiram de registros de peso à desmama (WW) e AFC de 847 animais da raça Nelore, sendo 529 destes animais genotipados (24,572 SNPs). Foi utilizado nas análises o modelo hierárquico Bayesiano bicaracterístico ajustado via MCMC via metodologia em passo único (ssBLUP). Foram identificados os 0,05% (12) mais relevantes SNPs para AFC bem como QTLs que podem estar relacionados com essa característica. As estimativas de herdabilidades foram 0,18 e 0,41 para AFC e WW, respectivamente. Já a estimativa de correlação genética foi de 0.06. Os 0,05% SNPs mais relevantes foram detectados nos cromossomos 7, 9, 14, 16, 18, 21, 24, 26 e 29. O SNP mais relevante foi detectado em BTA14 onde foi também obervado um pico nos efeitos dos SNPs que pode revelar a importância deste cromossomo para AFC. Além disso, novas regiões cromossômicas que podem estar relacionadas com a característica estudada foram detectadas.

Palavras–chave: Acurácia de predição, genes candidatos, parâmetros genéticos.

Abstract: In the genomic-wide selection (GWS) era, the identification and use of molecular markers such as SNP allows the prediction and accuracy gain of genomic estimated breeding values (GEBV) for economically important traits. The objectives of this study were to estimate genetic parameters for age at first calving (AFC), to perform genome-enabled predictions in Nellore and well as to identify QTLs associated to the most relevant SNPs. Phenotypic data included records of weaning weight (WW) and AFC from 847 Nellore whereas genotypes were acquired on 529 of these animals (24,572 SNPs). A multi-trait model was fitted under a MCMC Bayesian approach using a single step BLUP methodology. We identified 0.05% (12) of the most relevant SNP for AFC as well as reported QTLs related with AFC. Heritability estimates were 0.18 and 0.41 for AFC and WW, respectively. The genetic correlation between AFC and WW was 0.06. The top 0.05% most relevant SNPs were detected on chromosomes 7, 9, 14, 16, 18, 21, 24, 26 and 29. The most relevant SNP marker was detected on BTA14, when we also observed a peak which could reveal the importance of this chromosome for AFC. Moreover, we identified new regions that might be related with AFC.

Keywords: Candidate genes, genetic parameters, prediction accuracy.

Introduction

The most used reproductive trait to evaluate female fertility in beef cattle is the age at first calving (AFC), which this trait is easily measured and it is also expressed in almost all cows under genetic evaluation. In the genomic-wide selection (GWS) era, the identification and use of molecular markers such as single nucleotide polymorphism (SNP) allows the prediction and accuracy gain of genomic estimated breeding values (GEBV) for economically important traits. As a sex limited trait, the breeding values in males for AFC can be estimated, although not measurable directly.

Another point we may highlight is the Quantitative Trait Loci (QTL) detection derived from relevant SNP markers. Therefore, the objectives of this study were to estimate genetic parameters for age at first calving, to perform genome-enabled predictions in Nellore beef cattle by using a single step BLUP (ssBLUP) as well as to identify QTLs associated with the most relevant SNPs.

Material and Methods

Phenotypic data included adjusted weaning weight (WW) and age at first calving (AFC) on Nellore cattle. The 847 animals had records for weight and/or AFC and were born between 2000 and 2013. A total of 1,860 animals remained in the pedigree after removing those not related to the ones with records. The overall mean for WW and also for AFC during the evaluation period was 145.01 ± 25.79 Kg (range 54.53-256.25) and 1,208 ±191.18 days (range 628-1,811). Contemporary groups (CG) were defined by animals born within the same year and season. SNP Genotypes based on the BovineSNP30 Illumina v2 BeadChip uniformly distributed across the genome were acquired on 529 of these animals. Genotype quality control was implemented to remove samples with low call rates (≤ 0.95). Only SNPs with minor allele frequencies (MAF) ≥ 0.05 or not highly significant deviations from Hardy-Weinberg equilibrium were used for further analyses. After these quality control edits, 24,572 SNP markers remained which were used to estimate genomic relationship coefficients between animals.

These analysis was performed using a multi-trait GBLUP model ($\mathbf{Y} = \mathbf{X\beta} + \mathbf{Za} + \mathbf{e}$) fitted under a MCMC Bayesian approach, where **Y** is the vector of traits, **X** and **Z** are the incidence matrices of systematic (contemporary group, linear and quadratic animal age effect) and random additive genetic effects, respectively, **β** is the vector of systematic effect, **a** is the vector of random additive genetic effects, being **H** the genetic relationships based on pedigree adjusted for deviations due to genomic information as $\mathbf{H} = \begin{bmatrix} \mathbf{A}_{11} & \mathbf{A}_{12} \\ \mathbf{A}_{21} & \mathbf{G} \end{bmatrix} = \mathbf{A} + \begin{bmatrix} \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{G} - \mathbf{A}_{22} \end{bmatrix}$, where subscripts 1 and 2 represent ungenotyped and genotyped animals, respectively, **A** is a numerator (traditional pedigree) relationship matrix for all animals, **G** is a genomic relationship matrix which use the allele frequencies estimated from the genotyped individuals (Aguilar et al., 2010).

