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Association between single nucleotide polymorphisms and sexual precocity in Nellore heifers

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ABSTRACT

The aim of this study was to determine the extent (r^2) of linkage disequilibrium (LD) in the genome of Nellore cattle, and to examine associations between single nucleotide polymorphisms (SNP) and age at first calving (AFC) and early pregnancy (EP) using a panel of high-density SNPs and data from 1182 Nellore females. A total of 13 contemporary groups (CG) were used consisting of farm, season, and year of birth. For genome-wide association analysis, SNPs with a minor allele frequency (MAF) <0.05 and animals with a call rate <0.90 were excluded, totaling 431,885 SNPs. For statistical analysis, a linear model was used for AFC and a threshold model for EP. To estimate the significance of the associations for the two traits, the model included the categorical fixed effects of CG, SNPs, and sire. In addition, the polygenic effect was included in the analysis. The additive effects and dominance deviations of Bonferroni-adjusted significant SNPs for AFC and EP were estimated using orthogonal contrasts. The average estimate of r^2 for all autosomes was 0.18 at a distance of 4.8 kb and the mean MAF was 0.25 ± 0.13. The LD decreased as the distance between markers increased: 0.35 (1 kb) to 0.12 (100 kb). Eleven significant associations were detected in seven different chromosomes. Seven SNPs were associated with AFC and four were associated with EP. Three SNPs were significant for both traits. The identification of SNPs associated with AFC and EP may contribute for selecting sexually precocious animals.

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1. Introduction

The major focus of Zebu breeding programs are traits related to reproductive efficiency, such as sexual precocity. Developing bio-economic models, several authors concluded that reproductive traits are economically more important than growth traits (Brumatti et al., 2011; Krupa et al., 2005; Wolfova et al., 2005). In this respect, studies have shown that an increase in productivity (kg live weight sold/hectare/year) can be achieved with a reduction in the slaughter age of heifers, associated with an earlier age of heifers at first breeding (Beretta et al., 2001, 2002a,b; Pötter et al., 1998, 2000).

Age at first calving (AFC) and early pregnancy (EP) are related to the efficiency and profitability of beef production. Although AFC is easily obtained and is observed early during the animal's life, some breeders delay the start of the breeding season by predetermining a specific weight and/or age, impairing the identification of precocious animals and reducing genetic variability in this trait (Dias et al., 2004a). In addition, the fact that only animals that calve are included in the analyses and the low heritability estimates (Boligon et al., 2010; Dias et al., 2004b; Grossi et al., 2009; Mercadante et al., 2000; Pereira et al., 2000, 2005; Regatieri et al., 2012) result in a poor response to selection.

In an attempt to overcome the difficulties encountered when AFC is used as a selection criterion, EP has been employed in genetic breeding programs. According to Shiotsuki et al. (2009), EP is defined by the observation of a heifer that conceived and calved after she had been exposed to a bull during the breeding season. This definition results in a binary response of the trait (success or failure), a fact that permits the inclusion of data from all females in the analyses. In addition, this trait has greater heritabilities (0.50–0.73) for heifers exposed to bulls for the first time between 14 and 18 months of age (Boligon and Albuquerque, 2011; Eler et al., 2002, 2004; Silva et al., 2005; Van Melis et al., 2010), thus permitting a rapid response to selection.

Reproductive traits have quantitative genetic variation and the expression is influenced by some genes or a series of genes (quantitative trait loci, QTL). According to Höglund et al. (2009), the identification of a QTL for female reproductive traits can increase the response to selection. These genes can be identified based on the linkage disequilibrium (LD), which is calculated as the squared correlation of allele frequencies (r^2) at a given locus (Hayes, 2009). Molecular markers, called single nucleotide polymorphisms (SNP), are commonly used for the detection of QTL due to the ease of genotyping and the fact that these polymorphisms are present throughout the genome (Hayes et al., 2006).

The 50k SNP panels have been used in beef cattle to determine associations of SNPs with reproductive traits. Zhang et al. (2010) reported associations between several SNPs and age at puberty in Brahman females. Similarly, Hawken et al. (2012), working with Brahman Tropical Composite cattle, observed associations of SNPs with postpartum anestrus interval and the occurrence of postpartum ovulation before weaning. Using part of the data from the study of Hawken et al. (2012), Fortes et al. (2012) identified SNPs and chromosome regions that are directly associated with age at puberty of females and scrotal circumference in bulls. There have been some studies related to reproductive traits in zebu cattle such as: genome-wide association studies using 777k SNP panels (Irano et al., 2016; Nascimento et al., 2015; Costa et al., 2015), candidate gene/SNP studies (Fortes et al., 2013a,b), and combinations of methodologies (SNP association and gene expression; Fortes et al., 2014). The use of these technologies is being developed especially in tropical regions due to the importance of female performance in beef production profitability.

Genome-wide association studies using high-density panels are still scarce in zebu cattle. The objective of the present study, therefore, was to identify regions of LD in the bovine genome, and determine the presence of genetic markers that are associated with age at first calving and early pregnancy in Nellore cattle.

2. Materials and methods

A total of 1182 records of Nellore females born in 2007 and 2008 from 131 sires, which belonged to Agropecuária Jacarezinho Ltda. (Valparaíso, São Paulo – Brazil), were used. Genomic DNA was extracted from hair follicles obtained from the tail switch of females using the phenol/chloroform/isoamyl alcohol method (Sambrook and Fristch, 1989). Genotyping was performed using the high-density BovineHD BeadChip (Illumina, San Diego, CA, USA – 777,962 SNPs) according to the Illumina Infinium® II Assay Multi-Sample protocol in a HiScan™SQ System. The consistency of the genomic data was confirmed using the Genome Studio program. Bovine autosomes (BTA, $n = 29$) were considered for analysis and the genotypes were defined as AA and BB (homozygous), AB (heterozygous), and NA (not identified). The sex chromosome was not included in the analysis.

A total of 824 and 11,389 markers were excluded due to an unknown genome position and low mean cluster intensity (AB, AA or BB mean <0.3), respectively. In addition, 21,709 markers present on the sex chromosomes were also eliminated. Only markers with a minor allele frequency (MAF) >0.05 were considered for analysis. In addition, only markers with excess heterozygosity <0.30 were analyzed and animals with a call rate <0.90 were excluded.

The LD between two SNPs was calculated based on the r^2 measure (Hill and Robertson, 1968) as follows:

$$r^2 = \frac{(freq.AB * freq.ab - freq.Ab * freq.aB)^2}{(freq.A * freq.a * freq.B * freq.b)}$$

Where freq.A, freq.a, freq.B and freq.b are the frequencies of alleles A, a, B and b, respectively, and freq.AB, freq.ab, freq.aB and freq.Ab are the frequencies of haplotypes AB, ab, aB and Ab, respectively, in the population. If the two loci are independent, the expected frequency of genotype AB (freq.AB) is calculated as the product between freq.A and freq.B. A freq.AB that is greater or less than the expected value indicates that these two loci tend to segregate together and are in LD. The measure of LD (r^2) was calculated for all pairs of SNP markers of each chromosome using the SnppldHD program (Sargolzaei, M., University