Finally, for a linear GBLUP model, if we decompose the animal effects into genotyped (g_g) and ungenotyped (g_n) animals, the animals effects are a function of SNP effects ($g_g = \mathbf{Zu}$); where **Z** is a matrix relating genotypes of each locus and **u** is a vector of SNP effects. Therefore, the equation for predicting SNP effects is: $\hat{u} = \mathbf{Z}'[\mathbf{ZZ}']^{-1}\hat{g}_g$. From û we identified the top 0.05% of most relevant SNPs that presented the greatest absolute values for AFC as well as reported QTLs related with this trait.

Results and Discussion

The heritability estimate (h^2) for AFC was 0.18 and similar to those reported for Nellore cattle (range 0.13 to 0.18) in literature (Boligon et al., 2008; Boligon et al., 2010). It indicates small genetic variability in the expression of AFC as well as large influence of environmental factors. On the other hand, h^2 for WW was higher (0.41) suggesting that a considerable portion of the variation for these traits is due to the differences in the animal genetic merit. These results indicate that AFC and also WW might respond to individual selection. In addition, the genetic correlation estimate between AFC and WW was positive but close to zero (0.06). Negative correlations between these traits have already been extensively reported indicating that selection for larger WW would negatively affect the animal sexual precocity (Boligon et al., 2008; Boligon et al., 2010).

The Manhattan plots show the top 0.05% (12) SNP markers associated with AFC (Figure 1). The top 0.05% (12) most relevant SNPs were detected on chromosomes 7, 9, 14, 16, 18, 21, 24, 26 and 29 (Table 1). The most relevant SNP marker was detected on BTA14. Previously studies have reported QTL for AFC only in BTA2, BTA4, BTA19 and BTA29 (Clempson et al., 2011; Camargo et al., 2014; Sasaki et al., 2014).

Table 1. SNP marker (SNP), chromosome (Chr.) and position (Mb) for the top 12 SNPs for age at first calving.

SNP	Chr.	Position	Ranking	SNP	Chr.	Position	Ranking
BovineHD1400007539	14	26136726	1º	BovineHD2100019729	21	67172168	7º
BovineHD2600001600	26	7020897	2º	BovineHD1600024618	16	62695370	8º
BovineHD0700018018	7	62489638	3º	BovineHD1800013121	18	44297519	9º
BovineHD2900001343	29	4717549	4º	BovineHD1400006451	14	22331572	10º
UA-IFASA-8638	14	29109628	5º	BovineHD0900029031	9	100147391	11º
BovineHD1400010072	14	34873487	6º	BovineHD2400018502	24	22569408	12º

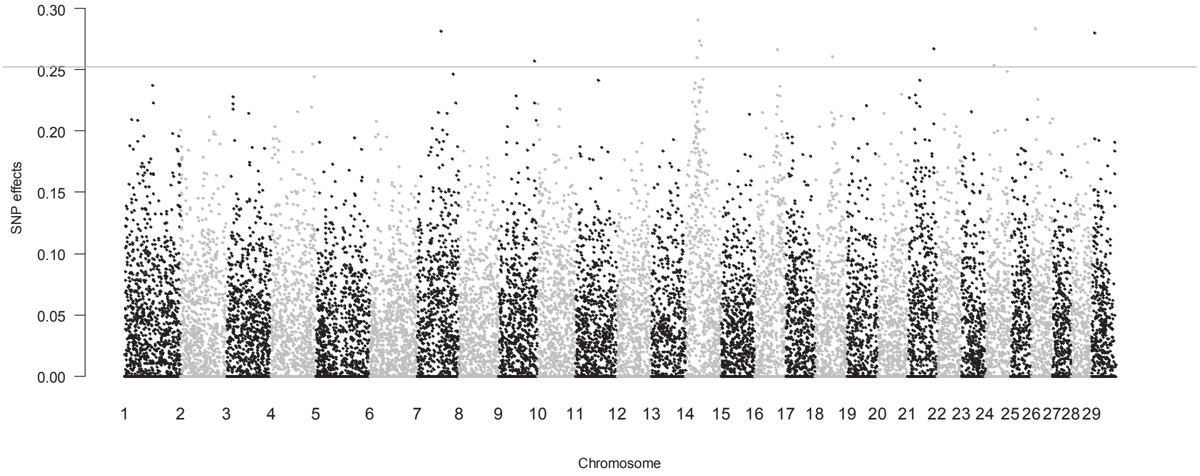

Figure 1. Manhattan plots reported for age at first calving (AFC). The corresponding horizontal line indicates the top 0.05% (12) most relevant SNP markers that affect AFC.

Conclusions

Age at first calving showed little genetic association to weaning weight. Both AFC and WW might respond to individual selection. We reported the most relevant SPNs for AFC with a peak on BTA14, which might detect the presence of QTLs. Further investigation in the detection of genomic regions explaining part of the phenotypic variation is still needed.

Acknowledgements

We thank The University of Queensland and QAAFI for theoretical and technical support, CAPES by granting the scholarship and Associação Brasileira de Criadores de Zebu (ABCZ).

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